AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Eye Disorders

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OVERVIEW

The Eye Disorders treatment guideline is designed to provide health care providers with evidence-based guidance on the treatment of working-age adults with potentially work-related eye disorders, whether acute, subacute, chronic, or postoperative. While the primary patient population target is working-age adults, the principles may apply more broadly.

This treatment guideline discusses the initial assessment and diagnosis of patients with eye injuries and disorders that are potentially work-related, identification of red flags that may suggest the presence of a serious underlying medical condition, initial management, diagnostic considerations and special studies to identify clinical pathology, work-relatedness, modified duty and activity, and return to work, as well as further management considerations including delayed recovery. Algorithms for patient management are also included and schematize how to generally manage eye disorders. This guideline does not address certain eye disorder categories such as congenital disorders or malignancies. It also does not address specific intraoperative procedures. For those patients with allergies who also have work-related asthma, the Occupational/Work-Related Asthma Guideline may be of assistance. This includes recommendations on exposure management of sensitizer-induced asthma, irritant-induced asthma, and criteria for removal from exposure.

The objectives of this guideline include baseline evaluations, diagnostic tests and imaging, return to work, medications, patching, injections, and operative procedures. Comparative effectiveness is addressed where available. To be more inclusive, this guideline includes some disorders that may not be considered work-related by certain jurisdictions. It excludes disorders that are considered to be entirely nonoccupational. It is recognized that there are differences in workers' compensation systems [1] and regional differences in treatment approaches.[2-4]

The Evidence-based Practice Eye Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine and Reed Group, neither of which influenced the guidelines. The literature is routinely monitored and searched at least annually for evidence that would overturn this guidance. The guideline is planned to be comprehensively updated at least every five years, or more frequently should evidence require it.

A detailed methodology document used for guideline development including evidence selection, scoring, incorporation of cost considerations,[5, 6] and formulation of recommendations is available online as a full-length document[7] and has also been summarized elsewhere.[8, 9]

The health questions for acute, subacute, chronic, and postoperative eye disorders addressed by this guideline include:

1. What diagnostic studies have been used for pre/placement examinations? Screening examinations?
2. What evidence supports the initial assessment and diagnostic approach?
3. What red flags signify serious underlying condition(s)?
4. What diagnostic approaches and special studies identify clinical pathology?
5. What initial treatment approaches have evidence of efficacy?
6. What is the evidence of work-relatedness for various diagnoses?
7. When is patching appropriate?
8. What modified duty limitations are effective and recommended?
9. When is return to work status recommended?
10. When initial treatment options fail, what evidence supports other interventions?
11. When and for what conditions are injections and other invasive procedures recommended?
12. When and for what conditions is surgery recommended?
13. Which surgeries are recommended for which conditions?

All evidence in the prior eye disorders guideline garnered from four databases (Cochrane, PubMed, CINAHL, and Scopus) was included in this guideline. Additionally, new comprehensive searches for evidence were performed in those databases up through 2016 to help assure complete capture. There was no limit on year of publication. Search terms are listed with each table of evidence. Guidance was developed with sufficient detail to facilitate the assessment of compliance[5] and auditing/ monitoring.[6] Alternative options to manage conditions are provided.

Because few studies solely evaluate patients with work-related eye disorders, studies that include different populations were used to develop the recommendations. In addition, most studies that focus on pharmaceuticals, appliances, and specific devices are industry sponsored. In certain areas, this may have made little difference as the comparisons were between the medication and placebo and the results may be stark. However, in other studies, the comparison groups may have been suboptimally treated and produced a bias in favor of the medication or device. In addition, industry-sponsored studies have been shown to frequently have better results and lower complication rates than studies conducted by independent investigators.

This guideline has undergone extensive external peer review. This guideline includes all criteria for the AGREE[6], IOM criteria[5] AMSTAR [10], [11] [12] and GRADE II [13] criteria. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers.[5]

Definitions

The classifications of *acute* (<1 month), *subacute* (1 to 3 months), and *chronic* (>3 months) are used in this guideline where appropriate and are based on commonly accepted durations.

Rationales for recommendations may refer to costs, which are defined as *low* (<$100), *moderate* ($100-$500), and *high* (>$500).

Impact

Based on population-based data, it is estimated that 3.5-7.7% of the general US population does not have binocular visual correction of at least 20/50, with considerable differences based on race/ethnicity (Lee 00). The Centers for Disease Control and Prevention estimated that 3% of adults over 40 years are either blind, have visual fields less than 20 degrees, and/or have visual impairment (20/40 or less) [14]. Approximately 16% of adults over age 40 have cataract(s), 3% are blind (20/200 or less), and 2% have glaucoma [14]. Adequacy of visual acuity is a major criterion for many jobs, and visual impairments have been associated with increased risks of injuries [15]. Color deficiencies are common but highly variable, affecting approximately 8% of the male population with European ancestry [16]. Color perception is a requisite criterion for numerous occupations; specific requirements vary widely depending on job requirements.

The workplace is a common source of ocular injury [17-20] and emergency department surveillance data indicate males in their third decade of life have the highest incidence rates (64.8% *cf* females) [21]. Eye injury claims at the largest US workers compensation insurer constituted 5% of all workers compensation claims [22]. Some permanent eye disability cases are also occupationally related. For example, disabling ocular injuries (8.5%) are reportedly the second most common injury in construction workers after low back pain (14.8%) [23].

The average cost of an occupationally-related eye injury has been estimated at $1,463 (OSHA), although this is likely an underestimate due to inadequate inclusion of indirect costs to employers for rehiring and retraining replacement workers, the loss of productivity, reduced quality work, administrative costs, and losses to the patient and patient's family (including productivity at home).

Risk and Causation

The etiology of most ocular injuries is noncontroversial. The eye is well innervated with nociceptors (pain sensation). The mechanism of injury and onset of symptoms is thus acute, noticeable, and readily discernible. Ocular diseases are naturally more challenging, with many factors producing ocular diseases such as pterygia and cataracts (see Work-Relatedness Guideline).

Acute Trauma

Determining the work-relatedness of ocular injuries (e.g., foreign bodies, rust rings, corneal lacerations, abrasions, contusions, hyphemas, burns) is not difficult because the mechanism of injury and acuity of symptom onset generally begets a straightforward determination of work-relatedness [22, 24-46]. Chemical injuries are common [47-60].

The construction industry has many reported risks for ocular injuries [47, 61-66]. Manufacturing is also a common industry with reportedly elevated risks [47, 50, 67, 68].

Welding-related tasks constituted an estimated 8.2% of all workers' compensation claims at the largest US workers' compensation insurer, with actual welding as the most common cause of occupational eye injury (38.5%), followed by grinding (17.5%), multiple tasks (3.8%), standing/walking/observing (3.4%), cleaning/brushing (3.3%), manual material handling (2.6%), and numerous other activities [22].

Employment in that study was most commonly in manufacturing (60.7%), construction (13.7%), services (12.1%), and wholesale/retail trade (5.9%).

Eyewear is believed to be strongly protective for eye injuries, although quality studies are sparse (likely largely due to the ease of implementation of eyewear programs) [26, 68-77]. Barriers to eyewear usage and/or injury reportedly include younger age [78], lack of comfort/fit [79], fogging [79], scratching of the eyewear [79], being rushed [80], fatigue [80], faulty equipment [80], foreign workforces [56, 81-84], and lack of safety training [78, 79, 85]. A case-crossover trial found unfamiliar work to be a considerable risk for ocular injury [80]. An ecological study found an inverse relationship between unemployment conditions and risks of report of ocular injury [86].

Enucleation is a sequellae of severe work-related eye injuries [24, 87]. A university-based case series reported occupational causes in 13.5% of cases and motor vehicle crashes in 13.5% of cases [24]. Open globe injuries are similarly reported to commonly arise from occupational injuries [27, 32, 40, 56, 63, 75, 88-95].

Welder's Flash (Photokeratitis)

Acute, unprotected ultraviolet radiation exposures (UV-A, UV-B) are known to burn the cornea and conjunctiva [96-101]. Welding is the most commonly reported exposure. Other reported examples include ultraviolet lamps for poultry abattoir disinfection [102], germicidal medical lamps [103], and damaged protective covers on mercury vapor lamps [104].

Pterygia

The worldwide prevalence of pterygia is estimated at 10%. Men have an approximately 7% higher risk for pterygia compared with women [105, 106]. For individuals in their 40s to 60s, the risk for pterygia approximately doubles [105]. Cigarette smoking is estimated to *reduce* risk of pterygia by 18% [107]. Conjunctival tumors are more common among farmers compared with controls [108]. Outdoor activity has been associated with 76% higher risk of pterygia [105, 109-116]. There is a 3.6-fold higher risk of pterygia among those living at latitudes of 0°-10° compared with those at 40°-50° [105]. Other reported risks include alcohol [117], low educational status [117-119], high systolic blood pressure [120], dry eyes [117, 119], not using sunglasses [117, 119], not using a hat [117, 119], light complexion [110], and dark complexion [112]. Use of sunglasses has been estimated to reduce risk up to 5.6-fold [110].

Retinal Laser-Induced Damage

Lasers are highly variable in their intensity and ability to damage tissue [121-123]. Reports include associated retinal and other ocular damage [124-133] among military [134-136] and commercial pilots [137, 138].

Cataracts

A cataract is a lens opacity that obscures vision. Cataracts are typically subdivided according to their anatomic location (i.e., nuclear, cortical, posterior subcapsular) and severity (size and intensity) of visual impairments by various classification systems [139-148]. The different anatomic locations may occur simultaneously in one patient. Elderly individuals are most susceptible to nuclear cataracts, whereas younger patients are more susceptible to posterior subcapsular cataracts.

Age is a robust risk factor for cataracts [149-162], with National Health Interview Survey data suggesting that individuals older than 75 years have a 10-fold greater risk compared with young adults [163]. Low educational status is a risk for cataracts [163]. Genetic factors are reported risks [164-167].

Age-related and cortical cataracts have been associated with increased carbohydrate intake and glycemic index [168]. Microvascular retinal changes associated with hypertension reportedly predict the risk of nuclear cataracts [169], as does hypertensive status [170]. Diabetes mellitus increases cataract risk by approximately 67-80% [149, 163, 170-173]. Oral hypoglycemic agents and insulin have been associated with 2-fold and 3.4-fold increased risks, respectively, which appear to be markers for diabetes rather than additional independent risks [166]. Use of glucocorticosteroids also increases risk [166, 174].

Smoking and alcohol have both reportedly increased risk of cataracts [177]. Obesity has been found to increase the risk of age-related cataracts, particularly posterior subcapsular cataracts [166, 175]. Lipids have been associated with increased risk [171]. Statins have been found to reduce the risk of nuclear cataracts by 29% [171] and cataract extractions by 34% [176]. Kidney disease is a reported risk for cataracts [160].

Aspirin and thiazide diuretic use have been associated with reduced risk of cataracts [166]. Dietary lutein and zeaxanthin have been found to reduce the risk of cataracts [178]. Dietary but not supplemental vitamin E has been associated with a reduced risk of age-related cataracts [179, 180], although reductions of 9-60% in cataract risk associated with multivitamin use have been reported [181, 182]. Glutathione S-transferases polymorphisms have been associated with cataracts [183]. Cataracts have been associated with subsequent age-related maculopathy [150], as well as elevated mortality [170, 184, 185].

Ultraviolet (UV) radiation, especially UVB, has been associated with cataracts [186-189]. This risk may be limited to cortical cataracts [190-192]. Steelworkers and other open hearth workers exposed to heat on the job may have an increased risk of cataracts [193-195]. Airline pilots and astronauts are reportedly at increased risk [196, 197]. A large cohort study suggested that all three types of cataracts were interestingly less common in rural residents than urban or suburban residents [198].

Cataracts may be associated with acute exposures to radiation of 2 Grays [199, 200]. Chronic cumulative exposures above 1 Gray are associated with cortical but not nuclear cataracts [201]. Healthcare workers exposed to ionizing radiation are also reportedly at increased risk of cataracts [202-205]. Work with trinitrotoluene has been associated with cataracts [206].

Post-traumatic cataracts occur, although there is no classification system for these more heterogeneous cataracts. The outcomes are more varied, largely because of the diversity and severity of causes [207-209]. Prospective cohort data suggest that a recalled history of ocular injury was associated with increased risk of posterior subcapsular and cortical cataracts [210].

General Approach and Basic Principles

The principal recommendations for assessing and treating patients with eye symptoms are as follows:

- The initial assessment focuses on detecting indicators of potentially serious injury or disease, termed *red flags*, which require urgent assessment and treatment as indicated.

- The foci for the treatment of patients with eye symptoms include optimal medical care, monitoring for complications, facilitating the healing process, assisting stay at work or early return to work in a modified or full-duty capacity, and surgical intervention(s) when indicated.
- Patients recovering from eye problems may usually stay at work or consider early return to modified work as their condition permits.
- Occupational factors should be addressed when the disorder is believed to be caused by work.
- Prevention measures should be addressed when the injury or disorder has a means of ready prevention.
- Nonphysical factors (e.g., psychosocial, workplace, or socioeconomic problems) should be addressed in an effort to resolve delayed recovery (see Cornerstones of Disability Prevention and Management).

This guideline addresses the following eye injuries and disorders that may be encountered by health care providers.

Blunt Trauma: Ocular contusions are caused by blunt trauma to the eye or periorbital structures that may cause contusion of the globe and/or periorbita. Although there may be no symptoms, most patients have local pain, visual loss, diplopia, or a red eye. The clinician may observe any of the following: eyelid ecchymosis, corneal edema, subconjunctival hemorrhage, hyphema, reduced visual acuity, abnormal visual fields, lens dislocation, lens subluxation, retinal tears, retinal edema, retinal detachment, and/or restricted ocular motion (e.g., if extraocular muscles are trapped in a blowout fracture).

Retrobulbar Hemorrhage: A retrobulbar hemorrhage may increase the pressure on the globe such that the intraocular pressure may become greater than the perfusion pressure of the eye, leading to total ischemia of the retina. A relaxing incision at the lateral canthus must be completed within 10 minutes of the rise in IOP or the eye may be irreversibly damaged secondary to the high IOP.

Orbital Floor Fractures: Orbital floor fractures are susceptible to causing diplopia, which may or may not resolve without surgery [183, 211-215]. The initial treatment foci are on understanding the mechanisms of diplopia and enophthalmos in orbital floor fractures, the best way to evaluate a patient, and the best way to restore maximal function and appearance [215].

Diplopia caused by orbital floor blowout fractures is one of the major complications of orbital injuries. However, diplopia may also resolve without surgery. When ongoing vertical movement of the eye is impaired, surgery is indicated and is performed after complete resolution of orbital hemorrhage and edema. The maximal time before the first surgical procedure is often considered to be 2 weeks [216], and waiting is particularly indicated when there has been some improvement in diplopia over the first week. Better prognoses for non-surgical management include lack of diplopia, lack of entrapment of muscle, lack of enophthalmos, and lack of marked hypo-ophthalmos. Nonresolving oculocardiac reflex, the ‘‘white-eyed’’ blowout fracture, and early enophthalmos or hypoglobus are indications for immediate surgical repair. Surgery within 2 weeks is recommended in cases of symptomatic diplopia with positive forced ductions and evidence of orbital soft tissue entrapment on computed tomographic (CT) scan or large orbital floor fractures that may cause latent enophthalmos or hypo-ophthalmos [183, 211-215].

Hyphema: Traumatic hyphema involves an acute, most often blunt, injury sufficient to produce blood behind the cornea in the aqueous humor. Complications of traumatic hyphema include increased intraocular pressure, peripheral anterior synechiae, optic atrophy, corneal blood staining, secondary

hemorrhage, and accommodative impairment. The reported incidence of secondary anterior chamber hemorrhage, i.e., rebleeding, in the setting of traumatic hyphema ranges from 0 to 38%. The risk of secondary hemorrhage may be higher among Black/African Americans than among whites. Secondary hemorrhage is generally thought to convey a worse visual prognosis, although the outcome may depend more directly on the size of the hyphema and the severity of associated ocular injuries. Some issues involved in managing a patient with hyphema are using various medications (e.g., cycloplegics, systemic or topical steroids, antifibrinolytic agents, analgesics, and antiglaucoma medications), the patient's activity level, use of a patch and shield, outpatient versus inpatient management, and medical versus surgical management. Special considerations are widely accepted in managing children, patients with hemoglobinopathies (e.g., hemoglobin S), and patients with hemophilia). It is important to identify and treat ocular injuries that often accompany traumatic hyphema. Consider the following general recommendations:

1. Advise routine use of topical cycloplegics and corticosteroids, consider systemic antifibrinolytic agents or corticosteroids, and use a rigid shield.
2. Recommend activity restriction (quiet ambulation). If compliance (with medication use or activity restrictions), follow-up, or increased risk for complications (e.g., history of sickle cell disease or hemophilia) is a concern, inpatient management may be needed.
3. Indications for surgical intervention include the presence of corneal blood staining or dangerously increased IOP despite maximum tolerated medical therapy, among others.

Thermal Burns of the Eye: Thermal burns of the eye are caused by exposure to hot gases, liquids, or solids. Unless there is local contact only with the eye, the periocular structures are typically also involved. Damage may range from superficial burns of the lids and surrounding structures to superficial destruction of the cornea, conjunctiva, or sclera, to greater destruction including exposure of the globe. If damage exceeds superficial burns of the lids and surrounding structures, prompt intervention by a specialist is imperative.

Electromagnetic Radiation Injury to the Eye: Patients with electromagnetic radiation injuries to the eye may have no initial symptoms. Severe cases may show a marked decrease in central visual acuity, but there may be severe delayed consequences. Depending on the exact electromagnetic spectrum, the symptoms or signs may be localized to the anterior segment, lens, retina, and choroid. These types of injuries may cause scarring of the cornea or retina or cataracts. Visual field disorders also may result from damage to the retina or choroid. Burns from the blue end of the visible spectrum and ultraviolet A are discussed under nonionizing radiation exposure.

Chemical Burns: Toxic substances often begin to cause damage immediately upon contact with ultrasensitive eye tissues. Damage is related to the substance's properties, concentration, duration of exposure and speed of irrigation. Aside from general tissue damage, acids and alkalis can change the pH in the eye itself. From this detrimental change, severe eye damage, including blindness, may result. A history of significant chemical exposure is an emergency, and examination should be delayed until after the eye is flushed to dilute the chemical (see Chemical Burns below). It is imperative that emergency flushing begin immediately. To ensure the best chances for a minimal amount of eye damage, correct emergency equipment, proper placement, and knowledge of its use are necessary. The requirements governing medical services and first aid are covered in OSHA 1910.151(a)(b), whereas ANSI Z-358.1, Emergency Eyewash and Shower Equipment, provides guidance. At the site, water is the initial dilution

agent to flush the eye or body. Subsequently, an isotonic saline or balanced Ringer's solution is preferred and should be used, if available (otherwise, use sterile intravenous fluids), until a tear pH of about 7 is obtained after ceasing irrigation for approximately 10 minutes. Proper flushing usually takes at least 15 minutes, but can take as long as 24 hours.

Irrigation technique. ANSI Z-358.1, Emergency Eyewash and Shower Equipment, identifies guidance for having the facilities to dilute a chemical within 10 seconds of undergoing an industrial eye chemical hazard. Once at the site of an industrial injury, emergency medical personnel or first responders may resolve pain and blepharospasm by applying a topical ophthalmic anesthetic (proparacaine hydrochloride). If needed, the interpalpebral fissure may be widened by means of a lid retractor (e.g., Demarres). The eye should be irrigated directly with isotonic saline, Ringer's lactate or other ocular solutions. A contact lens should be removed to facilitate irrigation of the eyeball. The irrigation is not completed until the upper lid is double everted so that all cul-de-sacs (recesses) of the conjunctiva are thoroughly irrigated and visualized. Irrigation should continue until the conjunctival secretions show a consistent pH of approximately 7 after ceasing irrigation for 10 minutes.

Contact lenses. In the event of a contact lens, remove contact lenses as soon as practical. Do not delay irrigation while waiting for contact lens removal because the lens may come out with the irrigation or can be removed when irrigation is complete. Contact lenses adhere to the cornea and sometimes the paralimbal conjunctiva, depending on the type, and they have been shown to protect the cornea and/or conjunctiva beneath the lens. However, they do not fulfill the requirements of PPE. If a contact lens has not been washed out during the irrigation, it(they) may be removed following completion of irrigation.

Alkali burns. Alkali burns of the eye typically cause pain initially and may have disastrous consequences if not treated immediately. Alkali exposure can cause corneal ulceration or conjunctival, scleral, and/or anterior segment degeneration that is manifested as a blanched or "marbleized" appearance. The cornea may become opacified. The diagnosis is usually based on a history of exposure to alkaline chemicals, but occasionally testing the pH of tears or residual liquid is required. Immediate and copious irrigation should be performed. Irrigation in most cases should be continued until the patient is seen by the ophthalmologist on an emergency referral basis. The primary exception is a very minor amount of mildly alkaline material that may be addressable without ophthalmological evaluation. A casual examination of the eye may reveal that the globe is white because there is severe ischemia of the conjunctiva or episcleral vessels, a finding that would be noted during a slit-lamp examination.

Acid burns. Acid burns of the eye, caused by acid splashes or vapors, may have immediate effects of corneal erosion, corneal necrosis, and decreased visual acuity unless irrigation is accomplished immediately. In patients with acid burns, the eye appears inflamed immediately, unlike alkali burns, where the eye typically appears white due to necrosis of the superficial ocular vessels. Delayed effects are unusual in patients with acid burns, although hydrofluoric (HF) acid burns are the exception.

Hydrofluoric acid burns*.* Hydrofluoric acid causes delayed tissue destruction out of proportion to the apparent exposure. With an HF acid concentration of less than 20%, the onset of symptoms may be delayed up to 24 hours. With high concentrations, symptoms may begin relatively quickly. The patient's main complaint is severe eye pain out of proportion to the apparent exposure. HF acid penetrates tissue remarkably well and causes deep as well as superficial necrosis. HF acid exposure must be treated immediately with copious irrigation with water or isotonic saline solution for 5 minutes and then by calcium gluconate 1% solution or Ringer's lactate solution providing Ca2+ and Mg+ atoms to the cell

replacing the Ca^{++} and Mg^{++} atoms that were incorporated into insoluble calcium and magnesium fluoride molecules. Immediate referral to an ophthalmologist after emergency care is recommended while calcium gluconate is irrigated into the eye.

Corneal Ulceration: Corneal ulcers are considered an ophthalmologic emergency. They may result in permanent visual impairment. They may be bacterial, viral, fungal, or parasitic in origin and may occur following corneal lacerations, abrasions, and intrusion of foreign bodies. They may result from poorly fitted or inadequately cleaned contact lenses. Patients with corneal ulcers present with complaints of changes in visual acuity, photophobia and/or eye pain, tearing, and a sensation that a foreign body is in the eye. The presence of corneal ulcers can be determined by direct visualization, but magnified viewing with fluorescein staining is needed to completely rule out their presence.

Open Globe Eye Injury: Direct trauma to the eye from high-velocity objects can cause laceration or perforation of the globe. The trauma can be perforating or penetrating. Patients with damage to the integrity of the globe can present with decreased visual acuity, local pain, and bleeding. The cardinal sign is distortion of the globe with loss of tension or IOP; the pupil is not round, but rather is distorted and/or nonreactive. In addition, ecchymosis or other signs of damage to periorbital structures are usually evident. The clinician may observe subconjunctival hemorrhage, distortion of the iris or pupil, or herniation of the iris through the cornea. There also may be retinal damage. The injured eye should be protected with a metallic or plastic shield. Transfer by stretcher is recommended.

Initial Care

The principal recommendations for initial assessment and approach to the treatment of patients with eye injuries and disorders are as follows:

- Initial assessment should focus on detecting indications of potentially serious ocular pathology, termed red flags, and determining an accurate diagnosis. For these purposes, red flags are defined as a sign or symptom of a potentially serious condition indicating that further definitive care, support, consultation and/or specialized treatment may be necessary.
- In the absence of red flags, eye disorders may be safely and effectively treated in experienced primary care settings. Conservative treatment should generally proceed for 48 to 72 hours for superficial foreign bodies, corneal abrasions, conjunctivitis, and ultraviolet radiation burns. Normally, eye tissues heal rapidly. If eye damage is not well on the way to resolution within 48 to 72 hours, additional care and/or referral is indicated particularly if the provider is inexperienced with more complex care. Nonspecific eye disorders are often monitored for considerably longer periods of time while evaluations, ergonomic and other adjustments are made. The foci are on providing the most effective treatment(s), monitoring for complications, facilitating the healing process, and determining fitness for return to work in a modified- or full-duty capacity.
- Corneal discomfort can be relieved with a topically applied ophthalmic nonsteroidal anti-inflammatory drug (NSAID) or an oral analgesic. Intramuscular or intravenous opioids are rarely needed, typically for some severe ocular/face injuries. Topical anesthetics are generally avoided other than diagnosis or brief treatment because they may obscure worsening pathology and thus inadvertently cause further injury.
- Visual acuity should be assessed and documented carefully at each examination prior to other examinations or treatment, except for cases of chemical burns where immediate copious irrigation should be administered without delay.

- Patients recovering from acute eye injury or infection should be encouraged to return to modified work as their condition permits.

Nonphysical factors, such as psychosocial, workplace, or socioeconomic problems, should be addressed in an effort to resolve delayed recovery.

INITIAL ASSESSMENT

Presenting Symptoms

The patient will typically present with either: (i) an acute injury or event or (ii) an ocular disease. Acute injury or events generally have fairly simple mechanisms of injury that often beget a straightforward treatment approach (e.g., immediate irrigation for a chemical splash). If immediate treatment is not required, then a careful history and physical examination will commence to identify the most likely diagnosis of the patient's symptoms and signs.

History

Information obtained from a careful history and examination directs the approach to management. This section is separated into history elements for acute, ocular injury and for ocular diseases. However, it is recognized that there are many cases where both sets of questions are needed.

Elements of the History of Ocular Injury

While a detailed, accurate history is essential in all injuries, it is especially important to obtain a detailed history of an ocular injury because incorrect or misleading information may lead to blindness. Such information may be obtained from a variety of sources, including the patient, the first responder(s), and others involved in or associated with the accident. Information for acute trauma should include the four Ws:

1. Where: Location of the accident
2. When: Time and date
3. Who: Other individuals involved
4. What: A detailed description of the accident circumstances, including force and load. If chemical exposure was involved, seek available Safety Data Sheet (SDS) information. Critical data include:
    i. What chemical (SDS information‡)
    ii. Type of chemical (alkali, acid, solvent)
    iii. Type of exposure (liquids, solids, fumes)
    iv. Dose of exposure
    v. pH of the material
    vi. Concentration of the material
    vii. Solubility of the material
    viii. Contact time
5. Emergency medical care provided by first responder(s), with information from:
    i. Product manufacturer
    ii. Availability of chemical data
    iii. Safety Data Sheets
    iv. Regional poison control center
    v. Internet

Elements of the History of Ocular Diseases

Asking open-ended questions generally allows the clinician to assess the primary focus for the visit, diagnose the condition more accurately, and identify a preferred treatment approach.

1. What are your symptoms?
    a. Are you experiencing pain? Sensitivity to light? Blurry vision? Loss of vision? Headache?
    b. Is your problem located primarily in the eye or near the eye? Do you have pain or other symptoms elsewhere? Nose? Sinus? Throat? Ear? Head?
    c. Are your symptoms constant? Intermittent?
    d. What makes the problem worse or better?
2. How do these symptoms limit you?
    a. How long can you look at something?
    b. Can you see clearly?
3. When did your current limitations begin?
    a. How long has your vision been limited? More than a day or two?
    b. Have your symptoms changed? How?
4. Have you had similar episodes previously?
5. Have you had any previous testing or treatment? With whom?
6. What do you think caused the problem?
7. What are your specific job duties? How long do you spend performing each duty?
8. Do you have other medical problems? Diabetes? High blood pressure? Glaucoma?
9. What do you hope to accomplish during this visit?

The onset of a red eye, duration of the redness, and clinical course should be noted to help to distinguish the causative agents (see Table 1). The patient's chief complaint often identifies or suggests the cause of the red eye. For example, itching may signify allergies. A scratchy or burning sensation suggests lid, conjunctival, or corneal disorders, including foreign bodies, in-turning eyelashes, and dry eyes. Localized lid pain or tenderness is a common presenting complaint of a stye or an acute chalazion of the lid.

Deep, non-localizing, intense, aching pain may reflect disorders such as iritis, or acute glaucoma, as well as sinusitis, cluster headache, or ocular migraine. Photophobia suggests problems arising from the anterior segment of the eye, such as corneal abrasions, iritis, and acute glaucoma. A halo effect around lights is a sign of corneal edema commonly seen in acute glaucoma. Individuals who have corneal edema associated with contact lens wear may also experience halo vision.

Table 1. Symptoms of Red Eye

Symptom	Acute Glaucoma	Acute Iridocyclitis	Keratitis	Bacterial Conjunctivitis	Viral Conjunctivitis	Allergic Conjunctivitis
Blurred vision	3	1-2	3	0	0	0
Pain	2-3	2	2	0	0	0
Photophobia	1	3	3	0	0	0
Colored halos	2	0	0	0	0	0

Exudation	0	0	0-3	3	2	1
Itching	0	0	0	0	0	2-3

Note: The range of severity of the symptom is indicated by 0 (absent) to 3 (severe).
Modified from Bradford CA, ed. Basic Ophthalmology. 7th ed. San Francisco, Calif: American Academy of Ophthalmology; 1999.

Red Flags

For potentially occupationally-related eye injuries, the mechanism of injury usually provides the most important information regarding the potential for a "red flag" (see Table 2). Potentially serious eye conditions are listed below. Depending on the provider's training and experience in dealing with the particular disorder, early consultation with an eye specialist may be needed.

In general, sudden onset of loss of vision, loss of visual acuity, photophobia, flashing lights, painful eye, and trauma are all red flags. Other red flags include systemic symptoms such as loss of function of the face, a hand, or a leg; speech alterations; accompanying new headache; and scalp tenderness.

Table 2. Red Flags for Potentially Serious Eye Conditions Requiring Immediate Ophthalmologic Examination

Disorder	Medical History	Physical Examination
Ocular injury, open globe	• Trauma due to high-velocity foreign-body injury • Visual loss • Bleeding • Local pain	• Visible foreign body in globe; deformity of globe • Loss of globe pressure • Distorted pupil and/or iris • Subconjunctival hemorrhage
Ocular injury, closed globe	• Direct blow • Visual loss • Diplopia	• Eyelid ecchymosis • Subconjunctival hemorrhage • Vitreous hemorrhage • Lens dislocation • Retinal edema and/or tear • Decreased visual acuity • Hyphema • Retrobulbar hemorrhage • Extraocular motion deviation
Thermal burns	• Exposure of eyes to hot material/extreme heat • Superficial eye pain • Photophobia	• Burns of lids and/or surrounding structures • Damage to cornea, conjunctiva, and/or sclera • Decreased visual acuity
Radiation injury	• Exposure of eyes to ultraviolet, laser, or bright light • Delayed severe superficial eye pain (4-6 hours) • Tearing • Photophobia	• Blepharospasm • Tearing • Corneal punctate staining and/or sloughing of epithelium • Retinal damage
Chemical burns	• Alkali, acid, solvent splash • Painless visual loss	• Corneal erosion • Conjunctival chemosis • Necrosis of anterior segment of tissues and vessels • Decreased visual acuity

		• Circumcorneal vascular ischemia • Necrosis of cornea and/or conjunctiva • Glaucoma
Hydrofluoric (HF) acid burns	• HF acid splash • Delayed damage	• Necrosis of cornea and/or conjunctiva • Decreased visual acuity
Corneal ulcer	• Abrasion or infection • Superficial pain • Foreign-body sensation • Photophobia • Visual loss	• Corneal infiltrates and ulcers • Decreased visual acuity • Ulceration on slit-lamp exam and fluorescein staining

Examination

The eye examination differs somewhat based on whether the presenting problem is an acute, discrete injury or an occupational disease (including red eye not due to trauma).

A comprehensive examination is preferred in patients with ocular diseases. A more abbreviated and focused examination is typically initially performed for obvious, acute injuries. At a minimum, a visual acuity assessment is performed prior to any treatment. The main exception is with chemical injuries, where immediate irrigation is mandated.

Ocular Examination for Eye Injury

For chemical exposures, this examination occurs after decontamination or while it is in progress, if that is feasible. Otherwise, initial ocular (visual) screening is extremely useful as the initial test of choice.

The examination of the injured eye should include the following:

1. Visual acuity (each eye separately) with best correction or pinhole
2. Inspection of the ocular structure (If an open globe is suspected, no pressure should be exerted on the globe.)
3. Position of the eyes and eye movements (six cardinal positions) if the globe is intact
4. Examination of the pupils for size and reaction to light
5. Gross visual fields by confrontation
6. Ophthalmoscopy
7. Intraocular pressure (IOP) determination if the globe is intact
8. Injury to lid(s) or other adnexal structures

It is important for make immediate referrals to the closest specialist when eye injuries exceed the treating provider's capability. Make the patient comfortable (with intravenous analgesics, if necessary) and protect the eye from further injury by applying a rigid Fox shield or equivalent. Depending on the type of injury, transport the patient on a stretcher.

How to Examine for Ocular Disease, including Red Eye

Visual complaints from diseases, including red eye, are initially evaluated with a visual acuity chart, a penlight (slit lamp preferred), a tonometer, a sterile fluorescein dye strip, topical anesthetic drops, and an ophthalmoscope. Many clinics use a vision screening device screener, a noncontact "puff" tonometer, and a slit lamp or biomicroscope. A systematic approach to the examination is recommended, beginning by examining the face, orbital area, and lids and ending with a close view of the eyeball. The preferred method for examining the eyeball is with a slit-lamp biomicroscope and the

ophthalmoscope.

The American Academy of Ophthalmology specifies nine diagnostic steps to use when evaluating a patient with a red eye (Bradford):

1. Determine whether visual acuity is normal or decreased using a Snellen chart or (preferred) ETDRS chart at 20 feet or 6 meters, or the 1 meter ETDRS chart if required.
2. Inspect the pattern of redness present and determine whether it is due to subconjunctival hemorrhage, conjunctival hyperemia, ciliary flush, or a combination of these.
3. Ascertain the presence of conjunctival discharge and categorize it as to amount (profuse or scant) and character (purulent, mucopurulent, serous, or hemorrhagic).
4. Identify opacities of the cornea, including large keratitic precipitates, or irregularities of the corneal surface, such as corneal edema, corneal leukoma (a white opacity caused by scar tissue), and irregular corneal reflection. Conduct the examination using a slit lamp biomicroscope, or at least penlight and transilluminator. Biomicroscopy is the practice standard.
5. Search for disruption of the full thickness of the corneal epithelium by staining the cornea with fluorescein. Search for a lack of corneal epithelium vitality by staining with rose bengal.
6. Use a slit lamp (biomicroscope) to estimate the depth of the anterior chamber as normal or shallow and to detect any microscopic blood or white blood cells, which would indicate either hyphema or hypopyon, respectively. (A hypopyon is indicated by the presence of protein and white blood cells in the anterior chamber [e.g., when a corneal ulcer is present] and a hyphema is indicated by protein and red blood cells in the anterior chamber. These typically "layer" out in the inferior cornea.)
7. Detect irregularity of the pupils and determine whether one pupil is larger than the other. Observe the reactivity of the pupils to light to determine whether one pupil is more sluggish than the other or is nonreactive.
8. Determine whether the intraocular pressure is high, normal, or low by performing tonometry. This is especially important if acute angle closure glaucoma is suspected. (Tonometry is contraindicated when external infection or lack of globe integrity is obvious.)
9. Detect the presence of proptosis, lid malfunction, or any limitations of eye movement.

Methods of Testing

Visual Acuity: Quantitative Bilateral Tests. Acuity is measured at infinity (as a minimum) and near and intermediate distances (based on job description) and is performed with and without corrective devices (e.g., glasses or contact lenses) and without removing other corrective devices (e.g., intraocular lenses).

Slit-Lamp Biomicroscopy. Slit-lamp examination is the standard method of examining the eye. The slit lamp uses intense illumination and magnification. The general findings noted in a slit-lamp examination (biomicroscope) and their clinicopathologic correlations appear at the end of this Guideline under "Additional Resources."

How to Interpret the Findings of Red Eye. The associated signs and symptoms (see Tables 1 and 3) of various disorders overlap to some extent. Although many conditions may cause a red eye, several signs and symptoms signal greater concerns. The presence of one or more of these signals (i.e., a red flag) alerts the physician that the patient may have a disorder requiring definitive care that often includes referral if the examiner has insufficient experience with that particular condition. See Table 4 for differential diagnosis.

Table 3. Signs of Red Eye

Symptom	Referral Advisable if Present	Acute Glaucoma	Acute Iridocyclitis	Keratitis	Bacterial Conjunctivitis	Viral Conjunctivitis	Allergic Conjunctivitis
Ciliary Flush	Yes	1	2	3	0	0	0
Conjunctival Hyperemia	No	2	2	2	3	2	1
Corneal Opacification	Yes	3	0	1-3	0	0-1	0
Corneal Epithelial Disruption	Yes	0	0	1-3	0	0-1	0
Pupillary Abnormalities	Yes	Mid-dilated, nonreactive	Small; may be irregular	Normal or small	0	0	0
Shallow Anterior Chamber Depth	Yes	3	0	0	0	0	0
Elevated Intra-Ocular Pressure	Yes	3	-2 to +1	0	0	0	0
Proptosis	Yes	0	0	0	0		0
Discharge	No	0	0	Sometimes	2-3	2	1
Preauricular Lymph Node Enlargement	No	0	0	0	0	1	0

Note: The range of severity of the symptom is indicated by 0 (absent) to 3 (severe).
Modified from Bradford CA, ed. Basic Ophthalmology. 7th ed. San Francisco, Calif: American Academy of Ophthalmology; 1999.

Table 4. Differential Diagnosis – Red Eye

Acute angle-closure glaucoma	A form of glaucoma due to sudden and complete occlusion of the anterior chamber angle by iris tissue.	Uncommon, serious (The more common chronic open-angle glaucoma causes no redness of the eye.)
Iritis or iridocyclitis	An inflammation of the iris alone or of the iris and ciliary body; often manifested by ciliary flush.	Serious
Herpes simplex keratitis	An inflammation of the cornea caused by the herpes simplex virus.	Common, potentially serious; can lead to corneal ulceration
Conjunctivitis	Hyperemia of the conjunctival blood vessels; may be bacterial, viral, allergic, or irritative.	Common, often not serious
Episcleritis	An inflammation (often sectorial) of the episclera (the vascular layer between the conjunctiva and the sclera), without discharge; possibly allergic, occasionally painful	Uncommon, not serious

Modified from Berson FG. Basic Ophthalmology for Medical Students and Primary Care Residents. 6th ed. San Francisco, Calif: American Academy of Ophthalmology; 1993.

¥ Fluorescein, applied primarily as a 2% alkaline solution and with impregnated paper strips, is used to examine the integrity of the conjunctival and corneal epithelia. Defects in the corneal epithelium will appear green in ordinary light and bright yellow when a cobalt blue filter is used in the light path. Similar lesions of the conjunctiva appear bright orange or yellow in ordinary illumination. Fluorescein also has been used in the fitting of rigid contact lenses, although it cannot be used for soft lenses, which absorb the dye. Prepared sterile ophthalmic strips are used diagnostically for staining the anterior segment of the eye when: 1) delineating a corneal injury, herpetic ulcer, or foreign body; 2) determining the site of an intraocular injury; 3) fitting contact lenses; 4) making the fluorescein test to ascertain postoperative closure of a sclerocorneal (also referred to as corneoscleral) wound in delayed anterior chamber re-formation; and 5) making the lacrimal drainage test. Avoid using fluorescein while the patient is wearing soft contact lenses because the lenses may become stained. Whenever fluorescein is used, flush the eyes with sterile normal saline solution and wait at least 1 hour before replacing the lenses. Rose Bengal Ophthalmic Strips are particularly useful for demonstrating abnormal conjunctival or corneal epithelium; devitalized cells stain bright red, whereas normal cells show no change; the abnormal epithelial cells present in dry eye disorders are effectively revealed by this stain).

± A slit lamp features an oblique (condensed) illumination and a magnifying system. With refinements, this system is used in current slit lamps. All detail is seen by the viewer by reflected light. Substances that do not reflect light are not visible; they are termed optically empty, such as normal tears and the aqueous humor. Structures that transmit light, but can be seen in the beam, are termed reluctant, such as the cornea, lens, and vitreous. Structures that do not transmit light are opaque. The examiner must use special techniques for illumination and focusing that enhance the examination. The methods include: 1) diffuse illumination; 2) direct or focal illumination (the most useful and important type of slit-lamp illumination, whereby tissues such as the cornea are seen as an optical section or a block of tissue known as a parallelepiped); 3) retro-illumination, where the area is being illuminated by reflected rays (e.g., a corneal foreign body or corneal ulcer); and 4) indirect illumination.

DIAGNOSTIC APPROACH

If the patient does not have red flags for serious conditions, the clinician may then determine which other eye disorder is present. The criteria presented in Figure 1 follow the clinical thought process from the mechanism of illness or injury to unique symptoms and signs of a particular disorder and finally to test results, if any tests were needed to guide treatment at this stage.

Several symptoms and signs are common to a number of eye injuries or disorders (see Tables 1 and 3). Therefore, accurate diagnosis depends on linking the mechanism of injury or pathogenesis, symptoms, signs, and findings of the eye examination with findings on magnification and, if necessary, with fluorescein staining of the eye. In the following lists, an asterisk (*) after a symptom or sign indicates a red flag.

Special Studies and Diagnostic and Treatment Considerations

Special studies are not generally indicated during the first 2 to 3 days of treatment, except for in red flag conditions. Most patients with eye problems improve quickly once any red flag issues are ruled out. The clinical history and physical findings generally are adequate to diagnose the problem and provide treatment. If the patient's limitations due to eye symptoms, other than nonspecific symptoms, do not improve in 3 to 5 days, reassessment is recommended. After again reviewing the patient's limitations, history, and physical findings, the clinician may consider referral for further diagnostic studies and discuss these options with the patient. For patients with limitations after 3 to 5 days and unexplained physical findings, such as localized pain or visual disturbance, referral may be indicated to clarify the diagnosis and assist recovery.

Selection of Special Studies

Radiography of the globe may be indicated if the patient's history indicates the possibility of injury by a penetrating high-speed radiopaque foreign body. Ultrasonography can be used to locate non- and radiopaque foreign bodies. Computed tomographic (CT) scan of the orbit may be indicated in cases of significant blunt trauma and associated fractures at the time of initial evaluation and treatment. Magnetic resonance imaging (MRI) is never indicated when there may be a possibility of a metallic foreign body. Table 5 compares (generally) the abilities of different techniques to identify physiologic insult and define anatomic injury.

Table 5. Ability of Various Techniques to Identify and Define Ocular Pathology

Technique	Identify Physiologic Insult	Identify Anatomic Defect
History	+ + +	+
Physical examination, including visual acuity testing and fundoscopy	+ + + +	+ + + +
Fluorescein staining	0	+ + + +
Slit-lamp examination	0	+ + + +
Tonometry	+ + +	0

Imaging studies		
Plain-film radiography	0	+a
Ultrasonography	0	+ + + +b
CT scan	0	+ + + +a
MRI	0	+ + + +c

Note: Specificity and repetitiveness from 0 (absent) to (maximum).

[a]For evaluating suspected periorbital and other depressed fractures.

[b]For evaluating suspected retinal detachment, chamber dimensions, and intraocular foreign bodies.

[c]For evaluating foreign body and intracranial pathology.

If the patient does not have red flags for serious conditions, the clinician may then determine which other eye disorder is present. The criteria presented in Table 5 follow the clinical thought process from the mechanism of illness or injury to unique symptoms and signs of a particular disorder and finally to test results, if any tests were needed to guide treatment at this stage.

The clinician must be aware that several symptoms and signs are common to a number of eye injuries or disorders (see Tables 1 and 3). Therefore, accurate diagnosis depends on linking the mechanism of injury or pathogenesis, symptoms, signs, and findings of the eye examination with findings on magnification and, if necessary, with fluorescein staining of the eye.

Diagnostic Criteria

In the following lists, an asterisk (*) after a symptom or sign indicates a red flag.

Symptoms of Red Eye (see Table 1)

- **Blurred Vision.** Blurred vision often indicates serious ocular disease. Blurred vision that improves with blinking suggests a discharge or mucus on the ocular surface.
- **Severe pain.*** Pain may indicate keratitis, ulcer, iridocyclitis, or acute glaucoma. Patients with conjunctivitis may complain of a scratchiness or mild irritation, but do not have severe pain.
- **Photophobia.*** Photophobia is an abnormal sensitivity to light that accompanies iritis. It may occur either alone or secondary to corneal inflammation. Patients with conjunctivitis have normal light sensitivity.
- **Colored halos.*** Rainbow-like fringes or colored halos seen around a point of light are usually a symptom of corneal edema, often resulting from an abrupt rise in intraocular pressure. Therefore, colored halos are a danger symptom suggesting acute glaucoma as the cause of a red eye.
- **Exudation.** Exudation, also called mattering, is a typical result of conjunctival or eyelid inflammation and does not occur with iridocyclitis or glaucoma. Patients often complain that their lids are “stuck together” on awakening. Corneal ulcer is a serious condition that may or may not be accompanied by exudate. Mucoid discharge generally is related to allergic conditions. Watery discharge may occur with viral conditions, and a purulent discharge is related to bacterial conditions.
- **Itching.** Although a nonspecific symptom, itching most commonly indicates an allergic conjunctivitis.

Signs of Red Eye (see Table 3)

- **Reduced visual acuity.*** Reduced visual acuity suggests a serious ocular disease, such as an inflamed cornea, iridocyclitis, glaucoma, or vitreous hemorrhage. It never occurs in simple conjunctivitis unless the associated cornea is involved. Acceptable of passable visual acuity for driving and injuries without a known baseline is considered 20/40 or better in each eye separately and both eyes together.
- **Ciliary flush.*** Ciliary flush is an injection of the deep conjunctival and episcleral vessels surrounding the cornea. It is seen most easily in daylight and appears as a faint violaceous ring in which individual vessels cannot be seen by the unaided eye. These engorged vessels, whose origin is the ciliary body, are a manifestation of inflammation of the ciliary body and the anterior segment of the eyeball. Ciliary flush is a danger sign often seen in eyes with corneal inflammations, iridocyclitis, or acute glaucoma. Usually ciliary flush is not present in conjunctivitis.
- **Conjunctival hyperemia.** Conjunctival hyperemia is an engorgement of the larger and more superficial bulbar conjunctival vessels. A nonspecific sign, it may be seen in almost any of the conditions causing a red eye.
- **Corneal opacification.*** In a patient with a red eye, corneal opacities always denote disease. These opacities may be detected by direct illumination with a penlight, or they may be seen with a direct ophthalmoscope (with a plus lens in the viewing aperture) outlined against the red fundus reflex. Several types of corneal opacities may occur, including:
    - Keratic precipitates, or cellular deposits on the corneal endothelium, usually too small to be visible. Occasionally forming large clumps, these precipitates can result from iritis or chronic iridocyclitis.
    - A diffuse haze obscuring the pupil and iris markings. This may be characteristic of corneal edema. It is frequently seen in acute glaucoma.
    - Localized opacities. These may be due to keratitis or ulcer.
- **Corneal epithelial disruption.*** Disruption of the corneal epithelium, which occurs in corneal inflammations and trauma, can be detected in two ways. The first method uses fluorescein vital stain, which detects disruption of the epithelium.
    - The examiner should be positioned in such a way as to observe the reflection from the cornea of a single light source (e.g., window or penlight) as the patient moves his or her eye into various positions. Epithelial disruptions cause distortion and irregularity of the light reflected by the cornea. Apply fluorescein to the eye. Areas denuded of cells of the epithelium will stain a bright green with a blue filter.
    - The second method uses rose bengal vital stain, which detects degeneration or absence of one or more layers of the epithelium. The examiner should be positioned in the same manner as described above. Apply rose bengal vital stain. Diseased epithelium will stain a reddish purple color.
- **Pupillary abnormalities.*** The pupil in an eye with iridocyclitis typically is somewhat smaller than that of the other eye due to reflex spasm of the iris sphincter muscle. The pupil is also distorted occasionally by posterior synechiae, which are inflammatory adhesions between the lens and the iris. In acute glaucoma, the pupil is usually fixed, mid-dilated (about 5 to 6 mm), and slightly irregular. Conjunctivitis does not affect the pupil.
- **Shallow anterior chamber depth.*** In a red eye, a shallow anterior chamber (especially related to acute ocular pain, nausea, and sometimes vomiting) suggests the possibility of acute angle-closure glaucoma. Anterior chamber depth can be grossly estimated through side illumination with a penlight. The most exact technique and practice standard involves using a slit lamp with

or without a diagnostic anterior segment contact lens. Intraocular pressure (IOP) is then measured.

- **Elevated IOP.*** IOP is unaffected by common causes of red eye other than iridocyclitis and glaucoma. In any red eye without obvious infection, IOP can be measured to rule out glaucoma as clinically indicated (routinely at the time of all eye screening examinations generally after age 40); however, under some circumstances, routine screening for IOP should be part of the examination.
- **Proptosis.*** Proptosis is a forward displacement of the globe. Proptosis of sudden onset suggests serious trauma, orbital infection, or tumor. The most common cause of chronic proptosis is thyroid disease, especially Grave's disease, and is bilateral. Orbital mass lesions also result in proptosis and should be considered. Proptosis may be accompanied by conjunctival hyperemia or limitation of eye movement. Small amounts of proptosis are detected most easily by standing behind a seated patient and looking downward to compare the positions of the two corneas. Acute orbital proptosis secondary to trauma is an ophthalmologic emergency because it may cause severe pressure on the eyeball, which may lead to central retinal artery occlusion.
- **Preauricular nodes.** The type of ocular discharge may be an important clue to the cause of conjunctivitis. Preauricular node enlargement can be a prominent feature of common viral as well as some unusual varieties of chronic granulomatous conjunctivitis, known collectively as Parinaud's oculoglandular syndrome. Usually, such enlargement does not occur in acute bacterial conjunctivitis. The adenovirus is found most commonly, especially in epidemic keratoconjunctivitis, which generally is readily spread by direct contact with the secretions of affected individuals.

MANAGEMENT APPROACH

The principal recommendations for assessing and treating patients with eye complaints are as follows:

- Initial assessment should focus on detecting indications of potentially serious ocular pathology, termed red flags, and determining an accurate diagnosis. For these purposes, red flags are defined as a sign or symptom of a potentially serious condition indicating that further consultation, support, or specialized treatment may be necessary.
- In the absence of red flags, experienced healthcare providers can safely and effectively handle most work-related eye injuries. Conservative treatment can proceed for 48 to 72 hours for superficial foreign bodies, corneal abrasions, conjunctivitis, and ultraviolet radiation damage. Normally, eye tissues heal rapidly. If eye damage is not well on the way to resolution within 48 to 72 hours and the provider is not experienced with the condition, referral to a specialist is indicated.
- Ocular diseases and nonspecific eye complaints usually require longer treatment timelines.
- The treatment focus is on assuring optimal treatment, monitoring for complications, facilitating the healing process, and determining fitness for return to work in a modified- or full-duty capacity.

Follow-up Visits

The frequency of follow-up visits is determined by the diagnosis, stage and severity of the problem.

After successful treatment for simple corneal abrasions or minor foreign bodies, follow-up may be on a daily basis until the problem has resolved. As healing is rapid and minor abrasions do not generally

require follow-up, it is also acceptable to schedule follow-up for such cases as needed. The larger, deeper and more extensive the injury, the more likely follow-up will need to be scheduled.

Photokeratitis (e.g., welder's flash) is generally readily treated and resolves in 1 or 2 days. It frequently requires no follow-up appointments or at most one appointment the next day.

For chemical burns, daily follow-up is generally required until the problem has resolved. For minor volumes of non-acidic, non-alkaline insults, it is acceptable to schedule follow-up as needed.

Thermal burns depend on the severity and involvement of other structures. Minor cases may require one follow-up appointment within a day or two. More severe cases may need follow-up every one to two days until the burns are resolved.

Blunt trauma injuries that include orbital blowout fractures without red flags for immediate surgery require follow-up approximately every 3 to 5 days to ascertain improvements and resolution of diplopia or other problems.

Traumatic hyphema requires close follow-up that is generally determined by IOP on presentation. The larger the extent of the hyphema and the higher the IOP, the more frequently the follow-up is needed.

Corneal ulcers require follow-up initially every 1 to 2 days until the epithelium has healed and then every 1 to 6 months depending on the severity and frequency of the episode when multiple.

SCREENING AND DIAGNOSTIC RECOMMENDATIONS

Vision Screening

Vision screening is performed for a wide range of purposes. Categories of vision screenings include pre-placement, periodic surveillance, post-injury and postoperative [217, 218](AOA). It is also performed for motor vehicle driver licensure.

Vision Screening for Preplacement Examinations

Recommended.

Preplacement vision screening is recommended for jobs that require visual acuity.
Indications **–** Occupations that require visual acuity for performance. **Generally, most safety sensitive and safety critical jobs require corrected visual acuity of at least 20/40 in both eyes and each eye separately.**

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

Vision Screening for Periodic Surveillance Examinations

Recommended.

Periodic vision screening is recommended for jobs that require visual acuity.
Indications **–** Occupations that require visual acuity for performance. More frequent examinations are indicated for jobs with higher visual demands and/or higher risks and/or among those at higher risks for incident visual impairments. **Generally, most safety sensitive and safety critical jobs require corrected visual acuity of at east 20/40 in both eyes and each eye separately.**

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

Vision Screening for Post-injury Examinations

Recommended.

Vision screening is recommended for post-injury examinations.
Indications **–** All post-injury examinations, including subsequent follow-up examinations.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – High

Vision Screening for Postoperative Examinations

Recommended.

Vision screening is recommended for postoperative examinations.
Indications **–** All postoperative examinations, including subsequent follow-up examinations.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – High

Rationale for Recommendations
Vision screening is widely performed as a component of essentially all eye-related examinations, most commonly with either a Snellen chart or a vision screening device that is comparable to a Snellen chart. For preplacement examinations, there are data to suggest increased risk of motor vehicle crashes with reduced visual acuity that is usually worse with 20/40 corrected [219-222], thus indirect evidence that both preplacement examinations and surveillance examinations are likely successful. There are many protocols for screening, with the most frequent interval typically being either annual or biennial. For specific occupations, there is an absence of evidence of efficacy of visual screening, but strong belief it is successful. Occupation-specific visual acuity testing beyond Snellen tests is recommended for specific occupations. For post-injury and postoperative examinations, vision screening is used to track the recovery, but there are naturally no studies without vision screening being performed to assess its comparable utility. Vision screening is not invasive, is without adverse effects, is low cost and is thus recommended for pre-placement, periodic surveillance, post-injury and postoperative examinations.

Evidence for Vision Screening

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Maa 2014 [26] (score = 8.0)		Diagnostic	No industry sponsorship or COI.	*N* = 52 patients Tele-eye protocol		Clinical Diagnosis through face-to-face examination		The percentage agreement between the tele-eye protocol and the clinical diagnosis for cataract was 100%, for macular degeneration it was 96% and that for glaucoma suspect was 87%.	"The initial data suggest that the tele-eye program is feasible to execute and appears fairly accurate when compared with the gold standard face-to-face eye exam."	Pilot study with small sample size study suggests high correlation between tele MD protocol and face to face eye exam for cataract, macular degeneration and glaucoma/R/o glaucoma.
Ong 2003 (score = 7.5)		Diagnostic	No mention of sponsorship or COI.	N= 510 Diabetic subjects, 17 with retinopathy and 493 without retinopathy. Tritan Contrast Threshold testing (TCT)	Mean age was 60.8 years.	Best corrected Snellen visual acuity (BCVA test).		For TCT detection of retinopathy there were 16 positive tests among the 17 patients and 1 negative tests. This yielded a sensitivity of 94% and a specificity of 95% for the TCT test.	"Tritan color vision deficiency was observed in patients with STDR despite their normal BCVA. These results indicate that automated TCT assessment is an effective and clinically viable technique for detecting STDR, particularly diabetic maculopathy, before visual loss."	Study suggests automated TCT detects STDR especially diabetic maculopathy prior to visual loss. Also the test measures function and morphology which may be helpful in early identification prior to development of more severe disease. Test is less cost prohibitive than current

										diagnostic tools such as fluorescein photography.
Arnoldi, 2014 [27] (score = 7.0)		Diagnostic	Supported by a research grant from Research to Prevent Blindness, Inc. No mention of COI.	*N*= 23 patients; a group of orthotropic volunteers with normal vision, a group with small angle strabismus and a group of patient whose angle of strabismus was large enough to precluded stereopsis. Mean age was 32 years.		Titmus Fly test vs. Snellen Test		Mean visual acuity of the worse-seeing eye was 0.8. The sensitivity for the Titmus fly test was 79% but the specificity was only 26% due to the large number of false positive responses.	"If the Titmus fly test is the only stereoacuity measure that can be used due to the presence of manifest strabismus, modifying the presentation of the test plate with this method will improve accuracy and precision of results."	Although the Titmus fly test has a reasonable sensitivity, specificity is low with a large degree of false positives. Study suggests modification of test will improve accuracy.
Lim 2010 (score = 6.0)		Diagnostic	Supported by the Joseph and Geraldine LaMotta Research Fund of the New York Glaucoma Research Institute, New York. RBR is a member of the Scientific Advisory Board of OTI-Opko, Toronto, Ontario, Canada.	N= 40 eyes in 40 ophthalmic patients. Mean age was 67 years old.		ETDRS log MAR and compact reduced logMAR (cRLM) tests vs. Snellen Test		The median acuity of the ETDRS, cRLM and Snellen charts were 0.42, 0.41 and 0.41 respectively. There was no statistically significant difference between groups (p=0.9865).	"[T]he theoretical advantages of logMAR charts compared to Snellen charts are measurable in a simulated clinical setting but the magnitude of the benefit of using an improved chart design appears to be small and the cost-effectiveness of introducing such charts into routine clinical practice is uncertain."	Relatively small sample size. ETDRS had a measurable advantage over Snellen but ETDR tool 1.86 times as long to complete as Snellen test making it likely cost prohibitive.

Arora 2014 (score = 6.0)		Diagnostic	No industry sponsorship. COI: Dr. Friedman is a consultant for Alcon, Bausch & Lomb, Merck, and QLT Inc. Manu Lakkur helped develop the iPod application used in this study.	N= 104 subjects with a wide range of visual acuity. Mean age was 67.3 years		Early Treatment Diabetic Retinopathy Study (ETDRS) using either a chart or iPod screen vs. Snellen Test		When a positive test was getting only 1 of 4 letters incorrect, the ETDRS test showed 100% and specificity was 60.9%. When getting 3 of 4 letters incorrect was a positive test the sensitivity was 98.3% and specificity was 91.3%. When getting all 4 letters incorrect was a positive test there was 98.3% sensitivity and 93.5% specificity.	"An iPod application requiring about a 1-minute testing time provides an objective, portable, rapid, and low-cost method to determine approximate VA, allowing VA testing to be performed efficiently in large surveys and other settings where approximate VA should be measured."	iPod visual acuity testing is relatively low cost and portable although the test does not represent total measurement of visual dysfunction which can be assessed in a clinical setting with more sophisticated technology.
Bock 2012 (score = 6.0)		Diagnostic	Supported by the German Research Foundation (DFG Exc 257 to JD, SO, CFP and FP) and grant KF2286101FO9 from the German Ministry of Economics to NeuroCure Clinical Research	N= 120 subjects (240 eyes), 85 multiple sclerosis (MS) patients and 35 healthy controls; Mean age was 37 years.		Functional Acuity Contrast Testing (FACT) vs. Snellen visual acuity test.		Area Under the Log contrast sensitivity function (AUC) was calculated for all data points of each FACT session. Retinal nerve fiber layer thinning (RNFLT) and Total Macular volume reduction (TMV) both correlated	"[O]ur study shows that functional contrast vision in MS is influenced by morphological changes in the anterior visual pathway, and that contrast vision testing with the Optec 6500 contrast box is capable of detecting differences from HC."	In MS, RNFL and TMV as measures of retinal axonal loss predict contract sensitivity as measured by FACT with Optec 6500P. Unable to readily calculate sensitivity and specificity.

			Center. No COI.					significantly with AUC day; (p=0.001) and (p<0.001), as well as with AUC night; (p=0.017 and (p=0.003). These assessments were corrected for age, gender and Snellen score.		
Kushner, 1995 [28] (score = 5.5)		Diagnostic	No mention of industry sponsorship or COI.	N= 69 literate patient with amblyopia or other cause of vision loss. Mean age was not provided.		Teller Acuity Card Test vs. Snellen test		There was a significant correlation between Teller card visual acuity and distance Snellen visual acuity (r =0.508, (p<0.001). Teller visual acuity had a low sensitivity for detecting a vision deficit of 20/40 or poorer (58%), 20/70 or poorer (39%) or legal blindness (24%).	"Teller Acuity Cards may underestimate the presence of amblyopia of all types, legal blindness, and a specified level of vision impairment (20/70). Even in the presence of normal visual acuity measurements with Teller cards, significant visual loss as assessed by standard Snellen optotypes may be anticipated in many patients."	Study suggests that both Snellen visual acuity and teller cards may underestimate vision lots in patients.
Sobaci 2009 (score = 5.0)		Diagnostic	No mention of industry sponsorship or COI.	N= 46 participants (23 patients with multiple sclerosis (MS) and 23 matched healthy		Randot Steroacuity (RSA) test vs. Snellen Test		The RSA score was much lower in the MS group compared to the control group; 80.7 arc seconds vs. 22.3	"Based on this study, patients with MS without optic neuritis have considerable abnormalities in stereopsis. RSA testing may be a	Very small sample. Study suggests MS patients had delayed PVEP and worse stereoacuity when compared

				controls. Mean Age was 35.1 years.				arc seconds (p<0.001). There was a significant correlation between P 100 latency (at 15 min) and RSA score; r=0.653 (p=0.001).	useful marker of subclinical disease activity in this condition."	to controls suggesting MS patients without optic neuritis have abnormal stereopsis such that RSA testing may aid in selecting those with subclinical disease.
Terry 2010 [29] (score = 4.5)		Diagnostic	No mention of sponsorship. No COI.	N= 2529 participants aged 40 years were evaluated for visual field loss.		Frequency doubling technology (FDT) methodology vs. Visual Field (VF) testing		The mean time was for the entire exam was 9.7 minutes. The average time of a single FDT test was 42 seconds. When defining reliability based on ≤ 1/3 blind spots, ≤ 1/3 false positive tests, and technician noted proper fixation, 90.1% of examined subjects had 2 reliable FDT tests for both eyes, and an additional 13.4% had 2 reliable tests for 1 eye.	"FDT is a feasible, fast, and reliable method for visual field loss screening in a population based U.S. study, with an 86.2% response rate, median exam time ~9 minutes, and nearly 95% of examined participants having complete, reliable results in 1 or both eyes."	Study suggests FDT is a fast alternate method for visual field loss screening in large populations.
Barsam 2006 [30]		Diagnostic	No mention of sponsorship. No COI.	N= 20 patients with who had		ETDRS acuity and Humphrey		The Humphrey field analyzer showed a mean	"Vitrectomy potentially allows retention/restoration	Small sample size. Study suggests that

(score = 3.5)				undergone a vitrectomy on at least one eye for hemorrhage or retinal detachment. Mean age was 50.8 years.		binocular Esterman Visual field testing vs. Snellen test		number of abnormal stimuli of 71.2% (p<0.005). 70% of patients had sufficient binocular acuity to drive and 71.4% were shown not to have a minimum visual acuity for safe driving.	of good visual acuity in patients with complications of proliferative diabetic retinopathy."	post vitrectomy patients may still have undetected visual impairment which may compromise safe driving.
Cacho-Martinez, 2013 [31] (score = 3.5)		Diagnostic	No mention of industry sponsorship or COI.	N= 66 patients with either large exophoria or normal heterophoria. Mean age was 24.83 years.		Diagnostic validity of clinical signs associated with Exophoria, using alternate cover test (ACT) and the Colon survey. EXO-MHVD group- Patients with large exophoria at near and moderate or high visual discomfort (N=33) vs. NH-LVD- Normal heterophoria and low visual		The NH-LVD group showed a significantly higher score compared to the EXO-MHVD group for the Monocular accommodative facility (MAF); 12.86 vs. 7.28 (p<0.001), the binocular accommodative facility (BAF); 10.82 vs. 4.45 (p<0.001), the monocular estimated method (MEM); 0.61 vs. 0.34 (p=0.002), the negative relative accommodation (NRA); 2.30 vs. 2.07 (p=0.02) and the	"In summary, this study shows that for subjects with a large near exophoria and moderate to severe symptoms, the accommodative and binocular tests that show a higher diagnostic accuracy are NPC and BAF."	Small sample, study suggests that people with a large near exophoria with moderate to severe symptoms, the NPC and BAF tests show a higher degree of diagnostic accuracy.

						discomfort (N=33).		vergence facility (VF); 15.91 vs. 10.35 (p<0.001).		
Cooper 1977 [32] (score = 2.5)		Diagnostic	No mention of industry sponsorship or COI.	N= 49 subjects tested with Titmus Stereo test. Age range was 8-55		Titmus Stereo test using both the circles and animals tests. Group 1 (N=30)- Look at each of the 4 circles and tell me which one looks different Vs. Group 2 (N=9)- Look at each of the 4 circles and tell me which seems to be closer Vs. Group 3- (N=10) Do any of the circles look like they pop off the page towards you?		The mean number of correct responses for the circle test was 3.3. The probability of guessing 4 consecutive right answers in group 1 was very small (0.004). 78% (7 of 9) of group 2 subjects and 70% (7 of 10) of group 3 subjects responded correctly to 1 or more of the circles. Scores obtained by the animal test were similar to those expected by chance.	"Responses obtained on the Wirt Stereo test with axis-135 Polaroid filters before both eyes was better than predicted by chance."	Study suggests administration of the animal test first, which has bene noted to be uninfluenced by lateral displacement cues. After that, study suggests numbers 4 and 9 of the circle test to decrease individuals responding to displacement cues. Authors report that the above will improve the validity of the Titmus Stereo test.

Color Vision Testing

Color vision screening is commonly performed as a component of preplacement and periodic examinations. It is sometimes performed prior to return to work for post-injury and postoperative patients, particularly for those in safety critical jobs.

Color vision is critical for countless occupations that require varying degrees of color detection. Color vision testing is also performed for motor vehicle driver licensure. Color detection is commonly segregated into several discrete categories including normal, deutranopia (difficulty detecting red/purple from green/purple), protanopia (difficulty detecting blue/green from red/green), tritanopia (difficulty detecting yellow/green from blue/green), and achromatopsia (absence of ability to detect colors) [223]. Although often categorized into these categories, there is an unappreciated and tremendous degree of heterogeneity within these groups. This heterogeneity has functional impacts such that some individuals within a given group can accurately perform a given occupation's tasks while others cannot [224, 225].

An added complication is that, there is a widespread misconception that color signals are of uniform color hue when they are not. This produces further difficulties with determining safety to perform a given job. There is yet another a common misperception that color detection is fixed for life, but multiple retinal intracranial diseases, metabolic disorders and pharmaceuticals all may result in serious, functional color vision impairments [226-231]. Such examples include diabetic retinopathy [230], multiple sclerosis, [232, 233], chloroquine, and amiodarone [234-236]. There also are some decrements in color vision discrimination ability with aging [237], mercury toxicity [238], and use of petroleum-based solvents [239].

As an example of the consequences of failure to detect color vision deficiencies, acquired color vision deficiencies have resulted in transportation injury fatalities [240-242]. Yet, color vision deficiency is also associated with advantages in discerning camouflaged objects, animals or humans [243, 244].

Color Vision Screening for Preplacement Examinations

Recommended.

Preplacement color vision screening is recommended for jobs that require color vision detection.

> *Indications* **–** Occupations that require color visual detection for accurate performance. Generally, most safety sensitive and safety critical jobs require some degree of color detection, although the discrimination requirements vary widely. These include almost all jobs requiring commercial operation of motorized equipment. Pseudochromatic plates are generally the most efficient way to screen a population and are thus recommended. Functional tests (e.g., on-the-job test) are of unclear validity and, if used, must test a wide array of circumstances (e.g., array of hues to be encountered, time of day/night, varying backgrounds) to have the potential to be valid.
> *Strength of Evidence* – **Recommended, Evidence (C)**
> *Level of Confidence* – High

Color Vision Screening for Periodic Surveillance Examinations

Recommended.

Periodic color vision screening is recommended for jobs that require color vision detection.

Indications **–** Occupations that require color visual detection for accurate performance. Generally, most safety sensitive and safety critical jobs require some degree of color detection, although the discrimination requirements vary widely. These include almost all jobs requiring commercial operation of motorized equipment. Pseudochromatic plates are generally the most efficient way to screen a population and are thus recommended. Functional tests (e.g., on-the-job test) are of unclear validity and, if used, must test a wide array of circumstances (e.g., array of hues to be encountered, time of day/night, varying backgrounds) to have the potential to be valid.
Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

Color Vision Screening for Select Post-injury Examinations

Recommended.

Color vision screening is recommended for select post-injury examinations.

Indications **–** Post-injury examinations for safety critical jobs that also require color vision detection.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Moderate

Color Vision Screening for Select Postoperative Examinations

Recommended.

Color vision screening is recommended for postoperative examinations.

Indications **–** Postoperative examinations for safety critical jobs that also require color vision detection.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Moderate

Rationale for Recommendations

Color vision deficiency is well associated with increased failures on signal detection [224, 225]. Fatalities in the transportation sector have been attributed to operator color vision deficiencies [240-242]. Thus, this is a strong basis for screening for color vision deficiency. There is also a potential basis for screening in favor of those with color vision deficiency for jobs requiring superior camouflage or animal detection [243, 244].

There are many color vision screening tests used, including: Ishihara, Farnsworth Panel D-15, Farnsworth Munsell 100 Hue (FM-100), Roth 28-hue desaturated, L'Anthony's desaturated D-15/D-15DS, Medmont C100, Color Assessment and Diagnosis Test; Nagel anomaloscope, Bowman's Color Confusion Index, Cambridge Colour Test (CCT), Color Assessment and Diagnosis test (CAD), Vingrys test, King-Smith's test, SPP-2, Nagel anomaloscopre, Color Vision Testing Made Easy (CVMET); City University Colour Vision Test (CUT); Waggoner computerized color vision test (CCVT) Richmond Hardy-Rand-Rittler (HRR), American Optical Hardy-Rand-Rittler (AO-HRR), Malbrel's chromatometer and luminance perception; Lantern test [237] [245-249] [236, 238, 250-255] [256-266] Cole 06a,b,c [267-269] [270-273] [218, 274, 275]. Pseudoisochromatic plates are the most commonly administered tests used to screen for color

deficiency, with Ishihara b eing the most widely used. Functional tests, such as the lantern test, a signal detection test, or on-the-job function tests are often used to attempt to ascertain sufficient discriminant abilities to perform a job after failure on pseudoisochromatic plate testing.

Functional tests have not been validated for determination of ability to both accurately perform the job tasks and prevent injuries/fatalities. Thus, they are generally of unclear ability to properly determine safe and accurate job performance. Carefully performed, functional testing that includes the array of circumstances likely to be encountered (e.g., array of hues to be encountered, time of day/night, season of year, varying backgrounds) may be sufficiently accurate for some jobs. The use of unvalidated functional tests is particularly concerning for safety critical jobs. Validated functional tests should be validated for both accuracy under a wide array of performance circumstances (e.g., array of hues to be encountered, time of day/night, season of year, varying backgrounds), as well as for ability to perform without elevated accident crash or other critical outcome performance measure(s).
Color vision screening is recommended for pre-placement and periodic screening for all jobs that require color vision detection. For safety sensitive and safety critical jobs, greater frequency of periodic screening is recommended, generally either annually or biennially. For safety critical jobs, screening post-injury and postoperative is also recommended. For those with risks for acquired color vision deficiency, greater frequency of color vision screening may be considered.

Color vision screening is not invasive, is without adverse effects, is low cost and is thus recommended for pre-placement, periodic surveillance, as well as select post-injury and postoperative examinations.

Evidence for Color Vision Screening

Author/ Year	Score	Study Design	Population/ Case Definition	Investigative Test	Comparative Test	Results	Conclusion	Comments
Hackman 2001	7.5	Diagnostic	N= 200 subjects. Age range from 17 to 53.	Farnsworth Lantern (FALANT)	Ishihara test.	167 subjects who passed the short-six Ishihara test also passed the FALANT test (0 failed). Of the 33 who failed the short-six Ishihara test, 30 failed the FALANT and 3 passed it. For the 14-plate test the 166 subjects who passed also passed the FALANT. The one borderline subject also passed the FALANT. Of the 33 who failed the 14-plate test, 30 failed the FALANT and 3 passed it.	"It appears that a 6-plate series of Ishihara pseudoisochromatic plates can predict FALANT success."	Study suggests that using a smaller number of Ishihara pseudoisochromatic plates can successfully predict FALANT testing success but at a much lower costs as study showed all subjects using either a 6 plate or 14 plate series of Ishihara plates passed the FALANT.
Shoji, 2009	7.0	Diagnostic	Criterion A (N=959). Mean age, 38.0±8.7 vs Criterion B (N=884). Mean age, 37.8±8.7. Subjects in criterion B were classified as normal subjects (N=729) Vs Acquired color vision impairment (ACVI) suspects (N=155) after Ishihara test.	D-15 panel (D-15DS)	Ishihara pseudoisochromatic plates, standard pseudoisochromatic plates part 2	The Bowman's Color Confusion Index (CCI) did not have normal distribution in the worse eye even after transformation ($p<0.001$). The 90^{th} percentile (95^{th} percentile) scores in the worse eye were 1.70(1.95) in criteria A and 1.59(1.73) for criteria B. AUC was 0.951 (95% confidence interval (CI), 0.931-0.971). Specificities of 80, 85, 90, and 95% were reached for sensitivities of 96.8, 93.3, and 71.0%.	"[O]ur study provided the normal healthy distribution in a large number of working-aged men on active duty using the D-15DS test with the CCI scoring system. Our results could be helpful for clinicians and patients when the D-15DS test is performed for screening purposes".	Study suggests D-15DS may be useful in screening as CCI correlated well with ACVI.
Birch 2010	6.5	Diagnostic	N = 486 male anomalous trichromats identified with the Nagel anomaloscope. 70 protanomalous trichromats and 416 deuteranomalous trichromats.	The Ishihara plates and of the American Optical Company (Hardy, Rand and Rittler) plates (HRR plates)	The Nagel anomaloscope	Based on 5/ 4/ 3 errors for the Ishihara plates, the sensitivity for 70 protanomalous trichromats was: 98.6%/ 100%/ 100%. The sensitivity for 416 deuteranomalous trichromats was: 87.7%/ 94.1%/ 98.1%. The overall screening sensitivity for Ishihara test based on 5/ 4/ 3 errors was: 94.7%/ 97.7%/ 98.4%.	"The Ishihara test and the HRR tests have different aims and it can be useful to give both tests in a clinical setting to provide accurate identification of red–green colour deficiency, with the Ishihara plates, and an estimate of severity together with confirmation of protan/deutan	Ishihara plates superior to HRR. In clinical settings using both tests may be of use in identification of red-green color deficiency. However, Ishihara plates associated with a sensitivity between 97.7%-98.4% in this

						The overall screening sensitivity for HRR plates was based on 2 and 3 errors: 92.8% and 87.0%.	classification when the HRR test is failed."	study and identified slight trichromatism.
Cole 2007	6.5	Diagnostic	99 participants with CVD diagnosed by the Ishihara, the Richmond HRR, the Farnsworth D15, the Medmont C100 and the Nagel anomaloscope.	Color naming task: 10 surface colors. The participants were asked to name 10 surface colors (red, orange, brown, yellow, green, blue, purple, white, grey and black). The colors were presented in two shapes (dots and lines) and three sizes.	The Ishihara, the Richmond HRR, the Farnsworth D15, the Medmont C100 and the Nagel anomaloscope.	The color naming task based on 1 error had a predictive value of passing of 0.73 and predictive value of failing of 0.90. The predictive value of passing and predictive value of failing based on no more than 1 error for Farnsworth D15/ Farnsworth D15 plus Medmont C100 or anomaloscope to exclude protans/ Richmond HRR/ Anomaloscope range were: 0.73 and 0.90/ 0.84 and 0.85/ 0.87 and 0.70/ 0.66 and 0.97.	"A 'mild' classification with the Richmond HRR test, especially if no more than two errors are made on the HRR diagnostic plates, identifies patients with abnormal colour vision who are able to name surface colour codes without error or only the occasional error. A pass of the Farnsworth D15 test identifies patients who will make no or few (up to 6%) errors with a 10 colour code, but who will be able to name the colours of a seven colour code that does not include orange, brown and purple."	Study suggests patients who fail the Farnsworth D-15 are likely to make errors on surface color code tests and patients with an anomaloscope range of >35 units will identify surface color code failures.
Ng 2015	6.5	Prospective, observational, multicenter trial	Subjects with color vision deficiency (CVD) (N=59) Vs Subjects with normal color vision (N=361) For subset subjects (24 CVD and 7 CVN), CCVT was administered twice using default setting of the computer monitor and another time after computer screen had been set to a correlated color temperature (CCT) of 6500 K. Mean (±SD) age for all subjects was 22.3 (±8.4) years	Waggoner computerized color vision test (CCVT) and the Richmond Hardy-Rand-Rittler (HRR)	24-plate Ishihara test	The HRR test classified 29 of 54 (54%; 95% Confidence Interval (CI), 0.40 to 0.67) subjects the same as the CCVT. When CCVT was used as a screening test only, the default (78% passed; 95% CI, 72 to 83%) vs Set CCT (*&% passed; 95% CI, 82 to 91%) conditions were different (p=0.017).	"The Waggoner CCVT is an adequate color vision screening test with several advantage and appears to provide a fairly accurate diagnosis of deficiency type. Used in conjunction with other color vision tests, it may be a useful addition to a color vision test battery".	Study suggests CCVT performs similarly to Richmond HRR with high sensitivity and specificity. It generally classified color defects as having a more severe defect than other tests.

Cotter 1999	6.5	Diagnostic	N=41 with normal color vision (N=20) or hereditary red-green color deficiency (N=21). Age range 22-31 years	Pseudoisochromatic color plate test, "Color Vision Testing Made Easy" (CVMET)	Ishihara, Panel D-15, anomaloscopic Rayleigh	Specificity CVMET: 100% for all 12 test plates (from color normal subjects. Sensitivity CVMET: ranged from 67-90% (from color deficient subjects); compared with anomaloscope, 90.5%.	"[T]he results of our investigation of the CVMET indicate that the test appears to be just as sensitive as the Ishihara test in identifying red-green color deficiencies in adults."	Preliminary study with small sample shows CVTMET to be potentially promising as a screening tool for red-green color deficiency Study reports 90.5% sensitivity and 100% specificity.
Ganley 1997	6.5	Diagnostic	N=111 university students. Age range 19-56 years.	Ishihara and Hardy-Rand-Rittler (H-R-R) pseudoisochromatic color plates projected on 35mm slides as a group in a moderately darkened auditorium	Ishihara and H-R-R color plates shown individually under natural daylight	Individuals identified as color blind: projected slides Ishihara 7, H-R-R 89; individual color plates Ishihara 6, H-R-R 5. Projected slides: Ishihara plates sensitivity 100%, specificity 98.1%; H-R-R plates sensitivity 100%, specificity 20.8%.	"[T]his study projected 35mm color slides, under well-controlled conditions, can be used to screen large population groups for red-green color deficiencies."	Study suggests that if conditions are well controlled, 35mm color slides might be used to screen large populations for red-green color defects.
Hovis 2000	6.5	Diagnostic	N=81 participants with normal color vision and N=74 participants with congenital red-green defects. Age range 18-67 years.	Lantern test (CNLAN) administered under room illumination levels of 300 lux; repeated after 10 days	Ishihara test, Nagel anomaloscope, simulation	CNLAN and simulation results: 70% of color-normals and no color-defectives had a perfect score for simulation; 90% of color-normals and 5% of color-defectives had a perfect score on the lantern test. Comparison with Ishihara test: 100% of color-defectives and 3.7% of color-normals failed the Ishihara test; all the color-normals that failed Ishihara passed both the lantern and simulation. Ishihara vs simulation results 1st session: ƙ=0.94±0.028. Predictive value: Ishihara test for passing 0.98 for lantern when color-normals included and predictive value of Ishihara for failing 0.99 for lantern.	"[T]he CNLAN is a reasonable substitute for a field trial of identifying wayside signal light colors."	Study suggests lantern test appears to be a "reasonable assessment" of the ability to correctly detect rail signal colors but lantern test is not as "strict" as Ishihara since Ishihara failed 3.7% of individuals passing both simulation and lantern. Study is biased against FRA criteria for 38 plate Ishihara.
Huna-Baron 2013	6.5	Diagnostics	N=43 patients (48 eyes) with newly diagnosed optic neuropathy and N=33 patients (33 right eyes) controls. Mean	Hardy-Rand-Rittler (HRR) 4th edition	Ishihara color plate tests	Mean±SD Ishihara scores: study group 10.1±2.5 vs controls 11.73±0.42 (p<0.001). Mean±SD HRR scores: study group 2.5±1.7 vs. control 5.3±0.5 (p<0.001). ROC area	"[W]e found the HRR 4th edition test to be more sensitive in detecting acquired dyschromatopsia due to optic neuropathy,	Small study sample. Study suggests 4th edition HRR test superior to Ishihara in detection of acquired

			age study group 47±19 years, control group 33±13 years.			under the curve (AUC): Ishihara 0.77±0.05; HHR 0.93±0.03 (p=0.0006). Specificity-sensitivity balance: HRR 100% and 79% respectively; Ishihara 100% and 48% respectively. AUC of ROC curve using age to separate study and control groups: 0.72±0.05; Ishihara did not perform better than age (p=0.5); HRR better than age (p=0.0006).	than the Ishihara plates test."	dyschromatopsia due to optic neuropathy, stating better sensitivity and specificity.
Ing 1994	6.0	Diagnostic	N= 32 subjects; 21 with normal color vision, 10 with congenital red-green defect and 1 patient with an acquired mixed color defect. Mean age was 34.5 years.	City University Colour Vision Test (CUT) and American Optical Hardy-Rand-Rittler (AO-HRR)	Ishihara	Subjects completed the three computer tests in an average of 20 min. Sensitivity for the CUT was 34% for the conventional test and 27% for the computer test. CUT showed a 99% specificity for the conventional test and 98% for the computer test. The AO-HRR showed 45% and 55% sensitivity for the conventional and computer tests, respectively. AO-HRR also showed a 100% and 99% specificity for the conventional and computer tests, respectively.	"[O]ur computer emulations of the CUT, Ishihara, and AO-HRR tests screen subjects with normal color vision with high specificity and delineate congenital color defects with a sensitivity comparable to that of their conventional counterparts"	Small sample size so generalizability of results cannot be ascertained. Computerized color images did not have identical color to their corresponding color plates but study suggest this difference did not effect performance.
Birch 1997c	6.0	Diagnostic	N = 401 males with green-red color deficiency diagnosed with the Nagel anomaloscope. There were 83 protanopes, 30 protanomalous trichromats, 96 deuteranopes and 192 deuteranomalous trichromats	The American Optical Company (Hardy, Rand, and Rittler [HRR]) plates.	Nagel anomaloscope, D15 test	HRR test sensitivity was 98% overall or 96.4% for the 222 anomalous trichromats. HRR screening plates identified 35 color deficient participants by a single error (6 protanopes, 2 protanomalous trichromats, 1 deuteranope and 26 deuteranomalous trichromats).	"The three tests compared in this study have very different examination procedures, and visual tasks, and the results obtained should not necessarily be expected to show precise agreement. However if all three tests are used a clear indication of practical hue discrimination ability can be obtained."	Study suggests Ishihara test is the most efficient test in determination of color deficiency with a high sensitivity and specificity.
Seshadri, 2005	6.0	Diagnostic	Normal color vision (N=30). Mean age: 26±5.4 years Vs Congenital red-green deficiency (N=30). This includes	Color Assessment and Diagnosis test (CAD),	Ishihara, Standard Nagel (model 1)	The specificity of the CAD test for normality was 100%. The sensitivity was 93.33%. The concurrent validity of the CAD test for normal colors, given by TN/TN+FN was 93.75%.	"These results showed that the CAD test is a valid test for identifying congenital red-green color deficiency".	Small sample so further testing necessary to validate preliminary results.

			11 protanopes (P), 7 deuteranopes (D), 11 deuteranomals (DA) and 1 protanomalous (PA) subjects. Mean age: 35±7.67 years		anomaloscope, Hardy, Rand and Rittler (HRR: 4th ed) pseudoisochromatic test, and the Farnsworth Munsell 100 (FM-100) hue test.	The concurrent validity of the CAD test for color defects, given by TP/TP/+FP was 100%. The sensitivity for Ishihara was 96% with a specificity of 100%. The sensitivity for HRR was 100% with a specificity of 33.33%. For FM-100 and Nagel anomaloscope, the sensitivity was 100% with the specificity of 83.33%.		
Chauhan 1986	6.0	Diagnostic	N= 455 male subjects	Both editions of the City University Colour Vision Tests (Cit y 1 and City 2)	Nagel anomaloscopre.	The anomaloscopre classified 42 subjects (9.23%) as abnormal. Shared information City 1 weighted score was 13.74% and the City 2 weighted score was 7.26%.	"Despite this, even the improved City 2, like its origin, the D-15, is shown to be poorer than most of the commonly used PIC tests."	Study suggests that a weighted scoring system
Squire, 2005	6.0	Diagnostic	Normal color vision (N=24) Vs Color vision deficient (N=55). This includes 36 deuteranomalous trichromats, 5 deuteranopes, 9 protanomalous trichromats, and 5 protanopes.	Nagel anomaloscope	Ishihara test	All 55 color-deficiency subjects failed the Ishihara plates by making at least 1 mistake in the 1st 15 plates of the 24-plate version. All dichromats failed the 2nd tests and all the protanomalous failed all 3 lantern tests except 3 who passed the Nagel anomaloscope. 7 of the 24 normal trichromats made between 1 and 3 mistakes on the 1st 15 plates of Ishihara test. 12 out of 24 normal color vision subjects passed the Nagel test.	"Consistency is lacking in color vision testing and an aspiring professional pilot may be accepted without limitation in one country, and rejected outright in another. The different tests also reveal different aspects of color deficiency and the severity of outcome may or may not relate directly to the subject's ability to discriminate colors".	Study demonstrates variability between all tests in terms of results for color vision testing. A consistent and quantifiable test is necessary to set standards for pass/fail criteria in the aviation industry.
Aroichane 1996	5.5	Diagnostic	N= 178 consecutive patients (349 eyes) reffered to the Wilmer Eye Institute examined by the two authors. Mean age was 45 years.	Hardy-Rand-Rittler test	Ishihara test.	Testing with the HRR plates showed no evidence of a color vision defect in 168 of the 202 healthy eyes (83.2%) compared to 196 (97.0%) in the Ishihara test (p<0.0001). For those with a visual acuity ≥ 20/25	"For patients with unilateral or bilateral NGON, HRR plates are more likely than Ishihara plates to detect a colour vision defect,	Neither HRR nor Ishihara plates are very sensitive in detecting nonglaucomatous optic neuropathy although Ishihara plates were

						with nonglaucomatous optic neuropathy, the color vision deficit on testing was higher in the HRR test vs. Isihara; 13 (76.5%) vs. 6 (35.3%) (p=0.008).	particularly when the visual acuity is 20/25 or better."	superior to HRR plates in detecting normal vision and HRR plates were more likely to detect color vision defects in persons with a 2-/25 visual acuity or better.
Atchison 1991	5.5	Diagnostic	N= 99 congenital red-green color defective subjects. Mean age was 33 years.	Farnsworth's standard D15 and L'Anthony's desaturated D-15 panel tests.	Ishihara	The correct diagnostic rates were 45% for the standard D15 test and 58% for the desaturated D15 test. The desaturated D15 test had a misclassification rate of 5% for dichromates compared to <0.1% for the standard D15 test.	"We suggest that quantitative scoring techniques are of limited benefit for the clinical diagnosis of congenital color vision defects but that they are of use in clinical trials or for the monitoring of changes in color vision over time."	Quantitative scoring methods to detect congenital color vision deficiencies are of little value. Study supports Ishihara plates to make congenital color vision diagnoses.
Cole 2003	5.5	Diagnostic	N = 102 participants with abnormal color vision. 48 deuteranomals, 18 deuteranopes, 16 protanomals and 19 protanopes.	The Farnsworth D15 test	The Ishihara test, and the Nagel anomaloscope.	The Farnsworth D15 had a sensitivity and specificity of 0.80 and 0.69 (large stimuli), and 0.75 and 0.71 (small stimuli). The Nagel anomaloscope < 35 scale units had a sensitivity of 0.85 (large and small stimuli), and specificity of 0.56 at large stimuli, and 0.63 at small.	"About 40 per cent of those with abnormal colour vision can name the main colours correctly under good visibility conditions. The D15 test is an imperfectpredictor of those who can name surface colour codes correctly but it does provide useful information for general counselling. It is not suitable as a single test for occupational selection because it will pass 20 per cent who cannot name surface colours correctly and fail 30 per cent who can. In occupations in which recognition of surface colour codes is of critical importance, it may be best not to select people with abnormal colour vision because of the lack of a colour vision test that is a	Study supports other literature stating that no one single test is a perfect predictor of a person's ability to name colors.

							perfect predictor of the ability to recognise surface colours."	
Cole 2006 Optometry and Vision Science	5.5	Diagnostic	100 participants with color vision deficiency (CVD) and 20 color vision normal (CVN) participants. CVD was diagnosed by the Ishihara test, the Richmond HRR test, the Farnsworth D15 test, the Medmont C100, and the Type 1 Nagel anomaloscope,	Color Naming Task: 10 surface colors (red, orange, brown, yellow, green, blue, purple, white, gray, and black) that were presented in two shapes (dots and lines) and in three sizes for each shape.	The Ishihara test, the Richmond HRR test, the Farnsworth D15 test, the Medmont C100, and the Type 1 Nagel anomaloscope.	Only 37% of the CVD participants named the colors without any errors. There was a significant factor in the class of color deficiency ($p<0.001$). There were significant interactions between shape and 1/area ($p<0.001$), and between class of CVD and 1/area ($p<0.001$).	"Mild deuteranomals will make very few errors with a seven-color code that omits orange, brown, and purple and will make very few errors (approximately 0.3%) with a 10-color code when the stimuli are reasonably large (area >20 mm^2)."	Study suggests that various types of color vision deficiency have different error rates when naming surface colors (mild deuteranomals 0.3%) and mild protanomals but dichromats and anomalous trichromats make more errors than both mild deuteranomals and mild protanomals.
Cole 2006 Clinical and Experimental Optometry	5.5	Diagnostic	100 patients with abnormal color vision and 50 patients with normal color vision. The color vision was diagnosed by the Ishihara test, the Farnsworth D15 test, the Medmont C-100 test and the Type 1 Nagel anomaloscope.	The new Richmond HRR pseudoisochromatic test	The Ishihara test	The mean number of errors on the protan-deutan screening plates was 4.97 ± 0.86. When the fail criterion was 2 or more errors for the Richmond HRR test had a sensitivity of 1.0 and specificity of 0.96. When the fail criterion was 3 or more for the Richmond HRR test had a sensitivity of 0.98 and specificity of 1.0. The Richmond HRR test correctly classified 86% of participants as protan or deutan.	"The test is as good as the Ishihara test for detection of the red-green colour vision deficiencies but unlike the Ishihara, also has plates for the detection of the tritan defects. Its classification of protans and deutans is useful but the Medmont C-100 test is better. Those graded as 'mild' by the Richmond HRR test can be regarded as having a mild colour vision defect but a 'medium' or 'strong' grading needs to be interpreted in conjunction with other tests such as the Farnsworth D15 and the anomaloscope. The Richmond HRR test could be the test of choice for clinicians who wish to use a single test for colour vision."	Study suggests new Richmond HRR is comparable to Ishihara plates in detection of red-green color deficiency but also has a specific plate for the detection of tritan plates.

Good 2005	5.5	Diagnostic	N=126 color vision normal. Mean age 34.5 years	Lanthony Desaturated D-15 retested after 3-6 weeks.	Nagel anomaloscope, HRR Pseudoisochromatic color plates, Farnsworth D-15	Mean Color Confusion Index (CCI): Lanthony Desaturated D-15 first session 1.12±0.12 vs. second session 1.10±0.12 with regard to age (p=0.04); median scores males 1.05 vs females 1.10 (p=0.05). Intraclass correlation coefficient (ICC) test-retest reliability of CCI score: 0.56 (95% CI 0.43-0.67).	"[T]he Lanthony Desaturated D-15 test can be used to quickly assess fine color discrimination, although there is considerable within-subject variability in discriminating subtle differences in color."	Although Lanthony desaturated D-15 test is quicker to administer and score, when compared to Farnsworth Panel D-15, there is significant inter-subject variability when detecting subtle differences in color. Authors recommend administration of Lanthony D-15 test at least three times and calculating mean of the three values because the test, retest reliability is only average at best.
Gündoğan 2005	5.5	Diagnostic	N=104 students with no known history of ocular pathology, ocular operations, and occlusion or penalization therapy, median age 21 years.	Ishihara projected slides, mass screening testing	Ishihara printed plates, individual testing a few weeks after mass screening	Incidence of color-blindness: 13.6% male, 6.7% whole population. Concordance between mass screening and classical method: k=1.00 (p=0.000). Sensitivity and specificity of mass screening: 100% for both.	"Using projected slides of Ishihara plates instead of the authentic method is an effective and timesaving method for detecting color-blindness."	No comparative test. Ishihara gold standard. Study suggests there is 100% sensitivity and 100%specificity in using Ishihara slides in mass screening of individuals with no known ocular disease for color deficiency.
Birch 2008	5.0	Diagnostic	107 protanomalous and 410 deuteranomalous trichromats identified by failure of the Ishihara plates.	The Farnsworth D15 test	The Nagel anomaloscope	186/517 anomalous trichromats failed the D15 (36%). In total, 42% protanomalous trichromats and 35% deuteranomalous trichromats failed Farnsworth D15 test.	"The ability of many severe protanomalous trichromats to pass the D15 might be attributed to perceived luminous contrast and the poor performance of a significant proportion of subjects with "minimal" deficiency demonstrates them true loss of practical hue discrimination ability when this is not available."	Study suggests protanomalous trichromats with slight color deficiency have poor practical hue discrimination ability measured by the Farnsworth D15 test.

Cole 1998	5.0	Diagnostic	N = 286 people with defective color vision.	The Farnsworth lantern test	The Ishihara Test, the Farnsworth D 15 test, and the Nagel anomaloscope	Sensitivity and specificity of the Farnsworth D 15 Test in predicting a pass or fail at the Farnsworth lantern was 0.67 and 0.94. The sensitivity and specificity of a Nagel Range with a fail criterion of >10 was 0.87 and 0.57.	"[N]either the D-15 nor the Nagel Anomaloscope matching range are satisfactory predictors of performance on the Farnsworth Lantern."	Study suggests neither the D-15 nor Nagel are good predictors of performance on Farnsworth lantern test. D-15 has good specificity (94%) but marginal sensitivity (67%) where Nagel test has poor specificity (57%) but good sensitivity (87%). Study would support use of a combination of tests.
Rabin, 2011	5.0	Diagnostic	(N=1446) Pilot applicants who had normal color vision (CVN). Mean age ±SD, 24.3±3.2 years.	The Cone Contrast Test (CCT), Pseudoisochromatic plate (PIP) that includes Dvorine PIP, Standard Pseudoisochromatic Plates Part 2 (SPP2), and Farnsworth F2 Plate	Ishihara test	L, M, and S CCT specificity was 100% in 92 participants on all tests, based on the concordance between passing scores on the CCT (≥75) and on Rayleigh and Moreland anomaloscope and PIP tests. Sensitivity of individual PIP tests for detecting hereditary color vision deficiency (CVD) ranged 40% to 68%, vs 40(80%) of 49 for the combined PIP battery. Deutan CVDs showed decreased M cone CCT scores (2-sample t-test, unequal variance, t=18.4; p<0.0001), but the protans showed decreased L cone CCTs (t=9.0; p<0.0002)	"[T]he CCT offers an intuitive, robust index of color vision that accurately detects type of CVD and capable of grading severity of CVD as well as color ability in the CVN population. The rapid, threshold letter-recognition task is well-suited for clinical application".	Study suggests CCT is a quick color vision test with sensitivity and specificity comparable to anomaloscope. Additionally, the CCT can detect color disability type and severity.
Abramov 2009	4.5	Diagnostic	N= 7 subjects with normal color vision. Mean age was 26 years.	Vingrys and King-Smith's tests	Rayleigh Matches using an anomaloscope. As well as distances. Standard distance	Values for the C-index (confusion) and S-index (polarity of an individual's pattern of cap reversals) began to decrease when view distances increased past 2 m. At 0.5 m all participants had perfect scores. After 2 m, error in the indices scores increased slightly for most participants.	"An individual's color vision performance can be interpreted by relating it to performance of color-normals viewing the test caps at some non-standard distance. This is similar to Snellen notation for acuity."	P-values were not reported with the data. Study suggests high degree of correlation between Farnsworth D-15 and Lanthony desaturation D-15 panels for interpreting an individual's color vision and the cut off index values correspond to

					was 0.5 m.			values of 2.5-3.0m viewing distance.
Birch 1997 Opthal. Physiol. Opt.	4.5	Diagnostic	N= 401 subjects with red-green color deficiency. Mean age was 28.3 years.	Ishihara test (Transformation and Vanishing plates)	Nagel anomaloscope	The sensitivity for the Ishihara test was 88.2% for a fail criteria of 12 errors, 95.5% for 8 errors, 97.5% for 6 errors, 99.0% for 3 error 100% for 2 errors. For the 222 anomalous trichromats the sensitivity was 78.8% for 12 errors, 91.9% for 8, 95.5% for 6, and 98.2% for 3 errors.	"The specificity of the Ishihara test was determined in a previous study (Birch and McKeever, 1993) and the results combined with the present data to obtain the overall efficiency of the Ishihara plates for a representative cross section of colour-deficient subjects."	Study suggests that HRR plates be used in conjunction with Ishihara plates but not as a stand-alone test for color deficiency subjects.
Birch 1997 Ophthal. Physiol. Opt.	4.5	Diagnostic	N= 222 subjects with congenital red-green color deficiency. Mean age was not reported.	City University test (TCU test)	Nagel anomaloscope	Of the 222 subjects examined, 149 (67.1%) failed the TCU test. All 47 deuteranopes failed the TCU, but 2 of the 52 protanopes examined passed the test. The TCU test was failed by 52 of the 123 anomalous trichromats examined (42.3%) and 48 of the 108 deuteranomalous trichromats (44.4%) failed the TCU test.	"Detection and classification rates varied on all the plates of the TCU test. Mixed protan and deutan classification errors were made by 61% of subjects with the majority result correct in 80%. The most efficient plates are identified and recommendations are made for the optimum use of the TCU test in clinical practice."	Study suggests Ishihara plates should be used for screening of color defects but that both the TCU and D-15 be used for determination of color defect severity. The D-15 is better in detection of acute protan color deficiency.
Cole 2006c	4.0	Diagnostic	100 male subjects with abnormal color vision diagnosed by the Ishihara test, the Farnsworth D15 test, the MedmontC100 test, and the Nagel anomaloscope.	Two versions of the Farnsworth Lantern test	The Ishihara test, the Farnsworth D15 test, the MedmontC100 test, and the	24% participants passed the old version of the Farnsworth Lantern test and 19% passed the new version. There were agreements between the two tests for 89% participants. The median number of errors on runs 2+3 was 9.5 in the new lantern test vs. 6.5 errors in the old version ($p<0.0001$). Most participants who	"The Optec 900™ can be considered equivalent to the Farnsworth lantern and might be preferred because it is slightly more stringent, reducing the risk of passing those who will make errors with signal lights. The practice of passing applicants who make no	Study suggests new lantern test (Farnsworth Optec 900) is slightly better than old Farnsworth lantern test in detecting color vision deficiency.

					Nagel anomalo scope.	failed the Farnsworth D15 test (n = 41) failed both Farnsworth lantern tests	errors on the first run should be abandoned since 10% of those who pass in this way make many errors when additional runs are given."	
McCulley, 2006	4.0	Clinical experiment study	Healthy Subjects tested at lesser degrees of fogging, 0.1 logMAR intervals. (N=12)	D-15 panel and Hardy-Rand-Rittler (HRR) plates	Ishihara color vision test	Single factor repeated measures analyses that was conducted separately at each acuity found a difference between the color vision testing devices for acuities 20/188, p=0.01. D-15 panel and HRR had fewer percentage of errors than Ishihara, p<0.01).	"Color vision testing is accurate up to logMAAR 1.40 (20/501) with D-15 panel, 1.10 (20/252) with HRR plates, and 0.71 (20/106) with Ishihara plates".	Study suggests color vision testing may be attributable to visual acuity loss. Color vision testing with Ishihara plates was most dependent and Farnsworth D-15 panel least dependent upon visual acuity.
Gaudart 2005	4.0	Diagnostic	N=158 patients aged 20-28 years, mean age 22.6 years.	Malbrel's chromatometer and luminance perception	Ishihara plates and Farnsworth 28-hue test (I-28H), Lanthony desaturated 15-hue panel used when required	Chromatometer evaluation with Ishihara plates and Farnsworth 28-hue tests to detect anomalous color vision (sensitivity/ specificity/ positive predictive value/ negative predictive value: 158 eyes of sample 1 – Blue-Yellow 100/83.7/16.7/100; Green-Red 100/83.0/16.1/100; Blue-Yellow and Green-Red 100/96.7/50.0/100; sample 2 – Blue-Yellow 40.0/79.1/5.9/97.6; Green-Red 60.0/80.4/9.1/98.4; Blue-Yellow and Green-Red 40.0/92.8/15.4/97.9.	"[C]hromatometer is a complementary test with regard to conventional tests. This new device allows color vision deficiency to be detected early and monitored."	Study suggests new chromatometer may assist conventional tools in screening for color deficiency especially for early onset disease as a first line tool.
Rodriguez-Carmona, 2012	4.0	Diagnostic	Subjects with normal color vision (N=236) Vs. Subjects who had deutan deficiency color vision. (N=340) Vs Subjects who had protan deficiency color vision. (N=166) The mean age for all subjects was 31.0±11.7 years with a median pf 28 years.	Color Assessment and Diagnosis (CAD) test	Ishihara test	80.9%(191) of normal trichromats made no errors on the 1st 25 plates of 38-plate version and al normals except for 1 got all 25 plates correct with 3 or less errors. 29% of deutan subjects make 12 or less errors compared to protan subjects with only 8%. 70% of deutan subjects make 20 or less errors compared with only 39% of protan subjects.	"Color thresholds can provide a good measure of the severity of both RG and YB color vision loss. Neither the number of IT plates failed nor the SI value computed in this way can be used to determine reliably the severity of color vision loss".	Study suggests that the number of IT plates failed nor the SI value can serve as a reliable method to determine color loss severity.

Bailey, 2004 Diagnostic Article	3.5	Diagnostic	N= 52 subjects. 29 normal color vision subjects (18 male and 11 female) and 23 color deficient Caucasian male subjects. Mean age was 29 years.	2002 edition of the HRR color vision test.	Ishihara test.	100% of the normal vision subjects tested as normal on the HRR test. 100% of the subjects with color vision deficiency were diagnosed as having a color vision deficiency using the HRR. 100% of subjects classified as dichromats were rated as "severe" on the new HRR.	"Among those with moderate and severe defects the new test was highly accurate in correctly categorizing subjects as protan or deutan. In addition, a mild tritan subject made a tritan error on the new test whereas he was misdiagnosed as normal on the original."	Small sample size. New HRR color vision test appears to be more sensitive than older version.
Melamud, 2006	3.5	Prospective clinical laboratory study	Subjects with normal trichromatic vision or with congenital color vision defects underwent various color vision tests. (N=59 subjects)	D-15 Farnsworth-Munsell test (D-15), Farnsworth-Munsell 100-Hue test (FM 100-Hue) and the Portal Color Sort Test (PCST)	15-plate Ishihara test	The FM 100-Hue and the PCST scores were highly correlated, 0.8(95% confidence interval (CI) 0.6-0.9, p<0.001. The median time of 3 minutes to complete the PCST was faster than the FM 100-Hue (p<0.001) but slower than both the Ishihara and D-15 (p<0.001)	"This study suggests that the PCST, a test of color vision deficiency, can be used effectively and reliably as a tool for screening (comparable to the Ishihara plates and the D-15) and grading (comparable to the FM 100-Hue) color discrimination ability."	Study confirms limitations of all color testing. Study suggests PCST may be used a confident alternative to both the Ishihara and D-15. However, future study is needed to compare PCST against the anomaloscope.
York, 2008	3.5	Diagnostic	Subjects with normal color (N=44) vs Subjects with color deficiency (CDs) (12 deutans, 4 protans, and 3 unclasified) (N=19).	Red light increment threshold test	Farnsworth D-15 arrangement test and the Hardy-Randy-Rittler (HRR) plate test	The differences between normal observers (1.21 cd/m²) and the CD observers (7.58 sd/m²) is 0.80 log units and highly reliable (ANOVA, F=127, dF=3, p<0.001). The protans were reliably less sensitive to the red test than deutans (p<0.001). The unclassified CDs were less sensitive than the deutans (p<0.001) whereas marginally different from the protans (=0.047). White increments detection threshold overlapped between the two groups, but the normal observer's average (7.02 cd/m²) and the difference was reliable (ANOVA, F=5.119, dF=3, p=0.003).	"The red test measures red light increment threshold, a characteristics of color vision not asses by conventional tests of color vision which are based upon measuring loss of color discrimination. All CD observers have raised red light increment thresholds and the test clearly differentiates CD observers from those with normal color vision".	Small sample. Study suggests red light test measures a red light increment threshold which is not typically assessed by traditional color vision tests because most of the tests are tests of loss of color discrimination.
Biersdorf, 1977	3.0	Diagnostic	N= 112 subjects (14 color vision impaired subjects and 98 normal vision subjects. Age	Davidson and Hemmendinger (DH) color rule test	Nagel anomaloscope, Farnswor	The DH color rule performed as accurately as the Nagel anomaliscope and better than the Farnsworth D-15 and HRR tests in	"The DH color rule has both advantages and disadvantages in screening	Results presented were not clear and statistics were not used to analyze differences between the

Diagnostic article			range from 10 to 50, most between 18-30.		th D-15 and the HRR test.	detecting anomalous trichromats and in discriminating protanomalous subjects from deuteranomalous subjects.	congenital color vision defects. When used with the proper illumination, the color rule is very sensitive in detecting small degrees of color defect (anomalous trichromats) and correctly classifying them."	different diagnostic tests. Study suggests there are both advantages and disadvantages to the PH Color Rule. For severe color vision subjects (dichromats and achromats), thus, DH color rule is more time intensive and less discriminatory. For less severe color vision defects, when used with proper illumination it appears to be quite sensitive.
Hovis 2002	3.0	Diagnostic	N=31 adults with normal color vision and N=21 adults with congenital red-green defects	The University of Waterloo Colored Dot Test (UWCDot) for Color Vision Testing	Nagel anomaloscope, Lanthony D-15	UWCDot agreement with D-15: with various versions, 80% of subjects pass and fail each test; UWCDot less sensitive vs. D-15 when only errors on Chroma 4 hues are considered. UWCDot compared with anomaloscope: agreement over 0.95. UWCDot: more sensitive than both D-15 tests when scored based on number of eye movements.	"The results show that when any mistake is considered to be a failure, the UWCDot test has a clinical utility approaching the Desat D-15."	Study underscores difficulties in accurately detecting color vision deficits.
Cole 1983	2.5	Diagnostic	N = 100 observers with defective color vision. 17 protanomals, 51 deuteranomals, 9 protanopes and 17 deuteranopes.	Lantern tests: the Farnsworth lantern and the Holmes-Wright Type A and Type B lantern.	The Farnsworth dichotomous test (Panel D15), the H-16 test, L'Anthony's desaturated test, the City	The sensitivity and specificity for the Farnsworth lantern test with D15 in the fail criterion of 5/ 4/ 3/ 2/ 1 xings were: 0.58 and 1.00/ 0.68 and 1.00/ 0.71 and 0.91/ 0.74 and 0.85/ 0.88 and 0.44. The sensitivity and specificity for the Farnsworth lantern test with City University based on 1/ 2/ 3 errors were: 0.74 and 0.85/ 0.62 and 0.97/ 0.56 and 1.00. The sensitivity and specificity for the Holmes-Wright Type A with D15 in the fail criterion of 5/ 4/ 3/ 2/ 1	"The lack of a strong correlation between clinical tests and the recognition of the small colored stimuli presented by the lantern tests suggests that clinical tests do not test the same aspect of color vision that is important to the recognition of signal lights. For this reason lantern tests should be retained for occupational testing of color vision."	Study suggests that Farnsworth D-15 test and City University tests were the best predictors of performance on lantern test but it appears that the lack of correlation between multiple color defective subjects suggests these tests of color vision test different aspects.

					University test, the Farnsworth-Munsell 100 Hue test and the Nagel anomaloscope.	xings were: 0.44 and 1.00/ 0.52 and 1.00/ 0.56 and 0.86/ 0.59 and 0.79/ 0.81 and 0.50. The sensitivity and specificity for the Holmes-Wright Type A with City University based on 1/ 2/ 3 errors were: 0.62 and 0.93/ 0.49 and 1.00/ 0.44 and 1.00.		
Davison 2011	2.5	Diagnostic	N=102 healthy subjects. Age range 18-40 years.	Macular pigment (MP) optical density (MPOD) using customized heterochromatic flicker photometry.	Farnsworth-Munsell 100-Hue test (FM100), Moreland match on the HMC anomaloscope, customized short wavelength automated perimetry (SWAP) technique at foveola and at 1, 2, 3, 4, and 5º eccentricity	Mean±SD hue discrimination total error scores (TES): not significantly correlated. % partial error scores (PES): short wavelength hue discrimination in region of peak absorption by MP and discrimination at the short wavelength end of the expected axis of type III acquired color vision defect were non-significantly correlated to MPOD at all eccentricities. Anomaloscope Moreland match midpoints: negatively correlated to MPOD at all eccentricities indicating shift toward green mixtures to match cyan (p=0.001 at MPOD 0.25, 1, 1.75, and 3º). Foveal cSWAP data eccentricities: negatively correlated with MPOD at 1.75 and 3º (p=0.000).	"Our findings suggest that dietary supplementation to increase MPOD is unlikely to adversely affect hue discrimination. The association of MPOD with cSWAP may be a temporally limited effect to which the visual system normally adapts. We suggest that cSWAP may provide a clinical tool for assessing short-wavelength foveal sensitivity."	Study suggests that CSWAP "may" be useful in detecting foveal SWS-cones sensitivity but strong conclusions are limited.

Hovis 2004	2.5	Diagnosis	N=100 subjects with normal color vision and N=64 subjects with defective color vision, congenital red-green. Mean age color normal 30±10 years, color defectives 29±11 years.	Adams D-15, two sessions at least 10 days apart	Nagel anomaloscope	Passing agreement: any mistake – significantly lower than other values for both groups and for color-defectives at more than one transposition. Failing agreement: color-normals increased as more errors were allowed; color-detectives values were constant. Failure criterion of more than 6 crossings: repeatability of Adams D-15 was significantly higher than the Farnsworth D-15. Confusion index (C-index) pass/fail criteria: correlation coefficients 0.90 for first session and 0.93 for second session. Inter-session classification: agreement between sessions k=0.38; 85% of subjects classified as protan at both sessions by Adam D-15 were classified correctly. Coefficient of repeatability: C-index/ specificity index (S-index)/ Angle/ Crossings: color-normals 0.71/0.70/49.8/0.20; all color-defectives 1.26/1.22/57.45/3.49.	"Approximately 98 per cent of the colour-normals and 82 per cent of the colour-defectives would have the same pass/fail outcome on the Adams D-15 test conducted several days apart when the failure criterion was either one or more or two or more crossings."	Study suggests that approximately 98% normal color vision individuals would have similar pass/fail outcome and about 82% of color defectives on Adams D-15 if tests repeated several days apart if failure criterion was either one or two or more crossings but individuals who make less than four Adams D-15 crossmap need repeat testing to confirm results. Also, the CDV analyses is more accurate in correct defect classification.
Mantere 1995	1.0	Diagnostic	N=85 color caps	Farnsworth-Munsell 100-hue test	Ishihara color vision test	There were differences in absolute values of the eigenvalues though no greater importance over another eigenvector for human color vision. The results for anomalous trichromats did not differ from those of dichromats.	"Our results show the efficiency of eigenvector analysis in color representation and in approximating color-vision deficiencies".	Study suggests efficiency of eigenvector analysis in color representation and approximating color deficiencies similar to the Farnsworth-Munsell 100 hue test.

Peripheral Vision Testing

Peripheral vision is particularly required to appreciate objects that are approaching the person or for situations where the person is moving and thus needing peripheral vision for accident avoidance. This is necessary for motor vehicle accident avoidance, avoidance of injury from a forklift driven by another worker, avoidance of injury from moving parts (e.g., suspended parts from an overhead crane), operation of overhead cranes, etc. Some safety sensitive and non-safety sensitive jobs require full visual fields to function.

Peripheral Vision Screening for Preplacement Examinations

Recommended.

Preplacement peripheral vision screening is recommended for jobs that require peripheral vision.

Indications **–** Occupations that require peripheral vision, generally including most safety sensitive and safety critical jobs. Optimum means for testing are unclear. Screening the temporal field of vision with simple equipment that can measure degrees of visual field is a reasonable option. Confirmatory testing with standard automated perimetry testing equipment is required for definitive determinations, particularly those with reductions in visual fields or glaucoma.

Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Moderate

Peripheral Vision Screening for Periodic Surveillance Examinations

Recommended.

Periodic peripheral vision screening is recommended for jobs that require peripheral vision.

Indications **–** Occupations that require peripheral vision, generally including most safety sensitive and safety critical jobs. Frequency is generally every year or biennially. Optimum means for testing are unclear. Screening the temporal field of vision with simple equipment that can measure degrees of visual field is a reasonable option. Confirmatory testing with standard automated perimetry testing equipment is required for definitive determinations, particularly those with reductions in visual fields or glaucoma.

Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Moderate

Peripheral Vision Screening for Select Post-injury Examinations

Recommended.

Peripheral vision screening is recommended for select post-injury examinations.

Indications **–** Post-injury examinations for jobs that also require peripheral vision. This is particularly needed where the injury may have reduced peripheral vision capabilities.

Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Low

Peripheral Vision Screening for Select Postoperative Examinations

Peripheral vision screening is recommended for select postoperative examinations.

Indications **–** Postoperative examinations for jobs that also require a peripheral vision. This is particularly needed where the injury may have reduced peripheral vision capabilities.

Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Low

Rationale for Recommendations

Peripheral vision is necessary for most safety sensitive and safety critical jobs and job tasks, although unsurpringly, there are no studies identified that address risks in those occupations. Cohort and longitudinal studies reported elevated crash risks among subjects with reduced useful field of view [276-278]. Other study designs have suggested visual field and/or useful field of vision [279, 280] are associated with crashes [279, 281-283]. Yet, multiple studies suggest no increased risk for peripheral vision [221, 276, 284, 285]. Driving simulator studies [286, 287] [288-290] and road tests [291, 292] suggest performance problems with one finding participants with bilateral central scotomas had higher risks of failing to detect pedestrians, slower and missed responses [287]. Another found performance impairments associated with peripheral vision impairments [288].

The degree of peripheral vision required varies among occupations. The most common screening tests used in primary care are manual kinetic testing (typically, “finger wiggle” moving from the lateral side forward) and confrontation fields. There are multiple tests that have been used mostly in comparative studies, including: Standard automated perimetry, Short-wavelength automated perimetry (SWAP), Frequency-doubling technology perimetry (FDT), High-pass resolution perimetry (HPRP), Scanning Laser Polarimetry (SLP, GDx VCC), Optical coherence tomography (OCT), pattern-electroretinography (PERG), Pattern Electrand Heidelberg Retina Tomography (HRT), Octopus tendency-oriented perimetry (TOP), and the Humphrey Swedish Interactive Threshold Algorithm (SITA)-fast (HSF), SITA 24-2 SAP, and Humphrey Matrix perimetry [293-309] [310-313] [314-330] [92, 320, 331-350]. There are no validated tests that demonstrate a given test is able to predict both inability to accomplish normal peripheral vision as well as to not successfully avoid crashes or accidents. Thus, the means to accomplish screening are unclear. Automated equipment is commonly used for confirmatory testing (or for monitoring glaucoma) and Wagner is most commonly used.

Peripheral vision screening is nevertheless recommended for pre-placement and periodic screening for jobs that require peripheral vision. This includes most safety sensitive and safety critical jobs. When injuries or surgeries potentially impair peripheral vision, peripheral vision screening of post-injury and postoperative patients is also recommended. For those in jobs requiring peripheral vision who also have risks for acquired or progressive loss of peripheral vision (e.g., glaucoma), greater frequency of peripheral vision screening is recommended.

Peripheral vision screening is not invasive, is without adverse effects, is low cost and is thus recommended for select pre-placement, periodic surveillance, as well as select post-injury and postoperative examinations.

Evidence for Peripheral Vision Testing

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Population Description	Case Definition	Investigative Test	Comparative Test	Results:	Conclusion:	Comments:
Robin 2005 (8.5)	FDT	Diagnostic	No mention of COI.	N=659	Mean age: 64.6±0.7 years. 281 males, 378 females.	Participants 50 years and older in the Seymour community	Individuals 50-90 years old with visual acuity <20/40, a family history of glaucoma or abnormal FDT, no history of stroke or previous diagnosis of glaucoma.	FDT	HRT	Optimal screening strategy combining visual acuity and family history with FDT and HRT had sensitivities at 96.8%, specificities at 89.7%, positive predictive values at 31.9%, and negative predictive values at 99.8% for detecting glaucoma.	"By combining assessments of presenting visual acuity and family history of glaucoma with Frequency Doubling Technology perimetry and Heidelberg Retina Tomography, we devised a community glaucoma-screening algorithm that showed a high sensitivity and specificity for detecting glaucoma in the general population."	This study supports a combination community based glaucoma screening algorithm using visual acuity, family history, FDT perimetry and HRT yielding both high sensitivity and specificity to detect glaucoma.
Sample 2006 (6.0)	FDT	Diagnostic	Sponsored by National Eye Institute Grants EY 08208 (PAS) and EY11008 (LMZ) and	N = 111	Mean age for controls / OHT / GON / and PGON: 51.81 ± 13.70 / 60.27 ± 11.61 /	(N = 71) FDT with glaucomatous optic neuropathy, (N = 37) ocular hypertensive eyes, and (N = 28) age-	A best corrected acuity of 20/40 or better, a spherical refraction within and inclusive of ± 5.0 D	Short-wavelength automated perimetry (SWAP), Frequency-doubling technology	Standard automated perimetry (SAP).	Controls vs GON group, the FDT pattern SD (PSD) area was larger than the HPRP PSD (= 0.020), and the FDT area of total deviation (TD) <5% was larger than	"At equal specificity, no single perimetric test was always affected, whereas others remained normal."	Data suggests the same quadrant of the retina shows damage for all tests first no one test was always affected in GON or PGON

			participant retention incentive grants in the form of glaucoma medication at no cost: Alcon Laboratories Inc, Allergan, Pfizer Inc, and SANTEN Inc. P.A. Sample, Carl Zeiss Meditec, Inc., Welch-Allyn, and Haag-Streit (F); F.A. Medeiros, Carl Zeiss Meditec, Inc. (F); no other COI reported.		65.59 ± 11.42 / and 66.85 ± 10.57, gender not specified.	matched normal control.	(transposition allowed), and cylinder correction within ± 3.0 D.	perimetry (FDT), High-pass resolution perimetry (HPRP).		the HPRP mean deviation (MD, p = 0.004). 2 (PSD) and 3 (PD) show the agreement among the 4 tests in identifying abnormality in eyes with GON and PGON combined (*n* = 142), using the 80% specificity criterion.		patients suggesting a combination of tests may be needed to confirm early loss.
Chauhan, 1986 (6.0)	Visual Field Test	Diagnostic	No mention of sponsorship or COI.	N=455	455 males between the age 17 and 30 years	Participants have very low incidence of congenital red/green and blue/yellow defects.	Method of weighting PIC plates is utilized for the information theory to check the frequency of animals and	City test that a derivatives of the Farnsworth D-15 sequence and the color samples on each plates	City University tests (Colour Vision Tests) vs PIC test (pseudoisochromatic plate tests) City 1 = Fletcher 1975	Anomaloscope classified 413 subjects as normal = 90.77%, and 42 patients as abnormal = 9.23% using Ishihara plates. Percentage information	"The concept of utilizing weighted responses is a powerful tool and has direct clinical implications. By extracting a	Study suggests that a weighted scoring system might provide better information about a person's true state of color vision

							defects passinf or failing the plates.		and City 2 = Fletcher 1980	increased from 25.4 to 31.6% (p=0.984) in City 1 and 34.2 to 45.9% (p=0.991) in City 2. GER decreased from 9 to 5.5% in city 1 and 5.9 to 4% in City 2.	selected amount of information and by reducing the level of spurious information or noise, tests can be made more efficient and as a consequence a good deal of time and effort can be saved."	when compared to using one unique test. Via the use of informational analysis, a cutoff point separated normal from defectives city 2 appeared to perform better than City 1, but still inferior to most PIC tests. ALL men were used due to low incidence of red or green color blindness in women.
Landers 2000 (5.5)	FDT	Diagnostic	No mention of sponsorship or COI.	N = 62	Mean age 58 years, 26 male and 36 female.	With ocular hypertension and normal AAP visual fields.	An IOP > 21 mmHg when not receiving medication, visual acuity 6/12 or better, five dioptre or less of sphere and three dioptre or less of cylinder in refractive error, no previous intraocular surgery, no other systemic illness.	Achromatic automated perimetry (AAP), Short wavelength automated perimetry (SWAP).	Frequency doubling perimetry (FDP).	Of the 53 that tested normal with SWAP 51 were normal with FDP. Mean time to complete SWAP was 11 minutes and 37 seconds vs 4 minutes and 32 seconds for FDP, (p < 0.0001). Sensitivity of 88.9% (8/9) a specificity of 96.2% (51/53), a positive predictive value of 0.8 (8/10), and a negative	"These results suggest that as SWAP may be predictive of AAP visual field loss, FDP may be similarly predictive."	Data suggest high degree of concordance between SWAP and FDP.

										predictive value of 0.98 (51/52).		
Wu 2011 (5.5)	FDT	Diagnostic	No mention of sponsorship or COI.	N = 49	Mean age 56.4 ± 9.8, 19 male and 30 female.	With open-angle glaucoma with visual field defects only in one hemifield.	Visual acuity greater than 20/28.6 and clear ocular media; reliable visual field test results (fixation losses <20% and false positives and false negatives <33%) that showed a hemifield defect.	With normal hemifields by FDT.	With abnormal hemifields by FDT.	The sensitivity of the FDT hemifield abnormality criteria was 98%, the specificity of the FDT hemifield abnormality criteria was 88%. HFA-intact hemifields that were abnormal on FDT testing compared with those with normal FDT results (unpaired t test, p = 0.013–0.024).	"Frequency doubling technology can detect glaucomatous damage earlier than conventional static perimetry can."	Data suggest FDT detects glaucomatous damage earlier than standard static perimetry and is associated with a 98% sensitivity and 88% specificity.
Zeppieri 2010 (5.5)	FDT	Diagnostic	No sponsorship or COI.	N = 319	Mean age for: POAG / GON / OHT / and Controls; 65.9 ± 11.0 / 63.9 ± 9.3 / 63.6 ± 10.3 / and 53.4 ± 13.2.	(N = 87) ocular hypertensives (OHT); (N = 67) glaucomatous optic neuropathy (GON); (N = 75) primary open-angle glaucoma (POAG); and (N = 90) healthy subjects.	Best-corrected visual acuity better than or equal to 0.7; open anterior chamber angle; absence of ocular pathology other than glaucoma; reliable SAP, FDT, and Pulsar test results; good GDx and HRT image quality.	Pulsar perimetry (Pulsar), Frequency Doubling Technology (FDT), Scanning Laser Polarimetry (SLP, GDx VCC), and Heidelberg Retina Tomography (HRT).	SAP	The greatest AROC for discriminating between glaucomatous and healthy eyes were respectively: sLV for Pulsar; no. p < 5% in the PDP for FDT; CSM for HRT; and NFI for GDx. Accuracy in discriminating between POAG and healthy eyes the AROCs were significantly higher for Pulsar sLV and FDT no. p < 5% than for structural parameters. POAG	"Pulsar T30W test is a rapid and easy perimetric method, showing higher sensitivity than SAP in detecting early glaucomatous VF loss."	Data suggest comparable efficacy between FDT, HRT and GDx. Data suggests T30W has a higher sensitivity then SAP and is better detecting early glaucomatous disease.

										eyes, Pulsar (AROC, 0.90) appeared vs FDT (0.89) and vs HRT (0.82) and GDx (0.79). For GON, Pulsar ability (0.74) was higher than GDx (0.69) and lower than FDT (0.80) and HRT (0.83). The agreement among instruments ranged from 0.12 to 0.56. Pulsar test duration was shorter vs SAP and FDT, (p < .001).		
Choi 2009 (5.5)	FDT	Diagnostic	No mention of sponsorship or COI.	N = 221	Mean age of the preperimetric glaucoma was 63.25 ± 14.50 and that of the normal group was 62.04 ± 14.16 years, gender not specified.	(N = 99) with preperimetric glaucoma and (N = 122) healthy controls.	BCVA of 20/40 or better, a spherical-equivalent refractive error between −6 and +6 diopters, without clinically significant cataracts, a normal open angle on gonioscopy, no previous intraocular surgical	Optical coherence tomography (OCT) parameters flagged as < 0.05, Retinal nerve fiber layer (RNFL).	Normal standard automated perimetry (SAP).	BCVA (logMAR) of the preperimetric glaucoma group was 0.11 ± 0.68 vs normal group 0.09 ± 0.77, (p = 0.154). MD from SAP was −2.66 ± 2.75 dB in preperimetric glaucoma patients and −2.12 ± 1.66 dB in controls (p = 0.092). The mean PSD from SAP was 2.14 ± 1.01 dB in preperimetric glaucoma and 1.88 ± 0.98 dB in	"FDT Matrix seems to be a valuable clinical tool in the detection of preperimetric glaucoma."	Data suggest Humphrey Matrix 24-2 may be valuable in detecting preperimetric glaucoma.

							history, and no systemic disease or medication that affect visual acuity.			controls, (p = 0.063). Discriminating power by the modified Anderson criteria showed the highest sensitivity and hit ratio (75.76% and 76.92%, χ^2 = 63.24).		
Horn 2012 (5.5)	FDT	Diagnostic	Sponsored by Deutsche Forschungsgemeinschaft, Bonn, Germany. No COI.	N = 588	Age range 34 to 71 years, gender not specified.	(N = 334) open angle glaucoma patients and (N = 254) controls.	A visual acuity of 20/40 or better, and a myopic refractive error not exceeding –8 D.	Heidelberg Retina Tomography (HRT).	Frequency doubling technology (FDT).	Highest sensitivities at a fixed specificity (95%) were: HRT = 32%, FDT = 19%, combined analysis = 47% in preperimetric patients and HRT= 76%, FDT = 89%, combined analysis = 96% in perimetric patients. HRT had a higher diagnostic power for early glaucomas and FDT perimetry for glaucoma patients with visual field loss.	"The feasibility of machine learning for medical diagnostic assistance could be demonstrated in patients from 2 independent study populations."	Data suggest combining morphology and function (HRT with FDT) translates into better diagnostic power.
Kaushik, 2011 (5.5)	FDT	Diagnostic	No mention of sponsorship. No COI.	N=114	Mean age was 47.3 years. 72 males, 42 females.	60 ocular hypertensive patients (OHT) and 54 subjects with suspicious	Patients with OHT were required to fulfill the following	Frequency-Doubling Technology (FDT) perimetry and Optical	Optic disc size	In Disc suspects, FDT-Mean Deviation correlated with retinal nerve fiber layer (RNFL)	In OHT, optic discs with larger VCDR and thinner RNFL had lower FDT-MD	Data suggest both OCT and FDT are useful detecting those types of changes which may be

						glaucoma (disc suspects).	criteria in both eyes: best-corrected visual acuity 20/40 or better (refractive error ±5.0D spherical and ±3.0D cylinder); IOP greater than 22mm Hg and less than 32mm Hg. Disc suspects were included if they had features suggestive of glaucomatous optic neuropathy as described above; IOP less than 21.0mm Hg on at least 2 successive measurements spaced 2 weeks apart	coherence tomography (OCT).		thickness measurements (p<0.001 and p=0.003) and disc area (p<0.001). In OHT patients the FDT-Mean Deviation also significantly correlated with mean RNFL thickness (p=0.038).	values. In disc suspects, smaller-sized discs had thinner RNFL and lower values of FDT-MD.	associated with glaucoma.
Wadood 2002 (5.0)	FDT	Diagnostic	No COI. No mention of sponsorship.	N=98	Mean±SD age 69.5±8.7 years. 59 female, 39 male.	With glaucoma.	With typical glaucomatous optic disk damage.	Humphrey–Welch Allyn frequency-doubling technology (FDT).	Octopus tendency-oriented perimetry (TOP), and the Humphrey Swedish Interactive Threshold Algorithm	Mean test time was 1.08±0.28 minutes, 2.31±0.28 minutes, and 4.14±0.57 minutes for the FDT, TOP, and HSF, respectively, p<0.0001.	"The C-20 FDT, G1-TOP, and 24-2 HSF appear to be useful tools to diagnose glaucoma. The test C-20 FDT and G1-TOP take	Data suggest all tests (FDT, TOP, HSF) have moderately comparable sensitivities and specificities. However, test time is significantly less

									(SITA)-fast (HSF).	Sensitivity for FDT: 91.4%; TOP 94.2%; HSF 98.5%	approximately 1/4 and 1/2 of the time taken by 24 to 2 HSF."	with HSF followed by FDT and TOP.
Heeg 2009 (5.0)	FDT	Diagnostic	Sponsored by the Dutch Health Care Insurance Council (CVZ) and the University Medical Centre Groningen, the Netherlands.	N = 174	Mean age was 60 (13), 80 male and 94 female.	With ocular hypertension or a positive family history of glaucoma without visual field abnormalities at baseline.	Suspected optic disc, vertical cup–disc ratio 40.6, Glaucoma hemifield test (GHT) outside normal limits, Pattern SD, ($p < 0.05$), Or, 3 adjacent non-edge points, ($p < 0.05$).	Frequency doubling perimetry (FDT) / Nerve Fibre analyser (GDx).	Standard automated perimetry (SAP).	Relative risk for FDT was 1.8 (CI: 0.9–3.7; $p = 0.10$) and of an abnormal baseline for GDx 2.7 (CI: 1.2–6.3; $p = 0.01$). Positive predictive value was 0.22 for both and FDT and GDx; negative predictive value was 0.88 for FDT and 0.92 for GDx.	"In a clinical setting, especially GDx may be helpful for identifying glaucoma suspect patients at risk of developing glaucomatous visual field loss as assessed by SAP."	Data suggest that in SAP test patients, GDx "may" aid in identifying glaucoma at risk patients.
Salvetat 2010 (5.0)	FDT	Diagnostic	No mention of sponsorship or COI.	N = 105	Mean age for Controls and POAG 58.7 ± 12.3 and 60.2 ± 11.7.	With primary open-angle glaucoma (POAG).	Best corrected vision acuity better or equal to 0.7 decimal, open anterior chamber angle, absence of ocular pathology other than glaucoma, reliable VF test results.	Control group, normal intraocular pressure (IOP), ONH and RNFL appearance.	POAG group (54 eyes): IOP 421mmHg before medication, reproducible glaucomatous SAP VF defects.	All significant perimeters between the groups, ($p < 0.0001$), except PP test duration, ($p = 0.73$). Number of locations in pattern deviation probability (PDP) plot with $p < 5\%$ for FDT (0.93); mean hit rate for RBP was 0.95 and mean defect for PP was 0.94. PP test		Data suggest FDT, PP and RBT are rapid and easy methods for detecting early glaucomatous disease and PP took half as much time to perform vs. SAP.

										duration was shorter than FDT and RBP, (p < 0.002).		
Bayer 2002 (5.0)	FDT	Diagnostic	No mention of sponsorship or COI.	N = 36	Mean age was 59.1 ± 6.5 and 59.8 ± 6.6 years, 13 male and 23 female.	With POAG	Optic disc cupping with a cup-to-disc ratio of 0.6 and untreated IOP of more than 21 mmHg on at least three occasions.	Short-wavelength automated perimetry (SWAP), perimetry, and pattern-electroretinography (PERG), and Frequency-doubling technology (FDT).	Standard automated perimetry (SAP).	SWAP-MD / FDT-MD / SAP-MD / and PERG amplitudes N1P1: (paired t test, p = 0.0003) / (p = 0.0008) / (p = 0.0001) / (p = 0.0001) and P1N2 (p = 0.0001) between contralateral POAG eyes. Sensitivities of 80.6% and 66.7% and specificities of 61.1% and 50.4% achieved with PERG P1N2-amplitude (AROC score 0.776; p < 0.0001) and N1P1-amplitude (AROC score 0.628; p < 0.062), respectively.	"A test battery of SWAP-MD and PERG P1N2 amplitude could detect glaucomatous optic neuropathy in POAG eyes with normal standard visual fields, whereas FDT-MD and SWAP-MD significantly correlated with each other and with SAP-MD."	Data suggest SWAP and PERG detected glaucomatous optic neuropathy. There was good correlation to SAP between SWAP and FDT.
Redmond 2013 (5.0)	FDT	Diagnostic	Sponsored by the Glaucoma Research Foundation (Dr Artes) and by grant MOP-11357 from	N = 64	Mean age 65 years and in patients and 62 years in controls, gender not specified.	With open-angle glaucoma (OAG).	SAP mean deviation (MD) between −2 and −10 dB, optic disc damage consistent with the clinical diagnosis, and	Frequency-doubling matrix perimetry (FDT2).	Standard automated perimetry (SAP).	Agreement between FDT2 and SAP was moderate with TD for both patients, (k = 0.44) and controls, (k = 0.34), but lower with PD for patients, (k = 0.03)	"No evidence was found that FDT2 is more sensitive than SAP in identifying visual field deterioration."	Data suggests similar efficacy for detection of visual field deterioration between FDT2 and SAP.

			the Canadian Institutes of Health Research (Dr Chauhan). No COI.				no other ocular disease.			and controls, (K = 0.00). Significant deterioration was identified in 16%of patients with FDT2, in 17%of patients with SAP.		
Shah 2006 (5.0)	FDT	Diagnostic	Sponsored by the National Institutes of Health, Bethesda, Maryland. No mention of COI.	N=123	SAP Definition: Glaucoma – Mean age of 68.3, 23 Males, and 20 Females. Control – Mean age of 58.6, 22 males, and 36 females. Stereophotography Definition: Glaucoma – Mean age of 65.5, 27 males, and 38 females. Control – Mean age of 60.1, 18 males, and 31 females.	One eye from each participant was included in the study.	No history of intraocular surgery, with exception to uncomplicated cataract or glaucoma surgery. All subjects with non-glaucomatous secondary causes of elevated IOP, other intraocular eye diseases, other diseases affecting VF, medications known to affect VF sensitivity, or problems other than glaucoma affecting color vision.	Scanning laser polarimetry	Optical coherence tomography (OCT), scanning laser polarimetry, frequency-doubling technology (FDT) and short-wavelength automated perimetry (SWAP)	The sensitivity and specificity in detecting glaucomatous VF damage is 41.9 and 98.3 for scanning laser polarimetry, 58.1 and 98.3 for OCT, 58.1 and 84.5 for confocal scanning laser ophthalmoscopy, 44.2 and 98.3 for FDT perimetry and 65.1 and 86.2 for SWAP. The addition of FDT significantly increases ($P<0.05$) sensitivity without significantly changing specificity when compared to structural parameters. The addition of SWAP significantly increases the	"A combination of parameters from structural tests and functional tests can improve the sensitivity of glaucoma detection."	This data suggests a combination of tests determining both structure and function increases the sensitivity for the detection of glaucoma.

										sensitivity, but also significantly decreases the specificity of structural parameter.		
Tafreshi 2009 (5.0)	FDT	Diagnostic	No mention of sponsorship or COI.	N=338	Control Group – Mean age of 59.6, 59 males, and 105 females. Glaucoma group – Mean age of 56.9, 81 males, 93 females.	With glaucomatous appearance of the optic disk on simultaneous stereophotographs.	Participants were excluded if they had previous history of intraocular surgery, elevated intraocular pressure caused by non-glaucomatous causes, coexisting retinal disease, other diseases affecting visual field, taking medication that affects visual field sensitivity or problems affecting color vision other than glaucoma.	SAP	SWAP, FDT	There is no significant difference in single test sensitivities when measured with the McNemar test: SAP vs SWAP (P=0.67), SAP vs FDT (P=0.39), SWAP vs FDT (P=0.71). SAP had a sensitivity of 30%, FDT had a sensitivity of 28% and SWAP had a sensitivity of 29%. When combined, SAP/SAP had the highest sensitivity and SWAP/FDT had the lowest sensitivity.	"Confirming VF abnormality is important and optima when an abnormal SAP is confirmed by a subsequent SAP or SWAP test."	Data suggest the presence of visual field defects is consistent in terms of location across all 3 tests (SAP, SWAP or FDT) and areas of loss equate into disease. If there exists an abnormal SAP, this should be confirmed with either SWAP or FDT to maximize sensitivity and specificity.
Thomas 2000 (5.0)	FDT	Diagnostic	No mention of sponsorship of COI.	N = 162 patients, 248 eyes	No mention of mean age or sex.	With glaucoma.	With glaucomatous defects and with "typical" neuro-ophthalmic field defects.	Frequency doubling perimetry.	Automated perimetry using Swedish Interactive Threshold Algorithm	When using the frequency doubling perimetry 20-5, a single point pressed to the less than 1%	'neuro-	Data suggest FDP detects neuro-ophthalmic VF defects with good sensitivity and specificity.

							visual acuity of 6/60 or greater.			probability yielded a sensitivity of 97.1% and a specificity of 95%, 2% probability yielded 98.6% and 85%, and 5% yielded 99.3% and 53.3 %. The 20-1 test with a single point pressed to the less than 1% probability yielded a sensitivity of 95.7% and a specificity of 95%. Two abnormal points depressed to <1% probability in the 20-1 had a specificity of 100% and a sensitivity of 84.8%.	ophthalmic' field defects."	
Kim, 2007 (4.5)	FDT	Diagnostic	Supported by the National Institutes of Health, Bethesda, Maryland (grant nos. EY11008 [LMZ], EY08208 [PAS]). COI: research support from Carl	N=93	Mean age was 63.2 years. 51 males, 42 females.	93 glaucoma patients.	Open angles, spherical refraction within ±5 diopters, cylinder correction within ±3 diopters and best-corrected acuity of 20/40 or better.	Frequency doubling technology perimetry (FDT)	Standard automated perimetry (SAP)	38 eyes showed a normal SAP and normal FDT (Group 1), 19 eyes showed a normal SAP and abnormal FDT (Group 2), 4 eyes showed an abnormal SAP and a normal FDT (Group 3), and 32 eyes showed an abnormal result in both SAP and FDT (Group 4). The mean deviation	"When SAP is within normal range, some patients with VF loss detected by FDT show a decreased RNFL thickness, possibly indicating the presence of glaucomatous damage. These results support	Data suggest FDT may be able to detect early glaucoma as there is thinning RNFL detected by FDT when SAP results are normal.

			Zeiss Meditec (LMZ, PAS, RNW), Heidelberg Engineering (LMZ, RNW), Welch-Allyn (PAS), and Haag-Streit (PAS). Honoraria from Heidelberg Engineering (LMZ, RNW) and Carl Zeiss Meditec (RNW).							was -2.59 dB in the SAP group compared to -3.90 db in the FDT group. The FDT MD was significantly worse in group 4 than groups 1 and 2 ($p<0.05$).	the validity of FDT as a tool to detect early glaucoma."	
Tafreshi 2010 (4.5)	FDT	Diagnostic	Sponsored by research grants NIH EY018190, NIH EY008208, NIH EY011008, and participant incentive grants in the form of glaucoma medication. No	N = 96 patients N= 175 eyes	Healthy patients (n=42 patients and 83 eyes) had an average age of 63.6, and glaucoma patients were 70.4. Healthy: 55 female eyes and 28 male eyes. Glaucoma:	Patients with glaucomatous appearing optic discs such as glaucomatous optic neuropathy.	Central 48 degrees (52 test points) of the visual field. . Best-corrected acuity better than or equal to 20/40. The spherical refraction within ± 5.0D and cylinder correction within ± 3.0D, and open angles on	Pattern Electroretinogram Testing (PERGLA was used to measure the pattern ERG response)	Psychophysical Testing: Standard Automated Perimetry 24-2, Short-Wavelength Automated Perimetry (SITA) 24-2, and Frequency-Doubling Technology (FDT) 24-2.	At high specificity (95%) the sensitivity obtained for pattern ERG amplitude was significantly lower than that obtained for SAP and FDT PSD and was similar to that of SWAP PSD. The diagnostic accuracy of pattern ERG was of lower quality than that of FDT	"Overall, our results suggest that pattern ERG amplitude using the pattern ERG for glaucoma detection paradigm is significantly different between healthy eyes and early glaucoma eyes, and the diagnostic	Data suggest FDT had a diagnostic accuracy than pattern ERG, SAP or SWAP.

			mention of COI.		53 female eyes and 39 male eyes		gonioscopy. Pattern ERG tested all eyes for good quality stereo-photography of the optic disc and reliable SAP, SWAP and FDT, within 9 months			with a ROC curve=0.818. The diagnostic accuracy of pattern ERG amplitude ROC curve=0.744 was statistically similar to that of SAP PSD and SWAP PSD ROC curves = 0.786 and 0.732 respectively. The area under the ROC curve for FDT PSD was 0.818 significantly greater than that obtained for pattern ERG amplitude 0.744. (p = 0.04). No statistically significant differences between pattern ERG ROC curve area and SAP PSD curve (0.786; p = 0.17) and SWAP PSD (0.732; p = 0.41).	accuracy of pattern ERG amplitude likely is similar to that of SAP and SWAP and somewhat worse than FDT. Pattern ERG (and other electrophysiological techniques) has the advantage of being a mainly objective visual function test and may be useful for patients who are unable to perform reliably on psychophysical tests."	
Bowd, 2001 (4.5)	FDT	Diagnostic	No mention of COI. Supported by National Institutes of Health	N= 94	Sex is not mentioned. Mean age: 61.91 years.	Healthy subjects or patients with glaucoma, prospectively enrolled as longitudinal	All subject eyes had open angles, best corrected acuity of 20/40 or better, sphere within	Frequency doubling technology (FDT) perimetry.	Scanning laser polarimetry (SLP) Optical coherence tomography (OCT) short-wavelength	The largest area under the Receiver operating Characteristic (ROC) curve was found for	"In conclusion, the largest ROC curve area for OCT (inferior quadrant thickness) was larger than the	Data suggest OCT and FDT parameters more sensitive than SWAP and SAP parameters. The instrument

			Grants EY11008 (LMZ) and EY08208 (PAS), the Glaucoma Research Foundation (PAS), the Research to Prevent Blindness Lew R. Wasserman award (PAS), and the Foundation for Eye Research (EZB, CV).			study participants.	65.0 diopters (D), and cylinder within 63.0 D at time of testing. Healthy eyes in this study (n 5 38) had a measured IOP of 22 mm Hg or less with no history of elevated IOP.		automated perimetry (SWAP) Standard automated perimetry.	OCT inferior quadrant thickness (0.91 for diagnosis based on SAP, 0.89 for diagnosis based on disc appearance), followed by the FDT number of total deviation plot points of ≤5% (0.88 and 0.87, respectively), SLP linear discriminant function (0.79 and 0.81, respectively), and SWAP PSD (0.78 and 0.76, respectively). For diagnosis based on SAP, the ROC curve area was significantly larger for OCT than for SLP and SWAP. For diagnosis based on disc appearance, the ROC curve area was significantly larger for OCT than for SWAP. For both diagnostic criteria, at specificities of	largest ROC curve area for SLP (LDF) and SWAP (PSD) when diagnosis was based on SAP, and the largest ROC curve area for OCT (inferior quadrant thickness) was larger than the largest ROC curve area for SWAP (PSD) when diagnosis was based on disc appearance. ROC curve areas among other instruments were not significantly different for either diagnostic criterion. Sensitivities were best (although not always significantly so) for OCT and FDT measurements	with best sensitivity and specificity not recommended for as a sole screening test in the general population.

										≥90% and ≥70%, the most sensitive OCT parameter was more sensitive than the most sensitive SWAP and SLP parameters. For diagnosis based on SAP, the most sensitive FDT parameter was more sensitive than the most sensitive SLP parameter at specificities of ≥90% and ≥70% and was more sensitive than the most sensitive SWAP parameter at specificity of ≥70%. For diagnosis based on disc appearance at specificity of ≥90%, the most sensitive FDT parameter was more sensitive than the most sensitive SWAP and SLP parameters. At specificity ≥ 90%, agreement among	followed by SWAP and SLP. However, the sensitivity and specificity of even the best parameter of the best instrument are probably not sufficient to warrant use as a sole screening method in the general population. In contrast, for screening in situations in which treatment is at a premium (e.g., developing nations), a sensitivity and specificity of 79% and 92% (for several OCT measures, for example) may be acceptable, assuming that the technique is relatively simple	

										instruments for classifying eyes as glaucomatous was poor.	and quick. The poor diagnostic agreement found among instruments suggests that different techniques may identify different characteristics of glaucomatous damage."	
Cioffi, 2000 (4.5)	FDT	Diagnostic	No mention of COI.	N=130	The mean age was 55.5 years. 88 females, 42 males were in the study	116 eyes (45%) were normal. Fifty-five eyes (21%) had evidence of cataractous lens changes, while only 9 (3.5%) of these eyes had best corrected visual acuity worse than 20/30. Sixteen eyes (6%) had open-angle glaucoma, 44 (17%) were diagnosed as "glaucoma suspects," and 27 (11%) had an intraocular	A participant was considered to be a "glaucoma suspect" if a suspicious optic nerve examination or intraocular pressure above 20 mm Hg was noted.	Frequency doubling technology (FDT) perimetry	standard achromatic automated perimetry (SAP), anterior segment biomicroscopy, tonometry, and dilated Ophthalmoscopy.	On clinical examination, 116 eyes (45%) were normal, 9 eyes (3.5%) had a cataract with best corrected visual acuity worse than 20/30, 16 eyes (6%) had open-angle glaucoma, and 17 eyes (7%) had retinal findings or lesions that were likely to cause a visual field defect. For FDT perimetry, 22 (8.6%) of 257 tests were unreliable, and for SAP, 65 (25.3%) of 257 tests were	"Finally, in a separate study, we have demonstrated that the FDT (C-20-5 test) sensitivity varied between 94% and 100%, depending on the severity of glaucoma in a controlled clinical population of glaucoma patients.'8 In these well-controlled studies with defined patient populations in a clinical setting, FDT	Data suggests FDP shows promise as a community screening tool for eye disease.

						pressure greater than 20 mm Hg. Seventeen eyes (7%) had retinal findings or lesions that were believed likely to cause a visual field defect (				unreliable. The sensitivity and specificity of FDT perimetry for detecting an abnormal clinical examination were 55% and 90% and for detecting an abnormal examination that included an abnormal SAP, 64% and 86%.	perimetry demonstrated better sensitivity, which correlated well with standard automated perimetric testing. In this "real world" screening of individuals from the community, lower sensitivities may reflect differences in the populations."	
Corallo, 2008 (4.5)	FDT	Diagnostic	No conflict of interest. No mention of industry sponsorship	N=60	Mean age: 42 years in ocular hypertension group, 40 in the control group. Sex not mentioned.	30 subjects with ocular hypertension were matched with 30 healthy subjects	Subjects included had intraocular pressure (IOP) greater than or equal to 21 mm Hg on no treatment, on at least two occasions; normal white-on-white automated perimetry findings; normal-appearing optic nerve	frequency-doubling technology (FDT) perimetry	rarebit perimetry (RP)	The mean (SD) SAP (standard automated perimetry) MD was –1.08 (0.79), the mean (SD) SAP PSD was 1.63 (0.27), the mean (SD) FDT MD was 0.5 (2.1), the mean (SD) FDT PSD was 4.2 (1.6), and the mean (SD) RP MHR was 81.4 (6.7) in the OHT group. The corresponding values of control	"RP and FDT showed VF defects not shown in standard automated perimetry in the OHT group. This may be indicative of an increased risk in developing glaucoma, even if a gold standard for detecting subtle defects	Data suggest RP and FDT detected some suitable defects which SAP did not detect in OHP group. RP is inexpensive but both RP and FDT are only moderate in detecting early damage.

							head (ONH) and retinal nerve fiber layer (RNFL); and central corneal thickness (CCT) ≤550 µm.			group were the following: mean (SD) SAP MD –1.04 (0.68), mean (SD) SAP PSD 1.60 (0.31), mean (SD) FDT MD 1.1 (1.4), mean (SD) FDT PSD 3.0 (0.3), mean (SD) RP MHR 96.2 (2.0). The differences between the two groups were not significant for all studied indexes (Figs. 3-5). According to the abnormality criteria we adopted, 11 (36.6%) out of the 30 OHT eyes had abnormal RP results; 12 (40.0%) eyes had abnormal FDT results (Fig. 6); 5 (16.6%) eyes had abnormal RP and FDT findings. Only 1 eye (3.3%) in the control group had abnormal RP results and 3 eyes (10.0%) had	is not currently available. RP has the additional advantage of not requiring any expensive device to be used. The poor agreement between these techniques in identifying eyes with early damage warrants further investigations. Large longitudinal studies are needed before defining the role of RP in early glaucoma diagnosis."	

										abnormal FDT results (Fig. 7). RP and FDT showed a moderate agreement (Kappa = 0.43; 95% CI: 0.42 to 0.51) (28). Mean (SD) CCT was 532 (8) µm (range 510-548 µm) in the OHT group and 561 (22) µm (range 515-607) in the control group (a cutoff level was adopted for CCT only for OHT patients).		
Hirashima, 2013 (4.5)	FDT	Diagnostic	No conflict of interest. The study was supported in part by a Grant-in-Aid for Scientific Research (20592038) from the Japan Society for the Promotion of Science (JSPS),	N=26	Mean age: 54.66 years 25 females, 21 males	26 patients with preperimetric glaucoma (PPG) and 20 healthy eyes of 20 volunteers.	subjects with normal open angles and normal visual field results on standard white on white perimetry. The eligible eyes were assigned to the preperimetric group when glaucomatous optic disc appearance was evident. Volunteer eyes	frequency-doubling technology (FDT) perimetry	Heidelberg retina tomography-2 (HRT2), standard automated perimetry (SAP), and RTVue-100.	SAP and FDT indices, HRT parameters, and circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (mGCC) thicknesses were correlated using Pearson's test. Areas under the receiver operating characteristic curves (AUROCs) and sensitivity/specifici	"In conclusion, although PPG eyes have significantly worse FDT indices and thinner cpRNFL and GCC thicknesses compared to healthy control eyes, the correlations between the functional and structural parameters were poor.	Data suggest poor correlation between structure and function as these changes are not uniform.

			Tokyo, Japan.				were assigned to the healthy control group when they had normal optic disc appearance, an intraocular pressure of 21 mmHg or lower, and no family history of glaucoma in a first-degree relative.			ty based on each parameter's definition of abnormalities were compared between parameters. Significant differences were found in FDT-MD, FDT-PSD, SAP-PSD, cpRNFL, and mGCC parameters (p< 0.001–0.015), but not in SAP-MD or HRT parameters, between PPG and control groups. Significant correlations were not found between visual field indices and structural parameters, except between FDT-MD and HRT rim area (r00.450, p00.021) and between FDT-PSD and temporal cpRNFL thickness (r00.402, p00.021). AUROCs for cpRNFL (p0 0.0047–0.033) and mGCC (p00.0082–0.049) parameters	In addition, neither of these functional or structural parameters strongly discriminated PPG eyes from healthy eyes, and both had a complementar y relationship. Collectively, these findings suggest that detectable damages to retinal function and structure due to glaucoma are not uniform (high inter-individual variability) even at the preperimetric stage. A combination of functional and structural parameters may potentially improve the ability to diagnose PPG."	

										were significantly better than those of HRT parameters, whereas significant differences were not found between FDT indices and cpRNFL or mGCC parameters or between cpRNFL and mGCC parameters. Adding average cpRNFL or mGCC thickness to FDT-MD significantly increased sensitivity compared to single parameters (p=00.016–0.031).		
Hollo, 2001 (4.5)	FDT	Diagnostic	No COI. Supported by Hungarian national grant for medical research ETT 293/2000 (G.H.).	N=11	Mean age: 55.1 years 7 females, 4 males	11 patients with preperimetric POAG (primary open angle glaucoma) patients	The participants had undergone no ocular surgery and the eyes were free of any corneal or anterior segment diseases. None of the	frequency-doubling technology (FDT) perimetry	scanning laser polarimetry (SLP), conventional automated perimetry (AP).	Intraocular pressure (IOP), AP and FDT measurements showed no statistically significant changes during the 12-month follow up period. In contrast to this, a tendency for a glaucomatous type decrease was	" In conclusion, we were not able to find any statistically significant alteration in perimetric global indices in medically controlled, preperimetric primary open angle glaucoma	Small Sample. Data suggest SLP useful in detection & measurement of early glaucoma which may go undetected in perimetry and FDT testing.

							patients was a contact lens wearer. All eyes originally had intraocular pressure higher than 21 mmHg before treatment but it was reduced to be consistently lower than 22 mmHg by the use of topical medication.			seen with SLP in the retinal nerve fibre layer (RNFL) thickness parameters (mean superior and inferior sector thickness values, ellipse average thickness and maximal modulation). The mean decrease of RNFL thickness in the superior and inferior sectors was 2.77 mm and 2.48 mm, respectively. Using the two-way nested ANOVA, which considers the relation between the right and left eyes of the subjects, the decrease was statistically significant (p=0.021) for the inferior sector RNFL thickness	during a one-year follow-up, using the sensitive FDT method. However, a statistically and clinically significant thinning of the RNFL was detected with scanning laser polarimetry. Our results suggest that SLP is able to detect fine progression in glaucoma, and that the GDx Nerve Fiber Analyzer is a superior technique for detecting and quantifying the progression of preperimetric glaucoma in comparison to the FDT method."	
Horn, 2014 (4.5)	FDT	Diagnostic	No COI. Supported by Deutsche Forschungsgemeinsch	N=202	Mean age= 58.8 years, 105 females, 97 males	64 healthy subjects, 45 ocular hypertensive patients, and	All individuals included in the study had an open anterior chamber angle, clear optic	flicker-defined form (FDF) perimetry	standard automated perimetry (SAP)	The age-corrected sensitivity values and the local results from the controls were used	" In conclusion, in this cohort of trained participants the FDF	Data suggest the functional changes detected with FDF perimetry correlated with

			aft, Bonn, Germany (SFB 539).			97 ‘‘early’’ open angle glaucoma (OAG) patients participated in this study	media, a visual acuity of 20/40 or better, and a myopic refractive error not exceeding _8D.			to determine FDF mean defect (FDF MD). The FDF perimetry and SAP showed high concordance in this cohort of experienced patients (MD values, R = -0.69, P < 0.001). Of a total of 42 OAG patients with abnormal SAP MD, 38 also displayed abnormal FDF MD. However, FDF MD was abnormal in 28 of 55 OAG patients with normal SAP MD. The FDF MD was significantly (R =-0.61, P < 0.001) correlated with RNFL thickness with a (nonsignificantly) larger correlation coefficient than conventional SAP MD (R =-0.48, P < 0.001)	stimulus was able to detect patients with glaucomatous nerve atrophy at an early stage and was correlated strongly with loss of RNFL thickness. This technique might be a new method in diagnosis of glaucoma that should compete against other sensory tests in the same patients to compare feasibility and performance.”	RNFL thickness changes.
Clement, 2009 (4.5)	FDT	Diagnostic (prospective case	No COI. No mention of industry sponsorship.	N=148	Mean age= 66.9 years 76 females, 72 males	115 participants with glaucomatous	Only patients with open-angle glaucoma (OAG) with reproducible	Humphrey Matrix perimetry	standard automated perimetry (SAP), original FDT perimetry.	The matrix perimetry sensitivity and specificity were up to 100% for moderate and	“Matrix perimetry is excellent for detection of moderate to advanced	Data suggests Humphrey Matrix frequency doubling perimetry is

		control study)				visual-field loss and 33 normal controls	visual-field defects on SAP tested within 12 months of this study were included			advanced glaucomatous visual-field loss. A receiver operator characteristic area under the curve (AUC) analysis revealed MD to be slightly better than pattern standard deviation (PSD) for defining moderate (AUC: MD 0.997; PSD 0.987) and advanced defects (AUC: MD 1.000; PSD 0.987). Matrix was less sensitive (up to 87.3%) for detecting early glaucomatous visual-field loss compared with SITA 24-2 SAP (AUC: PSD 0.948; MD 0.910	glaucomatous visual-field loss but may miss some early defects. It may be well suited to following progression of early to moderate field loss because of a smaller target size compared with original FDT perimetry."	useful for the detection of VF loss in moderate to advanced glaucoma but likely misses some early defects.
Taravati P 2015 (4.5)	FDT	Diagnostic	No mention of COI. Supported by institutional research grants from Welch-Allyn, Inc. to the University	N=33	Mean age=57 years. Sex: not mentioned	Thirty-three patients with hemianopias and 50 normal participants	The included subjects had either undergone a complete eye examination within 12 months before this study or were examined by an	Humphrey Matrix frequency-doubling perimeter	standard automated perimetry (SAP)	The sensitivity for hemianopic defects by total deviation probability plots was 75% for SAP and 59% for Matrix (not statistically significant, P= 0.29). The	"Although there was no statistically significant difference between the Matrix and SAP in the detection of hemianopias, the sensitivity of SAP was	Data suggest SAP had higher sensitivity then matrix but no statistically significant between the 2 methods to detect hemianopias

			of Iowa and University of California Davis; a VA Merit Review Grant; and an unrestricted grant to the Department of Ophthalmology, University of Iowa, and the Department of Ophthalmology and Vision Science, University of California Davis School of Medicine, Sacramento, California, from Research to Prevent				ophthalmologist on the day of testing to ensure normal ocular health.			sensitivity of hemianopic defects by pattern deviation probability plots was 88% for SAP and 69% for Matrix (not statistically significant, P= 0.13). The specificity of total deviation probability plots was 84% for SAP and 86% for Matrix. The specificity of the pattern deviation probability plots was 68% for SAP and 74% for Matrix.	higher, probably because of the obscuration of defects by scattered abnormal test"	

			Blindness, Inc.									
Nomoto H 2009 (4.5)	FDT	diagnostic	No mention of COI and no industry sponsorship.	N=123	Mean age: 60 years, 64 females, 59 males.	Fifty-nine eyes of fifty-nine patients with open-angle glaucoma, 24 eyes of 24 glaucoma suspects (GSs), and 40 eyes of 40 healthy age-matched subjects.	The inclusion criteria for glaucoma and GS groups were: best visual acuity of 0.7 or better; within a refractive error of -7.0D (spherical) and -3.0D (cylindrical); no tilted optic nerve head (ONH); and a reliable field defined as false-positive, false-negative, and fixation loss all <33%.	frequency doubling technology (FDT),	standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP), and flicker perimetry, and structural changes using optical coherence tomography (OCT).	The area under the curve (AUC) for FDT 30-1, 30-5, 24-2-1, 24-2-5, flicker perimetry, SWAP (MD), and SWAP (number of abnormal points) were 0.95, 0.94, 0.88, 0.89, 0.99, 0.88, and 0.88 in the early glaucoma group and 0.67, 0.69, 0.65, 0.70, 0.80, 0.64, and 0.66 in the GS group, respectively. In the early glaucoma and GS groups, all OCT parameters had an AUC >0.81 except the disc area parameter. Especially, average NFLT had the highest AUC of 0.94 in the OCT parameters.	"In conclusion, though we may take into account the selection bias of GS group, which may affect the better result of OCT, our results demonstrated the usefulness of detecting functional changes by FDT, SWAP, and flicker perimetry and substantiated the usefulness of measuring NFLT to evaluate structural damages in earlier stage of glaucoma. For the GS, FDT 24-2-5, flicker perimetry, and OCT show good performance to detect abnormalities.	Data suggests OCT has best sensitivity for detection of early glaucomatous changes although SAP, FDT, SAP and flicker perimetry are all good methods for discriminating between normal healthy eyes and enough early glaucoma eyes.

											Among all OCT measurements , NFLT has the highest sensitivity to detect early glaucomatous changes. NFLT measured by OCT provides us with valuable information to diagnose and examine the patients with earlier stage of glaucoma."	
Cello 2000 (4.5)	FDT	Diagnostic	Sponsored by National Eye Institute, Bethesda, Maryland (Dr Johnson) research grant EY-03424. COI, Dr. Johnson is a paid consultant for, and receives research support from,	N = 484	Age ranges between 18 and 85 with mean and SD for age at 46.8 ± 16.5 years for control patients. And Age ranges between 18 and 85 with mean and SD for age at 69.1 ± 11.3 years for glaucomatous visual loss	Normal subjects and Glaucoma patients without any history of ocular or neurologic disease other than glaucoma.	Normal subjects with visual acuity of better than 20/40 in both eyes, normal results of an eye examination, Humphrey Field Analyzer and 30-2 full-threshold visual fields with normal visual field indices P>05. Glaucoma patients had glaucomatous visual field loss	Frequency-doubling technology (FDT).	Previous Humphrey Field Analyzer (HFA) results.	The receiver operating characteristic (ROC) curve for the FDT of control group against glaucomatous patients has an area ROC curve equal to 0.9751, corresponding to a sensitivity of approximately 96% and a specificity of approximately 96%. Using a new test strategy, the Swedish interactive test algorithm, has	"In its present form, frequency doubling technology perimetry provides a useful complement to conventional automated perimetry test procedures and can serve as an effective initial visual field evaluation for detection of glaucomatous visual field	Data suggest FDT perimetry detects VF loss associated with glaucomatous eyes for early, moderate and advanced VF loss.

			Welch Allyn, Skaneateles, New York.		patients. No Gender details.		in one or both eyes, a history of elevated intraocular pressure of > 22 mm Hg before treatment, best-corrected visual acuity better than 20/40 in the eye to be tested, and no history of ocular or neurologic disease other than glaucoma.			been introduced by Humphrey Systems reduces threshold testing time by approximately 50%. This changes the area under ROC curve equal to 0.9261, corresponding to a sensitivity of approximately 85% and a specificity of approximately 90%.	loss. Frequency doubling technology perimetry demonstrates high sensitivity and specificity for detection of early, moderate, and advanced glaucomatous visual field loss."	
Landers 2003 (4.5)	FDT	Diagnostic	No mention of sponsorship. COI, J Landers is affiliated with Eye Associates, whom supports and aids the study.	N = 63	Control: mean age=52, SD=15, 7 males and 8 females; Glaucoma suspects: mean age=56, SD=16, 5 males, 3 females; Ocular hypertension mean age=60, SD=9, 1 male, 7 females,	Patients attending an urban glaucoma clinic having ocular hypertension or open angle glaucoma.	Glaucoma patients had no definite structural changes and normal intraocular pressure (IOP <21 mm Hg) and visual fields. Ocular hypertension was diagnosed as IOP >21 mm Hg. Open angle glaucoma patients had optic disc changes with or without a	Humphrey Field Analyzer (HFA) 24-2 full threshold, central 24-2 SITA standard and central 24-2 SWAP tests.	Medmont M600 automated perimeter 30 degree threshold and 15/22 flicker perimetry and Zeiss Frequency-doubling technology (FDT).	HFA was significantly faster than Medmont central Threshold ($p<0.001$). Medmont central threshold and HFA full threshold had no significant difference in test time ($p=0.53$). HFA SWAP compared to Medmont flicker showed a strict criteria of 0.65 and loose criteria of 0.62. FDP was significantly faster than Medmont	"We conclude that Medmont and Humphrey perimetry correlated favourably with one another, and therefore, both may be used for clinical and research purposes with similar confidence."	Data suggest Medmont and Humphrey correlate well for perimeters results.

					and Open angle glaucoma: mean age=64, SD=9, 16 males, 16 females. 34 females, 29 males, and average age of 60 with SD =13.		visual field abnormality using HFA 24-2 testing.			flicker (p<0.001), while Medmont flicker was significantly faster than HFA SWAP (p<0.01).		
Anderson 2005 (4.5)	FDT	Diagnostic	No COI. Supported by National Eye Institute Grant EY03424 (CAJ), the Oregon Lions Sight and Hearing Foundation (CAJ), National Institute on Aging Grant AG04058 (JSW), and a Jules and Doris Stein RPB Professorship (JSW).	N>275	Ages ranged from 10-90 years. No gender details reported.	Subjects judged to be normal by a battery of clinical procedures.	With refractive errors of <5 D sphere and <3 D cylinder, normal white-on-white fields (HFA Swedish interactive threshold algorithm, no explicit criterion for false responses or fixation losses), acuity of better than 6/12 (20/40).	Humphrey Matrix perimeter 30-2 test	Humphrey Matrix perimeter 24-2 test. Humphrey Matrix perimeter 10-2 test. Macula test.	Sensitivity decreased by 0.7 dB per age decade across all eccentricities; sensitivity decreased with eccentricity, typically by <5 dB at the most peripheral points tested.	"The performance of the test strategy in the Matrix perimeter is appropriately matched to the response characteristics of the normal population. The finding of a spatially nonuniform difference in sensitivity between left and right eyes is attributable to light-adaptation differences between the eyes. This effect is	Data suggest Matrix perimeter is matched to a normal populations response characteristics.

											accounted for in the perimeter's normative database."	
Lamparter, 2013 (4.5)	FDT	Diagnostic	No mention of sponsorship or COI.	N=73	60.6 years. 24 males, 49 females.	44 ocular hypertensive subjects and 29 health age-matched control subjects.	Participants had to have best-corrected visual acuity of at least logMAR 0.3, spherical refraction within 65.0 D, and astigmatism of less than 63.0 D.	Matrix frequency doubling technology (Matrix FDT)	Standard automated perimetry (SAP)	In Ocular hypertension subjects the SAP and Matrix-FDT significantly correlated (r=0.47 (p<0.005)). The SAP and Matrix-FDT also showed a significant correlation for healthy subjects (r=0.68 (p<0.001)). The comparison of SAP MD and FDT MD was significant for both Ocular hypertension (p=0.03) and control subjects (p=0.02).	"In both, ocular hypertensive and healthy subjects SAP and Matrix-FDT correlate well. In ocular hypertensive subjects, both techniques showed good correlation in the supero-temporal, supero-nasal, and nasal sectors of the disc."	Data suggest SAP and Matrix FDT correlate well in ocular hypertensives and normal.
Fredette 2015 (4.0)	FDT	Diagnostic	No COI. Supported in part by a fellowship scholarship from Laval University; an unrestricted donation from Carl Zeiss Meditec	N=53	Mean±SD age: 68±11 years. No gender details reported.	With glaucoma.	With a best-corrected visual acuity of 20/40 or better, had less than 5 diopters (D) of spherical and less than 3 D of cylindrical refractive errors, had a pupil diameter of 2mm or	Swedish Interactive Thresholding Algorithm.	Humphrey Field Analyzer II (HFA).	Mean deviation on the HFA ranged from -31 to +2.5dB. Medians of SAP sensitivity CVs (n = 53 subjects) were lower (p<0.05) than the medians of Matrix sensitivity CVs for 37 of the 55	"The decibel values reported by the two machines are not equivalent. Variability of sensitivity determinations is affected more by the sensitivity level with HFA than	Data suggest since decibel values are non-equivalent between the Humphrey and the Matrix, it is imperative to recognize this variability when making any type of diagnosis or determination

			Humphrey; a donation from Welch Allyn; an unrestricted donation from Allergan, Inc (Irvine, CA); an investigatorinitiated grant from Pfizer, Inc; and an unrestricted grant to the University of Miami from Research to Prevent Blindness, Inc (New York, NY).				more, had no history of disease or surgery that might affect visual field results, and agreed to participate as subjects in the study by attending all five sessions of testing.			evaluated locations	with Matrix. Duplicate measurements for baseline and follow-up evaluation could be important, especially for Matrix. Further information on learning effects is needed, as is commercially available progression software for Matrix.'	of disease progression. Additionally there was an observed learning effect in the Matrix.
Horn 2002 (4.0)	FDT	Diagnostic	No COI. Supported by Deutsche Forschungsgemeinschaft, Bonn, Germany (SFB 539).	N=173	Mean±SD age was 43.6±14.6 years (normals); 56.6±106 years ("preperimetric" glaucoma; 55.5±11.3 years perimetric	Ocular hypertensive eyes.116 "preperimetric" open-angle glaucoma eyes.	With open anterior chamber angles, clear optic media, and visual acuity of 20/25 or better.	FDT perimeter protocol (C-20-5).	Conventional white-on-white perimetry.	There was a correlation between FDT results of nasal quadrants and corresponding visual field losses in 78 left perimetric glaucoma eyes (Spearman's rank correlation was significant	"Point-wise analysis of FDT screening results can be helpful for classification of patient groups and consideration of the individual learning curve in repeated	Data suggest FDT perimeter protocol (C-20-5) can detect a proportion of glaucoma patients.

					glaucoma. No gender details reported.					(p<0.001) for lower (left, r=0.7) and upper areas (right, r=0.72).	measurements. The C-20-5 protocol of the FDT perimeter is able to detect a considerable proportion of glaucomatous patients."	
Sakai 2007 (4.0)	FDT	Diagnostic	No COI. No mention of sponsorship.	N=40	Mean age of 38.9 years (affected eye group). Gender not reporter.	With resolved optic neuritis.	Optic neuritis in 1 eye, but visual acuity had recovered to 1.0 or better (affected eye group).	Frequency-doubling perimetry (FDP).	Standard automated perimetry (SAP).	Correlations between SAP and FDP were statistically significant for mean deviation (P<0.001) and pattern standard deviation (P<0.005)	"(F)DP detects characteristics of slower recovery more effectively than SAP in the fovea and extrafoveal areas. These properties may allow more accurate detection of visual field defects and may prove advantageous for monitoring of patients with resolved optic neuritis"	Small sample. Data suggest FDT comparable to SAP in detecting VF defects associated with optic neuritis and is more sensitive.
Brusini 2006 (4.0)	FDT	Diagnostic	No COI. No mention of sponsorship.	N=318	Mean age control group: 63±11 years. OHT group: 64±11	N=108 patients with ocular hypertension (OHT), N=150 patients with high-tension	Corrected visual acuity Z20/30, open anterior chamber angle, absence of ocular	Standard automated perimetry (SAP) Humphrey Field Analyzer 30-2.	Frequency doubling technology (FDT) N-30 and Humphrey Matrix 30-2 tests.	FDT-N-30 test showed a greater percentage of areas with P<5% in the OHT, preperimetric	"FDT perimetry appeared more sensitive than SAP in detecting early glaucomatous	Data suggest FDT more sensitive than SAP in detecting early VF loss associated with glaucoma.

					years. Gender not reported.	primary open-angle glaucoma (POAG), N=60 healthy individuals as a control group.	pathologic condition other than glaucoma, mild nuclear sclerosis, and rare drusen.			POAG, and early POAG groups.	VF loss. The FDT-N-30 test showed a slightly higher ability to detect early glaucomatous damage in patients at risk for the development of glaucoma, whereas the Matrix-30-2 test provided a more detailed characterization of the glaucomatous VF loss pattern, although it required 30% more time.'	Humphrey Matrix 30-2 test took about 30% longer to perform but provided more details.
Bayer 2002 (4.0)	FDT	Diagnostic	No COI. No mention of sponsorship.	N=138	52 males, 86 females. Mean age (Study Group) 53.4±9.5 years. Control Group 51.6±8.6 years.	With primary open-angle glaucoma (POAG).	Glaucomatous visual field defects and concentric optic disc cupping with a cup-to-disc ratio of 0.5 or more as judged by slit-lamp biomicroscopy using the 78-D lens and untreated (wash	Short wavelength automated perimetry (SAP).	Frequency doubling technology perimetry (FDT), and pattern electroretinography (PERG).	SWAP and PERG P1N2-detected 88.9% of eyes before a prediction of field loss on SAP. When comparing the results of the two functional tests, SWAP and FDT in the 84 eyes without progression of field	"All three tests (SWAP, FDT, and PERG) have been successful in detecting glaucoma eyes with a future progression of standard visual field defects. A test battery of SWAP and PERG P1N2-amplitude	Data suggest SWAP, FDT and PERG successfully detect progressive damage associated with glaucoma.

							out) IOP of more than 21 mmHg on at least three occasions with the Goldmann applanation tonometer in both eyes.			loss on SAP between baseline and at 30 months, SWAP and FDT showed progressive deficits in 34.5% and 35.7%.	improved the power to predict these progressive defects on SAP. It remains to be seen whether the long-term follow-up in POAG eyes will improve the false-positive rate of SWAP and FDT."	
Haymes 2005 (4.0)	FDT	Diagnostic	No COI. Supported by Grant MOP-11357 from the Canadian Institutes for Health Research and by an unrestricted grant from Welch Allyn Inc.	N=65	34 males, 31 females. Mean age at baseline was 63±11 years.	With glaucoma.	With open angle glaucoma with glaucomatous optic disc damage (e.g., notching or progressive thinning of the neuroretinal rim), open angles by gonioscopy, a visual field with an SAP MD index between _2 and _10 dB, a best corrected visual acuity of 6/12 (20/40) or better, and a minimum of 6 examinations	Frequency-doubling technology (FDT).	Standard automated perimetry (SAP).	Least conservative GCP criterion: 32 (49%) had progressing visual fields with FDT vs. 32 (49%) with SAP. FDT identified progression before SAP (median, 12 months earlier).	"Using GCP, more patients showed progression with FDT than with SAP, yet the opposite occurred using LRA. As there is no independent qualifier of progression, FDT and SAP progression rates vary depending on the method of analysis and the criterion used."	Data suggest FDT detected glaucomatous VF progression but FDT and SAP identified different patient subgroups suggesting progression rates vary depending upon method and criteria used.

							with both FDT and SAP.					
Artes 2005 (4.0)	FDT	Diagnostic	Supported by Grant 41340 from the E. A. Baker Foundation of the Canadian National Institute for the Blind (PHA) and an unrestricted grant from Welch-Allyn (BCC). COI, one author indicated Welch-Allyn (F).	N=15	Mean age, 66.3 years. No gender details provided.	With glaucoma.	Open-angle glaucoma, refractive error within 5 D equivalent sphere or 3 D astigmatism, best-corrected visual acuity ≥6/12 (+0.3 logMAR), and prior experience with FDT1 perimetry and SAP.	Second-generation Frequency-Doubling Technology perimetry (FDT2, Humphrey Matrix).	Standard automated perimetry (SAP).	High correlation for global visual field indices mean deviation (MD) and pattern standard deviation (PSD) of FDT2 and SAP; P<0.001.	"The test–retest variability of FDT2 is uniform over the measurement range of the instrument. These properties may provide advantages for the monitoring of patients with glaucoma that should be investigated in longitudinal studies."	Small sample. Data suggest the variability of test-retest of FDT-2 is uniform.
Wong 2000 (4.0)	FDT	Diagnostic	No COI. Supported by Medical Research Council of Canada Grant MA15362 and by the E. A. Baker Foundation, Canadian National Institute	N=12	9 male, 3 female. Mean age of 57.5 years.	With homonymous hemianopia	Patients with well-defined occipital infarcts on MRI were included in the study.	Manual kinetic perimetry.	Tangent screen and Goldmann techniques and automated static perimetry with the Humphrey Field Analyzer.	Visual fields obtained from tangent screen and Goldmann perimetry were similar and corresponded well with the location of lesions on MR images in all 12 patients.	"All three perimetric techniques are satisfactory screening tests to detect occipital lesions. However, tangent screen and Goldmann perimetry provide information	Small sample. Data suggest Tangent screen, Goldmann and Humphrey Perimetry are comparable but location and degree of damage best with Goldman Tangent Screen.

			for the Blind.								about the location and extent of lesions that is more consistent with prevailing knowledge of the effects of the lesion in the post-geniculate visual pathway"	
Wall 2002 (4.0)	FDT	Diagnostic	No COI. Supported by a research grant from Welch-Allyn, Inc., by a VA Merit Review Grant, and by an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness.	N=139	Mean age: Patients 46.6±16.8 years. Normal subjects 44.9±18.9 years. No gender details reported.	With damage to the neuro-ophthalmic sensory visual pathways.	Perimetry with a field analyzer (program 24-2, or in the case of the patients with temporal lobectomies, program 30-2; Humphrey Systems, San Leandro, CA) and FDT perimetry (C-20 threshold) performed in both eyes on the same day.	Frequency-doubling technology (FDT).	Conventional automated perimetry (CAP).	The sensitivity of FDT was 81.3%, with a specificity of 76.2%.	"FDT has sensitivity and specificity similar to that of CAP for detecting visual field defects in patients with optic neuropathies. However, defects in patients with hemianopias may be missed because of the presence of scattered abnormal test locations and failure to detect test locations along the vertical	Data suggest that in patients with non-glaucomatous neuro-ophthalmic disease, both CAP and FDT have comparable sensitivities and specificities. Both CAP and FDT would need some additional modifications to successfully detect hemianopias.

											meridian. The defects demonstrated by both tests in patients with optic neuropathies are similar in number, extent, and shape of the defects. This suggests FDT may not be isolating the magnocellular (M) cells with nonlinear responses to stimulus contrast (My cells) in patients with visual loss"	
Artes 2009 (4.0)	FDT	Diagnostic	No COI. Supported by an E. A. Baker Foundation Project Grant (PHA) and Canadian Institutes of Health Research Grant.	N=15	Mean age 66.3 years. No gender details reported.	With open-angle glaucoma.	Clinical diagnosis of open-angle glaucoma, refractive error within 5 D equivalent sphere or 3 D astigmatism, visual acuity better than or equal to 6/12 and prior experience	Signal-tonoise ratios (SNRs) frequency-doubling technology (FDT2) perimetry.	Standard automated perimetry (SAP).	Moderate correlation between the signals of FDT2 and SAP (P<0.001), but no correlation of noise (P=0.16).	"The higher SNRs of FDT2 suggest that this technique is at least as efficient as SAP at detecting localized visual field losses. Signal/noise analyses may provide a useful approach	Small sample. Data suggest comparable efficacy between SAP and FDT-2 for the detection of localized VF losses.

							with frequency doubling technology (FDT) perimetry (i.e., FDT1) and SAP.				for comparing visual field tests independent of their decibel scales and may provide an initial indication of sensitivity to visual field change over time."	
Zein 2010 (4.0)	FDT	Diagnostic	No mention of COI or sponsorship.	N=78 eyes.	Mean age 53±20 years.33 males, 45 females.	With open-angle glaucoma.	Mean intraocular pressure ≥21 mmHg in a diurnal curve, open angle by gonioscopy, neuroretinal thinning in the optic nerve head (ONH) (i.e. cupping), and corresponding visual field defects.	Frequency doubling technology (FDT) perimetry.	Standard automated perimetry (SAP).	SAP detected abnormalities in 74 (79%) of the superotemporal, and inferotemporal quadrants. FDT figures were 70 (69%) for the same quadrants ($p<0.05$ each).	"As well as the already established lower sensitivity of FDT compared to SAP, this study also demonstrated the significantly poorer ability of FDT in detecting the same field quadrant defects, especially in the early stages of glaucomatous damage."	Although test time with FDT is significantly shorter than with SAP, FDT has a lower sensitivity than SAP and in early glaucomatous disease, FDT has poor ability to detect same field quadrant abnormalities.
Kogure 2002 (3.5)	FDT											Data suggest good agreement between FDT and HFA in NT

												eyes using threshold of HFA.
Allen 2002 (3.5)	FDT											Data suggest FDT comparable in performance to Humphrey 24-2 SITA fast with a relatively low FP rate, FDT may be a potentially useful screening device.
Bozkurt 2008 (3.5)	FDT											Data support combination of VF test results and optic nerve head parameters to improve glaucoma diagnosis as well as follow-up.
Zarkovic 2007 (3.5)	FDT											Data suggest good correlation between MATRIX and SAP.
Brusini 2006 (3.5)	FDT											Data suggest N-30-F comparable to N-30 for early to moderate defects but in subjects with significantly large VF loss, the N-30 was

												better. The test time for N-30-F was 25% shorter.
Wang 2007 (3.5)	FDT											Data state that FDT perimetry has a sensitivity of 64% for detecting glaucoma and that in approximately 50% of persons with abnormal FDT perimetry the precise cause may not be detected.
Yenice 2005 (3.5)	FDT											Data suggest there is a learning effect which occurred for both tests with suggestion that SITA standard may have less of a learning effects than FT.
Saric, 2005 (3.5)	FDT											Data suggest FDP better than SAP in the detection of early glaucoma.
Spry, 2001 (3.5)	FDT											Small Sample. Data suggest FDTP shows less variability than SAP in regions

												of VF sensitivity loss and may be beneficial in detection of progressive glaucoma vision loss.
Maddess, 2000 (3.5)	FDT											Data suggest HFA perimetry, MFP and FDT provide evidence of diffuse loss which occurs in early glaucoma and later glaucoma scotomas.
Joson, 2002 (3.5)	FDT											Data suggest learning effects must be considered during screening for all ocular diseases including glaucoma in FDT perimetry.
Numan 2008 (3.0)	Slit Lamp											Unequal group size for unexplained reasons. Appear to have uneven follow-up length. Patients not well described.
Anderson 2009	FDT											Data suggest cataracts

(3.0)												introduce increased stray light but GRP is the most insensitive to stray light effects.
Gardiner 2006 (2.5)	FDT											Data suggests variability among VF tests must be considered when evaluating glaucoma since tests have different predictive power, performance and detection speeds. SWAP>FDT for aging and practice effects and SAP had the least. RAP showed high variability followed by TMP.
Bernardi 2007 (2.5)	FDT											Data suggest fusion frequency diminishes with age and flicker perimetry is associated with a learning effects.

Mukai, 2004 (2.5)	FDT											Data suggest FDT perimetry results of the second eye were far less reliable than results of the first eye. Possible factors influencing there results are: delayed light adaptation, the learning effect, fatigue, reduced concentration, visual afterimage, ect.
Mansberger, 2007 (2.5)	FDT											Data suggest that if an FDT test is abnormal initially, the test should be repeated. Results showed dependence upon age and screening locale but repeat test results unavailable on 38% of initial abnormal results.
Pierre-Filho, 2010 (2.5)	FDT											Data suggest a significant learning effect on Humphrey

												Matrix FDT perimetry in glaucoma patients who have no perimetric experience. Data suggests it is probably necessary to hull out the presence of a learning effect by repeating the test 3 times.
Yoshii 2008 (2.0)	FDT											Data suggest results of Humphrey Matrix perimetry VF results are influenced by inverse myopic astigmatism of ≥2D.
Casson 2006 (2.0)	FDT											Data suggest cataracts produce false positive results from FDT perimetry screening due to the cataract degrading the retinal image via scattered light.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Population Description	Case Definition	Investigative Test	Comparative Test	Results:	Conclusion:	Comments:
Kerr 2010 (6.5)	SAP	Diagnostic	Kerr is supported by the Maurice and Phyllis Paykel Trust, Alcon, and the Neurological Foundation of New Zealand. Chew is supports by Allergan, Inc. Funded partially by Pfizer Inc.	N = 163 patients, 301 eyes	Mean age 58.9, 91 female and 72 male	Patients from specialist neuroophthalmology clinic	Best-corrected visual acuity of 6/60 (or better) Ability to perform both confrontation testing and automated statis perimetry SITA-standard 24-2 Humphrey visual field analysis.	Confrontation testing (7 common confrontation visual field tests and combinations)	Automated Perimetry	Mean sensitivy for the seven confrontation visual field tests was 52.2%. Probability of detecting visual field defects was dependent on density of field defect. While using the kinetic red target test, there was a 50% probability of detecting a defect. When detecting mild defects the sensitivity was low (0.0 – 67.9%) for all of the tests. Specificity ranged from 27.8 – 100%. Combining the static finger wiggle and kinetic red target tests produced the highest sensitivity (78.3%) and specificity (90.3%) when compared to individual tests.	"Confrontation visual field tests are insensitive at detecting visual field loss when performed individually and are therefore a poor screening test. Combining confrontation tests is a simple and practical method of improving the sensitivity of confrontation testing."	Data suggest use of a combination of confrontation tests is superior to any single confrontation test for visual field test diagnostic accuracy.
Rao 2014 (6.0)	SAP	Diagnostic	Rao and Garudadri are consultants with Allergan. Garudadri consults with Alcon and Merek as well. Funded by grant from Optovue.	N = 291	Median age 52.5, no gender distribution mentioned	Patients referred to tertiary eye care facility	glaucoma suspects based on the optic disc appearance best corrected visual acuity of 20/40 (or better)	False positive and false negative rates of Standard automated perimetry (SAP) using Humphrey field analyzer, model 750i,	Fixation losses of Standard automated perimetry (SAP) using Humphrey	Median fixation loss response rate was 7% while the median response rate for false-positives and false-negatives were 1% and 2%, respectively. 241 patients had reliable visual field test	"This study suggests that FN response rates have an effect on the ability of automated VF assessments to rule out glaucoma. Since	Data suggests the ability to defect and diagnose glaucoma is effected by the FN response rates.

							refractive error within ± 5 diopter sphere and ±3 diopter cylinder	with the SITA standard 24-2 algorithm.	field analyzer, model 750i, with the SITA standard 24-2 algorithm.	results, meaning the fixation loss response was < 20% and false-positive response rate was < 15%. Of these 241 patients, visual field testing determined 78% were normal and 22% had glaucoma. False-positive response rate for visual field testing was related to the false-negative response rate (OR = 1.36, CI 95% 1.25-1.48, p < 0.001). However, it was not associated with the fixation loss response (OR = 0.96, CI 95% 0.90-1.03, p = 0.30) or false-positive response rate (0R = 0.96, CI 95% 0.83-1.12, p = .64).	FN response rates are ignored by the manufacturer while flagging a test as unreliable, clinicians and researchers may benefit by realizing that FN response rates can lead to FP VF classification, even when their frequencies are small."	
Siatkowski 1996 (6.0)	SAP	Diagnostic	Partially funded by the National Glaucoma Research, the United States Public Health Service, the United States Public Health Service Clinical Vision Research Development, the National Eye	N = 159	No mean age or gender distribution mentioned	Participants who had visual field exam while attending the neuro-ophthalmology	Right eye of participants Classification by 6 reviewers: Normal, borderline, abnormal (whatever standard criteria used in clinical practice by reviewers) To be abnormal must present one of the following: general or patchy depression,	76-point, central 30° suprathreshold with central reference level set at 2 or 4 dB lower than estimated normal median central reference	76-point, central 30° automated static threshold perimetry, on Humphrey Visual Field Analyzer	Final clinical diagnoses revealed 70 patients had bona fide ophthalmologic disease. Out of all eyes classified as abnormal, 26 had patchy depression, 34 had nerve fiber layer defects, 9 had nasal defects, 13 had temporal defects, and 3	"The central 30°, 76-point, 2-dB offset suprathreshold automated perimetry is more rapid and nearly as effective as the full-threshold test in detecting visual	Data suggest comparable efficacy between suprathreshold automated perimetry as full threshold but is less time intensive. Data suggests borderline test results (in either test) should be

			Institute, the Research to Prevent Blindness, Inc. Author Anderson received a Senior Scientific Investigators award from the Research to Prevent Blindness, Inc.			service at Bascom Palmer Eye Institute	nerve fiber layer defect, nasal or temporal defect, or enlarged blind spot Clinical diagnosis using history and examination data, central 30-2 threshold tests of Humphrey Visual Field Analyzer, kinetic visual fields on Goldmann perimeter, fluorescein angiography, and neuroradiological evaluation Reviewer classifications were compared to final diagnostic ruling and if both agreed the reviewer's decision was listed as "correct"	level (CRL), adjusted for age ranges		had enlarged blind spots. The full-threshold test produced a sensitivity of 93% (borderline results considered normal) or 99% (borderline results considered abnormal). It produced a specificity of 71% or 91%. The 4-dB test produced a sensitivity of 79% or 87% and a specificity of 81% or 89%. The 2-dB test the 2-dB test produced a sensitivity of 87% or 94% and a specificity of 73% or 85%. Difference between sensitivities of two screen fields was significant ($p < 0.01$).	field abnormalities due to neuro-ophthalmologic disease. More quantitative, full-threshold perimetric strategies should be used in all equivocal cases and to follow progression of established disease."	repeated with the full threshold test.
Fan 2010 (6.0)	FDT	Diagnostic	No COI.	N=68	Mean age group 1: 59.95± 12.11 years. Mean age group	OAG	Glaucomatous optic neuropathy and visual field defects in at least 1 eye and having normal or elevated intraocular pressure without secondary causes	FDT N-30	SAP	Twenty-one eyes showed normal FDT results, 39 eyes showed abnormal FDT results at baseline. No significant difference in SAP and FDT groups at baseline except in FDT for first affected eyes ($p<.05$). Twenty of	"In perimetrically normal eyes of OAG patients, FDT detected visual field loss in almost 2 of every 3 of these eyes and also predicted to some extent	Data suggest that in OAG perimetrically normal eyes FDT predicted future VF loss on SAP and correctly detected this about 2/3 of the time.

					2: 59.33± 13.82 years. 30 males, 30 females.					perimetrically normal eyes developed visual field defects on SAP at 12.40±6.76 months after study. Twenty eyes were converters (greater cup to disc ratio) in group 2 and no eyes were converters in group 1. Twenty-eight patients were diagnosed with primary open-angle glaucoma and the other 32 patients were diagnosed with normal-tension glaucoma. During 3-year follow-up, 25 of 28 perimetrically normal eyes in POAG patients and 27 of 32 such eyes in NTG patient were treated with medication. Both POAG and NTG patients taking medication had used eye drops including prostaglandins, β-adrenergic receptor blockers, α-2-adrenergic receptor agonists, and topical carbonic anhydrase inhibitors. Seven of 17 initial perimetrically normal eyes with abnormal FDT results in POAG patients and 13	future visual field loss on SAP. Severity of glaucomatous neuropathy at baseline was related to conversion of abnormalities on FDT to visual field loss on SAP."	

										of 22 NTG patients were converters, but no significant difference (p>.05). At baseline, ther were 1140 FDT sectors in 60 eyes with normal SAP results. Superior nasal quadrant 35%, superior temporal quadrant 28%, inferior nasal quadrant 21%, and central 5° 1% was the distribution. During follow-up, 22% of abnormal FDT developed an SAP abnormality, whereas only 4% of normal FDT developed SAP abnormality (p<.05). RR of subsequent SAP abnormality to abnormal FDT was 5.38 (95% CI, 3.61-8.04; P<0.05).		
Leeprechanon 2007 (6.0)	FDT	Diagnostic	No mention of COI.	N=127	Mean age of Glaucoma group: 62.2±9.0 years. Mean age of control group: 58.2±1	OAG	Patients over the age of 40 with no history of eye trauma, best corrected visual acuity of 20/40 or better, spherical refractive error of 0±6 diopters, astigmatism of 0±3 diopters, +1 or less nuclear sclerosis on a scale of 1-4, open angles on gonioscopy, and no history of systemic disease or	SITA 24-2 SAP	FDP	No statistically significant difference in number of unreliable fields with SAP compared to FDP. At baseline, glaucoma group had slightly worse visual acuity than control group (p=.04). No significant difference in performing tests, but mean test time between the groups	"FDP and SAP perform similarly in their ability to detect visual field defects in early to moderate glaucoma. Larger and deeper defects detected with FDP suggests the possibility of	Data suggest FDP and SAP have comparable performance efficacy in detection of visual field defects in early to moderate glaucoma. The high sensitivity and specificity of FDP may suggest earlier detection

					2.0 years. 34 males, 58 females.		medication that could influence visual function.			(P<.01 for SAP and P<0.96 for FDP). SAP took 5.89 minutes and FDP took 5.23 minutes (P<0.001). Significant correlation with MD and number of defects on TD at P<.05 (r=.56, P<.001; r=.68 p=.001).In TD, FDP had significantly higher defect score than SAP in glaucoma group (P=.028) and oppositely for the normal group (P=.004). And the same results in PD occurred, except only significance in the glaucoma group (P=.01).GHT provided highest specificity (98 %) and highest sensitivity (92%). Location of visual field defects for glaucoma group found on FDP showed moderate agreement with SAP defects. (κ=.48±.04) This was not seen in the normal group. (κ=.16±.05)	earlier detection at high specificity."	of glaucoma associated with presence of larger and deeper structural defects.
Thomas 2002 (6.0)	FDT	Diagnostic	No mention of COI.	N=133	Mean age: 50.39 years. 60 males, 66	85 eyes of 85 patients with established field	Patients with primary open- or chronic closed-angle glaucoma with best corrected Snellen chart visual acuity of 6/9 or greater. No patients	C-20-5	C-20-1	The best sensitivity 85.9% and specificity 95.1% were provided. For moderate and severe cases, sensitivity improved to 91%. Detection was not	"FDP is a valid screening test for glaucoma. The scoring system described by Patel et al.	Data suggest FDP as a valid screening test for glaucoma.

					female s.	defecte d in automa ted perimet ry and 48 eyes of 48 control subject s.	with posterior subcapsular cataract in the pupillary area, no fellow eyes of chronic closed-angle glaucoma without field defects, proliferative diabetic retinopathy, no patients treated with laser photocoagulation, cataracts considered responsible for best-corrected vision less than 6/9.			improved by quantification of defect.	provided the best results."	
Soliman 2002 (6.0)	FDT	Diagn ostic	No COI.	N=123	Mean age: 58.14 years. No menti on of gender .	42 patient s with early to modera te glauco ma, 34 ocular hyperte nsives, 22 glauco ma suspect s, and 25 normal control s	Only subjects with an open anterior chamber angle, minimum best-corrected visual acuity 20/25 and clear ocular media, no history of intraocular surgery, no secondary cause of elevated intraocular pressure, no patients with history of diabetes, no neurological disorders that might affect VF, no medications that might affect the color vision or retinal sensitivity, and no patients with a history of congenital color vision defects, and no patients with lens	SAP	SWAP FDT	SWAP gave a significantly larger defect than both SAP and FDT in the glaucoma group and larger defects than FDT only in suspects. For the VF index PSD in SWAP was significantly larger than SAP in all groups (P=.0001 for all groups except glaucoma P=.01) and SWAP only in the glaucoma and OHT group (P=.002 and P=.004 respectively). No significant difference was detected in the suspects group. In normal controls the abnormal point in	"SWAP in its existing condition is markedly less efficient than either SAP or FDT in detecting VF defects, especially in glaucoma patients and ocular hypertensives (defects detected with SWAP are less than both SAP and FDT). Defects detected with FDT are equivalent to SAP and sometimes larger, especially in ocular	Data suggest SWAP does not perform as well as either SAP or FDT in the detection of VF defects (especially glaucoma and ocular hypertension patients) FDT detects larger defects making it useful for population screening.

							opacity >1. Normal patients without history of glaucoma, clinical evidence of glaucomatous damage on exam, and no abnormal IOP.			SWAP were significantly lower than in SAP for (p=.01 and p=.05). FDT detected significantly larger defects than SAP in OHT and suspects. (p=.01 and P=.004 respectively).	hypertensives and glaucoma suspects; this makes it a useful tool for picking up early glaucomatous defects in populations at risk."	
Su 2003 (6.0)	SAP	Diagnostic	No mention of sponsorship or COI.	N = 24	Mean age 38, 10 females and 14 males	Possibility of glaucoma, experience with automated visual field tests	Best-corrected visual acuity of 20/30 or better Intraocular pressure 21 mmHg Clear ocular media Normal ocular exam except for suspicious optic disc No other ocular or systemic condition that may affect visual field Two or more normal or equivocal visual field tests on standard white-on-white automated perimetry	SWAP, Humphrey Field Analyzer (HFA II 750i), 30-2 program with full-threshold performance	W-W perimetry, Humphrey Field Analyzer (HFA II 750i), 30-2 program with full-threshold performance	The average mean deviation (MD) for the SWAP group was 6.55 ± 3.31 db. For the W-W group the average MD was 2.69 ± 1.76 db. Using the Wilcoxon signed rank test these average MDs were statistically difference ($p < 0.001$). The average pattern standard deviation (PSD) for the SWAP group was 3.49 ± 0.80 db. The average PSD in the W-W group was 2.40 ± 0.95 db in the W-W group. Again these results were statistically different ($p < 0.001$). The average test time in the SWAP group was 905.68 ± 70.03 seconds.	"This study showed that greater MD and PSD were demonstrated with SWAP. The test time was longer for SWAP. However, in order to conclude that SWAP is an early indicator of glaucomatous damage, longer follow-up and further analyses are required."	Data suggest similar test reliability between SWAP and W-W just that SWAP, while longer in testing time was associated with greater MD and PSD. Small sample.

										It was 788.26 ± 69.93 seconds in the W-W group ($p < 0.001$) Average fixation loss in the SWAP group was 6.57% ± 7.98%, and 6.41% ± 8.43% in the W-W group ($p = 0.95$). False-positive rate was 0.72% ± 1.95% in the SWAP group. For the W-W group it was 2.37% ± 5.00% ($p = 0.07$); For the SWAP group the false negative rate was 2.14% ± 4.06% and 1.28% ± 3.70% for the W-W group ($p = 0.57$). The SWAP group had 3.42 ± 3.12 average number of test points depressed below the 5% sensitivity level on the pattern deviation probability plot. The W-W group had 3.29 ± 3.13 ($p = 0.84$). The SWAP group with test points under 1% was 0.67 ± 1.13		

										and 0.71 ± 1.04 for the W-W group (p = 0.85).		
Delgado 2002 (6.0)	SAP	Background	No mention of sponsorship or COI.	N = 60		Effectiveness in diagnosing glaucoma and detecting disease progression.		Short wavelength automated perimetry (SWAP), Frequency doubling technology perimetry (FDT), High-pass resolution perimetry (HPRP), and Motion automated perimetry (MAP).	Swedish interactive threshold algorithm (SITA) and SITA fast.		"Short wavelength automated perimetry detected visual field loss earlier than standard threshold automated perimetry, with a sensitivity and specificity of about 88% and 92% respectively."	Data suggest that SWAP, while having high sensitivity and specificity, it is time intensive and subject to large long term fluctuations. FDT is useful for the detection of early to advanced glaucoma and is resistant to blur and pupil size and less time intensive.
Terry 2010 (5.5)	FDT	Diagnostic	No COI.	N=2529	Participants over the age of 40. 1302 males, 1227 females.	No patients who are blind, have eye infection, or had an eye patch on both eyes.	VFL defined as at least 2 fields in the first test <.01 threshold, and at least 2 fields in the 2nd test were <.01 threshold level, and at least one field was the same on both tests.	FDT C-20	Humphrey Matrix N-30-5	Of eligible participants, 86.2% received VF exam. The average exam time was 9.7 minutes, with a median time of 9.1 minutes. Twenty-five percent of exams conducted for visual acuity (<20/40) exceeded 12 minutes. Average time of FDT test was 42 seconds with median time of 37 seconds. When defining reliability based on ≤1/3 blind spots, ≤1/3 false positive tests, and technician noted proper fixation, 80.1%	"FDT is a feasible, fast, and reliable method for visual field loss screening in a population-based U.S. study, with an 86.2% response rate, median exam time ~9 minutes, and nearly 95% of examined participants having complete, reliable results in 1 or both eyes."	Data suggests FDT a reliable testing method for VF screening and was a fast method for screening a large population.

										of examined adults had 2 reliable tests for both eyes; an additional 13.4% had 2 reliable tests for 1 eye. Increasing age, test times, decreasing visual acuity, data reliability, and presence of self-reported glaucoma resulted in decreased exam rates. Sensitivity and specificity to detect persons with glaucoma was 54.8% and 91.9% respectively.		
Liu 2011 (5.5)	FDT	Diagnostic	No mention of COI.	N=132	Mean age:54.1 years.	132 eyes of 95 glaucoma patients and 37 normal subjects	Visual acuity of at least 20/40, spherical refractive error within the range of ±8.0 diopters. No clinical evidence of macular disease, no refractive or retinal disease, no neurological disease, and no diabetes.	SAP	SITA SWAP Matrix FDT	Sensitivity was highest for Matrix FDT perimetry, followed by SAP, and then SITA SWAP. Analysis of only patients with early glaucoma sensitivity decreased to 52%, 46%, and 34%, respectively, with a significant difference between Matrix FDT perimetry and SITA SWAP (P=.034). The specificity was ≥97% for all perimetries. AUCs of MD and PSD followed a similar order, with Matrix FDT perimetry having the greatest (.89-.94) then SAP (.87-.94), and then SITA SWAP (.69-.90). There	"The performance for glaucoma detection was comparable between FDT perimetry and SAP. FDT perimetry had a higher sensitivity for detecting glaucoma than did SWAP at a comparable level of specificity."	Data suggest both FDT and SAP were comparable for the detection of glaucoma. SWAP and FDT had similar specificities but FDT had higher sensitivity of detection of glaucoma.

										were significant differences in sensitivities at 90% specificity between Matrix FDT perimetry and SITA SWAP (p≤.005 for MD, p≤.039 for PSD)		
Liu 2014 (5.5)	FDT	Diagnostic	No mention of COI.	N=217	Mean age: 52.53 years. No mention of gender.	179 eyes of 148 glaucoma patients and 38 eyes of 28 normal subjects	Visual acuity of at least 20/40, no evidence of macular disease, no refractive or retinal surgery, no neurological disease, and no diabetes.	SAP	Matrix FDTP	Of the 217 eyes, 6.1% and 3.9% progressed with conservative criteria, 14.5% and 5.6% of eyes progressed with the moderate criteria by FDTP and SAP. FDTP detected more progressing locations than SAP. Rate of change of visual field mean deviation was significantly faster for FDTP (P<.001). No eyes showed progression in the normal group using the conservative and the moderate criteria.	"With a faster rate of change of visual sensitivity, FDTP detected more progressing eyes than SAP at a comparable level of specificity. Frequency doubling technology perimetry can provide a useful alternative to monitor glaucoma progression."	FDTP and SAP have comparable specificity in glaucoma detection, but FDTP detected more progressing glaucoma locations than SAP.
Sample 2000 (5.5)	SAP	Diagnostic	Funded by grant from the National Eye Institute, the Foundation for Eye Research, and the Joseph Drown Foundation. No mention of COI.	N = 136	Mean age 62.46, no gender distribution mentioned	Glaucomatous optic neuropathy (GON), ocular hypertension (OHT), or control	Open angles in stereoscopic photographs Best corrected acuity of 20/40 (or better) Spherical refraction within 65 D Cylinder correction within 63 D	Short-wavelength automated perimetry (SWAP), frequency-doubling technology perimetry (FDT), motion-automated	SAP	71 eyes had GON. FDT identified 70% as abnormal, SWAP identified 61%, MAP identified 52%, and SAP identified 46%. For the eyes with OHT, FDT identified 46% as abnormal, SWAP identified 22%, MAP identified 30%, and SAP identified 5%. SWAP (p	"For detection of functional loss standard visual field testing is not optimum; a combination of two or more tests may improve detection of functional loss in these eyes; in an individual, the	The data suggest that using standard visual field testing is not ideal for detecting functional loss. It is suggested that combination of tests may be more appropriate for increasing the

							Glaucomatous optic neuropathy participants had to have asymmetrical cupping, presence of rim thinning, notching, excavation, or nerve fiber layer defect Ocular hypertensive participants had to have intraocular pressure of 23 mm Hg (or more) on at least two occasions and normal-appearing optic disc stereophotographs	perimetry (MAP)		= 0.003), FDT (p = 0.002), and MAP (p = 0.005) all significantly identified more abnormality in eyes than SAP according to a chi-squared analysis. There was no visual function loss in 10% of the GON eyes. 27% only showed loss in one test. 63% showed loss in two or more test. 30% of OHT eyes showed visual function loss in two or more tests. 4% of eyes from the controls showed any loss. For eyes with GON, 97% that were detected as abnormal for the SWAP and FDT tests had one quadrant in common. 97% also overlapped quadrants in the MAP and FDT tests. 92% also overlapped in the MAP and SWAP tests. The mean number of quadrants that were detected abnormal in GON eyes were as follows: SAP 0.59 ± 1.10, SWAP 1.18 ± 1.38, FDT 1.67 ± 1.62, MAP 0.79 ± 1.34. The mean	same retinal location is damaged, regardless of visual function under test; glaucomatous optic neuropathy identified on stereophotographs may precede currently measurable function loss in some eyes; conversely, function loss with specific tests may precede detection of abnormality by stereophotograph review; and short-wavelength automated perimetry, frequency doubling perimetry, and motion-automated perimetry continue to show promise as early indicators of function loss in glaucoma.”	sensitivity with a slight loss of specificity.

										number detected in OHT eyes were as follows: SAP 0.02 ± 0.16, SWAP 0.47 ± 1.10, FDT 1.00 ± 1.27, MAP 0.95 ± 1.61. The mean number in the control eye group was about 0.25 or less for SWAP, FDT, and MAP.		
Plummer 2000 (5.5)	SAP	Diagnostic	Funded by grants from the NIH, Core Grant for Vision Research, and Research to Prevent Blindness. No mention of COI.	N = 23	No mean age or gender distribution mentioned	Glaucoma patients and controls	Glaucoma patients and controls	Scanning laser entoptic perimetry	Standard Humphrey automated visual field perimetry (SAP)	SAP detected abnormality in all 29 glaucomatous eyes. 19 were detected as having entopic perimetry disturbances. All controls presented no abnormality in either test. With the entoptic perimetry, the sensitivity was high for moderate/severe patients (0.71-0.90). Specificity was 1.00. The sensitivity for those considered to less severe conditions or none were moderate (0.27-0.67). Specificity was high (0.78-1.00).	”Scanning laser entoptic perimetry may be an effective and inexpensive screening test in hospitals and community clinics for diagnosing visual field loss caused by glaucoma.”	Data suggest entopic perimetry “reasonably estimates” moderate- severe scotomas in visual field loss although this method is not as sensitive in detecting early visual field defects. It is less costly than SAP.
Laron 2010 (5.5)	SAP	Diagnostic	Sponsored by NIH grants P30 EY07751, T35 007088, a pilot grant from the National	N = 69	Age range from 21 to 57 years, gender	With clinical definite MS.	MS diagnosis ranged from just diagnosed to 21 years, in particular optic neuritis (ON). 47 MSON eyes (last optic neuritis (ON) attack ≥ 6 months	MfVEP (amplitude/latency) and Humphrey visual field (HVF).	Optical coherence tomography (OCT).	MfVEP identified more abnormality in MS-ON eyes (89%) vs HVF (72%), OCT (62%), mfVEP amplitude (66%) or latency (67%) alone. 18% of MS-no-ON eyes	“The mfVEP, HVF and OCT provide complementary information in detecting visual pathway	Data suggest that in MS patients, MFVEP letter at detecting deficits that either HVF or OCT.

			Multiple Sclerosis Society, a University of Houston GEAR grant, and the Minnie Flaura Turner memorial fund. No mention of COI.		not specified.		prior) and 65 MS-no-ON eyes without ON history.			were abnormal for both mfVEP and HVF compared to 8% with OCT. MfVEP categorized additional 15% of MS-ON eyes as abnormal vs HVF and OCT combined.	abnormalities in MS."	
Hood 2004 (5.5)	SAP	Diagnostic	Sponsored by National Eye Institute Grants R01-EY02115 and R0 - EY09076 and by the Steven and Shelley Einhorn Research Fund of the New York Glaucoma Research Institute, New York, New York. D.C. Hood, Carl Zeiss Meditec (C), and no other COI reported.	N = 50	Mean age 59.9 ± 11.5, gender not specified.	With open-angle glaucoma (OAG) and relatively mild visual field defects.	Abnormal HVF if the pattern standard deviation (PSD) was significant at, ($p < 5\%$ and or glaucoma hemifield test (GHT) outside normal limits.	Multifocal visual evoked potential (mfVEP).	Automated perimetry	The mean value of the MD for this group was –2.72 dB (range, 1.56 to –7.84). For the mfVEP test 74 (37%) of the 200 hemifields had abnormal mfVEP clusters vs 75 (37.5%) had abnormal HVF clusters. The HVF and mfVEP results agreed on 74% of the hemifields, and 90 normal and 58 abnormal hemifields on both the mfVEP and HVF cluster tests.	"[T]he HVF and monocular mfVEP tests showed a comparable number of defects, and, with the addition of the interocular test, the mfVEP showed more abnormalities than the HVF."	Data suggestion both multifocal VEP and HVP detect abnormalities that are distinctly different a comparable number of the same defect.
Goldbaum 2002 (5.5)	SAP	Diagnostic	Sponsored by	N = 156	Mean age 50.0 ± 6.7, gender not specified.	With advanced open-angle glaucoma	The glaucoma category based on optic nerve damage and not visual field defects.	Humphrey Field Analyzer with program 24-2 or 30-2.	Standard Automated perimetry (SAP).	Correlation between MD and PSD, ($p = 0.55$) and MD vs CPSD, ($p = 0.42$). MoG with PCA had 0.922 area under the ROC curve vs MoG constrained to QDF (0.917) with the full	"MoG, using the entire visual field and age for input, interpreted SAP better than the global indices of STATPAC."	Data suggest MoG better than STATPAC in interpreting SAP.

										data set, MoG constrained to QDF that was significantly higher vs PSD, (p = 0.0009). No significant difference in the number of false negative of each classifier (41, 39 and 41). False negatives 0.94 between MoG and PSD, 0.92 between MoG and expert 1, and 0.94 between expert 1 and PSD.		
Girkin 2000 (5.5)	SAP	Diagnostic	Sponsored in part by the National Eye Institute, National Institutes of Health, Bethesda, Md (Dr Sample), the Glaucoma Research Foundation, San Francisco, California from the National Eye Institute, National Institution of Health , Bethesda, Md (Dr Zangwill), the Heed Ophthalmic	N = 47	Mean age for non-progressive and progressive patients: 64.3 (14.5) and 66.9 (11.4), 21 male and 26 female.	With progressive glaucoma.	With high refractive error, >±5.00 spherical equivalent or ± 3.00 cylinder, lens changes, loss of > 1 line of visual acuity with nuclear sclerotic cataract, or development of any degree of posterior sub-capsular cataract.	Short-wavelength automated perimetry (SWAP).	White-on-white (standard) perimetry.	22 or 47% considered progressive and 25 or 53% nonprogressive. The mean intraocular pressure in the ophthalmic record was 5.4 mm Hg higher in progressive vs nonprogressive group, (p < 0.04). AGIS score for SWAP was higher vs baseline score, (p = 0.81). Standard perimetry showed progression in 7 or 32% of 22 patients vs SWAP progression in 12 or 55% of 22 patients using AGIS criteria for visual field progression. The mean difference of AGIS scores for both	"Short-wavelength automated perimetry identified more patients than standard perimetry as having progressive glaucomatous changes of the optic disc."	Data suggest SWAP detected more individuals with progressive glaucomatous changes in the optic disc than did standard perimetry.

			Foundation, Chicago, Ill, and Joseph Drown Foundation, Los Angeles, California (Dr Weinreb). No other COI reported.							standard perimetry, ($p < 0.004$) and SWAP, ($p < 0.001$) between progression and nonprogressed group.		
Bowd 2009 (5.5)	SAP	Diagnostic	Sponsored by NIH EY018190, 011008 and 008208. Financial disclosure, Carl Zeiss Meditec: PAS (S), RNW (S, C), LMZ (S), Haag-Streit: PAS (S), Heidelberg Engineering: RNW (S), LMZ (S), Lace Elettronica: CB (S), Optovue: LMZ (S), Welch-Allyn: PAS (S).	N = 71	Mean age of healthy individuals and PERGLA; 63.3 and 43.8 years, gender not specified.	With glaucomatous optic neuropathy (GON). N = 42 healthy individuals and N = 29 with GON.	Best-corrected acuity better than or equal to 20/40, spherical refraction within ± 5.0D and cylinder correction within ± 3.0D, and open angles on gonioscopy.	Pattern electroretinograms optimized for glaucoma detection (PERGLA).	Standard Automated perimetry (SAP).	PERGLA accuracy was 0.66 and SAP accuracy was 0.80. PERGLA and SAP significant differences for all parameters, ($p \leq 0.001$) except PERGLA phase, ($p = 0.582$). Sensitivities at or near the chosen specificities of 0.75, 0.85 and 0.95 were generally better for SAP than for PERGLA parameters.	"Pattern electroretinograms recorded using the PERGLA paradigm can discriminate between healthy and glaucoma eyes, although this technique performed no better than SAP at this task."	Data suggest PERGA does not perform as well as SAP in discriminating between healthy eyes and glaucomatous optic neuropathy (GON) eyes.
Iwasaki 2002 (5.5)	FDT	Diagnostic	No mention of COI.	N=14,814	Mean age: 40.7±9.7 years. 12660 males, 2154 females.	103 consecutive glaucomatous patients and 14,814 persons.	Patients without chronic ocular disease, distance refraction less than 700 diopters, and no systemic disease or medication known to affect the visual field.	FDT-GSP	30-2 SITA	FDP-GSP detected 83.3% of early stage glaucoma and 100% of advanced stage glaucoma. Of the 14,814 patients, 660 tested positive for FDT-GSP. 13,650 showed a negative FDT-GSP. Of the 660 with positive results, 370 were examined and 148 were	"Frequency-doubling technology-based screening with only a visual field test showed reasonable performance on mass screening for detection of definitive	Data suggest FDT screening showed good performance for glaucoma detection.

										already under medication for glaucoma or other diseases. Definitive glaucoma was diagnosed in 167 patients, 46 with suspicious, 53 with at-risk, 39 were normal, 55 with other diseases, and 10 were undiagnosed.	glaucoma in this study population, considering the glaucoma prevalence."	
Ferreras 2007 (5.5)	FDT	Diagnostic	No mention of COI.	N=202	Mean age: 60.78 years. No mention of gender.	92 healthy control subjects and 110 patients with varying degrees of glaucomatous visual field loss on SAP	Patients with best corrected visual acuity ≥ 20/30, refractive errors of <3 diopters sphere and <2 D cylinder, transparent ocular media, open anterior chamber angles, and patients without previous ocular surgery, diabetes, or other systemic diseases, without a history of ocular or neurological disease, and without current use of any medication that might affect VF sensitivity.	C-20	C-20-1	Best criterion for C-20-1 test is with 1 or more altered points with a p-value of< .01 and a sensitivity of 57.81% sensitivity and 100% specificity. Best criterion for glaucoma diagnosis for C-20 test is with 5 or more altered points with a p-value of <.05 or 2 or more altered points with p<.02, or 1 altered point with p<.01. Sensitivity at 79.68% and 94.2% specificity is best. Test duration for C-20-1 was 51±18 seconds. Test duration for C-20 was 279±30 seconds. Performance times for FDT were lower than SAP test (651±192 seconds).	"By using the C-20-1 strategy, a p < 1% defect anywhere showed 100% specificity with the lowest test duration. The criteria proposed for the threshold C-20 algorithm presented a good sensitivity) specificity balance. The threshold C-20 test provides higher sensitivity than the C-20-1 strategy but takes about five times longer to perform."	Data suggest C-20 test takes 5 times longer to perform with a higher sensitivity than C-20-1 has 100% specificity and short testing time.
Nehmad	FDT	Diagnostic	No mention of COI.	N=1253	Age: ≥45	1253 persons	Patients with an IOP of ≤21 mmHg in either	FDT	C-20-1	IOP and direct ophthalmoscopy were	"In the community	Dada suggest FDT was reliable for

2008 (5.0)					years old. No mention of gender.	over age 45 who are either black or have family history of glaucoma	eye or an IOP difference between the eyes ≤ 3mmHg, and no abnormality or suspicion of abnormality in media opacity, retinal disease, optic nerve disease, or the inability of the examiner to get a clear view of the fundus because of media opacity or small pupil.			passed by 1043 people. Of the 1043, 159 met high-risk criteria. Of the high-risk 19 failed FDT and 8 had unreliable FDT tests.	screening, FDT performed reliably and identified abnormalities in a significant number of persons in the high-risk group passing the eye health part of the screening. However, with the exception of the poor sensitivity shown by strategy 4, results from the simulated screening did not support the usefulness of one strategy over another."	the screening of most individuals in community vision screenings except it lacked good sensitivity for the group of persons with no direct ophthalmologic exams or IOP.
Nam 2009 (5.0)	FDT	Diagnostic	No mention of COI.	N=115	Mean age: 55.16 years. 67 males, 48 females.	47 healthy subjects and 68 glaucomatous subjects.	Patients with best-corrected visual acuity of 20/30 or better, with spherical equivalent ±5 diopters, cylinder correction +3D, presence of a normal anterior chamber and open-angle on slit-lamp and gonioscopic examination, reliable	Humphrey Matrix	SAP	Of the 68 glaucomatous eyes, 45 were diagnosed with normal-tension glaucoma and 23 with primary open-angle glaucoma. Overall AUC score was .857 for Matrix data and .881 for SAP data. No significant difference was observed (p=0.538) for Matrix or SAP	"Both Matrix and SAP showed good diagnostic performance with glaucoma defined as structural loss. Matrix and SAP data showed similar discrimination capability for	Data suggest Humphrey MATRIX and SAPP perform well in detecting structural loss associated with glaucoma.

							SAP and matrix results with a false-positive error of <15%, a false-negative error of <15%, and a fixation loss of <20%. No subjects with any other ophthalmic disease that could result in VF defects and those with a history of diabetes mellitus.			cluster score and for early-advanced stages of glaucoma (p=.831; p=.237).	different stages of glaucoma determined by cluster analysis."	
Sekhar, 2000 (5.0)	SAP	Diagnostic	No mention of sponsorship. No COI.	N= 48	No mention of mean age or gender.	48 Glaucoma Patients.	Glaucoma	SITA Fast (SF)	Standard Full Threshold (SFT), SITA Standard (SS)	The sensitivity of the SS test was 95.12% and the sensitivity of the SF test was 92.68%. Both were compared to the standard full threshold test. The SS test was 53.12% faster than the SFT test (p=0.001) and the SF test was 70.69% faster than the SFT test (p<0.0001).	"Swedish interactive threshold algorithm strategies have good sensitivity and are significantly faster as compared with the standard threshold algorithm. The repeatability of the SFT and SS strategies are excellent, whereas that of the SF strategy is variable."	Data suggest SITA is a faster VF test with good sensitivity and SFT and SS testing resulted in excellent repeatability.
Miranda, 2008 (5.0)	SAP	Diagnostic	No mention of sponsorship or COI.	N= 10	No mention of mean age or	10 glaucoma patients.	Glaucoma with previous experience with SSAP; visual acuity (VA) ‡ 0.3	Single-Stimulus automated perimetry (SSAP)	Multiple-stimulus perimetry (MSP)	The MSP showed an increase in sensitivity (mean = 1.9 dB (p<0.01)) and a reduction in variability (mean range from 3.7	"Patients have a higher sensitivity and less variability in their visual field when tested with MSP	Small sample. Data suggest MSP combined with verbal feedback led to increased sensitivity and

					gender.		logMAR (6/12); refractive error within ±5.00 D sphere and <3.00 D cylinder			to 2.5 dB, (p<0.01)). The mean MSP test time took 5.4 min, and the SSAP test took 4.3 min.	with verbal feedback than with SSAP."	less variability in visual field testing of glaucoma patients compared to SSAP although test performance time, on average, was longer.
Newkirk, 2006 (5.0)	SAP	Diagnostic	No mention of sponsorship. No COI.	N=10	Mean age was 53.8 years. Gender was not provided.	5 normal subjects and 5 patients with glaucoma.	Glaucoma patients were included based on clinical diagnosis of glaucoma.	Humphrey Field Analyzer's Swedish Interactive Threshold Algorithm (HFA II).	Clinical Diagnosis of Glaucoma	The mean false positive tests for normal and glaucoma patients were 0.4% and 0.93%, respectively. The greatest change in mean deviation in glaucoma patients at 33% error frequency was 2.4 dB. The mean test duration for normal subjects increased by 54 seconds and the mean test time increased by 69 seconds in glaucoma patients.	"HFA II SITA-S underestimates patients' FP errors, particularly among normal patients. High FP error frequencies can have adverse effects on MD and PSD, leading clinicians and researchers to an inaccurate determination of the amount and severity of visual field loss."	Small sample. Data suggest HFA II SITA-S in normal eyes underestimates FPs to a greater extent than when MD & PSD were abnormal as in glaucomatous eyes.
Park, 2009 (5.0)	SAP	Diagnostic	No mention of sponsorship or COI.	N= 202	Mean age was 55.5 years. 102 males, 100 females.	202 glaucomatous eyes.	90 Glaucomatous eyes were identified with SAP. 112 eyes were diagnosed using the Humphrey Matrix.	Humphrey Matrix (Matrix)	Standard Automated Perimetry (SAP)	No average RNFL thickness measured by OCT was significant between the matrix and SAP groups (p>0.05). The S1 (MD> -6dB) and S2 (-12<MD<-6dB) subgroups within the SAP group had significantly different average, superiori and	"SAP subgroups showed a good correlation of structural and functional defects when assessed using OCT and GDx VCC. These correlations were weaker in the	Data suggest SAP subgroups were highly correlated between structural and functional defects with OCT and GDx VCC assessments. This was not as strongly

										inferior RNFL thickness measured by OCT ((p=0.001), (p=0.011), and (p<0.001)) respectively. Only the average and inferior RNFL thicknesses were significantly different in M1 and M2 groups ((p=0.016) and (p=0.013)) respectively.	Matrix subgroups, especially in the early stages of glaucoma."	correlated in the Matrix subgroups for early to moderate glaucoma stages.
Kim 2013 (5.0)	SAP	Diagnostic	Sponsored by a grant of the Korea Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea. No COI.	N = 106	Mean age 52.93 ± 20.93, 51 male and 55 female.	With glaucoma	BCVA >20/30, a spherical equivalent within ±6D with a cylinder within 3D, presence of open-angle on slit lamp, gonioscopic examinations, and reliable visual field test results.	SD-OCT volume scans	SAP tests	The VFS of each test point was significantly correlated with the corresponding MRT (R^2 = 0.133-0.383, all (p < 0.001). The quadratic model than linear model when the MRT was plotted against the decibel VFS (superior hemisphere, p = 0.002; inferior hemisphere, (p = 0.012).	"The VFS showed a significant reciprocal relationship with corresponding macular thickness at each test point."	Data suggest that although the VFS showed a significant reciprocal relationship (correlation) to macular thickness, the strongest correlation was in the arcuate area whereas other areas showed variability. The SD-OCT may be useful as another way of assessing structural damage associated with glaucoma.
Fortune 2007 (5.0)	SAP	Diagnostic	Sponsored by the M. J. Murdock Charitable Trust, Vancouver WA;	N = 185	Mean age 60.9 ± 11.0, 78 male	With high-risk ocular hypertension	Corrected visual acuity ≥ 20/40 and spectacle refraction < ± 5.00 D sphere and < ± 2.00 D cylinder.	Multifocal visual evoked potential (mfVEP).	Standard automated perimetry (SAP).	The abnormality rate for mfVEP ranged from 14% to 45%. The average SAP MD was +0.3 ± 2.1 dB (range +3.9 to +10.1 dB)	"The diagnostic performance of mfVEP was similar to that of SAP."	Data suggest similar performance for the detection of GON between mfVEP and SAP

			Good Samaritan Foundation, Portland, OR; National Eye Institute Grants R01-EY03424 (CAJ) and R01-EY02115 (DCH); and the Legacy Good Samaritan Foundation. No COI.		and 107 female.	or early glaucoma.				and the average PSD was 2.3 1.9 dB (range, 1.0 – 16.1 dB). 54/185 eyes graded as GON abnormal SAP and 152/181 graded as normal SAP. The sensitivity of SAP-OHTS had higher sensitivity and lower specificity, of the SAP clusters only "44" or 2 points and "444" or 3 points performed better vs SAP-OHTS, ($p < 0.05$).		for 80% of individuals suggesting the 2 tests may vary in type of functional deficits detected.
Lima 2009 (5.0)	SAP	Diagnostic	Sponsored by the Joseph and Geraldine LaMotta Research Fund of the New York Glaucoma Research Institute, New York. RBR is a member of the Scientific Advisory Board of OTI-Opko.	N = 20	Mean age and VF mean deviation were 60.8 (13.4) years and -7.3 (6.1) dB, 8 male and 12 female.	With characteristic optic neuropathy and a paracentral VF defect.	VF defect 1% within the central most 16 points of the 24–2 visual field (Humphrey Field Analyzer II, SITA Standard 24–2).	Scanning laser ophthalmoscope microperimetry (SLO-MP).	Standard Automated perimetry (SAP).	Correlation between SLO-MP and SAP in all quadrants (inferotemporal, r^2= 0.84; inferonasal, r^2= 0.73; superonasal, r^2 = 0.68; superotemporal, r^2= 0.70, ($p < 0.001$). All abnormal SAP quadrants had corresponding abnormal SLO-MP quadrant.	"Macular sensitivity evaluated by SLO-MP correlates significantly with SAP paracentral VF defects."	Data suggest SLO-MP significantly correlates with SAP paracentral VF defects for macular sensitivity.
Asman 1997 (5.0)	SAP	Diagnostic	Sponsored by grants from the Herman Jrnhardt Foundation, the Inez and Joel	N = 51	Mean age 63 years, gender not	N = 23 normal subjects and N = 31 with	Humphrey 30-2 threshold, Dicon 76-point threshold test	Humphrey visual-field test perimeters	Dicon perimeters	The average of sensitivity/specificity was higher with the Humphrey vs Dicon probability maps, ($p <$ 0.05).	"The Dicon perimeter appears to yield excessive false-positive findings in normal	Data suggest Dicon perimeter results in high numbers of false postures compared to

			Carlsson's Foundation, and the Ingeborg and Ernst Ydman's Foundation, Malmo, Sweden. No COI.		specifi ed.	glauco ma or cerebro vascula r disease.				Blind spot was correctly detected as an absolute defect more often with Humphrey vs Dicon perimeter, (p < 0.012).	subjects, resulting in poor sensitivity/specifi city combinations, while at the same time failing to properly measure defect depth in scotomas."	Humphrey perimeter, thus, sensitivity and specificity is marginal and there is failure in accurately measuring defect depth in blind spots.
Bengtss on 2008 (5.0)	SAP	Diagn ostic	Sponsored by the Jarnhardt foundation, Malmo¨ University Hospital Foundation, Foundation of Visually Impaired in former Malmohus lan, Sweden, and by the Crown Princess Maragreta Foundation for the Visually Handicapped. No mention of COI.	N = 50	Mean age 54 years, gender not specifi ed.	With diabete s mellitus and differen t degrees of retinop athy.	Retinopathy stages 10–75 according to the ETDRS severity scale, visual field assessed by the 24-2 SITA standard SAP program.	Short-wavelength automated perimetry (SWAP) with short intervals.	Standard Automate d perimetry (SAP).	The average visual field threshold sensitivity decreased to 0.46 dB per ETDRS step using SAP (p = 0.001) and 0.72 dB per ETDRS step using SWAP, (p = 0.011). Mean deviation (MD) test with SAP vs SWAP, (p < 0.0001). The variability increased, with 0.06 dB per dB worsening of MD for both SAP (p = 0.04) and SWAP (p = 0.003). The median local test–retest variability for all points was 2.07 dB with SAP and 2.67 with SWAP, (p = 0.83).	"[C]hange in diabetic retinopathy can be monitored using conventional SAP, as well as SWAP, thus adding useful information to the conventionally used photographic documentation, particularly at early stages."	Data suggest similar performance between SAP and SWAP for monitoring visual field loss in diabetic retinopathy patients but a slight performance for SAP due to less test-retest variability.
Monteir o 2008 (5.0)	FDT	Diagn ostic	No mention of COI.	N=30	Mean age: 48.2 years. 12 males, 18	15 patient s with DON and 15 healthy	Patient must have a least one eye with DON documented by an abnormal SAP test result (3 adjacent abnormal points at P<.05 level or 2	C-20-5	C-20	For C-20-5 test sensitivity ranges were 40-86.7% and 53.3-100% total deviation and 20-93.3% partial deviation for C-20 test. Respective specificity	"FDT perimetry is a useful screening tool for DON in eyes with normal or only slightly	Data suggest FDT is useful for detecting DON in eyes with normal VA or slightly diminished VA.

					female s	control eyes	adjacent points with one abnormal at the p<.01 level), best-corrected VA of 20/25 or better in the study eye, above 20 years old, good cooperation for VF, spherical refraction within ±5 D, cylinder correction within ±3 D, intraocular pressure <22mmHg, reliable VF, reliable Humphrey VF with fixation loss <25%, and <25% false-positive or false-negative responses, and no patients with clinical signs of glaucomatous optic neuropathy or optic disc anomaly.			ranges were 86.7-100, 33.3-93.3, and 26.7-100. Best sensitivity/specificity ratios for 1 abnormal point depressed <.05 in C-20-5 test (86.7/86.7%), 1 point depressed <.01 in the total deviation (80.0/86.7%) and 1 point depressed <.02 in pattern deviation (80/86.7%). DON eyes showed significantly lower than normal average sensitivity in central, pericentral, and peripheral areas.	reduced visual acuity."	
Fogagnolo 2005 (5.0)	FDT	Diagnostic	No mention of COI.	N=80	Mean age: 65.7 years. 58 females, 62 females.	40 glaucomatous patients and 40 controls	Patients without FDT experience, patients with visual acuity of at least 20/25, lack of media opacities, retinal abnormalities, and systemic diseases potentially affecting visual field results	N-30	C-20	Both C-20 and N-30 best criteria to detect glaucoma was with 1 point with P<.05 at sensitivity= 87.5% for both tests and specificity of 90% and 95% for C-20 and N-30 respectively. Both tests obtained a lower sensitivity (75%) while FDT was able in all cases. Mean duration for C-20 was 60.0±33.3 seconds and 88.1±39.4 seconds for N-30.	"N-30 and C-20 screening procedures obtained similar results in well-defined glaucoma patients in terms of sensitivity and specificity. In the presence of a standard automated perimetry nasal step, diagnostic ability with both frequency-	Small Sample. Data suggest similar sensitivity and specificity between N-30 and C-20 screening methods. In the presence of a SAP nasal step, both N-30 and C-20 methods did not perform well.

										Difference in duration was significant P=.01.	doubling technology screening strategies decreased and one quarter of nasal steps went undetected."	
Leeprechanon 2007 (4.5)	FDT	Diagnostic	No mention of COI.	N=77	Mean age:60.41 years. 41 males, 36 females.	42 patients with preperimetric glaucomatous optic nerve damage and a normal SAP in 1 eye, but with contralateral SAP abnormalities, and 35 normal patients	Patients must be 40 years or older, have best-corrected visual acuity 20/40 or better, spherical refractive error of 0±6 diopters, astigmatism of 0±3 D, no more than 1+ nuclear sclerotic cataract (1-4) scale, no history of eye disease or eye trauma, and no other systemic disease or medication use that could influence color vision or the visual field. Normal patients must not have risk factors for development of glaucoma or other eye disease (positive family history, previous eye disease, previous intraocular surgery, previous ocular trauma, and retinal or neurological abnormalities that may affect the visual field).	FDT	SWAP	Normal group did significantly worse on SWAP MD (P=.0003) and SWAP TD <.05 (P=.001). Defects on the TD and PD plots were more frequent by FDP in glaucoma group, but significant for only PD at P<.01 (P=.024). Areas under curve for MD of SWAP and PSD of FDP were .74 and .67 respectively. (P=.37) Early glaucoma group performed significantly worse on FDP PSD (P=.01) and FDP PD <.05 (P=.005). FDP had a significantly higher sensitivity (72% vs. 54%; p=.02) and also in specificity (53% vs. 44%; P=.12) compared with SWAP. Agreement on defect location was moderate (k=.46). Testing time was longer for SWAP than FDP in both normal and glaucomatous groups.	"Short-wavelength automated perimetry and FDP showed similar ability to detect visual dysfunction in patients with preperimetric glaucoma. Long-term follow-up is required to define their role in predicting subsequent SAP defects."	Data suggest similar abilities to detect early glaucoma between SWAP and FDT.

Iester 2000 (4.5)	FDT	Diagnostic	No mention of COI.	N=23	Mean age: 29.1±6.3 years. 12 males, 11 females.	23 healthy subjects	Patients free of ocular disease, refractive errors ranged between +5 and -7 dopters with corrected visual acuity equal to or better than 0.7.	Short-term C-20	Long-term C-20	Average mean sensitivity of the 3 examinations of 2nd session was 30.4±1.24 dB and average short-term fluctuation of subjects was 2.16±0.5 dB. Short-term fluctuation of each point tested ranged 1.4-3.4 dB. Average mean sensitivity for all session was 32.4±1.14 dB. Average long-term fluctuation of each tested point range 2.5-4.4 dB.	"Short-term and long-term fluctuations were similar to those known to occur with the conventional threshold perimetry when they were compared with the literature data. A learning effect was also observed and should be taken into account for the clinical use of this test."	Data suggest short and long term fluctuations were similar to those known to exist in conventional threshold perimetry. There was also the observance of a learning effect which should be accounted for in clinical settings.
Iwase 2007 (4.5)	FDT	Diagnostic	No COI.	N=4000	Mean age: 57.7±11.3 years. 1281 males, 1611 females.	4000 random subjects form Tajimi City	Subjects over 40 years old with visual acuity >20/40, no ocular disease except glaucoma, and no brain diseases	C-20-1	HFA 30-2	Of 5784 eyes in 2892 participants, 5707 eyes obtained reliable results (≤33% fixation loss and ≤33% false positive errors). Significant bilateral difference was observed in 2871 right eyes and 2836 left eyes ($p<0.001$). In 5582 eyes with reliable FDT results, FDT showed 1 or more abnormal point in visual field in 502 eyes (388 of 5295 normal eyes; 19 of 116 of glaucoma subjects; 95 of 171 eyes with definite glaucoma).	"In a population-based glaucoma screening study, FDT perimetry with the C-20-1 screening protocol was reliably performed in more than 98% of participants. The sensitivity for detecting glaucomatous visual field damages, especially early damage, was not sufficiently high, whereas the	Data suggest the C-20-1 screening protocol of FDT perimetry testing performed well although sensitivity for detecting early damage related to glaucoma was not high, but specificity was good.

										Sensitivity and specificity values for detecting definitive glaucoma were 55.6% and 92.7% respectively. Predictive values in mean deviation of HFA, sensitivities were 32.1%, 48.4%, 73.7% and 96.6% for detecting definitive glaucoma with an MD of more than -2dB, an MD of -2dB or less and more than -5dB, an MD of -5dB or less and more than -8dB, and an MD of -8 dB or less, respectively.	specificity was high."	
Wall, 1991 (4.5)	SAP	Diagnostic	Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY. No mention of COI.	N=36	Mean age was 36.1 years. Gender not provided.	18 patients with pseudotumor cerebri (PTC) and 18 age-matched controls.	All patients met the modified Dandy criteria: Signs and Symptoms of increased intracranial pressure, absence of localized finings, deformity, displacement, or obstruction of ventricular system. No other cause of increased intracranial pressure (Table 1)	Humphrey perimetry test 24-2	Ring Test and Goldmann perimetry test.	Goldmann perimtery test was abnormal in 9/18 patients, the ring test detected abnormalities in 13/18 and the Humphrey perimtery showed 15/18 abnormalities. The Ring test found 16 controls to not have a defect (detecting 2/18 defects) compared to 4/18 in the Humphrey perimetry. The Humphrey test had a specificity of 78% and a sensitivity of 83% compared to the ring test with specificity of	"In conclusion, the sensitivity and specificity of the ring test is similar to differential light sensitivity automated perimetry. Most of the defects found with the ring test had a similar defect present with at least one of the other two tests. The ring test has the characteristics	Data suggest ring test (high-pass resolution perimetry) has comparable sensitivity and specificity to Humphrey automated perimetry in pseudotumor cerebri patients.

										89% and a sensitivity of 89%.	of an excellent screening test for patients with optic neuropathies"	
Wang, 2012 (4.5)	SAP	Diagnostic	Supported by the Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre. No COI.	N=6696 eyes in 3586 patients.	Mean age was 66 years. No mention of gender.	6696 eyes in 3586 patients with suspicious/diagnosed glaucoma.	Normal eyes (Brusini stage 0) and defective eyes (Brusini stage 2-3) were analyzed from the sample.	SITA 24-2	SITA 30-2	10, 20, 30, and 54 test locations were used for the defective group. Sensitivity for the test locations were 70.2%, 91.0%, 95.5%, and 97.4%, respectively. Specificity was 96.0%, 86.2%, 76.3%, and 58.6% respectively. The estimated test time in minutes for each number of testing location was: 0.8-0.9, 1.6-1.8, 2.4-2.7, and 4.3-4.9, respectively. With increasing number of test locations the mean deviation became less negative and the pattern standard deviation became less positive (p<0.001).	"Good diagnostic performance can be obtained with optimized subsets of the standard 24-2 test pattern that can provide substantial savings in test times."	Data suggest subtests can provide both good diagnostic performance as well as saving time.
Patel, 2007 (4.5)	SAP	Diagnostic	Supported in part by the National Institutes of Health, Bethesda, Maryland (grant nos.: RO1-EY013178-	N=50	Mean age was 58.8 years. 18 males, 32	50 glaucomatous eyes in 50 patients.	Subjects had a best-corrected visual acuity of >20/40 and had a SITA VF defect.	Matrix Perimetry (Matrix VF)	Swedish interactive thresholding algorithm (SITA)	The matrix test was significantly shorted than the SITA test; 319.5 sec vs. 357.0 sec (p=0.0002). All subjects showed visual field defects on the SITA test, but 18 subjects (36%) did not show any	"The Matrix examination did not detect 36% of abnormal SITA fields. Matrix field defects were smaller and deeper than those appearing	Data suggest comparative accuracy of matrix perimetry inferior to SITA perimetry as abnormal field detection was missed in

			5, P30-EY008098); the Eye and Ear Foundation, Pittsburgh, Pennsylvania; and an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York. COI: Dr Schuman receives royalties for intellectual property licensed by Massachusetts Institute of Technology to Carl Zeiss Meditec, Inc.		female s.					defects on the Matrix test. The mean deviation was significantly different between the SITA and matrix groups as well; -4.14 vs. -5.34 (p=0.03).	in SITA perimetry."	greather than 1/3 of abnormal fields detected by SITA.
Mutlukan, 1994 (4.5)	SAP	Diagnostic	The author was supported financially by The International Glaucoma Association, The Royal National Institute for the Blind, The Ross Foundation of Prevention of	N=25	Mean age was 68 years. 13 males, 12 females	25 glaucomatous eyes in 25 perimetrically experienced patients.	All patients had 6/6, N5, or better visual acuity. None had non-glaucomatous ocular disorders or systemic disease.	Computer-Assited moving eye campimeter (CAMEC) using dark stimuli.	Humphrey visual field analyzer 30-2.	All four contrasts of the CAMEC dark stimuli test showed the abnormal areas in the central visual field of the glaucomatous eyes. The highest contrast (-76% black) had a specificity of 93%, and a sensitivity of 49%. The lowest contrast (-10% light gray) had a specificity of 86% and a sensitivity of 35%.	"In conclusion, dark stimuli allowed the delineation between glaucomatous field defects and the normal regions in the central visual field."	Data suggest that testing dark stimuli on a bright background identified glaucoma related defects and normal areas of the central visual field.

			Blindness, and McCunn Trust. No mention of COI.									
Katz 1995 (4.5)	SAP	Diagnostic	Sponsored by grants, and RR04060 from the National Institutes of Health, Bethesda, Maryland. No mention of COI.	N = 543	Mean age 57.0 ± 13.6, gender not specified.	With intraocular pressure and glaucoma (plus 41 normal subjects).	Intraocular pressures below 22 mm Hg.	The Glaucoma Hemifield Test.	Single and Repeated Visual Field Testing.	The average difference in MD between the 1st and 2nd fields was 0.5 dB (p = 0.28) for normal group, -0.5 dB (p < 0.001) for ocular hypertension, and – 1.0 dB (p < 0.01) for those with glaucoma. 17% of normal, 16% with ocular hypertension, and 18% of subjects with glaucoma had 2 unreliable fields (false-negative or false-positive rate ≥33%, or fixation loss rate ≥20%.	"Although mere is concordance of Glaucoma Hemifield Test results on consecutive testing, there is enough disagreement to result in improved specificity from the use of a second test in a clinical trial setting."	Data suggest repeat testing on the glaucoma Humphrey Field Test improves specificity.
Bergin 2011 (4.5)	SAP	Diagnostic	Sponsored by the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology At Moorfields Eye Hospital NHS Foundation	N = 6	Age range 21 to 29 years, gender not specified.	Healthy volunteers	Optic disc rim area classified as within normal limits and intraocular pressure < 21 mm Hg. Visual acuity for each observer was 20/17 (6/5) or better.	SITA-Standard 24-2 Program 24-2 ZEST Program 24- 2 ASTA Program Weighted Binary Search Program.	Moorfields MDT, Weighted Binary Search Program.	With a white opacity filter (WOF) greater than grade 4, SAP (p < 0.001), FDT (p < 0.003), and FDF (p < 0.001) significantly affected; MDT TMS values did not have a significant association with the density of WOF filter used (p = 0.73; ANOVA). MDT threshold show little to no association with IOS (slope = -	"The Moorfields MDT shows greater resilience to the effects of additional straylight compared with SAP, FDT, or FDF."	Small sample, N = 6. Data suggest MDT is less influenced by IOS than SAP, FDI or FDF.

			Trust and the UCL Institute of Ophthalmology (DFGH). No COI.							0.01), SAP weak association with IOS (p = 0.02), strong association with FDT, (p < 0.01) and FDF, (p < 0.01).		
Landers 2007 (4.5)	SAP	Diagnostic	No sponsorship and no COI.	N = 63	Average age 60 years, 29 male and 34 female.	With suspected glaucoma, ocular hypertension, open angle glaucoma.	Visual acuity of 6/12 or better, IOP, 21 mm Hg.	Humphrey Field Analyzer II (HFA), used to perform central 24-2 full threshold visual field tests.	Medmont Automated Perimeter (MAP) visual fields, used to perform central 30° threshold tests.	There was an association when MD is compared to AD, (p < 0.001). MD and PSD results strongly correlated with AD and PD, (p-value not given).	"The AD and PD results obtained from the MAP may be substituted for the MD and PSD results from the HFA after appropriate conversion."	Data suggest comparable performance efficacy between MAP and HFA.
Kwon 1998 (4.5)	SAP	Diagnostic	Sponsored by Research to Prevent Blindness, Inc, New York, New York, and the Alcon Research Institute Award, Fort Worth, Texas (Dr Caprioli). No mention of COI.	N = 64	Mean age for Humphrey and Octopus groups: 35.5 ± 6.6 and 34.6 ± 5.5, gender not specified.	No history of ocular disease.	Corrected Snellen visual acuity of at least 20/25, and astigmatism of less than 3 diopters.	Humphrey Visual Field Analyzer, white-on-white and blue-on-yellow perimetry (N = 31).	Octopus perimeter, white-on-white and blue-on-yellow perimetry (N = 33).	Humphrey perimeter, mean sensitivity declined with eccentricity for both blue-on-yellow (p < 0.001 and p < 0.001 for Octopus group) and white-on-white (p < 0.001 and p < 0.001 for Octopus group) perimetry. The long-term fluctuation for blue-on-yellow vs white-on-white, (p < 0.001) / the short-term fluctuation for blue-on-yellow vs white-on-white, (p < 0.001). The intersubjective	"Long-term fluctuation and short-term fluctuation of blue-on-yellow perimetry are greater than those of white-on-white perimetry in normal subjects."	Data suggest in normal individuals both long and short term fluctuations of blue-on-yellow perimetry are larger than white-on-white perimetry.

										variability was significantly greater in blue-on-yellow (13.2 6 2.8 dB^2) vs white-on-white perimetry (4.25 6 1.13 dB^2; $p < .001$) and similar results found with the Octopus perimeter.		
Hoffmann 2006 (4.5)	SAP	Diagnostic	Sponsored by a research fellowship from Deutsche Forschungsgemeinschaft Ho 3277/1 to 1 (E.M.H.), NIH grant EY08208 (P.A.S.), and NIH grant EY11008 (L.M.Z.). Drs Weinreb and Zangwill have received research support from Carl Zeiss Meditec. Dr Sample has received research support (instruments) from Carl Zeiss Meditec, Welch Allyn, and Haag Streit.	N = 245	Mean age was 66.8 ± 12.9 years, gender not specified.	With glaucomatous optic neuropathy in at least one eye defined by masked stereophoto review included.	Reliable fields had less than 25% false positives, 25% false negatives, and 25% fixation losses Corrected visual acuity of 20/40 or better, a spherical refraction within ± 5.0 diopters, and cylinder correction within ± 3.0 diopters.	2 SAP visual fields using the 24 to 2 program.	SITA thresholding algorithm of the Humphrey Field Analyzer.	In those with a normal superior hemifield in the worse eye, 75% of the normal eye had normal VF. In those with a normal inferior hemifield in the worse eye, 69% of the better eye had normal superior hemifield. The percentage of correspondence by hemifield location for (superior-superior) / (inferior-inferior) / (superior-inferior) / and (inferior-superior) was: 53% / 62% / 45% / and 55%.	"Patterns of visual field loss between eyes often corresponded within the same VF hemifield (superior-superior, inferior-inferior) as well as between opposite hemifields (inferior-superior), although opposite hemifield correspondence was less common."	Data suggest moderate correlation between patters of visual field loss and the same VF hemifield as well as opposite hemifields with opposite side hemifield correlation was less common. Also, more correlation was seen in eyes showing more progressive ocular defects.

Bizios 2011 (4.5)	SAP	Diagnostic	Sponsored by grants K2005-74X-1426-13A and K2005-74BI-15375-01A from the Swedish research Council, by the foundation of Crown Princess Margareta for visually handicapped, by the foundation for visually impaired in the former Malmöhus län, and by the Järnhardt foundation. No COI.	N = 260	Mean age 64.65 ± 8.11 for heathy group and 73.36 ± 7.81, 115 male and 145 female.	Healthy individuals (N = 125) and those with glaucomatous optic nerve head (N = 135).	Visual acuity ≥ 0.5 and refractive error ≥ 5 dioptres (D) sphere and < 3 D cylinder, intraocular pressure measured by a Goldmann applanation tonometer.	Humphrey 24-2 SITA standard SAP	Stratus OCT tests	Mean deviation of the SAP visual fields, the glaucoma group consisted of 49 patients (ca 36%) with early, 32 patients (ca 24%) with moderate and 54 patients (ca 40%) with advanced glaucomatous visual field loss. The fused OCT and the combined fused OCT and SAP data respectively provided almost identical AROC values of 0.978. For SAP GHT accuracy of 86.92%.	"Compared to the use of SAP parameters, input from the combination of fused OCT and SAP parameters, and from fused OCT data, significantly increased the performance of ANNs."	Data suggest combining both OCT and SAP (fused OCT and SAP parameters; and fused OCT data) may help to improve ANN accuracy in diagnosing glaucoma.
Bosworth 1998 (4.5)	SAP	Diagnostic	Sponsored by grant from the National Eye Institution, Bethesda, MD, and by the Samuel E. McLaughlin Foundation of Canada, Toronto, Ontario (Dr. Gupta). No mention of COI.	N = 105	Mean age 66.3 ± 11.18 years, gender not specified.	With primary open angle glaucoma (N = 21), suspected glaucoma (N = 28), OHT (N = 18)	Open angles cup-disc ration asymmetry between the 2 eyes of 0.2 mm or more, loss determined by visual field analysis, corrected pattern SDs outside the 95% CI or glaucoma hemifield test results outside the 99% confidence limits.	Motion automated perimetry (MAP), using RDKs in a direction discrimination paradigm.	Separated full-field foveally centered RDK and standard automated perimetry	Perimetric motion thresholds significantly distinguish the groups, ($p \leq 0.001$) vs foveally centered motion test motion test was unable to separate them, ($p \leq 0.32$). 90.5% with glaucoma, 39.3% with suspected glaucoma, 27.8% with ocular hypertension, and 5.3% of the normal subjects had abnormal	"Motion automated perimetry identifies visual field defects in patients who already show standard visual field loss as was as in a moderate percentage of those with suspected glaucoma and	Data suggest motion automated perimetry may be beneficial in identifying early glaucoma in patients with suspected glaucoma and ocular hypertension as this technique does positively

						and normal controls, (N = 38).				results on motion automated perimetry testing.	ocular hypertension, indicating that the testing of discrete locations might be necessary for increase diagnostic utility."	identify visual field defects in those who already present with standard visual field loss.
Turpin, 2007 (4.5)	SAP	Diagnostic	Supported by an Australian Research Council QEII research fellowship (AT). The project was supported by Australian Research Council Discovery Project Grant DP0450820. No mention of COI.	N= 428	Mean age was 52.3 years. No mention of gender.	265 control patients and 163 patients with glaucoma.	Glaucoma	Zippy Estimation by Sequential Testing (ZEST)	Full Threshold test (FT)	If sensitivity was stable from test to retest, the retest algorithms were faster by one presentation per location and were significantly more accurate ($p<0.05$). Retest minimizing uncertainty (REMU), which combined the suprathreshold and ZEST procedures, was faster and more accurate than other procedures from test to retest.	"The obvious approaches to retest, such as continuing the previous procedure or seeding with previous values, have limitations when sensitivity changes between tests. REMU, however, significantly improves both accuracy and precision of testing and displays minimal bias, even when fields change and patients make errors."	Data suggest REMU improves accuracy and precision in liew of changing fields, patient errors and minimal bias.
Rowe, 2010 (4.5)	SAP	Diagnostic	No mention of sponsorship. Potential COI: The Damato campimeter	N=100	Mean age was 62.8 years.	100 patients (197 eyes) identifi	"Glaucoma suspects were defined as patients with evidence of raised intraocular pressure but with no	Damato Campimetry	Humphrey automated perimetry	178 eyes were tested in both methods. 94 eyes (53%) had defects detected by both tests, 45 (25.5%) had normal	"We found Damato campimetry to be a useful portable device to assess	Data suggest Damato campimetry when compared to Humphrey

			used in this study was provided by Professor Bertil Damato, St Pauls Eye Unit, Royal Liverpool and Broadgreen University Hospitals, Liverpool, UK.		38 males, 62 females.	ed randomly from those on a waiting list for a visual field assessment.	prior evidence of optic disc or visual field defect."			results on both tests, 22 (12%) had normal results on the Damato test and defects on the Humphrey test, and 17 (9.5%) had a normal result on the Humphrey test and a defect on the Damato test. The sensitivity for Damato in comparison with the Humphrey test was 81% and the specificity was 72%.	the visual field, with an optimal sensitivity of 81% and a specificity of 72% based on comparison with a Humphrey 24-2 programme."	perimetry has a sensitivity of 81% and specificity of 72% The Damato compimetry is portable and may be useful in areas where sophisticated testing does not exist.
Roggen, 2001 (4.5)	SAP	Diagnostic	No mention of sponsorship or COI.	N=41	Mean age was 57.1 years. 13 males, 28 females.	19 normal subjects and 22 glaucoma patients.	"The diagnosis of glaucoma was based on the presence of at least two out of three of the following criteria: intra-ocular pressure before treatment s 22 mmHg, glaucomatous disc-excavation (cup/disc-ratio s 0.6), obvious visual field defect on previous visual field examinations."	FASTPAC (FP)	SITA Standard (SS) and SITA Fast (SF)	The FASTPAC test took an average of 8.1 minutes for normal subjects compared to the SITA standard at 6.1 min ($p<0.0001$) and compared to the SITA fast, 3.8 min ($p<0.0001$). For glaucoma subjects it was 10.6 min vs. 8.8 ($p=0.008$), and 10.6 vs. 5.5 ($p<0.0001$). There were no significant differences between SITA fast and FASTPAC for the mean deviation for both normal subjects and glaucoma patients ($p>0.05$).	"The SITA strategy causes a significant test time reduction without decreasing the test quality."	Data suggest SITA FAST takes approximately half as much time as FAST PAC although with increasing VF loss, time increases. Also, SITA FAST appears to maintain test quality while decreasing test time.
Goren 2013 (4.5)	SAP	Diagnostic	Sponsored by NEI EY19674 (SD) and The Legacy Good Samaritan	N = 209	Age range between 38 and 91	With high-risk ocular hyperte	Early to moderate ocular hypertension or diagnosis of glaucoma.	Retinal nerve fiber layer thickness (RNFLT) using three	SAP 24-2 test pattern and SITA-standard	The correlation with SLP was of intermediate strength, ($r = 0.40$) and weakest correlation	"Average RNFLT estimated from SDOCT predicts SAP status significantly	Data suggests that the coverage RNFLT from SDOCT is a significantly

			Foundation. SD was involved in a clinical training using the Spectralis OCT. The funding organization had no role in design or conduct of this research.		years, gender not specified.	nsion or a diagnosis of glaucoma.		techniques: CSLT, SDOCT and SLP.	threshold algorithm.	was found with CSLT, (r = 0.13). CSLT in models that included all three RNFLT measurements (p = 0.50), or bivariate models when included with SDOCT (p = 0.51) or SLP (p = 0.22).	better than average RNFLT estimated from SLP or CSLT."	better predictor of SAP than average RNFLT from either SLAP or CSLT.
Martinez, 1994 (4.5)	SAP	Diagnostic	No mention of industry sponsorship or COI.	N=107	Mean age was 62.5 years. No mention of gender.	34 patients with primary open-angle glaucoma, 37 glaucoma suspect patients, and 36 normal subjects.	Glaucoma: intraocular pressure exceeding 24 mmHG, abnormal optic disk, disk hemorrhages, localized rim defects.	Frisen Ring – High pass resolution perimetry	Humphrey perimeter	Both tests identified 19/34 (56%) of glaucoma eyes. High-pass resolution perimetry determined that 34/36 (94%) normal eyes were not outside normal limits. The Humphrey perimeter test determined that all 36 normal eyes were normal. Lastly, high-pass resolution perimetry determined 12/37 (32%) glaucoma suspect eyes were outside normal limits compared to 3/37 (8%) by the Humphrey Perimeter.	"With the Glaucoma Hemifield Test, high-pass resolution perimetry was comparable to standard perimetry in sensitivity and specificity, and identified a slightly higher percentage of patients at risk for glaucoma as abnormal. These results suggest that high-pass resolution perimetry should continue to be explored as an alternative to standard perimetry for the diagnosis and	Data suggest comparable performance between high pass resolution perimetry and SAP but high pass resolution perimetry identified more at risk for glaucoma patients.

											treatment of glaucoma."	
Medeiros 2004 (4.5)	FDT	Diagnostic	No mention of COI.	N=105	Mean age of Converters: 66.2±11.0 years. Mean age of Nonconverters: 58.3±12.5 years. 48 males, 57 females.	105 eyes of 105 glaucomatous suspect patients	Subjects had to have best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 diopters and cylinder correction within ±3.0 dipoters, and open-angles in gonioscopy. Could not have secondary cause of high intraocular pressure, other intraocular eye disease, other diseases possibly affecting visual field, or a history of refractive surgery. Must have Intraocular pressure higher ≥ 23 mmHg or glaucomatous optic neuropathy by stereophotograph assessment	FDT	SAP	Seventeen patients showed a change from normal SAP visual field to a visual field with a confirmed defect. Abnormal FDT exams at baseline predicted SAP visual field conversion in both univariate and multivariate models. Six of 14 converters developed FDT abnormalities. Fifty-nine percent of converters had FDT abnormalities that preceded SAP visual field loss by as much as 4 years. Twenty-one of the 88 nonconverters had repeatable FDT examination during follow-up. A significantly higher proportion of converters had repeatable abnormal FDT exams compared to nonconverters. (P<.001)	"Functional abnormalities detected by FDT perimetry were predictive of the future onset and location of SAP visual field loss among glaucoma suspect patients."	Data suggest FDT in suspected glaucoma patients correlated to SAP VF loss and was predictive of future onset.
Jansonius 2009 (4.0)	FDT	Diagnostic	No mention of COI.	N=70	Mean age: 58±12 years. 32 males, 38	70 glaucoma suspect patients	Patients with an HFA visual field was considered reliable if fixation losses were ≤ 20%, false-positives ≤ 10% and false-negatives ≤ 10%. No	SAP	GDx FDT	Of 70 glaucoma suspect patients, 3 converted on FDT, 14 on GDx, and 6 on SAP. These 3 proportions are significantly different (p=0.002). GDx versus	"The most frequent finding after a 4-year follow-up was conversion on GDx."	Data suggest GDX nerve fibre had the most conversions after 4 years compared to SAP and FDT

					female s.		glaucomatous visual field defects in either eye.			SAP (p=.033), GDx versus FDT (p=.002), and FDT versus SAP (p=.256) were the proportions.		
Schiefer, 2003 (4.0)	SAP	Diagnostic	Supported by MSD Sharp & Dohne GmbH, Haar, Germany, and Allergan Inc, Irvine, Calif. No mention of COI.	N=66	Age rang was 14-85 years. 32 males, 34 female s.	66 eyes in 66 patient s with suspect ed glauco ma.	Curcumscribed glaucomatous morphotic lesions with or without corresponding localized glaucomatous VFDs. Central visual acuity equal to or better than 10/20.	Fundus-Oriented perimetry (FOP)- Using the Tuebingen Computer Campimeter	Conventional automated perimetry (CAP)- Using Humphrey Field Analyzer (HFA 30-2)	In 23 patients, both tests showed normal findings. 27 patients had pathological findings in both tests. In 15 patients with normal visual fields according to HFA 30-2, the FOP revealed early glaucomatous functional damage. Only 1 patient had pathological HFA results where FOP results were normal.	"Fundus-oriented perimetry that uses individual condensed test grids significantly increases the detection rate of glaucomatous VFDs in morphologically conspicuous areas compared with CAP using equidistant targeting arrangements."	Data suggest FOP with condensed grads is superior to CAP for the identification of VFDs associated with glaucomatous areas where morphology is abnormal.
Wild, 2005 (4.0)	SAP	Diagnostic	No mention of sponsorship. No author has a proprietary interest in the Humphrey Field Analyzer. Dr Wild has received honoraria from Carl Zeiss Meditec for lectures.	N=35	Mean age was 60.5 years. No mention of gender.	22 patient s with ocular hyperte nsion (OHT). 13 patient s with open-angle glauco ma (OAG)	The classification of the severity of glaucoma was graded in terms of Hodapp et al. Also, visual acuity of 6/9 or better in either eye, a distance refractive error of _5 diopters (D) mean sphere and _2.5 D cylinder, lenticular changes not greater than NC2.0, NO2.0, C1.0, or P1.0 by the Lens Opacities Classification System III	Short-wavelength automated perimetry (SWAP)	Standard automated perimetry (SAP)	The mean deviation (MD) improved for all patients in both eyes occurred from visits 1 and 2 (P<0.001) and 2 and 3 (p=0.021). Other visits were not significant. The mean short-term fluctuation (SF) improved over all 5 visits (p<0.001), and Pattern Standard Deviation (PSD) varied between the OAG and OHT groups. It was the most postivei for the OAG groups with a mean difference of 3.56	"Care should be taken to ensure that, during the initial examinations, apparent field loss with SWAP in patients exhibiting a normal field by SAP is not the result of inexperience in SWAP. Apparently deeper or wider field loss in the initial	Data suggest there is a learning effect in SWAP and some patients may demonstrate VF loss initially due to inexperience. This is not as prevalent in SAP.

										and 4.58 for the right and left eye respectively. The ratio across the 2 eyes indicated that the learning effect was greater in the periphery with OAG by 20% and 25% in the patients with OHT who were experienced in SAP and in the region of 30% to 50% in those inexperienced with SAP.	examinations with SWAP compared with that exhibited by SAP in OAG also may arise from inexperience in SWAP."	
Wall, 2008 (4.0)	SAP	Diagnostic	Supported by a VA Merit Review Grant, and by an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness, New York, NY. No mention of COI.	N=180	Mean age was 62.4 years. 67 males and 113 females.	120 Patients with glaucoma and 60 control patients.	Glaucomatous visual field defects with a mean deviation of 0 to _20 dB on standard automated perimetry.	24-2 SITA Standard Test using the response time window procedure (RTW)	24-2 Full Threshold (FT) perimetric test using the blank presentation method (BP)	Glaucoma patients did not have significant differences comparing SITA vs. BP for false positive rates at both visits (1.99% vs. 1.99%). The overall difference between the RTW and BP tests were significant for glaucoma patients who had false positive responses on both SITA and FT tests; 3.58% vs. 7.72% (p=0.001). However glaucoma patients had higher mean false negative rates (4.11% vs. 1.69% (p=0.001))	"In summary, FP responses using the RTW technique underestimates the values found using BP. Although FP rates greater than 10% identify subjects with excessively liberal response criteria, FN in areas of damage and fixation losses are poor indexes of patient performance and should be replaced by use of an eye tracking system."	Data suggest RTW appears to underestimate false positives compared to BP method.

Salvetat, 2007 (4.0)	SAP	Diagnostic	No mention of sponsorship. No COI.	N= 75	Mean age was 52.9 years. 33 males, 38 females.	75 consecutive healthy adult subjects.	Healthy adult volunteers	Rarebit Perimetry (RBP)	Standard Automated Perimetry (SAP)	The mean hit rate (MHR) was 91%. The mean miss rate (MMR) ranged from 4.0% to 13.8%. No significant learning effect was found. Mean test time for RBP was 268 seconds, and the mean SAP test time was 433 seconds. No significant learning effect was observed. 28 patients underwent 4 repeated RBP tests. There were no significant differences for MHR or MMR across the 4 tests. Test-retest variability (TRV) ranged between 4.9% and 11.4% (p=0.001).	"RBP is a rapid and easily accessible VF test. RBP testing did not show a significant LE; however, inter- and intrasubject variability were consistent. Blur and media opacities may give false-positive results in RBP, especially in the central VF, and should be considered."	Data suggest rarebit perimetry is simple and fast without showing a significant learning effect but consideration needs to be given to central VF false positives.
Nakatani, 2012 (4.0)	SAP	Diagnostic	Supported by a Grant-in-Aid for scientific Research (20592034) from the Japan Society for the Promotion of Science. No mention of COI.	N=126	Mean age for 60 normal participants was 45.3 years, with 37 males and 23 females. Gender and age	60 Normal Controls, 37 with Pre-perimetric glaucoma (PPG), and 29 early stage of primary open-angle	Patients had a best correct visual acuity (BCVA) ≥1. No other pathologies other than glaucoma.	Automated Fundus-oriented small-target perimetry	Standard Automated Perimetry - (SAP)	The rate of negative response was significantly lower for the PPG group vs. the POAG group (9.2% vs. 21.2% (p<0.0001). The SAP mean deviation for PPG vs. POAG was 0.25 vs. -1.45 (p<0.0001) and the SAP-pattern standard deviation was 1.70 vs. 3.69 (p<0.0001). The mean test time for the fundus-oriented small-target perimetry was 13.8 min per eye.	"Fundus-oriented small-target perimetry is useful in detecting visual field abnormalities in PPG."	The data suggest automated fundus-oriented small-target perimetry is useful in detecting PPG via visual field defects before SAP can detect them.

					were not provided for the glaucoma patients (n=66).	glaucoma (POAG)						
Bengtsson 2006 (4.0)	SAP	Diagnostic	Sponsored by the Swedish Research Council; Carl Zeiss Meditec, Dublin, California; and funds administered by Malmö University Hospital, Malmö, Sweden. No mention of COI.	N = 101	Mean age of 70 years, 33 male and 68 female.	With ocular hypertension and manifest glaucoma.	Ocular hypertension of more than 24 mmHg. Manifest glaucoma, with no more than slight cataract, all lens grading ≤ 2. Threshold sensitivity at the p < 5% and the p < 2% levels in the pattern deviation probability maps.	Short-wavelength automated perimetry (SWAP) Lengthier full-threshold (SWAP) Standard automated perimetry (SAP).	Swedish interactive threshold algorithm (SITA).	The median number at the p < 5% limit was 9 for both full-threshold SWAP and SITA SWAP; 7 for SITA Fast SAP (p = 0.27); and 5, 5, and 4, respectively, at the p < 2% level (p = 0.18). The median false-positive frequency was 1% for SITA SWAP, 0% for full-threshold SWAP, and 3% for SITA Fast SAP. Full-threshold SWAP identified 1 or more cluster in 65% of all eyes, ITA SWAP detected clusters in 66% (95% CI, 57–76), and SITA Fast SAP detected clusters in 64% (95% CI, 55-74).	"The SITA SWAP identified at least as much glaucomatous visual field loss as the older full-threshold SWAP, although test time was considerably reduced."	Data suggest comparable performance between all 3 tests (SITA, SWAT & SAP) for the detection of early glaucoma limit the testing time was shortened with SITA SWAP.
Demirel, 2009 (2.5)	SAP											Data suggest there are patterns of visual field fundings in

												classification trees which are predictive for progressive glaucomatous optic neuropathy (pGON)
Bourne, 2007 (3.0)	SAP											Data suggest SITA and FT testing should be done within a short time (i.e. same day) to minimize data misinterpretation. Also, the glaucoma hemfield test (GHI) was more likely to be abnormal from SITA vs. FT.
Kamantigue, 2006 (3.5)	SAP											Data suggest C-20-1 FDT predictive of glaucoma in some patients but has a high false positive rate.
Johnson, 2012 (3.5)	SAP											Data suggest approximately twice as many false negatives resulted from FULL vs. SITA.
Hong, 1990 (3.5)	SAP											Data suggest comparable performance

												efficacy between Humphrey screening and Humphrey threshold for detection of glaucomatous usual field defects.
Bass, 2000 (3.5)	SAP											Small Sample (N=11) Data suggest comparable results between Humphrey and Dicon but Dicon took less time to perform in patients with well-defined lessons.
Bernardi, 2006 (3.5)	SAP											Data suggest increasing age decreases critical fusion frequency and that thicker perimetry is associated with learning in healthy individuals. Also study suggests a fairly high short term fluctuation is typical.
Mohammadi, 2004 (3.5)	SAP											Data suggest thinning SLP RNFL measurement were predictive

												for future visual loss independent of IOP, CCP, age, SAP PSD and vertical disk ratio.
Reus, 2003 (3.5)	SAP											Data suggest glaucoma patients with RNFL measurements which are mild to moderate, are highly correlated with DGx VCC measurements but not for normal healthy eyes. However, in severe glaucoma disease, SAP may be better.
Nowomiejska, 2009 (3.5)	SAP											Data suggest both SAP and SKP should be used to diagnose the variety of visual field defects in ONHD.
Zhu, 2010 (3.5)	SAP											Data suggest BRPB resulted in a statistically significant method to describe and relate function and structure in glaucoma compared to standard linear

												regression modeling.
Oleszczuk, 2012 (3.5)	SAP											Small Sample. Data suggest MDT less sensitive to additional straylight when compared to SAP or PP.
Wishart, 1993 (3.5)	SAP											Data suggest OKP is not useful for glaucoma screening due to low sensitivity and specificity but can detect advanced visual field loss.
Wall, 2000 (3.5)	SAP											Data suggest SITA standard had higher sensitivity at least in hemianopias & optic neuropathies and is comparable to FTT for funding visual loss.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Population Description	Case Definition	Investigative Test	Gold Standard/Comparative Test	Results:	Conclusion:	Comments:
Lee 2003 (6.0)	Manual Studies	Diagnostic/Prospective	No sponsorship or COI.	N=84	82 males, 2 females; mean age 66±12	All patients who were presented to complete a Visual field test.	All visual field test examiners were blinded to any previous diagnoses or visual field defects	Laster pointer visual field testing (LVF) and Confrontational visual field testing (CVF).	The Humphrey Visual Field Test(HVF)	Sensitivity LVF & CVF with defects in agreement with HVF (95% CI): LVF 0.73 (0.59-0.81), CVF 0.31 (0.17-0.38). Specificity of LVF and CVF in agreement with HVF (95% CI): LVF 0.82 (0.77-0.95), CVF 0.99 (0.92-1.00). Testing times: CVF 0.5 min, LVF 1.5 min, HVF 8.0 min.	"[W]e have demonstrated that LVF testing, performed using a commercially available laser pointer projected onto a tangent screen, and is significantly more sensitive than confrontation visual field testing with fingers in screening for HVF visual field defects in this cohort."	Data suggest LVF was significantly more sensitive than confrontation testing.
Wall 2010 (5.0)	Manual Studies	Diagnostic/RCT	Study supported by a Veteran Affairs Merit Review Grant and an unrestricted grant to the Departme	N=180	Control: 38 males, 22 females; mean age 57.2±7.9. Glaucoma group: No mention of gender;	N=120 patients with Glaucoma. N=60 Healthy participants.	Glaucoma patients enrolled with primary, secondary, or normal tension glaucoma with no other disease. Control patients had no history of eye disease, diabetes,	Comparing Effective dynamic range (EDR) of 4 perimetry 5 retests including: SAP III, SAP V, motion perimetry and Matrix perimetry.	All perimetry tests at baseline.	SAP III and SAP V tests had linear sensitivity of about 20 dB. Sap III had largest number of 0 dB trials, therefore the smallest dynamic range, while SAP V had largest with fewest 0 dB trials. Comparing least	"[S]tandard automated perimetry (SAP) III, motion perimetry, and matrix perimetry have similar effective dynamic range (EDR), but their associations are complex. SAP V stimuli may	Data would suggest that the SAP III range is far less than tested limits. Motion perimetry and matrix perimetry have complex associations even if EDR's are similar.

			nt of Ophthalmology from Research to Prevent Blindness.		mean age 64.9±9.5		stigmatism, or refractive error.			amount of dicsrimnable steps, SAP V appears to have greatest range.	therefore be useful in testing glaucoma patients with moderate to severe visual field damage."	
Morales 2000 (5.0)	Manual Studies	Diagnostic/Prospective	No sponsorship, one of the authors invented the Tendency-Oriented Perimetryalgorithm and has propriety interests in the corresponding software.	N=57	No mention of gender; age Range (20-70)	N=42 individuals with a variety of visual field abnormalities. N=15 individuals with normal ocular exam results.	Most of visual field abnormalities consisted of either glaucoma (N=12), advanced glaucoma (N=10). Exclusion criteria included multiple ocular pathologies, or vision worse than 20/40.	Tendency-Oriented Perimetry (TOP) perimetrc program.	The Octupus 32 Threshold Perimetry visual field test. (32)	Mean Sensitivity TOP v 32 (dB): 20.5 vs 19.45 (p<0.001). Mean deviation Top vs 32 (dB): 6.31 vs 7.36 (p<0.001). Time of test Top vs 32 (min): 4.05±0.55 vs 14.65±3.75.	"The TOP algorithm is the fastest strategy reported in the current literature. It is capable of obtaining a full estimate of the visual field threshold in the 76 points commonly tested in glaucoma and in different pathological conditions of the visual field."	Data suggests that TOP was four times faster than octopus program 32 and successful in the detection of visual field abnormalities.
Alniemi 2013 (5.0)	Manual Studies	Diagnostic/Prospective	No mention of sponsorship or COI.	N=20 patients	10 males, 10 females; mean Age 64±16	All patients were preoperatively diagnosed with blepharoptosis,	Blepharoptosis was defined as a marginal reflex distance of <+2.5 mm.INdividuals with glaucoma, neurologic disease, or visual field defects were excluded.	Humphrey automated perimetry visual field testing	Goldman manual perimetry visual field testing	Bilateral mean examination time, Goldmann vs Humphery: 12.1±2.9 vs 18.5±3.8, difference of 6.4 min (95% CI 4.5-8.3) (p<0.001). Seventy percent (14/20) patients preferred	"In comparison visual field testing techniques, Goldmann and Humphrey visual field techniques were comparable in their ability to detect superior	Data suggest that Goldmann and Humphery are comparable in terms of sensitivity for the detection of Blepharoptosis visual field defects but Goldmann Perimetry is

										Goldmann over Humphrey, chi quared test reveal (p=0.0253).	visual field loss due to ptosis. Goldmann testing offers advantages in examination time and patient preference."	better than Humphery for Blepharoptosis detection, takes less time and is the patient preferred method.
Kerr 2010 (5.0)	Manual Studies	Diagnostic/Randomized prospective	No sponsorship or COI.	N=163 patients	72 males, 91 females; mean age 58.9±16.3.	Study participants were consecutively recruited from a special neurooptahmology clinic at University of Auckland.	Inclusion criteria were a best correlated visual acuity of 6/60, and able to perform visual tests. Excluded if false-negatives or false positives were above 33%.	7 confrontation Visual field tests; Finger counting, finger comparison, red comparison, static finger wiggle, kinetic finger wiggle, Kinetic 5 mm red target.	Automated Humphrey visual field testing	Mean sensitivity of 7 confrontational tests, 52.2±%. Red comparison test highest sensitivity of 71% for detecting anterior visual pathways. Kinetic red target (90.9%) was most sensitive in detecting posterior lesions.	"The present findings suggest that the sensitivity of confrontation testing may be enhanced by combining 2 tests. However, even the best combination of tests will fail to detect more than 20% of lesions."	Data suggest as a standalone test confrontation visual field testing is a poor screening test but combinations of confrontation tests increase the sensitivity.
Jennings 1991 (4.5)	Manual Studies	Diagnostic/randomized prospective	No sponsorship or COI.	N=176 patients	113 males, 239 females; Mean age 50.7 (11-86)	All study participants were taken from the Vascular Clinic at the Southern College of Optometry.	All patients demonstrated any type of disease that would affect their visual field. Patients were put into 1 of 8 programs that matched their disease, (i.e. glaucoma,	The Marco MT-336 automated perimeter	Goldmann Perimetry visual field testing	Marco vs Goldmanns level of agreement chi-squared testing for all 8 groups: Glaucoma Screen X^2=1014.0 ($p<10^{-8}$), Full Field Screen X^2=770.8 ($p<10^{-8}$), Pseudo-kinetic X^2=815.5 ($p<10^{-8}$),Central 30 absolute	"In this study, chi-squared testing, as well as the accuracy ratios and predictive values, have demonstrated that the Marco MT-336 computerized perimeter demonstrates	Data suggests comparing different visual field tests to each other is challenging but that MarcoMT-336 automated perimetry correctly detected the presence of scotomas and

							macular disease, etc)			X^2=94.8 ($p<10^{-8}$), Glaucoma absolute X^2=954.1 ($p<10^{-8}$), Macula absolute X^2=43.6 ($p<10^{-8}$), Full Field Diagnostic X^2=526.4 ($p<10^{-8}$). Marco vs Goldmann disagreement, McNemar's test value: Glaucoma screener 45.1 ($p<10^{-8}$), Psuedo-kinetic 28.6 ($p<10^{-8}$), Glaucoma diagnostic 38.1 ($p<10^{-8}$), Glaucoma absolute ($p<10^{-8}$)	sufficient degrees of accuracy to serve as a diagnostic tool for evaluating the visual field	also detected areas of vision where present.
Trope 1987 (4.5)	Manual Studies	Diagnostic	No mention of Sponsorship or COI.	N=25 patients (42 eyes)	No mention of gender or age.	Patients who were diagnosed with Glaucoma.	Glaucoma was diagnosed by physicians by clinical standard. No detailed criteria for diagnosis of Glaucoma.	Automated Humphrey threshold visual field testing (program 30-2)	Goldmann Perimetry visual field testing	Patient preference: 60% Goldmann vs 17% Humphrey. Technician Preference: 67% Humphrey vs 13% Goldmann. Humphrey test Specificity was 91% and sensitivity 90.3%. Automated Humphrey test takes approximately 25% longer.	"The results of this section of the study indicate that Program 30-2 (Humphrey) is both highly sensitive and specific for detecting glaucomatous visual field defects."	Data suggest high sensitivity and specificity of Humphrey automated perimetry for Galucoma patients but patients preferred Goldmann over Humphrey

Bengtsson 2000 (4.5)	Manual Studies	Diagnostic	Study supported by grants administered by Malmo University Hospital, and by Jarnhardt foundation.	N=76 patients	26 males, 50 females; Mean age 72 (50-83)	Patients diagnosed with glaucoma.	Glaucoma being defined as typical field loss, paracentral and arcuate defects across the nasal horizontal meridian.	Reproducibility of automated test and patient reliability indices.	Humphrey II 30-2 SITA Standard program.	Threshold reproducibility was highly dependent on visual field status ($p<0.0001$). Second most importntt in reproducibility was False Negative ($p=0.065$). High frequencies of Field loss were more common than False Negatives. And False Positives being the least common.	"A general conclusion of the current study is that the reliability if glaucomatous visual fields expressed as their reproducibility can be reasonably well predicted by field status (MD) alone, and that traditional patient reliability indices contribute surprisingly little in this regard."	Data suggest in glaucoma patients, visual field loss can be directly correlated to threshold reproducibility, not patient reliability indices.
Marraffa 1989 (4.5)	Manual Studies	Diagnostic	No mention of sponsorship or COI.	N=104 patients (182 eyes)	45 males, 59 females; Mean age 54.3±13.8	Participants within the study were suspected to have glaucoma.	Patients had intraocular pressure of >21 mmHg in more than one measurement, as well as a suspicious optic disc. Excluded if they had already been previously diagnosed with glaucoma, or	Four different visual field exams including; Humphrey 630 perimeter, Octopus 2000 R perimeter, Perikon (opticon) perimeter, Henson CFS	Final diagnosis based upon clinical parameters including intraocular pressure, or presence of optic disc.	Final clinical diagnosis in 140 and absent in 42. Glaucoma screening (Henson test) sensitivity 51.4%, specificity 88.0%. Humphrey 630 test: sensitivity 64.2%, specificity 64.2%. Perikon: sensitivity 55.0%, specificity 90.4%.	"The Henson strategy has the definite advantage of the short examination time and lower cost of the equipment… however a specifically designed threshold measuring	Data suggest Henson method is quicker and less costly but with marginal sensitivity. It may be appropriate as a screening tool in large population where glaucoma is not highly prevalent.

							cannot perform field test.	2000 perimeter.		Octopus: 92.1%, specificity 83.3%.	strategy is needed."	
Wall 2009 (4.0)	Manual Studies	Diagnostic	Study supported by a VA Merit Review Grant by Department of Ophthalmology from Research to Prevent Blindness. No COI.	N=120 patients	Glaucoma group: 22 males, 83 females; Mean age 64.9±9.5. Control group: Mean age 57.2±7.9	First 120 patients were all previously diagnosed with Glaucoma. An additional 60 participants were healthy.	Glaucoma patients could have no other ocular disease. Included if they had abnormal glaucomatous, also included primary, secondary, and normal-tension glaucoma.	Study aimed to test the repeatability of automated Humphrey test with stimulu sized III, and V. Also the Matrix and Motion automated perimetry tests.	All baseline perimetry testing of previously described tests.	Standard automated Perimetry (SAP) III variability increased with a reduction in sensitivity. Retest variability of all 4 tests: SAP III 22%, SAP V 12%, Motion 2%, and Matrix 2%.	"In summary, our results show larger sized stimuli show more uniform variability in areas of visual field damage. A moderate reduction or variability and improvement of dynamic range can be accomplished using size V stimuli."	Data suggest substantial variability in damaged visual field locals in standard automated perimetry III but not as much in matrix or motion perimetry.
Vislisel 2011 (4.0)	Manual Studies	Diagnostic	Study supported by a VA Merit Review Grant by Department of Ophthalmology from Research to Prevent Blindness. No COI.	N=17 participants	3 males, 14 females; Mean age 44±14.	Subjects were healthy and had no prior history of ocular disease, apart from refractive error.	Participants were excluded if they had no eye exam within the past 2 years, did nto have minimum of 20/30 Snellan acuity, or had diabetes mellitus, systematic hypetesnions, or other diseases causing visual field loss.	Rarebit Perimetry (RBP). Patients performed test 5 times	Humphrey Automated Perimetry with Goldmann size I and III stimulus. Patients performed test 5 times	PR:M ratios of visual field tests; Size I, Humphrey automated tests, 3.42±0.62, Size III 2.29±0.55, RBP test, 0.29±0.10. Variance was significantly different ($p<0.0001$) favoring RB. All tests had decreasing sensitivity with an increase in age.	"[I]t appears that RBP might have lower test-retest variability than size III SAP, which in turn has lower variability than size I SAP in normal subjects. The test addresses some of the shortcomings of SAP and attempts to avoid the	Small sample, but 5 tests completed. Data suggest test-retest variability of rarebit perimetry less than both standard automated perimetry sizes 1 and 3 measurements of normal subjects.

											limitations imposed by using threshold measutres"	
Pandit 2001 (4.0)	Manual Studies	Diagnostic/Prospective	No mention of sponsorship or COI.	N=138 patients	No mention of gender; Mean Age 67.5 (17-88)	All outpatients of an eye clinic were consented for the study, a total of 89 (64%) had defects detected by automatic field testing.	No exclusion criteria for the participants of the study.	Confrontation tests, including: Description of examiners face, Quadrant finger counting, kinetic to finger, kinetic to 20 mm white target, kinetic to 20 mm red target, red colour comparison, central field test.	Automated Humphrey II 30-2 Perimetry.	Sensitivity and Specificity of confrontations tests: Descript of examiners face, 44% and 100%. Quadrant finger counting, 35% and 100%. Kinetic to finger, 40% and 100%. Kinetic to 20 mm white target 48% and 100%. Kinetic to 20 mm red target, 56% and 100%. Red colour comparison, 60% and 100%. Central Field test to 5mm red target, 76% and 100%.	"The central red field and the red-colour comparison tests should be essential components of the examination of visual fields to confrontation… The specificity of confrontation tests is high, suggesting that causes of identified field defects are usually real and therefore warrant explanation."	Data suggest most confrontation visual field tests are insensitive to detecting visual field losses compared with full threshold automated perimetry tests.

Shahinfar 1994 (4.0)	Manual Studies	Diagnostic/prospective	Supported by an unrestricted grant from Research to Prevent Blindness. No COI..	N=72 patients	No mention of Gender; Mean Age of 60.4±18.0	63 of the participants (87.5%) were diagnosed with abnormal field defects by automate.	Outpatients of a Neuro-Ophthalmology service during a 3 month-period. A variety of disorders were included. Patients included if they had 20/200 vision, could complete both tests, had a False Negative or False positive frequency < 20%.	Confrontation test (quadrant finger wiggle)	Automated Humphrey II 30-2 Perimetry.	Overall sensitivity of confrontation visual field tests was 63% However, it varied depending on visual field loss present, being most sensitive to Hemianopias (90%). Significant differences in field loss types ($p<0.0001$). Abnormal confrontation test in different quadrants; overall sensitivity (38%), highest sensitivity within the Ineferonasal quadrant sensitivity of 44%. All confrontation testing yielded high specificity of 97%, and positive predictive value of 96%.	"Confrontation visual field testing is sensitive for very dense visual field defects of either the anterior or posterior visual pathway. Confrontation visual field testing is insensitive for mild to moderate scotomas of up to -19 dB sensitivity loss."	Data suggest confrontation testing is poor at detection of visual field loss, is a poor screening test but cn detect moderate to large defects.

Szatmary 2002 (4.0)	Manual Studies	Diagnostic/Prospective	Study supported in part by a departmental grant from Research to Prevent Blindness Inc. One author is a recipient of an award from Research to Prevent Blindness Inc.	N=64 patients	36 males, 28 female; Mean age 53 (18-92)	Patients were evaluated by study if they had either severe neurological impairment or severe vision loss.	Severe Neurological impairment constituted as a score of 3-4 on Modified Rankin Scale (MRS) (requires help with or without walking). Severe vision loss defined by an acuity of 20/200 or worse in at least one eye.	Swedish Interactive Thresholding Algorithm(SITA) Fast static Perimetry	Manual Goldmann Kinetic Perimetry (GVF)	Overall, both results were similar for both testing strategies. Only discrepancies were in 8% (6 of 43 w/ neurological defects, 2/50 w/ vision loss) when GVF failed to show a defect SITA showed. Also, in 9% (3/43 w/ neurological defects, 6/50 w/ vision loss) SITA failed to show a vision field loss GVF showed. Test Time, GVF vs SITA: 7.97±3.2 vs 5.43±1.41. Patient Preference: 91% preferred the GVF test, and 9% preferred the SITA, based on difficulty of maintain concentration during exam.	"In conclusion, we believe that SITA Fast strategy of automated perimetry may be useful in the evaluation of central vision field defects associated with neuro-opthalmic disorders."	Data suggest although Goldmann perimetry has been the gold standard for testing, SITA Fast may be the preferred test due to it being faster and requiring less skill to perform. Patients appeared to prefer Goldmann due to concentration challenges in SITA Fast (91% vs 9%).

Topouzis 2003 (4.0)	Manual Studies	Cross-Sectional Study/ Diagnostic	No mention of sponsorship or COI.	N=88 patients	38 males, 50 females; Mean age 68.8±4.8	Participants came from those included in an ongoing epidemiological study (Thessaloniki Eye Study) of Glaucoma and age-related macular degeneration (AMD).	A test of visual field loss was considered unreliable is 76-STHR or 30-FTHR if the percentage of fixation losses or false-positive to false-negative errors exceeded 33%.	76-suprathreshold test (76-STHR)	Humphrey Threshold testing, 30-Full Threshold algorithm (30-FTHR)	Sensitivity and Specificity of 76-STHR with 1 test point missed: 85.2% and 70.0%. With 2 test points missed: 77.8% and 78.0%. With 3 test points missed: 74.1% and 86.0%. Higher sensitivity of 76-STHR was found after excluding eyed with Visual Field Defect not secondary to glaucoma.	"In conclusion, based on the results of our study, the 76-STHR test showed high sensitivity and low false-negative results at the "at least one point missed" cutoff level criterion to detect eyes with visual field defect by Humphrey threshold testing in a population-based study."	Data suggest the 76 STHR had high sensitivity but low specificity and would appear inappropriate for the screening test in a primary care setting.
Ong 2014 (4.0)	Manual Studies	Diagnostic/Prospective	Study supported by a Singhealth Foundation Project Grant, Singapore, Republic of Singapore. No COI.	N=426 patients	166 males, 260 females; Mean age, glaucoma group: 66.6±13.1. Control Group 55.2±9.2	N=78 participants who were diagnosed with glaucoma prior to the study. N=348 participants who were healthy controls.	Diagnosis of glaucoma was based on clinical examination with glaucomatous optic neuropathy defined by presence of neuro retinal rim thinning, notching, or excavation of the cup, cup thinning, or a combination	Moorfields Motion Displacement Test (MMDT)	Clinical Diagnosis (Described in Case definition) as well as the Heidelberg Retina Tomography (HRT) results.	Testing time, glaucoma vs control group (seconds): 112.7±39.7 vs 103.3±30.7. HRT results for diagnosing glaucoma, global probability of true damage (PDT) Area under receiver operator curve (AUC); 0.930 (95% CI, 0.893-0.967). MMDT sensitivity was 88.5% when	"In summary, the present study has shown that the MMDT shows good diagnostic performance in detecting structurally and clinically defined glaucoma. In view of MMDT's portability, accessibility, and relative affordability, its	Data suggests MMD highly correlates to structural criteria fro glaucoma with good sensitivity and specificity.

							there of. Confirmed by HRT Moorfields Regression Analysis.			specificity was 85%. MMDT sensitivity 83.3% when specificity was 95%. At PTD cutoff point value of 2.5, sensitivity was 85.9% and specificity was 94.5%.	good diagnostic performance underlies its potential asa new glaucoma diagnostic tool."	
Rowe, 2011 (3.5)	Manuel Studies											Data suggest Octopus perimeter is useful for assessment of uniocular ductions and binocular field of single vision but speed of stimulus alters test duration, and thus may overestimate field of rotations.
Hsu, 2010 (3.5)	Manuel Studies											Data suggest use of repeated III-4e isopter techniques during kinetic perimetry testing is fast and aids clinicians in

												diagnosing NOVFL.
Heijl, 1976 (3.5)	Manuel Studies											Data suggest manual and automatic perimetry similar in efficacy with a slight trend towards a higher rate of FPs in automatic perimetry which can be improved by using higher VF defect detection (optimization)
Katz, 1995 (3.5)	Manuel Studies											Data suggest there is concordance on consecutive testing of the glaucoma hemifield test but enough discordance whereby specificity increases from using a second test.

Johnson, 1991 (3.5)	Manuel Studies											Data suggest confrontation testing has a high specificity but modest sensitivity.
Kerr, 2010 (3.5)	Manuel Studies											Data suggest confrontation testing has low-medium sensitivity and high specificity.

Peripheral Vision Crash and Safety Risk

Peripheral Vision Crash and Safety Risk							
Name/Year Location	**Score**	**Study Design**	**Exposure**	**Population. Age range. Dropout Rate. Case Definition**	**Results**	**Conclusion**	**Comments**
Rubin 1997 Maryland, USA	II	Cross sectional baseline from longitudinal. Salisbury Eye Evaluation Study	Residents of Salisbury, MD, between September 16, 1993 and September 26, 1995 who completed examination.	N=2520 aged 65-84 yrs. Assessed visual acuity, contrast sensitivity, glare, visual fields.	Visual acuity impairment (worse than 20/40 to better than 20/200) in blacks vs. whites was 5.6% vs. 3.0%.	"[A] loss of visual function with age and potentially important racial differences for all the tests included in this study."	Visual impairments associated with age and greater with black than white. Especially includes VA, contrast sensitivity and visual field points missed
Rubin 2007 Maryland, USA	II	Longitudinal, population-based study Salisbury Eye Evaluation (SEE) Study	Vision tests (visual acuity, contrast sensitivity, glare sensitivity, stereoacuity, visual fields, test of attention, driving assessment)	1801 members of original cohort (N=2520) with current Maryland driver's licenses ages 65-84; sample included 100% of identified African American residents and 58% of identified Caucasian residents. Eligibility: score higher than 17 on Mini Mental State Examination (MMSE), able to travel to SEE clinic for examination	From 1991 to 1997, Maryland Automated Accident Reporting System (MAARS) recorded 290 crashes from SEE study participants. **Hazard Ratios.** (Variable: interval for hazard ration/HR/95% CI/p-value). Age: 5 years/1.20/1.00-1.44/p=0.05. Sex (adjusted for age): female = NS. Race (adjusted for age): African American/2.05/1.37-3.02/p=0.0007. Live alone: NS. Education: NS. Mental status (adjusted for age): 1 point/0.91/0.85-0.98/p=0.02.	"[B]inocular visual fields, glare sensitivity, and UFOV were significant predictors of crash involvement in our cohort of older drivers…Nevertheless, the data suggest that current vision screening for driver's licensure, which is based primarily on visual acuity, may miss important aspects of visual impairment about which the driver is not	Glare sensitivity, binocular visual fields and UFOV associated with elevated crash risk.

					Comorbidities: NS. Depression: NS. **Vision risk factors**. (interval for hazard ratio/adjusted for miles driven hazard ratio/adjusted for miles driven 95% CI/p-value). Acuity: NS. Low luminance acuity: NS. Contrast sensitivity: NS. Glare sensitivity <3: 6 letters/0.46/0.26-0.89/p<0.05. Glare sensitivity ≥3: 6 letters/2.32/1.14-16.78, p<0.05. Stereodeficient: NS. Binocular visual fields <20: NS. Binocular visual fields ≥20:15 points/1.31/1.13-4.27/p<0.05. Useful Field of Vision Test (UFOV): 40% lss/2.21/1.32-3.39/p<0.01.	sufficiently aware."	

Ball 1993 Jefferson County, Alabama, USA	III	Population-based cross sectional and retrospective study, with sampling of the population.	Visual sensory function, mental status, UFOV, driving habits questionnaire , eye health. VA, contrast sensitivity, disability glare, stereopsis, color discrimination and visual field sensitivity.	N=294 drivers ages 55-90. Stratified by age and crashes in prior 5yr. 33% had 0, 49% had 1-3, and 18% had 4+ crashes.	Diagnostic category (n=135 normal, 23 retinal disease, 6 glaucoma/ocular HTN, 5 DM retinopathy, 26 others) not related in final model. MMSE and UFOV most associated with the crash frequency variance.	"With the identification of a visual attention measure highly predictive of crash problems in the elderly, this study points to a way in which the suitability of licensure in the older adult population could be based on objective, performance-based criteria."	Not powered for most diagnoses. UFOV and MMSE most important of the factors.
Goode 1998 USA, Alabama Department of Public Safety	III	Case control design	Crash-involved older drivers	N = 239 with older adult driving population who had experienced a crash. Adults, 55 years of age and older. No dropouts, reported. The purpose of the present investigation was assess; visual sensory function, neurocognitive functioning, UFOV®, driving habits, and eye health.	First model; Traditional tests (MOMSSE, Trials A, B time, WMS-VR score) $X^2 = 20.02$, $p < 0.01$, indicating these variables as a set, distinguish between crashers and non-crashers. Second model; UFOV® reduction score to the neuropsychological variables, was	"In terms of cognitive assessment of driving risk, the results of the current investigation support the use of a stand-alone measure of visual attention (UFOV®) for assessing older adults' risk for automobile crashing."	Data suggest UFOV most strongly associated with crash.

					analyzed and found to be statistically significant, X^2 = (7, N = 239) = 84.24, p < 0.001. Third model; only the UFOV® score, found statistically significant X^2 = (1, N = 239) = 76.04, p < 0.001. All measures are significantly correlated with UFOV® score (ps < 0.001).		
Owsley 1998 Alabama USA	II	Prospective cohort study	To identify whether measures of visual processing ability, including the useful field of view test, are associated with crash involvement by older drivers.	N= 294 Ages 55-87. Single visit to the clinic in 1990 with visual sensory function, visual attention and processing speed, cognitive function and eye health; a questionnaire about driving exposure; and a review of demographic and health information.	Those driving <7 days/week 30% less likely to have had a crash vs. those driving daily. Crash risk in 5 prior years (RR=2.0;95% CI, 1.1-3.8). Older drivers with ≥40% field of view reduction 2.2x (95% CI, 1.2-4.1) more likely to crash during follow-up. Older drivers driving <7 days/wk had 45% (95% CI, 0.3-1.1) decreased crash risk.	"Reduction in the useful field of view increases crash risk in older drivers. Given the relatively high prevalence of visual processing impairment among the elderly, visual dysfunction and eye disease deserve further examination oas causes of motor vehicle crashes and injury."	Data suggest visual field impairments associated with increased crash risk.

Johnson 1982 California USA	II	Cohort	Visual field loss vs normal vision Visual Field: substantial depression of all or part of the peripheral field or 2 or more adjacent target missed in testing.	N= 10,000 Volunteers, 20k eyes from driver's license applicants at Dept. of Motor Vehicles (DMV) offices in El Cerrito and Redwood City, CA. Visual field screening and ophthalmic history.	Normal/abnormal visual fields in 96.7/3.3% of eyes. Severe visual field loss (eg, hemianopic defect or severe visual field constriction) in 0.5%. Increase in frequency of visual field loss between 61-65 yrs., and frequency of visual field loss is >4x higher for those >65 yrs. ~13% of >65 years had visual field defect.	"Drivers with monocular visual field loss had accident and conviction rates equivalent to those of a control group. Our results have important implications for mass visual field screening to detect eye diseases and for vision-related factors in traffic safety."	Large sample size, but relatively modest numbers affected. Age related to visual field losses.
Burg 1968 USA, California Department of Motor Vehicles		Large-scale research project	Vision and driving	N = ~ 17, 065 who participated in the vision and driving study of both genders, age from 16 to 92. The aim of this study was to administrate a distance phoria test utilizing a modified Thorington apparatus and red Maddox rod.	Results show slight but statistical significance trend toward exophoria with increasing age, for men r = 0.021, p = 0.06, and women r = 0.042, p = 0.01.	"Analysis of the resultant data reveals a slight but statistically significant trend toward exophoria with increasing age; however, this trend is not consistent one, and it more pronounced for women than it is for men."	
Council 1974 USA, North Carolina		Retrospective (accident experience)	Lateral vision	N = ~ 52, 000 drivers were measured. Age range, < 25 – > 70 years.	Visual field and accidents: < 0.0848% of the applicants had total visual fields ≤ 90	"Overall two year retrospective accident experience of those with	

Highway Safety Research Center				The aim of this study is to examine relationship between lateral vision and accident involvement.	degrees and < 1%, visual fields ≤ 120 degrees, ≤ 4.18% had visual fields less ≤ 140 degrees, and ~75% had total visual fields greater than 160 degrees. Distribution of visual fields of the accident-involved sample was different from the distribution of the accident-free sample, p < 0.001.	"limited visual fields" (140 degrees or less) does not differ from drivers with "normal" fields of view (greater than 160 degrees)."	

Evidence for Intraocular Lenses

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*	*Author Year (Score):*	*Category:*
Schmidinger 2008 (6.5)	Intraocular lens	Diagnostic	No COI.	N=31	Mean age: 73.4±7.64 years. No mention of gender,	62 eyes of 31 patients	Patients without history of corneal disorders, no abnormal pupil reaction, no sign of inflammation, no opacification of optic media apart from cataract, no retinal disorders, and no systemic disease or having	AF-1 (UV) IOL (Hoya)	AF-1 (UY) IOL (Hoya)	Visual acuity difference for both IOL groups was no significant. (p>.05) Central color contrast sensitivity also had no significant difference between eyes with clear IOL and yellow IOL at any tested spatial frequency. Peripheral color contrast sensitivity test	"In this intraindividual comparison, the implantation of a blue-light-filtering IOL did not lead to a clinically significant change in color contrast sensitivity."	Data suggest equivalency.

							treatment that might affect color perception, no evident signs of macular alteration or other ocular disease after surgery.			showed slightly higher color contrast sensitivity in eyes with yellow IOL, but no significant difference. Two patients reported subjective changes in color perception in the eye with yellow IOL.		

Depth Perception

Depth perception is the ability of the eye to help ascertain three dimensions and be able to judge the distance of an object. Depth perception is also involved in ascertaining the length, width, and the height of an object. When the head is held steady and the body is not moving, both eyes are required to ascertain depth perception, known as stereopsis. While depth perception is commonly thought to require both eyes, this is not completely correct. When the head and/or body is moving (e.g., moving the head or traveling by vehicle), some depth perception is possible based on experiences, the relative changes in the size and position of objects. Still, people with stereopsis will use these clues much less frequently.

Overall, there were two review articles that partially included the condition of monocular vision as a risk factor for occupational injury. One review found that balance issues related to problems of depth perception and visual ambiguity caused by monocular vision increased the risk of falling off a roof for roofers [351]. The second review showed little evidence that visual impairment increased risks for occupational injury and no studies were found that directly assessed monocular vision as a risk factor for occupational injury [352]. Overall, the lack of evidence for monocular vision as a risk factor for occupational injury seems to be related to not properly defining eye pathology in current research [352].

Depth Perception Screening for Preplacement Examinations

Recommended.

Preplacement depth perception screening is selectively recommended for jobs that require depth perception.

Indications **–** Occupations that require a high degree of depth perception for accurate performance. Optimum means for testing are unclear. A functional test that either accomplishes the required job functions or one that mimics the required job task(s) may be best.

Strength of Evidence – **Recommended, Evidence (I)**

Level of Confidence – Low

Depth Perception Screening for Periodic Surveillance Examinations

Recommended.

Periodic depth perception screening is recommended for select jobs that require depth perception.

Indications **–** Occupations that require a high degree of depth perception for accurate performance. Optimum means for testing are unclear. A functional test that either accomplishes the required job functions or one that mimics the required job task(s) may be best.

Strength of Evidence – **Recommended, Evidence (I)**

Level of Confidence – Low

Depth Perception Screening for Select Post-Injury Examinations

Recommended.

Depth perception screening is recommended for select post-injury examinations.

Indications **–** Post-injury examinations for jobs that also require a high degree of depth perception.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Low

Depth Perception Screening for Select Postoperative Examinations

Recommended.

Depth perception screening is recommended for select postoperative examinations.

Indications **–** Postoperative examinations for jobs that also require a high depth perception.
Strength of Evidence – **Recommended, Evidence (I)**
Level of Confidence – Low

Rationale for Recommendations

Depth perception is necessary for select jobs and job tasks. The degree of depth perception required varies widely. There are multiple tests that have been used mostly in comparative studies, including: Polarized Stereoscopic Monitor, Distance Randot Stereotest, Titmus stereo test (static depth perception), Frisby stereotest, Randot circles and FNS, Wirt Fly Stereotest, TNO test, steroacuity, stereogram [353-360] Leske 06. There are no validated tests that demonstrate a given test is able to predict both inability to accomplish normal depth perception as well as to not successfully perform job tasks. Thus, the means to accomplish the testing are unclear.

Depth perception screening is nevertheless recommended for select pre-placement and periodic screening for jobs that require a high degree of depth perception. For jobs that require a high degree of depth perception, depth perception screening of post-injury and postoperative patients is also recommended. For those in jobs requiring depth perception who also have risks for acquired or progressive loss of depth perception (e.g., keratoconus), greater frequency of depth perception screening may be considered.

Depth perception screening is not invasive, is without adverse effects, is low cost and is thus recommended for select pre-placement, periodic surveillance, as well as select post-injury and postoperative examinations.

Evidence for Depth Perception Screening

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Population Description	Case Definition	Investigative Test	Comparative Test	Results:	Conclusion:	Comments:
Yang, 2004 (6.5)	Depth Perception Testing	Diagnostic	Sponsored by the INJE University research grant 2003. No COI.	N=100	57 males, 43 females, and a mean age of 3.9 years	Normal patients without ocular or general diseases.	Stereoacuity test can confirm the absence of strabismus, suppression and amblyopia.	Test sheet of digitalized, random-dot stereogram through Random-dot production program	Randot preschool stereoacuity (stereoptical Co., Chicago), Titmus-fly (Stereo Optic Co., INC., IL, USA), and Lang (Western ophthalmic Co. USA)	Success rate percentage for random-dot = 90%, Randot prescholl stereoacuity = 83%, Titmustests = 71%, and Lang test = 80%. Percentage of sensitivity of stereoacutity test for digital random-dot (100(100/100)), Preschool (78(78/100)), Titmus (87(87/100)), and Lang (100(100/100)). Percentage of specificity of stereoacutity test for digital random-dot (100(100/100)), Preschool (96(96/100)), Titmus (90(90/100)), and Lang (98 (98/100)).	"In the future, we can use the digitalized, random-dot, stereogram test designed in this study over a wider range, and the group study results of this test will be more accurate if studies are conducted into favorite Korean numbers, letters and objects."	Study performed on children with strabismus suggests random dot stereoacuity test may be of use in chemical settings.
Kim 2011 (4.5)	Depth Percepti	Diagnostic	Funded by grant A092206	N = 64	Mean age 30.7,	Normal binocularity	20/20 vision or better, no manifest tropia	Polarized Stereoscopic Monitor	Distance Randot Stereotest	The two test result scores presented a significant	"The distance 3-D stereotest showed	Data suggest 3-D stereotest comparable to Randot stereotest

	on Testing		from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Seoul, Republic of Korea. No conflict of interest.		no gender distribution mentioned		with simultaneous and alternative prism cover test, 0.33 m and 6 . fusion in Worth 4-dot test			correlation (r = 0.324, p = 0.009). Results between the two tests were 64% identical and ranged within 1 disparity level for 97% of the adults.	good concordance with the distance Randot stereotest and relatively good test–retest reliability, supporting the validity of the distance 3-D stereotest. The normative data set obtained from the present study can serve as a useful reference for quantitative assessment of a wide range of binocular sensory abnormalities."	and it also demonstrated good test-retest reliability and was either similar to or better than conventional tests.
Watanabe 2008 (4.5)	Depth Perception Testing	Diagnostic	No conflict of interest. No mention of sponsorship.	N = 52	Mean age 16, 32 female and 20 male	Strabismic patients	Exotropia or esotropia	One random dot stereogram of rotating cylinder, three random dot stereograms of two parallel planes (motion-in-depth perception)	Titmus stereo test (static depth perception)	Data presented a weak correlation between scores of the stereo motion test and Titmus stereo test.	"This study indicates the importance of testing motion-in-depth perception as well as static depth perception in assessing stereopsis in strabismic patients."	Data suggest it is important to measure both static and motion in depth perception.
Leske 2004 (4.5)	Depth Perception Testing	Diagnostic	Partially funded by grant to Department of Ophthalmology of the Mayo Clinic and by the Research to Prevent	N = 186	Median age 11, 108 female and 78 male	Horizontal strabismus	Horizontal strabismus	Titmus Fly, Animals, and Circles tests	Preschool Randot test and Frisby test	The Titmus Fly resulted in a false-positive 6% of the time, Titmus Animals at 10%, Titmus circles 35%, and Randot at 10%. The Frisby test presented no false-positives.	"In summary, the Titmus Fly, Titmus Animals, and Titmus Circles (the first four circles) tests possess monocular clues that limit their usefulness for clinical testing. The Frisby test is particularly	Data suggest Frisby test useful for identifying the presence or absence of stereopsis where Randot is useful in the quantification of the stereopsis in both adults and children.

			Blindness in New York, New York. Holmes, the coauthor, was an Olga Keith Weiss Scholar at the Research to Prevent Blindness organization.								useful for rapid assessment of whether stereopsis is present or absent. The new Preschool Randot test is valuable for quantifying stereopsis in both children and adults. True stereopsis may be rare when a patient has a horizontal deviation > 4 PD."	
Leske 2006 (4.5)	Depth Perception Testing	Diagnostic	Funded by a grant, from the National Institutes of Health, to Department of Ophthalmology of the Mayo Clinic and by the Research to Prevent Blindness in New York, New York. Holmes, the coauthor, was an Olga Keith Weiss Scholar at the Research to Prevent Blindness	N = 182	No mean age or gender distribution listed. Age range 8-84	Variety of strabismic conditions	Visual acuity of 20/40 or better (in each eye) No more than 70 prism diopters of esotropia (pd) No more than 55 pd exotropia And/or No more than 30 pd of hypertropia	Near Frisby (nF), distance Frisby-Davis 2 (FD2)	Preschool Randot test, Distance Randot	Participants underwent finer disparities using the nF test compared to the Randot test ($p < 0.0001$). Participants also experienced finer disparities with the FD2 test compared to the Distance Randot test ($p < 0.0001$). No participants presented improved stereoacuity with the Distance Randot test compared to the FD2 and only 4% has an improved result with nF compared to the Randot test.	"The type of stereotest influences measurable thresholds, and the results from different tests are not interchangeable. The choice of test should depend on the question being asked; nF and FD2 would be appropriate for determining presence or absence of stereopsis and best measurable stereopsis. The more rigorous Randot tests would be appropriate for determining subtle changes."	Data suggest Randot test is better for detecting slight changes where the nF and FD2 tests are better for detecting presence of or lack of stereopsis. Therefore, data suggest the choice of stereotest is dependent upon what question is being asked.

			organization.									
Holmes 2005 (4.0)	Depth Perception Testing	Diagnostic	Funded by a grant from the National Institutes of Health and Research to Prevent Blindness Inc. Holmes is a scholar at the Research to Prevent Blindness Inc.	N = 95	No mean age or gender distribution mentioned. Age range 4-84	Variety of strabismic and nonstrabismic conditions	Variety of strabismic and nonstrabismic conditions	Distance Frisby-Davis 2 (FD2)	Preschool Randot Stereoacuity	28 participants, out of 66 tested at 3 meters, were able to pass at least one of the first levels of the FD2 test (monocular conditions). 7, out of 29 tested at 6 m, were able to pass one of two primary levels. 14 out of 21 stereoblind patients (who failed the Randot and near Frisby tests) were able to pass at least one level of the FD2 test (binocular conditions). The binocular test conditions were modified to include monocular phase afterwards. This resulted with no detection of stereopsis.	"The FD2 stereotest is a useful measure of distance stereoacuity, provided the presentation protocol accounts for monocular cues."	Data suggest FD2 is beneficial in testing distance stereoacuity if a monocular phase is part of the testing protocol.
Gharaibeh 2012 (4.0)	Depth Perception Testing	Diagnostic	No mention of COI or sponsorship.	N = 43 patients, 55 eyes	Mean age of 26.62, 21 male and 34	With keratoconus	Irregular astigmatism, at least one classical sign of keratoconus (fine deep	Intrastromal corneal ring segments (ICRSs), specifically	Penetrating keratoplasty	At six-month post operation the mean UCVA statistically improved from 0.10 to 0.32, the	"KeraRing implantation provided significant improvement in visual activity, spherical equivalent, and keratometry results.	Retrospective case series. Data suggest KeraRing implantation led to significant improvement in patients with all grades

					femal e.		stromal striae, localized corneal thinning, progressive corneal thinning, bulging of lower eyelid when looking down, conical reflection on nasal cornea when penlight shone from temporal side). At least two symptoms from the Pentacam corneal topography findings. Clear central corneas, severely affected visual acuity, contact lens intolerance	KeraRing segments		mean BSCVA statistically improved from 0.36 to 0.57 ($p < 0.05$), the mean spherical refractive error improved from -4.85 to -1.89 diopters, the mean cylindrical refractive error improved from -3.65 to -2.60 diopters, the mean spherical equivalent decreased from -6.68 to -3.19, and the mean keratometry value decreased from 51.83 to 47.27 (all significant with $p < 0.05$). The change in mean cylindrical refractive error was the only variable that was not significant ($p = 0.74$) for patients with grade 3 keratoconus. For participants with grades 1 and 2 keratoconus, all changes were	This ICRS is an effective treatment for managing keratoconus and might delay or even avoid the need for penetrating keratoplasty."	of Keratoconus during the first three months after surgery.

										statistically significant.		
Gomez 2011 (4.0)	Depth Perception Testing	Diagnostic	Partially funded by grant from the Science and Technology Ministry of Spain	N = 69	Mean age 23.43, 15 male and 54 female.	Students at the Technical University of Catalonia (volunteers)	With monocular and binocular distance and near visual acuity equal to 1.0 or better	Phoria measured with cover test and handheld prism bar	TNO test at 40 cm	Predictive accuracy overall was 66.67% (p = 0.024). Group 1 (having a minimum time of < 10 seconds) had 78.26% predictive accuracy while Group 2 (minimum time > 10 seconds) had 75.86% predictive accuracy. Group 3 (unable to perceive SIRDS) had a predictive accuracy of only 35.29%. Between-group differences were significantly different for the variables of stereoacuity (p = 0.001) and negative relative convergence (p = 0.003).	"The ability to perceive SIRDS was related to many visual parameters and skills, including, but not limited to, stereoacuity and negative relative convergence. It is uncertain whether SIRDS might be considered a useful tool in clinical practice."	Data suggest multiple visual parameters contribute to the ability to perceive SIRDS including stereoacuity and negative relative convergence.
Rosner 1984 (4.0)	Depth Perception Testing	Diagnostic	No mention of sponsorship or COI	N = 20	Mean age 27.4, no mention of gender	Determined by a pre-screening test to be binocular	All pre-screened with a Random-dot E stereotest (1.5 meters)	Frisby stereotest	TNO	A strong positive correlation exists between the test results of each test for each participant (Pearson r = 0.73, p < 0.001). Using a t-test it was	"The Frisby stereotest appears to be as sensitive to slight stereoacuity differences as are the other, better established tests of stereoacuity—at least when used with	Data suggest comparable sensitivity between the Frisby stereotest and the TNO.

					distribution					determined there was a significant difference between the mean scores of each group ($t = 2.14$, $p < 0.025$).	experienced adult observers. Its value with other groups—such as young children—has yet to be established, but such an effort appears to be clearly worthwhile."	
Lindstrom 2009 (4.0)	Depth Perception Testing	Diagnostic	No mention of sponsorship or COI	N = 12	Mean age and gender distribution not mentioned. Age range 18-23	Healthy eyes, good vision	6/6 vision in both eyes at near when measured with a reduced Snellen test Normal BSV	Wirt Fly Stereotest (at 40 cm)	Randot circles and FNS tests	Group mean depth for no lens was 42.8 mm. Mean perceived depth perception decreased as lens power increased ($p < 0.001$). When compared to each other all mean values from range +1.00 to +4.00 diopter spheres were statistically different ($p < 0.02$). FNS group means also showed a significant difference ($p < 0.01$). Increasing lens power during the Randot test showed significant reductions when analyzed with ANOVA ($p < 0.001$).	"The substantial individual and between-subject variation in Wirt Fly perceived depth causes us to doubt its value as a proxy for stereoacuity except as a rough estimate."	Data suggest Wirt Fly Stereotest has significant between subject variation.
Yoshitomi, 1999 (3.5)												Data suggest pupil perimetry may be valuable in the

												objective measurement of visual fields. However, study subjects had many different diagnoses which may involve differing pathways causing visual loss.
Matsuo, 2014 (3.5)												Data suggest significant correlation between 3-Rods test and eye-hand coordination and distance Randot Stereotest for depth perception.
Wang, 2010 (3.5)												Data suggest distance randot stereotest is a useful tool in the measurement of binocular sensory status.
Long, 2005 (3.5)												Data suggest Randot Stereoacuity Test does not perform well for accurately diagnosing depth perception abilities in subjects with normal binocular vision. N=48
Fu, 2006 (3.5)												Data suggest new distance Randot test better at detecting distance stereopsis abnormalities and may and in detection of distance stereoacuity for those with or without strabismus.

Fricke, 1995 (3.5)												Small sample. Data suggest RDE stereotest results should be used and interpreted with caution.
Keltner, 1995 (3.0)												Data suggest SWAP may be beneficial in detection of neuro-ophthalmological disorders and may be better than standard automated visual field testing.
Heijl, 1976 (3.0)												Data suggest automatic perimetry screening better than routine perimetry screening.
Brown, 2001 (3.0)												Data suggest Lang 1 Stereotest identified both children and adults with vision defects associated with diminished stereopsis.
Smith, 2012 (3.0)												Data suggest that stereoacuity measurements do not need to occur prior to visual acuity testing as thresholds do not deteriorate.
Bentley, 2012 (2.5)												Data suggest UFOV test shows some variability (greatest for glaucoma subset) as well as a “learning effect”.
Ooi, 2015 (2.5)												Data suggest that binocular depth perception information is required to locate a

												mid-air target but not when the target is on the ground.
Mousa, 2013												Data suggest multifocal visual evolved potential objective perimetry (mfVEP) shows promise in the early detection of glaucoma although it may not be practical to the average physician due to its testing length and specific knowledge regarding results.
Momeni-Moghadam, 2011 (2.0)												Data suggest presence of stereopsis is beneficial when determining symptomatic vs asymptomatic subjects.
Pugesgaard, 1987 (2.0)												Data suggest clinical examination in tandem with other stereotests is useful for accurately diagnosing eye conditions associated with stereopsis.
Shousha 2013 (5.5)		Diagnostic		54 eyes; 53 participants			Ocular surface lesions		"custom-build UHR OCT"	UHR OCT served as a valuable tool in analyzing and diagnosing ocular surface lesions similar to histopathologic specimens. UHR OCT also aided in guiding the diagnosis of primary	"This study found that UHR OCT images correlated remarkably with histopathologic results in all studied lesions. This novel, noninvasive diagnostic technique can reveal the structure and location of the lesion and can aid in guiding	Study suggests ultra-high resolution OCT imaging showed strong correlation to histopathologic specimens. Therefore this technique is a non-invasive tool which can help in diagnosing ocular surface lesions.

										histiocytosis, conjunctival amyloidosis and amelanotic melanoma.	the diagnosis and management."	
Rush 2013 (2.5)		Diagnostic		22 participants			Anterior corneal scarring		Spectral domain OCT (Cirrus HD-OCT), surgery performed, clinical outcomes assessed, long term follow-up.	In a comparison of preoperative versus postoperative means (95% CI), there were significant differences in BSCVA (LogMAR), topographic cylinder (diopters), topographic projected visual acuity (LogMAR), and crater depth by OCT (μm): BSCVA- 0.82 (0.61-1.02) vs. 0.40 (0.19-0.61), (p=0.007), topographic cylinder- 4.42 (3.54-5.30) vs. 2.90 (2.02-3.78), (p=0.0173), topographic projected visual acuity- 0.36 (0.30-0.43) vs. 0.26 (0.19-0.32), (p=0.0261), crater depth- 61.4 (49.5-73.5) vs. 12.5 (0.8-24.2), (p<0.0001).	"OCT-guided transepithelial PTK algorithm described in this study can result in excellent visual and anatomic outcomes in patients with anterior corneal scars, particularly with crater formation. The algorithm in this study may also restore the uniformity of the Bowman layer and normalize the epithelial thickness, thereby reducing postoperative residual irregular astigmatism. Because the corneal epithelium is photoablated at a rate similar to that of the corneal stroma, the corneal epithelium may effectively act as a masking agent during transepithelial PTK, obviating the need for masking agents such as sodium hyaluronate or biomask."	Small sample size case series suggesting new technique for managing anterior corneal scarring with preliminary favorable results.

Foreign Bodies, Rust Rings, and Corneal Abrasions

RELATED TERMS

- Corneal Abrasion
- Corneal Injury
- Corneal Scratch
- Corneal Laceration (not same as an abrasion)
- Corneal Foreign Body
- Adherent Corneal Foreign Body
- Embedded Corneal Foreign Body
- Metallic Foreign Body
- Rust ring
- Ferrous ring

OVERVIEW

Foreign bodies and corneal abrasions are the most commonly reported occupational ophthalmological conditions [59, 83, 361]. In experienced hands, they are usually relatively simple to manage. However, complications such as infections and other adverse sequella occasionally occur.

RISK AND CAUSATION

Risk Factors

Risks differ widely across occupational groups. Both foreign bodies in the eye and corneal abrasions may occur in nearly any occupational workgroup. Yet, those at highest risk tend to be employed in construction and metalworking occupations, especially where high impact and/or grinding occur. ([362], [363-368]. Work-related injury was the most common cause, accounting for 70% - 72% of all eye injuries [83]). More than 90% of injuries at work were by workers who worked with grinding/buffing, welding, working in dusty atmospheres, and drilling/hammering [83]. Those exposed to windy environments are also particularly susceptible. Protective eye wear reduces, but does not eliminate risks [72, 83, 369, 370]. In some studies, most workers were not wearing eye protection even though it was available [83, 370].

Causation

Causation is rarely at issue as the onset of symptoms is generally quite acute. When the onset is acute, the event at hand determines the cause.

Prevalence/Incidence

Population-based incidence data are not available. Males between the ages of 20-40 were more likely to be seen with ocular trauma than were women [83, 370, 371]. In an Australian metropolitan area, corneal abrasions were among the top five ocular emergencies [361]. US data are spares and eports

from Korea, Singapore and Nigeria found work was the most common causative factor for ocular traumatic emergencies [59, 83, 372]. Corneal abrasions are well known to occur in the peri-operative and intensive care settings due to lack of protective reflexes [373-377], but are beyond the scope of this guideline.

Work Relatedness

Work-relatedness is determined by whether the ocular event occurred out of, or in the course of employment. As these are acute events, such determinations of work-relatedness are rarely difficult or controversial.

SIGNS AND SYMPTOMS

Medical History

Symptoms of corneal abrasions, foreign bodies and rust rings both commonly include:

- A foreign body sensation.
- Acute onset of symptoms (usually)
- Pain. May be severe, especially if large foreign body or extensive abrasion(s).
- Tearing
- Redness
- Photophobia, especially if more severe
- Visual acuity usually preserved unless visual axis affected

Onset

- Symptom onset is sudden and timed with a known event such as metalworking. Abrasions often involve rubbing the eye, with or without a prior foreign body sensation.

Current treatments used

- Usually none, although may have included flushing of the eye.

Prior injuries and prior treatments

- Risk Factors
- Workers with corneal foreign bodies often have had the same in the past, as they tend to hold at-risk jobs (e.g., metalworking).

RED FLAGS

Red flags for potentially more serious injuries include [378, 379]:

- History of penetrating trauma or high impact metalworking without eye protection
- Suspected penetration of the globe
- Lacerated cornea
- Lacerated globe
- Ruptured globe
- Impaled globe
- Impaired extraocular eye movements
- Gradual onset of photophobia without an inciting event
- Systemic symptoms or diseases, especially rheumatological

- Purulence
- Abnormal visual acuity without objective foreign body and/or abrasion in the visual axis

JOB ANALYSIS AND PREVENTION

The employer's roles include primary prevention as well as facilitating secondary and tertiary prevention. Primary prevention activities include engineering interventions such as machine guarding to prevent exposure to the generation of projectiles from hammering, grinding, drilling, and use of other high-speed machines [371].

Education is an important component of prevention [371]. Most often, in higher risk settings, eye protection is still required after consideration of engineering controls to prevent ocular injuries. Safety eye wear, includes glasses, goggles face shields and splash guards, and should be selected based on the exposure(s) to adequately prevent work-related eye injuries.

The employer's roles include eyewear provision, education and promotion of the use of appropriate eye safety wear [368]. Employer's roles also include facilitating appropriate medical care for eye injuries that are incurred at the workplace. Employers sometimes also facilitate consultations when suboptimal clinical results occur.

One role of an employer is education of the susceptible workforce regarding ocular hazards [380, 381].

Education for Potential Eye Injuries

Recommended.

Education is recommendation for workers who have potential for eye injuries, e.g., from chemical splashes, impacting metal and/or wind-blown objects.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	All workers should be trained if they have potential for eye injuries, e.g., from chemical splashes, impacting metal and/or wind-blown objects.
Benefits:	Reduction in risk of injury
Harms:	Negligible
Frequency/Dose/Duration:	Pre-placement, periodic and post-injury
Indications for Discontinuation:	Lack of exposure
Rationale:	Behavioral and education training on injury prevention has been shown to be successful in a few studies, although it is combined with protective eye wear [73, 380, 381]. Training to prevent eye injuries is not invasive, has no adverse effects, is of negligible cost, has demonstrated efficacy and is thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits.
Comments:	

Evidence for Education

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Eime 2005 (score =)	Eye Injury Prevention	Field Study	Sponsored by NHMRC Translational Grant in Injury, R Eime was sponsored by NHMRC Public Health Postgraduate Research Scholarship, C Finch was sponsored by NHMRC Principal Research Fellowship. No COI.	N = 992 squash players --- 698 Males, 224 Females Median age = 38.2 years		N = 266 players at PEP venues completing the survey before the intervention VS N = 379 players at PEP venues completing the survey after the intervention VS N = 170 players at control venues completing the survey before the intervention VS N = 232 players at control venues completing the survey after the intervention. No follow-up mentioned.		There is no difference between PEP and control groups in pre/post intervention changes of players wearing PEP (OR = 0.77, CI 95% 0.14 - 1.45). PEP players had a 2.4 times greater odds (OR, CI 95% 1.3 – 4.2) of wearing appropriate PEP when compared to control players. Players at PEP venues were 2.1 times more likely to start wearing PEP "this year" than the players at the control venue (p = 0.04, 95% CI 1.1-4.2). PEP group had a larger increase in knowledge about open eye guards not providing adequate protection (p=0.05).	"Components of the PEP intervention were shown to be effective. The true success will be the sustainability and dissemination of the project, favourable eyewear behaviours, and evidence of the prevention of eye injuries long into the future."	

Forst 2004 (score =)	Eye Injury Prevention	Field Study	Sponsored by the National Institute for Occupational Safety and Health and by NIOSH Training Grant. No mention of COI.	N = 703 farm workers that received safety glasses and an information sheet --- 563 Males, 140 Females. Mean age = 32.9 years.		Block A: 256 received eyewear, worked alongside promoters, and were trained by promoters VS Block B: 298 received eyewear, promoters collected data and no training was provided VS Block C: 149 received eyewear with no training and research was conducted. No follow up mentioned		All blocks (A, B, C) were more likely to wear protected eyewear after intervention than before; meaning simply passing out safety glasses and making workers aware of dangers improves the use of protective eyewear. Those that received training by the promoters had the greatest improvement of eye safety/risk knowledge. The improvement was determined by pre/post intervention questions.	"CHWs were an effective tool to conduct research and to train farm workers in eye health and safety, improving in this case the use of personal protective equipment and knowledge about work-related injuries."	

Forst 2006 (score =)	Eye Injury Prevention	Field Study	No mention of sponsorship or COI.	N = 725 farm workers that received safety glasses and an information sheet --- No mention of age of sex.		Block A: 256 received eyewear, worked alongside promoters, and were trained by promoters VS Block B: 298 received eyewear, promoters collected data and no training was provided VS Block C: 149 received eyewear with no training and research was conducted. No follow up mentioned		The main reasons for wearing/not wearing safety glasses fell into one of the following categories: (1) perception of risk and effectiveness of eyewear reducing risks, (2) is the eyewear mandated and provided, (3) its impact on visual acuity, (4) comfort, (5) appearance, and (6) nuisance of carrying them. Many LFW mentioned the use of dark glasses obstructed their vision when it gets dark out (i.e. cloudy) and when working inside. Also, many workers were influenced by their co-workers using them.	"A successful program that promotes use of safety glasses among LFWs could be disseminated across the U.S. to significantly reduce eye injuries in this vulnerable population."	

Mancini 2005 (score =)	Eye Injury Prevention	Observational Study	No mention of sponsorship or COI.	N = 237 metal-ware factories with reported eye injuries with ~ 32000 workers. No mention of age or sex		~15000 Metal factory workers VS ~12000 Construction workers VS ~6000 wood/ceramic workers. 4 follow up time periods following first intervention: (1) 1991-1992, (2) 1993-1996, (3) 1997-2000, (4) 2001-2003.		Each group had an overall reduction in both eye/non-eye injuries, with the sharpest reduction in eye injury coming from metal workers. Metal workers had the greatest reduction in eye injury compared to non-injury, but not the wood/ceramic and construction workers. However, metal workers had a fivefold risk of an eye injury while construction workers had a twofold risk.	"Results suggest that a carefully coordinated, extensive, multicomponent intervention can lead to lasting reductions in the burden of eye injuries"	

Protective Eyewear for Prevention of Eye Injuries

Recommended.

Behavioral and Psychological Interventions

Protective eyewear is recommended for prevention of eye injuries.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Moderate and high risk occupations and at-risk workforces. The employer should educate the workers regarding the potential for ocular injury and the means of protection [71]. Especially in high-risk settings, it is recommended that this should then be followed by enforcement.
Benefits:	Proactive reductions in risks of injury
Harms:	Time to educate
Frequency/Dose/Duration:	Generally at baseline and at least annually in moderate and high risk settings.
Indications for Discontinuation:	At-risk exposure(s) have been engineered out
Rationale:	Protective eyewear promotion (PEP) has been shown to be effective for improving compliance, although not in some studies for reducing the rate of injuries [71, 381, 382], for which studies are likely underpowered. Other studies combining education and protective eyewear have shown reductions in injuries [380]. In one study, there was a 2.4-fold odds of wearing appropriate eyewear compared with controls. [382] Education is low cost, without adverse effects and likely effective and thus is recommended. This may require (re)inforcement for efficacy.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Educational interventions for the prevention of eye injuries, eye controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 4 articles in PubMed, 665 in Scopus, 1 in CINAHL, 1 in Cochrane Library and 2 in other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 1 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic study met the inclusion criteria.

Comments:

Evidence for Protective Eyewear

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Test Used:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Adams 2013 (score = 6.5)		RCT, Cluster-randomization.	Supported by an intra-mural research grant from the Fluid Research Fund of the Christian Medical College, Vellore, administered through the Office of Research. Protective eyewear was funded by a project grant from the Christoffel-Blindenmission (CBM) to the Department of Ophthalmology, Christian Medical College, Vellore.	*N* = 204 consenting adult stone quarry workers in India. Mean age was 39.1 years.	Enhanced education-same initial education as the standard education group as well as additional education in the form of pre-recorded, short street-plays and messages regarding prevention of ocular injuries. Individual counselling was provided by health workers occurring 1-2 h every week in the first month and often throughout 6 months (11 total sessions) (N = 103).		Standard Education group-Initial health education consisting of health education talk by educators; display and discussion showing major ocular injuries and consequences and instructions regarding care, handling and usage of protective eyewear. Single session lasting 1-2 h, and follow up for 6 months to replace protective eyewear and answer questions from workers and assess outcomes (N = 101)	6 months	Outcome measures: Compliance with protective eyewear. Compared to standard education, the enhanced education group significantly increased compliance with protective eyewear by 15% at 3 months (Odds ratio, 95% CI); 2.1 (1.2-3.8), and 25% at six months; 2.7 (1.5-4.8). At baseline, 80/103 (78%) in the enhanced education and 88/101 (87%) in the standard education group reported some sort of eye injuries in the past. The 3 month incidence of eye injuries was	"Provision of appropriate protective eyewear reduces the incidence of eye injuries in stone quarry workers. Periodic educational and motivational sessions with individuals and groups facilitates sustained use of protective eyewear."	Cluster randomized 6 quarries. Data suggest enhanced education (including more methods) effective for compliance but not eye injuries (both significantly improved).

									reduced by 16% in the enhanced education and 13% in the standard education group compared to three months before the study. At 6 months, 12% and 7% decrease in enhanced and standard educational groups, respectively, p<0.05.		
Eime, 2005 (score = 2.5)		RCT	Sponsored by an NHMRC Translational Grant in Injury. RE was funded by an NHMRC Public Health Postgraduate Research Scholarship. CF was supported by an NHMRC Principal Research Fellowship. No COI.	*N*= 992 total surveys were completed among squash players in Australia. 222 pre-intervention and 360 post-intervention in the PEP group and 146 pre- and 220 post-intervention in the control group. Mean age was 38.3 years.	PEP intervention group- Protective eyewear promotion (PEP), education about the benefits of wearing eyewear. (N=266 players pre- and 379 post-intervention)		Control group- no intervention was used (N= 170 pre- and 232 post-intervention). 4 centers in the northwest region of Melbourne received PEP and 4 centers in the southeast region of the city received no-intervention.	Follow-up for 4 months.	Outcome measures: Compliance with protective eyewear. At the PEP venues, 266 players completed the survey before the intervention and 379 after the intervention. At the control venues, 170 surveyed before the intervention and 232 after the intervention. There was no difference	"Components of the PEP intervention were shown to be effective. The true success will be the sustainability and dissemination of the project, favourable eyewear behaviours, and evidence of the prevention of eye injuries long into the future."	Cluster randomized but only two regions. Then sampled with unclear methods. Data suggest increased use of eyewear.

									between PEP and control groups from the pre- to post-intervention change in the number of players wearing protective eyewear while playing (Odds ratio (95% CI)); OR = 0.77 (0.41 to 1.45) (p>0.05).		

Safety Glasses in Most Employment Settings

Recommended.

Devices

Safety glasses suffice for most employment settings and are recommended for most low to moderate-risk exposure situations.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – High

Indications:	Workers at risk of penetrating trauma, hammering/pounding metal, chemical splashes or performing work that previously resulted in foreign bodies.
Benefits:	Injury Prevention
Harms:	Minor discomfort
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	Removal from at-risk task

Rationale: Safety glasses and/or safety eyewear have been shown to be effective for reductions in eye injuries [380]. Safety glasses are recommended for prevention of eye injuries and the specific type of protection is ideally selected to address the worker(s) specific job task(s). Safety glasses suffice for most employment settings. Where there are high-risks of penetrating eye trauma or chemical splashes, safety goggles, face shields and/or splash guards are generally preferable.

Evidence: A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: eye, safety glasses, safety eyewear, safety goggles, eye protective devices, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 117 articles, and considered 3 for inclusion. In Scopus, we found and reviewed 2,782 articles, and considered zero for inclusion. In CINAHL, we found and reviewed 40 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 10 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 3 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.

*Comment*s:

Safety Goggles, Face Shields and/or Splash Guards in High-Risk Jobs for Penetrating Eye Trauma or Chemical Splashes

Recommended.

Devices

Where there are high-risks of penetrating eye trauma or chemical splashes, safety goggles, face shields and/or splash guards are Recommended, Insufficient Evidence.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

Indications:	Workers at risk of penetrating trauma, hammering/pounding metal, chemical splashes or performing work that previously resulted in foreign bodies.
Benefits:	Injury Prevention
Harms:	
Frequency/Dose/Duration:	
Indications for Discontinuation:	Removal from at-risk task
Rationale:	There are no quality studies. There are no quality comparative trials. In settings were exposures risks and/or consequences of exposures are higher, safety goggles, face shields, and/or splash guards are recommended for prevention of eye injuries. However, Safety glasses likely prevent ocular injuries from splashes and injuries associated with penetrating eye trauma. Goggles, face shields and/or splash guards may be preferable where risk of splashes is high or where risks of projectile metal is quite high.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: eye, safety glasses, safety eyewear, safety goggles, eye protective devices, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 117 articles, and considered 3 for inclusion. In Scopus, we found and reviewed 2,782 articles, and considered zero for inclusion. In CINAHL, we found and reviewed 40 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 10 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 3 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	Goggles may be preferable where risk of splashes is high. Goggles may also be Indicated where risks of projectile metal is quite high. However, they are typically less well tolerated.

DIAGNOSIS

Initial Assessment

Visual acuity should be assessed in all patients. It may be impaired, particularly if the visual axis is involved with the injury or the injury is extensive, e.g., with heavy tearing. This is followed by a careful history of the event(s), including duration of the condition. An eye history should be obtained that includes prior trauma and diseases. A history of systemic diseases should be sought. Prior treatment should be recorded.

An eye exam should ensue. Findings on inspection typically include redness, tearing and difficulty using the eye. Larger foreign bodies are visible on direct inspection. Unless large, abrasions are usually not visible without staining. Direct inspection may provide initial identification of larger foreign bodies. Magnification should identify foreign body(ies) and, if present, rust rings. Slit lamp examination is best. Fluorescein staining should be performed after the initial eye examination has occurred.

Prompt referral for definitive care is recommended for cases with penetrating wounds, lacerations, impaired ocular movements, new pupillary defects, signs of infection, loss of visual acuity (unless a minor abrasion is in the visual axis), and signs of iritis.

Diagnostic Criteria

Corneal abrasion:

- Linear uptake on fluorescein staining, may be multiple. May have identifiable parallel linear streaks of uptake. May also have one large defect.

Foreign body:

- Visible foreign matter in the eye, either upon inspection or with slit lamp examination
- Foreign matter does not move with eyelid movement if it is embedded or fixed

Rust ring:

- Generally requires a ferrous foreign body in the eye for at least 3-4 hours and, most commonly, overnight. Often visible without magnification, however small rust rings may require slit lamp examination to observe

Classification

Minor abrasions, rust rings and foreign bodies are not commonly classified.

History

The history should include a careful ascertainment of the event(s), including duration of the condition. Particularly important aspects are whether high-impact was used to attempt to estimate the impact and probability of a penetrating foreign body. For example, hammering a nail or metal stamping have higher potential for penetrating trauma, while looking up under a car for routine muffler work with debris dropping in the eye does not. Use of eye protection (glasses, goggles) should be ascertained, and generally (re)recommended if the exposure is ongoing. An eye history should be obtained that includes prior trauma, diseases especially affecting the eye(s). Systemic disease should be sought. Prior treatment should be recorded, including whether the eye has been irrigated or otherwise treated.

Physical Exam

In general, physical examination for simple corneal abrasions, rust rings and foreign bodies should include the following elements:

- Distant visual acuity, usually Snellen
- Inspection, appearance (sclera, conjunctiva, blood)
- Signs of other potential foreign bodies in the eyelids, eye brows and on the skin
- Periorbital appearance
- Extraocular movements
- Pupillary reactivity, iris and appearance
- Slit lamp examination
- Fluorescein staining

Other physical examination components that are sometimes used for apparent work-related foreign body eye injuries include pinhole testing (particularly if there is a reduction in visual acuity), direct ophthalmoscopy, and occasionally, ocular pressure/manometry.

DIAGNOSTIC RECOMMENDATIONS

Visual Acuity Testing

Distance visual acuity screening is performed at the initial visit to document current visual acuity, guide clinical management, and as a baseline for follow-up visits. The Snellen chart test is considered the gold standard in visual acuity testing. Most tests are conducted at a distance of 20 feet away, however smaller letters may be used when the chart or card is less than 20 feet away ([383] http://www.nlm.nih.gov/medlineplus/ency/article/003396.htm). There are many other acuity tests that have been used including the Randot Stereoacuity test (RSA) [384], the Early Treatment Diabetic Retinopathy Study [385, 386], the Functional Acuity Contrast Test [387] and the Tritan Contrast Threshold test [388].

Visual Acuity Screening When Evaluating Eye Conditions

Recommended.

Vision screening is recommended for evaluation of eye function, including foreign body and corneal abrasion injuries.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

Benefits:	Provides clinical assessment of vision
Harms:	None
Indications:	For the evaluation of eye function after eye injury from foreign bodies and corneal abrasions.
Rationale:	There are no quality studies to directly address the utility of visual acuity testing. However, it is the primary screening test for all injured eye patients, serving as the main basis for evaluating visual acuity, and as it also is not invasive and has negligible costs is thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the

following terms: Visual Acuity Testing, Snellen Test, E-Chart, Titmus test, Eye Exam, Snellen Test, Titmus test eye, eyes, disorders, sensitivity, specificity, predictive value of tests, gold standard, accurate, accuracy, precision, precise, and test. We found and reviewed 824 articles in PubMed, 49 in Scopus, 292 in CINAHL, 20 in Cochrane Library and 0 in other sources. We considered for inclusion 16 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 21 articles considered for inclusion, 12 articles met the inclusion criteria.

Comments: N/A

Use of Slit Lamp and Fluorescein Stain for Evaluation and Diagnosis of Foreign Body and Corneal Abrasion

Recommended.

Slit lamp with fluorescein staining is recommended.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Benefits: Provides identification of foreign body and corneal epithelial defect. Observation of Seidel's sign indicates possible anterior chamber leakage or globe perforation.

Harms: None. Rare allergies

Indications: The slit lamp examination is the most common method for visualizing corneal abrasions and other ocular defects. It is also the preferred method for visualizing uptake with fluorescein staining.

Rationale: There are no quality trials comparing use of slit lamp with and without fluorescein staining. Some foreign bodies may be observed without a microscope or slit lamp. This technique requires modest practitioner skill. The procedure is moderately expensive, has no adverse effects for diagnostic purposes, is highly effective, and therefore is recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: slit lamp examination, slit lamp exam, eye, disorders, sensitivity, specificity, predictive value of tests, gold standard, accurate, accuracy, precision, precise, and test. We found and reviewed 1577 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library and 0 in other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Zero articles met the inclusion criteria.

Comments: N/A

X-ray

Roentgenograms (X-Rays) use x-ray beams to detect radiolucent objects, particularly metallic or calcified. They have been used to assess the eye's structural components and can be used to detect intraorbital foreign bodies (IOFBs), orbital and intraorbital fractures, orbital floor blow-outs and retinoblastomas [389-392].

X-ray for Evaluation of Orbital Fracture

Recommended.

X-rays have been used for evaluation of potential fractures, and penetrating eye trauma particularly if metallic [390].

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Benefits:	Detection of orbital fractures
Harms:	Mild radiation exposure
Indications:	Trauma sufficient to produce orbital fracture(s).
Rationale:	There are no quality studies of X-rays for the detection of orbital fracture, although they have been widely used. X-rays are not invasive, have no significant adverse effects and are low to moderate cost and are thus recommended for evaluation of potential orbital fracture.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Eye, Efficacy, Efficiency, Diagnostic, Sensitivity and Specificity, Predictive Value of Tests, Positive predictive value, Negative predictive value, Radiography, X-ray, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 225 articles in PubMed, 271 in Scopus, 3 in CINAHL, 1 in Cochrane Library and zero in other sources. We considered for inclusion 7 from PubMed, 1 from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 8 articles considered for inclusion, 0 trials and zero systematic studies met the inclusion criteria.
Comments:	N/A

X-ray for Evaluation of Ocular Foreign Bodies

Recommended.

X-rays have been used for evaluating the presence of ocular metallic bodies.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Benefits:	Detection of intraocular foreign bodies
Harms:	Mild radiation exposure
Indications:	High impact tool use likely to produce penetrating projectile(s) and thus risk of intraocular foreign bodies.
Rationale:	There are 2 moderate quality studies that included using x-rays for detection of intraocular foreign bodies. Clear superiority of one

	imaging method over another (e.g., CT, xray) has not been shown, and there is some evidence (i) CT is superior to xray for evaluation of trauma [393]; and (ii) MRI is superior to xray or CT to determine foreign body composition if non-ferrous [390]. X-rays are not invasive, have no significant adverse effects and are low to moderate cost and are thus recommended for evaluation of intraocular foreign bodies (especially metallic).
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Eye, Efficacy, Efficiency, Diagnostic, Sensitivity and Specificity, Predictive Value of Tests, Positive predictive value, Negative predictive value, Radiography, X-ray, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 225 articles in PubMed, 271 in Scopus, 3 in CINAHL, 1 in Cochrane Library and zero in other sources. We considered for inclusion 7 from PubMed, 1 from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 8 articles considered for inclusion, 0 trials and zero systematic studies met the inclusion criteria.
Comments:	N/A

X-Ray for Evaluation for Simple Abrasions, Rust Rings, and Non-Penetrating Foreign Bodies
Not Recommended.

X-rays are not recommended for routine evaluation of ocular abrasions, rust rings and foreign bodies.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – High

Benefits:	None for routine use
Harms:	Radiation exposure, cost
Indications:	Not indicated for simple abrasions, rust rings or foreign bodies.
Rationale:	There are no quality studies comparing use of xrays with evaluations without xray to ascertain differences in patient outcomes for simple abrasions, rust rings and/or foreign bodies. Xrays have no clear use for routine evaluation of foreign bodies that do not penetrate and thus are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Eye, Efficacy, Efficiency, Diagnostic, Sensitivity and Specificity, Predictive Value of Tests, Positive predictive value, Negative predictive value, Radiography, X-ray, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies,

	prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 225 articles in PubMed, 271 in Scopus, 3 in CINAHL, 1 in Cochrane Library and zero in other sources. We considered for inclusion 7 from PubMed, 1 from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 8 articles considered for inclusion, 3 trials and zero systematic studies met the inclusion criteria.
Comments:	N/A

Evidence for X-Ray

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Modjtahedi 2015 (score = 5.0)		Experimental	Supported by an unrestricted grant from Research to Prevent Blindness. B. S. Modjtahedi receives research support from the Heed Ophthalmic Foundation.	19 lamb cadaver eyes, Intraocular foreign bodies, 8-10 MHz probe, model: I3-ABD (Innovative Imaging, version 2)		CT, MRI, more than one rater.		Ultrasound and plain film x-ray had difficulty differentiating various IOFBs. Computed tomography could distinguish wood, CF6 spectacle plastic, polyvinyl chloride, slate, bottle glass, windshield glass, aluminum, steel, brass, copper, silver and lead.	"[M]RI is superior to CT in detecting nonmetallic IOFBs, and can also be used in conjunction with CT for the identification of their composition. We recommend MRI be considered in the evaluation of patients with a suspected IOFB and a negative CT, as well as in cases where the mechanism of injury suggest a nonmetallic IOFB."	Study suggests computed tomography is best for imaging intraocular foreign bodies showing superiority over plain x-rays. MRI, and ultrasound reserved as adjunctive tests.
Pasman 1995 [37] (score = 4.5)		Case Series	No mention of industry sponsorship or COI.	1218 patients, Possible head trauma, Plain skull radiography.		CT used.		Skull radiology had no significance in the low-risk group (No hematomas found). X-rays could not determine intracranial hematomas in the high-risk group, thus CT imaging was utilized.	CT imaging is superior to X-ray films in acute head trauma.	Study suggests plain skull x-rays are inferior to CT imaging in detecting intracranial hemorrhage post-head trauma.

Marshall 1978 [38] (score = 2.5)			No mention of sponsorship or COI.	19, Eye, Known or suspected facial fractures, Plain radiography, Xeroradiography, and Laminagraphy		Blinding of rater, surgery performed.		More sharply outlines discontinuities at bony, soft tissue interphases than plain films. Roughly twice as much radiation require per film compared to plain films.	Xeroradiograms provide a reliable alternative to plain radiograms. They can be useful alone and paired with other types of X-rays.	Small sample size in apparent pilot series. Study suggests advantage is "edge enhancement."

Computed Tomography (CT)

Computerized tomograms use x-rays but provide more detailed images with greater resolution [394]. It is considered superior to MRI for imaging fractures [395]. Its purported uses are similar to, but more extensive than xrays including detecting intraorbital foreign bodies (IOFBs), orbital fractures, orbital sepsis and traumatic optic neuropathy [39][396, 397].

CT for Evaluation of Ocular Foreign Bodies

Recommended.

CT imaging is selectively indicated for evaluation of penetrating and/or evaluation of potentially retained intraocular foreign bodies.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Benefits:	Improved diagnostic accuracy and potentially altered treatment plans
Harms:	Higher radiation exposure than x-rays, cost
Indications:	Selective use only in cases of 1) penetrating globe injuries, 2) penetrating corneal abrasions, with 3) concerns for potentially retained intraorbital foreign bodies (IOFBs).
Rationale:	There are no quality studies comparing use of CT scans with evaluations without CT scans to ascertain differences in patient outcomes. One small comparative study reported superiority of helical CT scans to conventional scans in the pre-operative setting (Lakits 1998). CT scans have been suggested to be helpful for evaluating intraorbital foreign bodies (IOFBs) [394, 396, 397] and thus are recommended for selective use.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: computed tomography, orbit injury, eye injury, eye foreign bodies, penetrating eye injuries, eye fractures, trauma, corneal abrasion, rust ring, hyphemia, conjunctivitis, bacterial infection, fungal infection, pterygium, surfer's eye, transplants, cataracts; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency, review. We found and reviewed 847 articles in PubMed, 13 in Scopus, 49 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 10 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 10 articles considered for inclusion, 2 diagnostic studies and 1 systematic studies met the inclusion criteria. Of these, 2 were of moderate quality.
Comments:	N/A

CT for Evaluation of Possible Orbital Fracture

Recommended.

CT imaging is selectively indicated for evaluation of penetrating globe injuries and/or abrasions accompanied by concerns for orbital fractures unaddressed by radiographs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Benefits:	Improved diagnostic accuracy and potentially altered treatment plans
Harms:	Higher radiation exposure than x-rays, cost
Indications:	Selective use only in cases of suspected fractures not seen on simple X-ray, suspected orbital sepsis or traumatic optic neuropathy or penetrating globe injuries. May be indicated for likely fractures with complications (e.g., impaired visual function). Simple orbital fractures without complications do not require CT (e.g., no impaired extraocular movements, normal visual function). (Pasman 95; Lakits 98)
Rationale:	There are no quality studies comparing use of CT scans with evaluations without CT scans to ascertain differences in patient outcomes. There is one large trial with a risk tool suggesting efficacy with CT for blunt trauma (Bodanapally 2014). CT scans have been suggested to be helpful for evaluating orbital fractures, orbital sepsis and traumatic optic neuropathy [394, 396, 397] and thus are recommended for selective use.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: computed tomography, orbit injury, eye injury, eye foreign bodies, penetrating eye injuries, eye fractures, trauma, corneal abrasion, rust ring, hyphemia, conjunctivitis, bacterial infection, fungal infection, pterygium, surfer's eye, transplants, cataracts; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency, review. We found and reviewed 847 articles in PubMed, 13 in Scopus, 49 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 10 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 10 articles considered for inclusion, 2 diagnostic studies and 1 systematic studies met the inclusion criteria. Of these, 2 were of moderate quality.
Comments:	N/A

Evidence for CT scan

Author Year (Score):	Category:	Study type:	Conflict of Interest	Number	Area	Diagnoses:	Type of CT	X-ray used	MRI used	More than one rater	Blinding of rater	Myelography	Surgery Performed	Clinical Outcomes	Long-term Follow-up (mean when noted)	Results	Conclusion	Comments
Lakits 1998 (score = 5.0)	[Previous table header, if any]	Diagnostic	No mention of sponsorship or COI.	18 Participants	Eye	Penetrating eye injuries and possible metallic intraocular foreign bodies	Helical CT (Tomoscan SR 7000 with a tube current of 250 mA) versus Conventional CT (Tomoscan SR 7000 with a tube current of 200 mA)	No	No	Yes	Yes	No	No	No	No	Both helical and conventional CT detected metallic intraocular foreign bodies for the coronal, axial and reconstructed planes. Similar quality images yielded for both scans on axial and coronal parameters. Examination times and radiation exposure less in helical CT compared to conventional CT.	"[H]elical CT multiplanar imaging is superior to conventional CT in the preoperative assessment of metallic intraocular foreign bodies in clinical practice. The main advantages of helical CT are shortened examination time, reduced radiation exposure, good multiplanar reconstruction capability, and reduced motion artifacts. The multiplanar reconstruction possible with helical CT affords useful sagittal and coronal images without the need for	Very small sample size so generalizability not possible. Further studies needed to validate these preliminary results. Initially helical CT imaging looks promising for reduced radiation exposure and there is shortened exam time (18 sec vs. 52 sec)

																	additional scanning, particularly in patients who cannot be positioned for conventional CT coronal views because of neck injuries or other reasons."	
Bodanapally 2014 (score = 4.5)	[Previous table header, if any]	Diagnostic	No mention of sponsorship. No COI.	1273 orbits; 637 participants	Eye	Traumatic optic neuropathy from blunt craniofacial trauma	40 or 64 section CT; Brilliance 40-channel or Brilliance 64-channel system	No	No	Yes	Yes	No	No	No	No	Significant CT predictor variables analyzed for traumatic optic neuropathy included intraconal emphysema, intraconal hematoma, optic canal fracture, hematoma along posterior globe and extraconal hematoma: Intraconal emphysema- OR 5.21, 95% CI 2.03-13.36, (p=0.001), intraconal hematoma- OR 12.73, 95% CI 5.16-31.42, (p<0.001), optic canal fracture- OR 4.45, 95% CI 1.91-10.35, (p=0.001), hematoma along posterior globe- OR 0.326, 95% CI 0.111-0.958, (p=0.041), extraconal hematoma (OR 2.36, 95% CI- 1.03-5.41, (p=0.052).	"Radiologists might suggest the possibility of TON on the basis of CT findings of craniofacial and intraorbital injuries after facial trauma. Such patients should be directed toward early ophthalmologic consultation to prevent delays in the diagnosis of TON as other life-saving treatments are performed in patients with severe trauma."	Study suggests that this risk model "may" help predict patients with traumatic optic neuropathy after blunt facial trauma but MRI is a better diagnostic tool for evaluating optic neuropathy.

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imagery (MRI) has been used especially for soft tissue imaging [398-402] that includes intraocular, non-ferrous foreign bodies [403, 404].

MRI for Diagnosis of Foreign Body and Corneal Abrasion

Not Recommended.

MRI is not recommended for routine evaluation of eye foreign body or corneal abrasion, particularly if there is concern of ferrous-metallic object penetration of the globe. MRI may be a reasonable option to evaluate intraocular foreign bodies when there is assurance that an intraocular foreign body is non-ferrous [390, 403] and/or there are concerns for fracture with visual impairment

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – High

Benefits:	Identification of foreign body(ies)
Harms:	Contraindicated with ferrous-metal foreign body due to potential further trauma, costs
Indications:	Not recommended for most ocular events. Rarely recommended for soft tissue injuries. However, MRI is useful for evaluation of other conditions including orbital fractures, and trauma with visual impairment.
Rationale:	There are no quality studies comparing use of MRIs with evaluations without MRIs to ascertain differences in patients outcomes. MRI may be a reasonable option to evaluate intraocular foreign bodies if they are known to be non-ferrous [403]. MRIs have been shown to be helpful for evaluating soft tissues, including retinal imaging, evaluating staphyloma [405]. Workers are usually unable to identify whether a potential metal foreign body is ferrous or not, providing further concerns about the use of MRI in that setting. When there is concern regarding detection of orbital fractures, CT is generally preferable.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Magnetic Resonance Imaging (MRI), eye, orbit, eye foreign bodies, eye injuries, penetrating, sensitivity and specificity, predictive value of tests, gold-standard, accurate, accuracy, precision, precise and test. We found and reviewed 275 articles in PubMed, 5 in Scopus, 5 in CINAHL, 9 in Cochrane Library and zero in other sources. We considered for inclusion 9 from PubMed, 0 from Scopus, 0 from CINAHL, 1 from Cochrane Library and 0 from other sources. Of the 10 articles considered for inclusion, 3 articles met the inclusion criteria.
Comments:	N/A

Evidence for Magnetic Resonance Imaging (MRI)

Author Year (Score):	*Category*	*Study type*	*Conflict of Interest*	*Number*	*Area*	*Diagnoses:*	*CT used*	*MRI used*	*T1 weighted images*	*T2 weighted images*	*X-ray*	*Myelography*	*More than one rater*	*Surgery Performed*	*Clinical Outcomes*	*Long-term Follow-up (mean when noted)*	*Results*	*Conclusion*	*Comments*
Mosisseiev 2015[48] (score = 5.5)		Diagnostic	No sponsorship or COI.	36 porcupine eyes; 30 with IOFBs; 6 control eyes	Eye	Intraocular foreign bodies (IOFBs)	1.5 T Interventional MRI (Optima 450w)	Helical CT Technology (Brilliance 64)	Yes	Yes	No	No	Yes	No	No	No	MRI proved to be more effective than CT in identifying various materials in the eye. Although CT detected a general appearance of IOFBs, MRI allowed for a more detailed analysis of the type of material embedded.	"[M]RI is superior to CT in detecting nonmetallic IOFBs. Moreover, the integration of information available from T1-, T2-, and GE-MRI and CT images may be used to identify the composition of such IOFBs."	Small sample suggests MRI superior to CT in the detection of nonmetallic IOFB's.
Nasr 1999[49] (score = 2.0)		Diagnostic	Supported in part by unrestricted grants from St. Giles Foundati	19 participants	Eye	Penetrating orbital injury with retainer organic foreign bodies	Not stated	Not stated	Yes	Yes	No	No	No	Yes	No	No	Preoperative CT identified foreign bodies in 42% of the participants, while MRI	"[T]he management of organic orbital foreign bodies, a detailed history coupled with careful examination as	Small sample study suggests that, when possible, identification of the foreign material is beneficial in preventing

			on, New York, New York (ZAK, BGH), and Research to Prevent Blindness, Inc., New York, New York (BGH, JCF). No mention of COI.													identified foreign bodies in 57% of the participants.	well as the identification of the foreign material before surgery is very helpful, but may not be possible in approximately 50% of the cases with the use of CT and MRI. Even at surgery, one may have difficulty in locating the foreign body under direct visualization. Fragmentation of the foreign body at the time of removal and soft tissue damage caused by exploration may also present problem."	long term complications associated with organic foreign bodies.

TREATMENT RECOMMENDATIONS

Foreign Body Removal

Depending on size and degree of embedding, foreign bodies are commonly removed through irrigation, cotton swab, hypodermic needle tip, burr tool, and natural tears [406-408]. Magnets are also successfully used for ferrous foreign body `removals [409, 410]. Rust rings also occur and are generally easily removed [411, 412].

Copious Irrigation for Removal of Superficial Foreign Body(ies)

Recommended.

Surgical Considerations

Copious irrigation (e.g., approximately 200mL to 1L) is recommended for removal of superficial foreign body(ies) in some circumstances. The use of a Morgan Lens is not recommended for simple foreign bodies and may cause (additional) abrasions unless there is concern related to chemical or other substance that may result in rapid corneal injury through pH imbalance or other mechanism (See Chemical Conjunctivitis Guideline below). Copious irrigation after removal of a foreign body (see below) is often included as an adjunct to attempt to assure removal of foreign body(ies).

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic

☒ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Foreign body sensation, especially with mechanism suspected to result in unembedded foreign body(ies), such as fiberglas, windblown debris. Also selectively used after foreign body removal, particularly if the foreign body fragments.
Frequency/Dose/Duration:	Irrigation with from approximately 200mL to 1L of either sterile saline or lactated Ringer's solution is recommended [413]. Experimental evidence suggests solution choice is unimportant [413].
Benefits:	Removal of foreign body or irritants.
Harms:	Negligible when irrigated without an appliance. May have minor irritation
Indications for Discontinuation:	After completion. May repeat until symptoms resolved.
Rationale:	There are no quality studies comparing irrigation with no irrigation for foreign bodies of the eye. Irrigation is low cost, minimally invasive, associated with negligible risks, is successful and is recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: nonpenetrating, superficial, ocular, corneal, penetrating, foreign body, eye foreign bodies, "rust ring, eye, eyes, removal, extraction, leaving in the eye, mydriatics, cycloplegic, meidiatric effect, extraction size, extraction

location, woods lamp, slit lamp, fibrin tissue adhesive, fibrin sealant, autologous fibrin tissue adhesive, fibrin klebe system immune, transglutine, crosseal, tisseel, tissel, tussucol, beriplast, seal fibrin, eye irrigation, irrigation, morgan lens, morgan lenses, patching, patch, treatment, eye magnet, eye burr, diamond burr, alger brush, ophthalmic burr, aaron burr, burr, contusion, Acuvail, acular LS, acular PF, acuvil, bromday, bromfenac ophthalmic, diclofenac ophthalmic, flurbiprophen ophthalmic, Ilevro, ketorolac ophthalmic, phenylephrine ophthalmic, nepafenac ophthalmic, nevanac, ocufen, omidria, prolensa, voltaren ophthalmic, ketoroloac tromethamine, topical NSAID, “Anti-Inflammatory Agents, Non-Steroidal", Gentamicin, tobramycin, besifloxacin, ciproflaxin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, azithromycin, erythromycin, bacitracin, polymyxin, natamycin, neomycin, gramicidin, trimethoprim, sulfacetamide, Neosporin, polytrim, natacyn, romycin, Azasite, ocuflox, vigamox, lquix, quixin, Zymar, Ciloxan, besivance, tobrex, Anti-Bacterial Agents, Anti-Bacterial, Agents, antibiotic ointment, antibacterial ointment, anesthetics, lidocaine, tetracaine, proparacaine, fluress, topical anesthetic, prednisolone, fluorometholone, steroids, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 85 articles, and considered 13 for inclusion. In Scopus, we found and reviewed 10,342 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed 137 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 173 articles, and considered 0 for inclusion. We also considered for inclusion 4 articles from other sources. Of the 18 articles considered for inclusion, 2 randomized trials and 0 systematic studies met the inclusion criteria.

Comments: N/A

Evidence for Foreign Body Removal

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/*	*Population:*	*Comparison:*	*Results:*	*Conclusion:*	*Comments:*
Jones 1998[54] (score = 5.5)	[Previous table header, if any]	RCT	Sponsorship, supported in part by a Geisinger Clinic Research Endowment Fund Grant.	No mention of COI.	N = 63 with no preexisting ophthalmologic abnormalities and at least 18 years old. Ages: 30.9±9.22 years.	Morgan therapeutic lens (MTL) and balanced salt solution (BSS) (N = 15) vs. No lens and BSS (N = 15) vs. MTL with lactated ringer solution (LR) (N = 16) vs. No lens and LR (N = 15). All patients with one eye as control irrigated with NS. Eye irrigation for 15 mins. Follow-ups at 5 min. intervals during irrigation and once 15 min. post irrigation.	A lens-solution interaction was found (p=0.023), indicating that the experimental groups experienced different levels of discomfort. No difference in Global Evaluations by patients or MDs in either treatment or control eyes in any of the treatment groups (p>0.05). Significantly higher ocular pH difference between pre- and post-irrigation for control eyes in those irrigated with MTL (p = 0.046).	"There does not appear to be any clinically important difference in discomfort scores between the tested ocular irrigation fluids when used without the MTL."	Experimental study in healthy adults. Data suggest comparability across all 4 groups.

O'Malley 2008[55] (score = 5.0)	[Previous table header, if any]	Experimental	No mention of COI or Sponsorship.	N = 10 healthy participants, > 18 years. Mean age not provided.	All eyes with tetracaine instilled. Then, Control Arm Irrigation with 1 NS at 35mL/min (N=NA) vs. Experimental Arm Irrigation with 1 L of NS with 10mL of 1% lidocaine HCL at 35 mL/min Subjects served as their own controls. (N=NA). Follow-ups at 5, 10,15,20,25 min during irrigation.	One-way analysis of variance p value for combined time sets significant ($p<0.0001$). Difference in mean Likert scores significant at 15 mins [1.22 (95% CI 0.16 - 2.28)], 20 mins [1.44 (95% CI 0.38 - 2.5)], and 25 mins [1.55 (95% CI 0.62 - 2.28)].	"Healthy volunteers were better able to tolerate eye irrigation with a 0.01% lidocaine-saline, solution compared with plain saline, with no reported adverse effects.	Experimental study in healthy adults. Small sample size. Data suggest lidocaine makes Morgan lens more comfortable.	

Foreign Body Removal of Superficial Foreign Body(Ies) with Cotton Swab, Needle or Magnet

Recommended.

Surgical Considerations

Foreign body removal is recommended. The device used (e.g., needle, tool, magnet, swab) is recommended to be based on expected foreign body composition, depth of embedding and clinician's experience. Copious irrigation after removal of a foreign body (see above) may also be included as an adjunct to attempt to assure removal of foreign body(ies) especially if fragmentation occurs on attempted removal. Use of slit-lamp examination is usually helpful, but is optional for simple removals, especially when the foreign body is visible without magnification and removal is easy (e.g., use of magnet). Slit-lamp is essential if prior removal attempts fail. [406]

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic
☒ Preoperative ☐ Perioperative ☒ Postoperative

Indications:	Foreign body visualized, and non-mobile.
Benefits:	Removal of foreign body
Harms:	Negligible in experienced hands. Rare infections, although that risk may not be associated with the foreign body removal, and instead is more associated with embedded organic matter.
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	With resolution of issue
Rationale:	Foreign body removal has not been evaluated in quality comparative trials. Use of a magnetized tool tip is quite simple and may result in less corneal damage, but its use is limited to ferrous bodies. Quality data do not clearly define that a slit-lamp examination is required [406], although for some removals it is essential. Foreign body removal is moderate cost, minimally invasive, associated with negligible risks, is highly successful and is recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: nonpenetrating, superficial, ocular, corneal, penetrating, foreign body, eye foreign bodies, "rust ring, eye, eyes, removal, extraction, leaving in the eye, mydriatics, cycloplegic, meidiatric effect, extraction size, extraction location, woods lamp, slit lamp, fibrin tissue adhesive, fibrin sealant, autologous fibrin tissue adhesive, fibrin klebe system immune, transglutine, crosseal, tisseel, tissel, tussucol, beriplast, seal fibrin, eye irrigation, irrigation, morgan lens, morgan lenses, patching, patch, treatment, eye magnet, eye burr, diamond burr, alger brush, ophthalmic burr, aaron burr, burr, contusion, Acuvail, acular LS, acular PF, acuvil, bromday, bromfenac ophthalmic, diclofenac ophthalmic, flurbiprophen ophthalmic, Ilevro, ketorolac ophthalmic, phenylephrine ophthalmic, nepafenac ophthalmic, nevanac, ocufen, omidria,

prolensa, voltaren ophthalmic, ketoroloac tromethamine, topical NSAID, “Anti-Inflammatory Agents, Non-Steroidal", Gentamicin, tobramycin, besifloxacin, ciproflaxin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, azithromycin, erythromycin, bacitracin, polymyxin, natamycin, neomycin, gramicidin, trimethoprim, sulfacetamide, Neosporin, polytrim, natacyn, romycin, Azasite, ocuflox, vigamox, lquix, quixin, Zymar, Ciloxan, besivance, tobrex, Anti-Bacterial Agents, Anti-Bacterial, Agents, antibiotic ointment, antibacterial ointment, anesthetics, lidocaine, tetracaine, proparacaine, fluress, topical anesthetic, prednisolone, fluorometholone, steroids, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 85 articles, and considered 13 for inclusion. In Scopus, we found and reviewed 10,342 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed 137 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 173 articles, and considered 0 for inclusion. We also considered for inclusion 4 articles from other sources. Of the 18 articles considered for inclusion, 12 randomized trials and 1 systematic study met the inclusion criteria.

Comments: [Can include harms, benefits, advantages, limitations, etc.]

Removal of Rust Ring

Recommended.

Surgical Considerations

Removal of a corneal rust ring is recommended. Rust rings can develop in as little as three to four hours after ferrous metal adheres to, or penetrates the cornea [56-58]. Due to its insolubility in the corneal tissues, oxidation occurs and rust infiltrates the surrounding corneal tissue [56-58]. However, it is usually readily removed [57, 58].

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☒ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications: Presence of rust ring with or without foreign body. If foreign body visualized, it must be removed and by definition, use of a magnet for an initial tool to attempt to remove the foreign body is preferred. For rust ring removal, use of a burr under slit lamp examination is the preferable procedure. [412] Use of a hypodermic needle may be adequate to successfully remove some tiny rust rings.

Benefits:	Removal of rust ring. Improvement in visual acuity if rust ring is in the visual axis. Removal is thought to also reduce scarring.
Harms:	Negligible in experienced hands.
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is no trial comparing rust ring removal with non-removal. Rust ring removal has been evaluated in one moderate quality trial that compared manual rust ring removal with use of an electric drill and found the drill superior [412]. A low quality trial found comparative results with an electric drill compared with a burr [412]. Delayed and/or inadequate rust ring removal has been associated with worse ocular rehabilitation. [414] Rust ring removal is minimally invasive, associated with negligible risks, generally quite successful, moderately costly, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Rust ring removal, cornea, corneal, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 12 articles in PubMed, 5 in Scopus, 0 in CINAHL, 2 in Cochrane Library and 0 in other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 4 articles considered for inclusion, 2 clinical trials and 0 systematic studies met the inclusion criteria.
Comments:	N/A

Evidence for Foreign Body Removal/Removal of Rust Ring

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/*	*Population:*	*Comparison:*	*Results:*	*Conclusion:*	*Comments:*
Brown 1975 [57] (score = 6.0)	Foreign Body Removal	Clinical trial	No mention of sponsorship or COI.	N = 121 with significant corneal rust rings and possible ferrous foreign bodies.	Ages not reported.	Slim electric drill treatment group removing foreign body with dental burr and drill (N = 64) vs. Manual treatment group removing foreign body with 40 mm x 0.8 mm disposable syringe and dental burr (Eyes treated with hyoscine and oc. chloramphenicol drops) (N = 57) Follow-up daily until eyes had healed.	Manual breakup of rust rings in the firm stromal tissue proved to be more difficult with manual treatment compared with electric, causing irregularities in the resulting crater and a need for more treatment. Zero participants receiving electric treatment required a second treatment, while five participants receiving manual treatment required secondary treatment. Electric drill treatment provided clean cut craters and enabled	"The dental burr rotated by an electric drill is the quickest, safest and most precise form of treatment for corneal rust rings. It enables complete removal of the corneal rust at a single treatment and leaves a smooth crater that is no larger than the original rust ring. Pain relief is more rapid after electric drill removal; this is probably related to the complete removal of the rust. Epithelial and stromal healing are marginally faster than after manual removal and the patients' duration of attendance is less. The ideal drill is a slim straight instrument, which rotates dental burrs and is operated by a light finger pressure. A brake which stops drill rotation on lifting	Unclear if blinded. Study trends re. rust removal via drill trended superior to manual removal, though not statistically significant.

							removal of all rust without further treatment. Persisting mean pain days significantly lower in electric drill group compared with manual treatment; 0.02 days vs. .64 days, (p value not reported).	the finger is a useful safety feature."	

Haynes 1996[60] (score = 5.0)	Foreign Body Removal	RCT	No mention of COI. Supported by Ciba Vision who provided the diclofenac and placebo preparations and administrative costs.	N = 26 with corneal rust ring for less than 96 hours. Mean age: 33.5 years.	4 hourly G diclofenac 0.1% and Oc. Chloramphenicol (N = 15) vs. 4 hourly G placebo and Oc. Chloramphenicol follow-up after 48 hours. 4 hours of patching was offered to all patients (N = 11).	At day 2, mean pain scores in the diclofenac group vs. placebo for VAS favored diclofenac (p = 0.0075) and Likert scale (p = 0.042). No other differences between groups.	"[D]iclofenac significantly reduces the pain experienced after the removal of a rust ring, without producing a delay in healing."	High dropouts. Data suggest efficacy.	

Eye Patching

Eye patching has been used as a treatment for corneal abrasion injuries related to foreign body or traumatic injury of the corneal epithelium [362, 415-419]. Patching for 24 hours has been traditionally prescribed to purportedly reduce pain and a theory of promoting healing through reducing eyelid movement across the wound [417].

Eye Patching for Corneal Abrasion

Moderately Not Recommended.

Devices

Eye patching for simple corneal abrasions is moderately not recommended, including after removal of foreign bodies or rust rings.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	None
Benefits: None demonstrated	
Harms: Inability to use the eye, elimination of binocular vision, reduced depth perception.	
Frequency/Dose/Duration:	
Indications for Discontinuation:	
Rationale:	There are five moderate quality trials that compared the use of an eye patch with no patch for simple corneal abrasions. [362, 416-419] There are no quality trials comparing patch to non-patching without cointerventions, as each of the trials utilized other treatments in addition to patching, including mydriatics, ophthalmic antibiotic drops or ointments, which may also have had some therapeutic effect. However, the trial results uniformly found no clinically significant differences demonstrated between the groups in healing times, pain control or adverse outcomes. The use of an eye patch did not demonstrate altered increased risk of infection in any of the trials. Use of an eye patch may be problematic for activities requiring binocular vision and good depth perception. Evidence is consistent that an eye patch does not provide faster healing or fewer complications, and therefore patching is not recommended for simple abrasions. There are 8 low quality trials comparing the use of an eye patch with no patch concomitant in the appendix, with mostly comparable results. [417, 418, 420-425]
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: nonpenetrating, superficial, ocular, corneal, penetrating, foreign body, eye foreign bodies, “rust ring, eye, eyes, removal, extraction, leaving in the eye, mydriatics, cycloplegic, meidiatric effect, extraction size, extraction location, woods lamp, slit lamp, fibrin tissue adhesive, fibrin sealant,

autologous fibrin tissue adhesive, fibrin klebe system immune, transglutine, crosseal, tisseel, tissel, tussucol, beriplast, seal fibrin, eye irrigation, irrigation, morgan lens, morgan lenses, patching, patch, treatment, eye magnet, eye burr, diamond burr, alger brush, ophthalmic burr, aaron burr, burr, contusion, Acuvail, acular LS, acular PF, acuvil, bromday, bromfenac ophthalmic, diclofenac ophthalmic, flurbiprophen ophthalmic, Ilevro, ketorolac ophthalmic, phenylephrine ophthalmic, nepafenac ophthalmic, nevanac, ocufen, omidria, prolensa, voltaren ophthalmic, ketoroloac tromethamine, topical NSAID, “Anti-Inflammatory Agents, Non-Steroidal", Gentamicin, tobramycin, besifloxacin, ciproflaxin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, azithromycin, erythromycin, bacitracin, polymyxin, natamycin, neomycin, gramicidin, trimethoprim, sulfacetamide, Neosporin, polytrim, natacyn, romycin, Azasite, ocuflox, vigamox, lquix, quixin, Zymar, Ciloxan, besivance, tobrex, Anti-Bacterial Agents, Anti-Bacterial, Agents, antibiotic ointment, antibacterial ointment, anesthetics, lidocaine, tetracaine, proparacaine, fluress, topical anesthetic, prednisolone, fluorometholone, steroids, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 85 articles, and considered 13 for inclusion. In Scopus, we found and reviewed 10,342 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed 137 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 173 articles, and considered 0 for inclusion. We also considered for inclusion 4 articles from other sources. Of the 18 articles considered for inclusion, 5 randomized trials and 5 systematic studies met the inclusion criteria.

Comments: N/A

Evidence for Eye Patching

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow up:*	*Results:*	*Conclusion:*	*Comments:*
Arbour 1997 (score = 5.5)	[Previous table header, if any]	RCT	Sponsored by Quebec Eye Bank Foundation Inc. No mention of COI.	N = 48 eyes 46 participants with epithelial erosion > 1 mm secondary to trauma or recurrent erosion syndrome sparing Bowman membrane.	Mean±SD age 41.6±11.5 years patch group, 39.8±17.1 years no patch group.	Patch (n=25) vs. No Patch (n=22). Each group received single drop of 2% homatropine hydrobromide, plus 10% sulfacet-amide sodium ointment.	Follow up was 6 months after the last visit.	No significant differences between groups on mean and maximal VAS scores, p = 0.80. No difference in linear and surface speeds of re-epithelialization between groups (p=0.78 linear speed; p=0.60 surface speed).	"[W]e found that patching corneal erosions did not significantly accelerate re-epithelialization and did not alter the epithelial wound healing pattern."	Details sparse. Data suggest no efficacy of patching in this population.
Le Sage 2001 (score = 5.0)	[Previous table header, if any]	Quasi-RCT	Sponsorship, supported by the Quebec Association of Emergency Medicine (AMUQ), the Foundation of the CHA (Enfant-Jesus Hospital), the CHA Research Center, the Quebec Federation of General Practitioners (FMOQ), and the Department	N = 163 with traumatic corneal abrasions with or without foreign bodies.	Mean (IQR) age: Patched 32 (28-38) years. Nonpatched 36 (31-46) years.	Patch plus erythromycin ointment QID) (n=82) vs. No patch (n=81) (erythromycin ointment QID).	Each group treated with topical erythromycin ointment to be applied 4 times a day.	Patch vs. no patch Healed (cumulative incidence): Day 1- 0.51 vs. 0.6; Day 2- 0.78 vs. 0.83, Day 3 - 0.92 vs. 0.88. All non-significant results were similar in both groups. Corneal healing probability after day 1, 2, and 3: (0.51, 0.78 and 0.92 vs. 0.60, 0.83 and 0.88 in group 2).	"[T]he use of eye patching…should be abandoned for its lack of efficacy. Our study confirms that the use of eye patching, although still widely used in primary care and in emergency medicine, should be abandoned for its lack of efficacy.	Quasi-randomization, allocation by every other patient. Data suggest no difference in treatment.

			of Family Medicine, Laval University. COI, NL and RV obtained research funding.							
Kaiser 1995 (score = 5.0)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N = 223 with traumatic corneal abrasion or removal of superficial corneal foreign body < 36 hours.	Mean±SD age 36.17±11.93 years.	Mydriatics and topical antibiotics ((2.5% phenylephrine/1% tropicamide); No patch. (N = 58) vs.	Pressure patch (control) along with mydriatics drops and topical antibiotics (2.5% phenylephrine/1% tropicamide) (N = 62).	No-patch vs. Patch: Traumatic Corneal Abrasions: 24hr pain change: 3.02+0.66 vs. 2.51+0.08 (p<0.01) 48hrs change: p<0.05 Days to heal: 2.33+0.66 vs. 2.60+0.77 (p<0.05) Blurred vision: 17% vs. 40% (p<0.01) Foreign Body Corneal Abrasions: 24hr pain change: 3.27+0.89 vs. 2.75+0.06 (p<0.01) 48hrs change: (p<0.05) Days to heal: 2.36+0.58 vs. 2.67+0.81 (p=0.049)	"Noninfected, noncontact lens-related traumatic corneal abrasions as well as abrasions secondary to foreign body removal can be treated with antibiotic ointment and mydriatics alone without the need for a pressure patch."	Data suggest less blurry at day 1 if not patched. Less pain at day 1 if patched.
Campanile 1997 (score = 4.5)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N = 74 with a corneal defect limited to the epithelium without evidence of	Mean age was 31 years (range 5-74).	Patched Group or PG received a one-time instillation of erythromycin ophthalmic ointment followed		After a 24 hour follow up there was a significant difference in the percent of abrasions	"Our study demonstrated a significant improvement in the healing rates of traumatic	Data suggest use of patch delays healing, although long term significance is

				ocular inflection or additional trauma		by the application of a semi-pressure patch for 24 hours (N = 31). Vs. Non-Patch Group or NPG received ophthalmic ointment applied in the affected eye every 6 hours for 24 hours (N = 33). All patients were re-evaluated at 24 hours.		healed favoring the Non-Patched Group (NPG: 97.091% vs. PG: 94.130%, p = 0.0283).	corneal epithelial defects in patients treated with an ophthalmic antibiotic ointment and mydriatic alone as compared to patients who received the same ophthalmic antibiotic ointment and mydriatic with the addition of a semi-pressure eye patch."	uncertain. Lack of study details for randomization, baseline comparability, control for cointervention s, assessor blinding.
Menghini 2013 (score = 4.5)	[Previous table header, if any]	RCT	No sponsorship. No COI.	N= 66 patients with work-related corneal foreign bodies without infectious keratitis.	Mean age was 31.4 years.	Pressure patch with ofloxacin (PG group) (N=18) vs. Contact lens with nonpreserved ofloxacin eye drops 4 times a day (CLG group) (N=20) vs. Ofloxacin ointment 4 times a day (OG group) (N=28)	Follow up was 1 day and 7 days later.	At day 1 follow up: Corneal abrasion reduction, mm PG vs. CLG vs. OG; 0.2 vs. 0.1 vs. 0.2 (p=0.789). Pain score at 24 hours: PG vs. CLG vs. OG; 4.0 vs. 3.9 vs. 2.2 (p=0.227).	"[T]reating traumatic corneal abrasions by pressure patching, a bandage contact lens or ointment alone was equal in terms of reducing the abrasion area and reducing pain. We believe that such a result is of significant practical value since it gives the treating physician complete liberty to choose the option best suited for each individual patient."	Data suggest no differences in the interventions. Lack of study details, dropout 38%, confusion in assessor masking limits conclusion.

Medications

The use of ophthalmic antibiotic solutions or ointments have been prescribed following traumatic corneal abrasion. The incidence of bacterial keratitis following corneal abrasion is thought to be low, however there may be increased risk with injuries associated with vegetative or organic matter. [72-74]. There also is a reportedly higher incidence of keratitis from foreign body injuries in the developing world than industrialized countries [75][426].

Topical nonsteroidal anti-inflammatory medications (NSAIDs) function as local analgesics and are administered to provide relief from pain associated with corneal abrasions [76], postoperative pain from various surgical procedures [77] and pain associated with many other disorders.

Topical antifungal medications, generally in ointment form, have been used to attempt to prevent (or treat) fungal keratitis that typically arises from corneal abrasions with unsanitary objects or sources. [427]

Prophylactic Ophthalmic Antibiotics for Simple Corneal Abrasion, Rust Rings, and Foreign Bodies

No Recommendation.

Medications (including topical creams)

There is no recommendation for or against the use of prophylactic ophthalmic antibiotics for simple corneal abrasion, rust rings, and foreign bodies that do not involve vegetative matter.

Strength of Evidence – **No Recommendation, Insuffcient Evidence (I)**
Level of Confidence – Low

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	None in the absence of vegetative matter (see below)
Benefits:	N/A
Harms:	Potential for allergic reaction
Frequency/Dose/Duration:	
Indications for Discontinuation:	
Rationale:	There are no quality studies suggesting efficacy of prophylactic ophthalmic antibiotics for prevention of eye infections in the setting of minor ocular trauma and not involving vegetative matter; vegetative matter is thought to significantly increase risk of infections and the recommendation is different (see below). There is only one low quality study using antifungals for corneal abrasions which showed lack of efficacy between treatment groups. As there is no quality evidence, antibiotics are not invasive, have few adverse effects and are low cost, there is no recommendation for or against use of antibiotics in the absence of vegetative matter.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents,

antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.

Comments: N/A

Prophylactic Ophthalmic Antibiotics for Organic Matter Injuries

Recommended.

Medications (including topical creams)

Prophylactic ophthalmic antibiotics are recommended for abrasions associated with significant organic or vegetative matter.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Abrasions due to organic or vegetative matter, regardless of whether a foreign body removal procedure was required.
Benefits:	Potential for reduced risk of infection.
Harms:	Allergic reactions in susceptible patients, intolerance
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	When the condition has resolved
Rationale:	There are no quality trials comparing prophylactic antibiotic use with placebo or non-use in the setting of trauma involving organic matter. However, there is thought to be considerably higher risk of infection when vegetative matter is involved due to potential microbial load/dose, and this is thought to increase risk of infection. Prophylactic use is widely practiced in this setting. Ophthalmic antibiotics are noninvasive with low risk for systemic effects, but do carry small risk of adverse events such as allergic reaction, eyelid itching and swelling, and conjunctivitis. Costs range from inexpensive to relatively high cost for new wide spectrum antibiotics. Eye injuries associated with plant or vegetative matter or organic matter likely have higher risk for bacterial or fungal infection and may warrant use

	of these medications, and thus they are recommended for this limited indication.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	N/A

NSAID Drops after Removal of Rust Ring or Foreign Body Removal

Moderately Recommended.

Medications (including topical creams)

NSAID ophthalmic drops are recommended for large abrasions and/or after removal of a corneal rust ring or foreign body, particularly if larger sized.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Rust ring with or without foreign body removal with larger sized ocular trauma.
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	Allergic reactions in susceptible patients, intolerance.
Frequency/Dose/Duration:	Per manufacturer's recommendations. Duration is until the abrasion is resolved.
Indications for Discontinuation:	When the condition and pain has resolved
Rationale:	There are 6 moderate quality trials comparing NSAIDs with placebo or drug vehicle for analgesia of simple corneal abrasion [428-433]. Ophthalmic drops were evaluated in one moderate quality study after rust ring removal and found evidence of efficacy [411]. Each of the

	trials suggest efficacy in providing analgesia, with no significant increases in adverse events or reduction in healing times. NSAID drops have been shown to reduce pain, have low adverse effects, are low cost, and are thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 8 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	N/A

Evidence for NSAID Drops

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Goyal 2001 (score = 7.5)		RCT	No mention of study sponsorship or COI.	N=85 patients with non-infective, non-contact lens related traumatic or foreign body removal related corneal abrasions. Mean age: 39.5 years.		Ketorolac trometamol group- 0.5% Ketorolac trometamol solution (N=43) Vs. Placebo Group- Liquifilm tearms 4 times per day. (N=42)	Follow-up took place 24 hours after treatment.	Mean VAS pain scores were not significant after treatment for treatment vs. control; 1.28 vs. 1.02 (p=0.76). The number of patients requiring oral analgesics was less in the treatment group vs. control group; 7 vs. 21 (p=0.002). There were no significant differences for photophobia (p=0.87), grittiness (p=0.27), watering (p=0.66) and blurring (p=0.18).	"We therefore assume our results to be a true reflection of the role of topical NSAIDs in the management of corneal abrasions. They may act as a substitute for oral analgesics in reducing pain levels."	Data suggest efficacy of topical NSAID in reducing oral analgesic intake. Although no differences in outcomes.
Brown 1975 (score = 6.0)		Clinical trial	No mention of sponsorship or COI.	N = 121 with significant corneal rust rings and possible ferrous foreign bodies. Ages not reported.		Slim electric drill treatment group removing foreign body with dental burr and drill (N = 64) vs. Manual treatment group removing foreign body with 40 mm x 0.8 mm disposable syringe and dental burr (Eyes treated with hyoscine and oc.	Follow-up daily until eyes had healed.	Manual breakup of rust rings in the firm stromal tissue proved to be more difficult with manual treatment compared with electric, causing irregularities in the resulting crater and a need for more treatment. Zero	"The dental burr rotated by an electric drill is the quickest, safest and most precise form of treatment for corneal rust rings. It enables complete removal of the corneal rust at a single treatment and leaves a smooth crater that is no larger than the	Unclear if blinded. Rust removal via drill trended superior to manual removal, though not statistically significant.

						chloramphenicol drops) (N = 57)		participants receiving electric treatment required a second treatment, while five participants receiving manual treatment required secondary treatment. Electric drill treatment provided clean cut craters and enabled removal of all rust without further treatment. Persisting mean pain days significantly lower in electric drill group compared with manual treatment; 0.02 days vs. .64 days, (p value not reported).	original rust ring. Pain relief is more rapid after electric drill removal; this is probably related to the complete removal of the rust. Epithelial and stromal healing are marginally faster than after manual removal and the patients' duration of attendance is less. The ideal drill is a slim straight instrument, which rotates dental burrs and is operated by a light finger pressure. A brake which stops drill rotation on lifting the finger is a useful safety feature."	
Szucs 2000 (score = 5.5)		RCT	No mention of sponsorship or COI.	N = 49 with corneal abrasions who presented to a community-based ED		Mean age was 38 years (diclofenac group), 41 years (control group).	1 drop of 0.1% diclofenac sodium plus 2 drops of topical antibiotic (gentamicin 0.3% solution) (N=25) vs. 1 drop of natural tears as control plus 2 drops of topical antibiotic (N=24). Follow up conducted by phone interview rather than	At 2-hour mean Numeric Pain Intensity Score comparing diclofenac vs. control (3.1 (95% CI 2.3 to 4.0) vs. 1.0 (95% CI 0.1 to 2.0; p=0.002. No further significant differences were found.	"[D]iclofenac ophthalmic solution appears to be safe and effective analgesic in the treatment of traumatic corneal abrasions in the ED."	Data suggest diclofenac plus gentamicin superior to natural tears plus gentamicin.

							ophthalmic examination.			
Jayamanne 1997 (score = 5.5)		RCT	No mention of sponsorship or COI.	N = 40 with a unilateral corneal abrasion. No data on age presented.			Diclofenac 0.1% drops QID 4 times/day in affected eye plus chloramphenicol ointment vs. normal saline QID. Daily follow-up until re-epithelialization occurred.	Wilcoxon rank sums for pain scores on day 1: diclofenac vs. control: 38 vs. 482, p<0.025. Day 2: 149.5 vs. 40.5, p<0.001).	"The treatment regimen of topical diclofenac sodium (0.1%) and antibiotic ointment 4 times daily as outlined in this article appears to provide a superior alternative to the traditional treatment of corneal abrasions."	Details sparse. Data suggest efficacy in pain control for corneal abrasion.
Kaiser 1997 (score = 5.0)		RCT	Sponsored by Allergen, Inc. No COI.	N = 88 simple epithelial defect without stromal edema, loss, or infiltrate, and no prior treatment before being entered into the study.		Mean±SD was 38.46±8.96 years.	Study Group: ketorolac tromethamine 0.5% ophthalmic solution, (N = 43). vs. Placebo (N = 45).	Day 1, Pain / Photophobia / Foreign body sensation: (2.44 ± 1.53 vs. 3.49 ± 1.32 , p = 0.002) / (12 (28%) vs. 22 (56%), p = 0.009) / (17 (40%) vs. 28 (62%), p = 0.003). Return to normal activity (2.09 ± 0.76 days vs.2.68 ± 0.63 days, p = 0.001).	"This study illustrates the effectiveness of ketorolac tromethamine 0.5% ophthalmic solution in providing improved comfort in traumatic, non-contact lens related corneal abrasions with minimal ocular side effects."	Details sparse. Data suggest efficacy in symptomatic relief for corneal abrasion.
Alberti 2001 (score = 4.5)	[Previous table header, if any]	RCT	No mention of study sponsorship or COI.	N= 123 patients with traumatic corneal abrasion with pain of >20mm on the Visual Analog Scale. Mean age was 38 years.			Indomethacin 0.1%/gentamicin sulfate drops (300,000IU/100ml); Indogenta group (n=62) Vs. Gentamicin sulfate drops alone; Gentamicin group (300mg/100ml) (N=61) Follow-up occurred on day 0 (same day as	There was a significant difference 1 hour after treatment in VAS score in favor of the Indogenta group vs. Gentamicin; -15.7 vs. -9.8 (p=0.007). At day 4/5, the difference was also significant with mean VAS	“[W]e observed rapid recovery of the corneal surface in both groups and better pain reduction in the indogenta group.”	Baseline differences in outcome measures favoring NSAIDs limits conclusions.

							treatment), day 1 and day 4	scores of 0.3 vs. 1.5 respectively (p=0.015).		
Patrone 1998 (score = 4.0)	[Previous table header, if any]	RCT	No mention of sponsorship. No COI.	N = 347 with traumatic corneal abrasion less than 12 hours before clinical examination			Group A: 0.3% netilmicin, plus 0.1% indomethacin eye drops (N = 178). vs. Group B: 0.3% netilmicin eye drops (N = 169).	Pain trend on days 1 and 2: (2.05 ± 1.36 vs. Group B: 3.70 ± 1.94, p < 0.0001 and 1.54 ± 1.00 vs. 2.92 ± 1.72, p < 0.0001).	"Our study highlighted the efficacy of indomethacin as a pain reducer for acute corneal pathology and suggested that the medication may act on the corneal nociceptors in a qualitative way."	Details sparse. Data suggest topical NSAID effective for analgesia.
Harris 1971 (score = 4.0)	[Previous table header, if any]	Clinical trial	Sponsored by the USPHS Research Grant (NS-07162-04) and the Sam S. Shubert Foundation, Inc. No mention of COI.	N = 20 with corneal rust rings, or stains verified through ophthalmoscopy, slit-lap examination, visual acuity and applanation tonometry.	No ages reported.	Lyophilized deferoxamine mesylate with 0.05% methylcellulose (4000 cps) treatment group (10% deferoxamine solution) receiving 6 applications per day. (N=20)	Follow up daily until rust ring disappearance and corneal lesion healing.	70% (n=14) of participants treated exhibited complete healing of corneal rust ring from treatment within 8 days; 4 between 3-4 days, 7 between 5-6 days and 3 between 7-8 days. No p-value statistics reported.	“Corneal rust is mobilized as a result of topical therapy with deferoxamine mesylate. Therapy, however, is effective only as long as re-epithelialization is not complete. This is explained by the poor penetrance of the drug through an intact epithelial barrier. Medical therapy offers significant advantages over surgical debridement in certain clinical circumstances.”	Small sample and sparse methods. Data suggest medical removal of rust rings with Deferoxamine dependent on size of presenting rust ring and larger rings require more days for removal. 6 Treatment failures (30%).

Prophylactic Ophthalmic Antifungals for Routine Prophylaxis of Simple Corneal Abrasions, Rust Rings, and Foreign Bodies

Not Recommended.

Medications (including topical creams)

The use of topical antifungal medications is not recommended for routine prophylaxis of simple corneal abrasions, rust rings and foreign bodies. They may be of benefit in select populations at risk for contaminated injuries such as from plants or organic matter.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Low

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Not indicated for simple abrasions, rust rings and foreign bodies. May be used for very select patients who sustained a contaminated exposure.
Benefits:	N/A
Harms:	N/A
Frequency/Dose/Duration:	N/A
Indications for Discontinuation	N/A
Rationale:	There are no quality trials of efficacy in a developed country. There is one moderate quality comparative trial comparing use of antibiotics and topical clotrimazole with antibiotics in a developing world tribal population [427]. There were no differences in healing rates. The study may be limited by power, generalizability from Southern India, potentially different foreign body source(s) and/or complications may have differed [427]. Topical prophylactic antifungal medications are noninvasive, have low risk for adverse events, low to moderate cost, and are not shown to be effective and thus are not recommended for routine use as prophylaxis for simple corneal abrasions.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and

	nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 1 randomized trial and 1 systematic study met the inclusion criteria.
Comments:	N/A

Evidence for Prophylactic Ophthalmic Antifungals

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/*	*Population:*	*Comparison:*	*Results:*	*Conclusion:*	*Comments:*
Srinivasan 2006 (score = 6.5)	[Previous table header, if any]	RCT	Sponsored by World Health Organization, Aravind Medical Research Foundation, Aravind Eye Care System, and Lions Aravind Institute of Community Ophthalmology. No COI.	N = 374 with corneal abrasion after ocular injury (confirmed by clinical examination with fluorescein stain and a blue torch), reported injury within 48 hours of the injury, aged > 5 years old.	Group A: received 1 % chloramphenicol and 1% clotrimazole ointment (N = 205) vs. Group B: received chloramphenicol and a placebo ointment (N = 169).	98.5% abrasion healed without complications.	Four patients had adverse events in treatment A, overall result lacks statistical significance between groups.	"Both fungal and bacterial ulcers that occur after traumatic corneal abrasions seem to be effectively prevented in a village setting using only antibiotic prophylaxis."	Study in Southern India. Data suggest no increased efficacy from addition of antifungal prophylaxis. Study may not be applicable to general populations.

Therapeutic contact lens accompanied with non-preserved Ofloxacin™ eye drops, also described as a contact bandage, have been used to treat corneal abrasions as a measure to purportedly aid in re-epithelialization of the corneal defect [419].

Therapeutic Contact Lens for Corneal Abrasions, Rust Rings, and Foreign Bodies

Not Recommended.

Devices

A therapeutic contact lens or contact bandage is not recommended for corneal abrasions, rust rings, or foreign bodies.

Strength of Evidence: Abrasions – **Not Recommended, Evidence (C)**
Strength of Evidence: Rust Rings, Foreign Bodies – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Generally not indicated for corneal abrasions, rust rings or foreign bodies as a stand-alone treatment
Benefits: None	
Harms:	N/A
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is one moderate quality trial that compares use of patching with therapeutic contact lens and topical antibiotic for healing rates of simple corneal abrasion. There was no difference between the two groups. [65] Thus, there is no evidence of efficacy of the therapeutic contact lens and it is not recommended for these purposes.
Evidence:	There are two low quality trials included in the appendix. [83, 84] A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12

in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 1 randomized trial and 1 systematic study met the inclusion criteria.

Comments:

Evidence for Therapeutic Contact Lenses

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Menghini 2013 (score = 4.5)		RCT	No mention of study sponsorship. No COI.	N= 66 patients with work-related corneal foreign bodies without infectious keratitis. Mean age was 31.4 years.	Pressure patch with Ofloxacin (PG group) (N=18) vs. Contact lens with nonpreserved Ofloxacin eye drops 4 times a day (CLG group) (N=20) vs. Ofloxacin ointment 4 times a day (OG group) (N=28)	Follow up was 1 day and 7 days later.	At day 1 follow up: Corneal abrasion reduction, mm PG vs. CLG vs. OG; 0.2 vs. 0.1 vs. 0.2 (p=0.789). Pain score at 24 hours: PG vs. CLG vs. OG; 4.0 vs. 3.9 vs. 2.2 (p=0.227).	"[T]reating traumatic corneal abrasions by pressure patching, a bandage contact lens or ointment alone was equal in terms of reducing the abrasion area and reducing pain. We believe that such a result is of significant practical value since it gives the treating physician complete liberty to choose the option best suited for each individual patient."	Data suggest no differences in the interventions. Lack of study details, dropout 38%, confusion in assessor masking limits conclusion.

Epidermal growth factor (EGF) reportedly accelerates the re-epithelialization process for traumatic corneal ulcers [434, 435]. EGF purportedly decreases epithelial defects, vascularization risks, infection, and rejection of graft. The encoded proteins act as a mitogenic factor that responds by initiating cellular growth. EGF may be found in the cell membranes of conjunctival epithelium, corneal epithelium and lens epithelium. Once EGF binds with the receptors, proliferation and differentiation of epidermal and cells occurs. [435]

Epidermal Growth Factor (EGF) for Corneal Abrasions, Rust Rings, and Foreign Bodies

Not Recommended.

Medications (including topical creams)

Epidermal growth factor (EGF) is not recommended in the treatment of corneal abrasion, rust rings and foreign bodies.

Strength of Evidence: Abrasions – **Not Recommended, Evidence (C)**
Strength of Evidence: Rust Rings, foreign bodies – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Low

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Not indicated for the treatment of corneal abrasions, rust rings and foreign bodies.
Benefits:	"Potential for faster re-epithelialization and healing.
Risks:	Possible allergic response to EGF
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is one quality trial comparing the use of EGF with placebo suggesting faster healing times measured in hours rather than days. [434] Topical ophthalmic EGF is not available on the U.S. FDA approved list of medications (accessed drugs@FDA 4/20/15). Thus, EGF is not recommended for simple corneal abrasions.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12

	in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 1 randomized trial and 1 systematic study met the inclusion criteria.
Comments:	N/A

Evidence for Epidermal Growth Factor (EGF)

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Pastor 1992 (score = 6.5)	[Previous table header, if any]	RCT	Sponsored by Laboratory Zambon, S.A. No COI.	N = 104 with a previously untreated traumatic corneal epithelial defect >5mm2 and of <6h duration, age range 18-80 years. Mean age not reported.	EGF 10µg/ml of vehicle (40mg of mannitol and 0.5mg of human albumin dissolved in 5ml of sterile 0.1M phosphate-buffered saline) (N = 47) Vs. Placebo, containing only the drug vehicle (N = 57). Gentamicin drops, 1% were prescribed 5 times daily, 10 minutes after the application of either the investigational drug or the placebo. Evaluation times: 24, 48, 72, 96, 120, and 144 hours.		Average healing: EGF-treated vs. placebo; 44.17±18.23 hours vs. 61.05±24.45 hours, ($p<0.05$).	"Our results indicate clinical efficacy of EGF eye drops in accelerating healing of corneal epithelial defects of traumatic origin and the drug may be useful in the treatment of other ocular surface disorders requiring substantial cell proliferation. Additional clinical trials of EGF topical application in other diseases would be promising."	Allocation method not described. Data suggest faster healing times with EGF.

Mydriatic medications such as topical anticholinergic preparations have been used to provide analgesic relief from corneal abrasion and foreign body removal through dilation of the pupil. These medications are typically applied directly to the eye to assist with eye examinations or surgeries, and to treat cyclitis and iritis.

Mydriatic Medications for Simple Corneal Abrasions, Rust Rings, and Foreign Bodies

Moderately Not Recommended.

Medications (including topical creams)

Mydriatic medications are not recommended for treatment of simple corneal abrasions, rust rings and foreign bodies.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	N/A
Benefits:	N/A
Harms:	N/A
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is one high quality trial demonstrating no efficacy of mydriatic medication compared with synthetic teardrops for analgesia after corneal abrasion. [436] Mydriatic medications are not invasive, but cause dilation of the pupil and potentially light sensitivity and decreased visual acuity that may be a safety concern for reading, driving, etc. They are low cost. The use of mydriatic medications for corneal abrasion is not recommended except in circumstances that require pupil dilation. There are 8 moderate and low quality trials that utilized mydriatic medications in conjunction with other treatments with no comparison of efficacy. These articles are found in other tables elsewhere in this guideline or the appendix. [362, 416, 420, 422, 423, 437-439]
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and

	nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 1 randomized trial and 8 systematic study met the inclusion criteria.
Comments:	N/A

Mydriatic Medications

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Meek 2010 (score = 8.0)	[Previous table header, if any]	RCT	Study supported by the Department of Emergency Medicine and the Pharmacy Department, Southern Health, Melbourne, Australia. No COI.	N=55 patients who had sustained a mechanical corneal abrasion in the previous 12 hours; Mean age: 38 years (Homatropine): 33.5 years (Placebo).	Homatropine Group (Homatropine 5% eye drops) (N=27) vs. Placebo Group (Hypomellose 0.5%) (N=28) Patients repeated use of study drug at 6, 12, and 18 hours and repeated VAS pain ratings at 6, 12, 18 and 24 hours.		There were no significant differences for mean VAS pain score change (mm) Homatropine vs. Placebo at 6 h; 8.4 vs. 16.7 (p=0.25) 12 h; 20.6 vs. 30.9 (p=0.21) 18 h; 26.1 vs. 35.7 (0.25) and 24h; 33.4 vs. 40.3 (p=0.39).	"In a general ED population presenting with mechanical corneal abrasion, we found no significant difference in the percentage of people reporting a significant level of pain reduction between those using 5% homatropine and those using a 0.5% hypromellose placebo preparation."	60 randomized but 5 withdrew before treatment. Data suggest lack of efficacy.

The use of artificial tears and lubricants is commonly used for eye irritation related to foreign body and corneal abrasion. Artificial tears or lubricants are often used to relieve eyes exhibiting dryness, or keratoconjunctivitis sicca, when the eyes are unable to produce adequate tears.

Artificial Tears or Lubrication for Extensive Corneal Abrasions, Rust Rings, and Foreign Bodies Recommended.

Medications (including topical creams)

Artificial tears or lubricants are selectively recommended for treatment of patients with extensive corneal abrasions, rust rings and foreign bodies, especially among those who do not tolerate ophthalmologic NSAIDs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Corneal abrasions of sufficient size and pain that require adjunctive treatment. However, NSAIDs are more effective [429, 433], thus artificial tears reserved for those not tolerating ophthalmological NSAIDs.
Benefits:	May potentially alleviate some symptoms.
Harms:	Negligible.
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	Resolution of the condition
Rationale:	There are two quality trials comparing artificial tears to topical NSAIDs, demonstrating greater efficacy of the NSAID than artificial tears [429, 433]. There are no quality trials for artificial tears or lubrication vs. placebo. Artificial tears are inexpensive, noninvasive, and have low adverse effects. There is insufficient evidence for or against use of artificial tears, and other interventions may be more beneficial. However, these may be a low cost, low adverse effect option for those who do not tolerate NSAIDs yet require some additional minor treatment. Low quality –[433, 438, 439].
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies,

epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 2 randomized trials and 2 systematic studies met the inclusion criteria.

Comments:

Artificial Tears or Lubricants

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Goyal 2001 (score = 7.5)		RCT	No mention of study sponsorship or COI.	N=85 patients with non-infective, non-contact lens related traumatic or foreign body removal related corneal abrasions. Mean age was 39.5 years.	Ketorolac trometamol group- 0.5% Ketorolac trometamol solution (N=43) Vs. Placebo Group-Liquifilm tears 4 times per day. (N=42)	Follow-up took place 24 hours after treatment.	Mean VAS pain scores were not significant after treatment for treatment vs. control; 1.28 vs. 1.02 (p=0.76). The number of patients requiring oral analgesics was less in the treatment group vs. control group; 7 vs. 21 (p=0.002). There were no significant differences for photophobia (p=0.87), grittiness (p=0.27), watering (p=0.66) and blurring (p=0.18).	"We therefore assume our results to be a true reflection of the role of topical NSAIDs in the management of corneal abrasions. They may act as a substitute for oral analgesics in reducing pain levels."	Data suggest efficacy of topical NSAID in reducing oral analgesic intake. Although no differences in outcomes.

Szucs 2000 (score = 5.5)		RCT	No mention of sponsorship or COI.	N = 49 with corneal abrasions who presented to a community-based ED Mean age was 38 years (diclofenac group), 41 years (control group).	1 drop of 0.1% diclofenac sodium plus 2 drops of topical antibiotic (gentamicin 0.3% solution) (N=25) vs. 1 drop of natural tears as control plus 2 drops of topical antibiotic (N=24).	Follow up conducted by phone interview rather than ophthalmic examination.	At 2-hour mean Numeric Pain Intensity Score comparing diclofenac vs. control (3.1 (95% CI 2.3 to 4.0) vs. 1.0 (95% CI 0.1 to 2.0; p=0.002. No further significant differences were found.	"In summary, diclofenac ophthalmic solution appears to be safe and effective analgesic in the treatment of traumatic corneal abrasions in the ED."	Data suggest diclofenac plus gentamicin superior to natural tears plus gentamicin.

Topical anesthetics are used during eye examinations and procedures to aide in hindering pain signals from nerve endings. Pain can be induced from the presence of foreign bodies, corneal abrasions and many other conditions [440].

Use of Topical Anesthetics for Corneal Abrasions, Rust Rings, and Foreign Bodies Moderately Recommended.

Medications (including topical creams)

The selective use of topical anesthetics as a patient treatment option is recommended for short-term analgesia for corneal abrasion, rust rings and foreign bodies. However, self-treatment by the patient at home is not recommended.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Particularly large and/or painful injuries. Short term use of only one or two days is recommended.
Benefits:	Immediate relief of corneal and conjunctiva irritation and pain
Harms:	Potential for systemic toxicity, mask retained foreign body or nonhealing defect
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	Resolution of the condition
Rationale:	There is one high quality trial and one moderate quality trial demonstrating analgesic efficacy over the first 24 hours after injury [440, 441]. The prolonged use of topical anesthetics is controversial, with concerns for toxicity from overuse, or complications from overtreatment of pain such as retained foreign body. Topical anesthetic is not invasive, has low but potentially important adverse effects and is generally low cost. Topical anesthetics are recommended for selective use.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12

	in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria.
Comments:	N/A

Topical Anesthetics

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Waldman 2014 (score = 9.0)		RCT	No industry sponsorship. No COI.	N= 122 patients with corneal abrasion from mechanical trauma or from removal of foreign body by a physician. Mean age was 37.5 years.	Saline Group- (N=61) vs. Tetracaine Group- 1.5 mL of undiluted 1% tetracaine hydrochloride (N=61)	Follow-up at 48 h and 1 week.	At 48 h, there was no significant difference in healing as identified by fluorescein uptake which was seen in 11 patients in the tetracaine group vs. 10 patients in the saline group (p=0.761). 10 patients in each group showed persistent symptoms at 48 h follow up (p=0.957). There was no significant difference in VAS pain score at 48 h; between group difference of 0.53 mm (p=0.149).	"The researchers recommend that the short-term use of tetracaine eye drops for 24 hours for pain relief from simple corneal abrasions should become routine practice."	Data suggest no differences in clinical outcomes including healing, no increase in compliance. However, pain scores significantly lower with tetracaine while under treatment.

Ball 2009 (score = 7.0)		RCT	No mention of sponsorship. No COI.	N = with corneal abrasions. Mean age 38.0 years for proparacaine and 38.3 years for placebo.	0.05% proparacaine (N = 15) vs. Color and smell matching placebo (N = 18). Patients: 2 to 4 drops on an as-needed basis for the next 7 days; pain log; topical fluoroquinolone and tablets of 325mg acetaminophen with 30 mg of codeine for breakthrough pain; topical gatifloxacin, 1-2 drops every 2 hours to the affected eye while awake for the duration of the study period; they were told to take 1 to 2 tablets with codeine every four hours if needed.	Follow up on days 1, 3 and 5 after enrollment.	Pain reduction 5 minutes after administration of study drug: proparacaine vs placebo: 3.9 cm vs 0.6 cm, (p=0.007). Satisfaction: proparacaine vs placebo: 8.0 vs 2.6, (p=0.027).	"Dilute topical anesthetic is an efficacious analgesic in patients with corneal injuries discharged from the emergency department. Treatment with dilute topical anesthetics may be effective and safe when prescribed for 1 to 2 days. Larger studies powered for safety are necessary before widespread adoption of this practice."	Small sample size limits conclusion. Numbers enrolled in study not mentioned. Data suggest pain reduction with proparacaine.

Topical opioids provide analgesic effects for severe ophthalmic pain on a short-term basis. Extended chronic use can result in adverse effects to the corneal tissues reportedly including alteration of lacrimation, corneal sensitivity loss, increased corneal permeability, disruption of corneal cell motility, swelling and corneal re-epithelialization inhibition [442]. See also Work-related Asthma Guideline.

Topical Opioids for Analgesia of Corneal Abrasions, Rust Rings, and Foreign Bodies Not Recommended.

Medications (including topical creams)

The use of topical fentanyl and opioids for analgesia of corneal abrasions, rust rings, and foreign bodies is not recommended.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	N/A
Benefits:	N/A
Harms:	Decreased lacrimation, corneal sensitivity loss, increased corneal permeability, disruption of corneal cell motility, swelling and inhibition of corneal re-epithelialization.
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is one quality trial comparing the use of topical fentanyl with no fentanyl that demonstrated no improved in analgesia at the dose tested. [442] There are no commercially available topical opioids approved for use in the eye in the U.S. These medications are not invasive, have reported adverse effects, and have no demonstrated efficacy and are thus not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cornea, corneal, corneas, eye injuries, scratch, scratches, abrasion, abrasions, defect, defects, anti-bacterial agents, antibiotic prophylaxis, contact lenses, anesthetics, injections, intravitrial injections, intraocular injections, analgesics, non-steroidal anti-inflammatory agents, narcotics, mydriatics, ointments, ophthalmic solutions, patch, patches, capping, rubbing, everting, flushing, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and nonexperimental Studies. We found and reviewed 163 articles in PubMed, 100 in Scopus, 78 in CINAHL, 143 in Cochrane Library and 12 in other sources. We considered for inclusion 29 from PubMed, 3 from Scopus, 2 from CINAHL, 3 from Cochrane Library and 1 from other sources. Of the 38 articles considered for inclusion, 26 randomized trials and 8 systematic studies met the inclusion criteria.

Evidence for Topical Opioids

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Zöllner 2008 (score = 6.5)		RCT	Sponsored by "Klinische Forschergruppe Grant" KFO 100 from the Deutsche Forschungsgemeinschaft (DFG). No mention of COI.	N = 40 with corneal damage, or corneal erosion; mean age 68±15 years for group A, and 66±12 years for group B. Mean±SD age: Group A 68±15 years. Group B: 66±12 years.	Group A: 0.02 g dexpathenol ointment (N = 20) vs. Group B: 0.02 g fentanyl plus 10 mg dexpanthenol ointment (N = 20). Paracetamol tablets (500/2000) were given upon request in a sealed envelope.	Follow-up at 24 hours.	Pain scores did not differ between groups: Group A vs. Group B: 6.8±0.5 vs. 6.5±0.6, ($p>0.05$). Pain scores decreased over time and were significantly different at 24 hours after surgical treatment compared with before ($p<0.05$).	"Both μ and δ-receptors are localized on nerve fibers within the cornea, which are accessible for topical opioid treatment. However, our formulation and dose of topical fentanyl in combination with dexpanthenol did not show any benefit in relieving pain from corneal erosion. Future studies are planned to determine the optimal protocol and dose of topical opioid treatment."	No details for compliance, dropout. Data suggest no benefit of topical fentanyl.

FOLLOW-UP VISITS

There are no quality studies on the frequencies of following up patients with these injuries, thus guidance is by expert consensus. Patients with minor abrasions may require no follow-up other than if symptoms persist and fail to resolve in one to two days. Patients with more extensive abrasions, abrasions from vegetative matter, large foreign body removals and/or large rust ring removals may require followups every 1-3 days until healed. The primary purposes of frequent followup appointments are to assess healing, detect complications and address work limitations all of which may change quickly.

Traumatic Injuries

OVERVIEW

Penetrating trauma and rupture of the globe are rare injuries, although work is an occasional cause of those injuries, particularly high impact or motor vehicle crashes [44, 90, 443-446]. These are diverse and complex injuries that include a range of injuries from simple corneal lacerations to deep structural injuries. Complications of these injuries include visual impairments, astigmatisms, endophthalmitis, infections, sympathetic ophthalmia, cataracts, blindness, and enucleation [371, 447, 448].

Corneal Lacerations

Corneal lacerations are deeper wounds than abrasions and include flap wounds. More extensive wounds may include injury to intraocular structures such as the lens. Retinoic acid has been used for adjunctive treatment of corneal lacerations [449], however, there are no quality studies and it is **Recommended, Insufficient Evidence (I)**. Rigid gas-permeable contact lenses have been used to attempt to provide better healing [450-453]. There are no quality studies of contact lenses for this purpose, and they are **Recommended, Insufficient Evidence (I).** Injuries with significantly impaired vision, e.g. due to uncorrectable astigmatisms or opacities may need corneal transplantation (see Corneal Transplantation below) [452].

Penetrating trauma and intraocular foreign bodies are **Recommended, Insufficient Evidence (I)** to be initially treated with stabilization of the intraocular foreign body without removal to avoid further trauma, and prompt, emergent referral for definitive treatment. Many small intraocular foreign bodies, particularly metallic, do not require removal, and instead can be conservatively managed [454-456].

This guideline does not address these penetrating eye injuries in detail that require referral for highly individualized, definitive care [367, 455, 457-470].

Blunt Trauma and Traumatic Hyphema

Blunt ocular trauma is most commonly due to transportation crashes, sports injuries and altercations [84, 471, 472]. Other occupational causes occur beyond those due to work-related vehicular crashes [84, 473]. Predictors of worse outcomes reportedly include afferent or nonreactive pupil, fracture, and inability to open the eye [474].

Blunt trauma injures are highly diverse and include contusions, fractures, hyphema, retinal detachments, anterior chamber angle recession, ocular hypertension, and other complications [72, 475, 476]. As multiple other injuries are potentially present, a comprehensive evaluation of the patient and his/her neighboring tissues/organ systems is required. Orbital blowout fractures most commonly involve the medial wall followed by the orbital floor [473]. Associated nasal fractures have been reported in 16% [473]. While x-rays are often performed for initial evaluations and are **Recommended, Insufficient Evidence (I),** CT scans are considered the main imaging procedure [396] and are **Recommended, Insufficient Evidence (I)**.

Traumatic hyphema is susceptible to recurrent bleeding in approximately 10-40% of patients. [477-483]. Prevention of re-bleeding is believed to be important to prevent worse outcomes and prednisone and aminocaproic acid have been utilized.

This guideline does not address those blunt trauma eye injuries that are complex, particularly those with pupillary defects, impairments and/or require definitive surgical care. Surgical approaches and techniques are diverse that are used for treating orbital fractures [211, 315, 484-492].

TREATMENT RECOMMENDATIONS

Topical Aminocaproic Acid for Traumatic Hyphema

Moderately Recommended.

Medications (including topical creams)

Topical aminocaproic acid is recommended for treatment of traumatic hyphema [493].

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Non-penetrating traumatic hyphema.
Benefits:	Improved visual acuity, reduced risk of corneal blood staining, glaucoma,
Harms:	Negligible.
Frequency/Dose/Duration:	Aminocaproic acid 30% in 2% carboxypolymethylene gel, 0.2mL applied in the inferior fornix Q6hrs for 5 days. Patients in the highest quality trial were also treated with 30º of head elevation, metal eye shield and moderate ambulation. [493, 494]
Indications for Discontinuation:	Completion of the treatment course.
Rationale:	The highest quality trial compared controls with oral or topical aminocaproic acid and found markedly superior visual acuity results with either aminocaproic acid treatment arm [493]. Other studies have also suggested efficacy compared with placebo [494-496] with another underpowered study also trending towards efficacy [497]. Another trial found comparable results between aminocaproic acid and prednisone [498], while another trial failed to find efficacy of glucocorticosteroid [499]. Topical aminocaproic acid is not invasive, has low adverse effects, is moderately costly, but is efficacious for preserving and/or recover visual acuity and thus is moderately recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: traumatic hyphemia, hyphema, hyphaema, eye, eyes, topical glucocorticoid eye drops, topical beta adrenergic blocker eye drops, patching, ophthalmic solutions, prednisone,, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized,

	randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 17 articles in PubMed, 2 in Scopus, 70 in CINAHL, one in Cochrane Library and 0 in other sources. We considered for inclusion 5 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 13 articles considered for inclusion, 11 randomized trials and 2 systematic studies met the inclusion criteria.
Comments:	N/A

Evidence for Topical Aminocaproic Acid

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Crouch 1997 (score = 8.0)	Aminocaproic acid vs. Topical aminocaproic acid	RCT	Supported by the Lions Medical Eye Bank and Research Center. No mention of COI.	N = 64 with nonpenetrating traumatic hyphema; mean ages not reported.	Systemic aminocaproic acid 50 mg/kg every 4 hours with a maximum dose of 30 g/day, plus placebo topical gel, (N = 35) vs. Topical aminocaproic acid 30% aminocaproic acid in 2% carboxypolymethylene gel, 0.2 mL applied in the inferior fornix of the involved eye every 6 hours and an oral placebo (N = 29) vs. Control (N = 54). Both groups with + 30º of head elevation, metal eye shield and moderate ambulation.	Follow-ups were everyday for the first 5 days and then up to 6 years.	Final visual acuity ≥20/40: topical group: 30 patients (86%) vs. 23 patients (43%) in the control group (p<0.001). Final	"Topical aminocaproic acid appears to be a safe, effective treatment to prevent secondary hemorrhage in traumatic hyphema."	Variable follow-ups. Data suggest strong efficacy of topical aminocaproic acid.
Farber 1991[116] (score = 8.0)	Aminocaproic acid vs. Prednisone		Supported by a grant from the National Eye Institute and an unrestricted grant from Research to Prevent Blindness.	N = 112 who sustained hyphema after blunt trauma. Mean±SD age: Aminocaproic acid 23.8±13.8 years. Prednisone group 23.3±13.4 years.	Aminocaproic acid 50 mg/kg every 4 hours for 5 days with maximum dosage at 30 g daily (N = 56) vs. Prednisone, 40 mg daily (N = 56). Both groups with head elevated to 30º, no reading, a patch/shield applied to the involved eye, topical application of 1% atropine sulfate 4x/day to the involved eye, oral administration of	Follow-up over 5 days.	Visual acuity after 5 and 10 days / IOP at admission and discharge / rebleeds / initial hyphemas size: (21 vs. 26 in placebo, and 10 vs. 7 who had visual acuity of 20/200 or worse) / (17.8 vs. 17.7 mmHg, and 13.1 vs. 13.3 mmHg) / (4 in each group	"Although it is not possible to determine whether aminocaproic acid or prednisone is the preferred treatment of traumatic hyphemas, our study suggests that both drugs are successful in reducing the	Data suggest oral aminocaproic acid is equivalent to prednisone for prevention of rebleed.

					acetaminophen as needed, no aspirin.		had rebleeds) / (43% vs. 75%, p=0.001).	incidence of rebleeds."	
Pieramici 2003[114] (score = 7.0)	Aminocaproic acid vs. placebo	RCT	Sponsored by Orphan Medical Inc., Covance Inc., National Eye Institute, and an unrestricted research grant from Research to Prevent Blindness. No COI.	N = 51 with traumatic hyphema. Mean±SD age for topical aminocaproic acid was 24±4 years and 23±3 years for placebo.	Topical, 30% in 2% gel, aminocaproic acid (ACA) (N = 24) vs. Placebo gel that looked like the ACA gel (N = 27). All patients received 1 drop of proparacaine hydrochloride (0.05%) in the involved eye and then the gel was given every 6 hours for 5 days and 1 drop of homatropine 2% was given topically 3 times a day.	Follow-ups were daily for 7 days.	Rebleeding occurred in 30% of the placebo group 8 of 27; 95% CI = 14-50% vs. 8% of the treatment group (2 of 24; 95% CI = 1-27%) (95% CI = -3-38%, (p=0.08). Median days to rebleeding was 6 in the ACA gel group and 3.5 in the placebo group, (p=0.02). At the last follow-up a higher percentage of patients in the ACA gel group (46%) than in the placebo group (33%) showed improved visual acuity (p=0.03).	"[T]opical aminocaproic acid is safe and demonstrates trends towards reducing the rebleeding rate in the management of traumatic hyphema."	Study terminated due to slow enrollment. Suggest trend toward efficacy.
McGetrick 1983[117] (score = 6.0)	[Previous table header, if any]	RCT	Sponsored by grants from the National Eye Institute and by an unrestricted grant from Research to Prevent	N = 49 with non-perforating traumatic hyphema; mean ages not reported.	Aminocaproic acid 100 mg/kg po every 4 hours up to a maximum dose of 30 g/day for 5 days (N = 28) vs. Oral placebo (N = 21).	Follow-up ranged from 0 to 9 months.	Drug related complications / clotted blood / rebelling / mean duration hospitalization: (6 vs. no complications in placebo, (p<0.05) /	"Aminocaproic acid, when used in a dosage of 100 mg/kg orally every four hours, up to a maximum dose of 30 g/24 hr,	Patients not well described. Variable follow-up. Data suggest efficacy.

			Blindness. No mention of COI.				(mean of 4.5 days vs. 6.3 in placebo) / (1 vs. 7 rebelled in placebo, (p>0.01) / (5.7 vs. 7.3 in placebo).	dramatically and significantly (p<.01) reduces the incidence of secondary hemorrhage."	
Spoor 1980[119] (score = 5.5)	Prednisone vs. placebo	RCT	No mention of industry sponsorship or COI.	N = 43 with traumatic hyphema. Average age of prednisone group: 20.1, and 21.2 years for placebo group.	Prednisone (40 mg/day for adults and children older than 10 years; 15mg/day for children aged 4 to 10 years; and 10mg/day for those aged 18mos to 4 years) (N = 23) vs. Placebo (N = 20).	Patients with intraocular pressure greater than 24 mmHg were treated with 30 mg/kg of oral sodium acetazolamide in divided doses.	Final visual acuity were very similar between groups, (p=0.85). Secondary hemorrhage occurred in 23 vs. 20 placebo patients, (p=0.85).	"[P]rednisone given for systemic effect is of no significant value in the treatment of traumatic hyphema."	Follow up period unclear. Larger hyphema not associated with worse outcome. Data suggest lack of efficacy.
Crouch 1976 (score = 5.0)	Aminocaproic acic vs Aromatic clixir vs Placebo	RCT	No mention of industry sponsorship or COI.	N = 59 with traumatic hyphemas. Mean ages not reported.	Aminocaproic acid 100 mg/kg of body weight) every four hours orally, for five days (N = 32) vs. Placebo. 200 ml of aromatic clixir per 1,000 ml of solution also given every four hours for five days (N = 27).	Follow-ups were at 1 week, 1/2/3/6/12/18/24 months.	Rebleed / clots: (9 placebo vs. 1 in ACA group. At the last follow-up 79% of the patients in the aminocaproic acid had 20/40 or better vision vs. 67% in the placebo group.	"Based on the statistically significant reduction (P < .01) in the incidence of rebleeding of traumatic hyphemas in our patients treated with aminocaproic acid, we think that aminocaproic acid can prevent secondary hemorrhage."	Variable follow-up. Patients not well described. Placebo somewhat better visual acuity at baseline. Data suggest efficacy.
Kutner 1987[113]	Aminocaproic acid (Amicar) vs Placebo	RCT	No mention of industry	N = 34 with nonperforating ocular injury	Aminocaproic acid Amicar, 100 mg/kg every four hours,	Not specified.	Rebleeding / residual blood present/	"Our findings confirm and strongly	Computer randomization but group size

(score = 5.0)			sponsorship or COI.	and traumatic hyphema. Mean age for aminocarproic acid group 18.9±7.7, and 22.8±7.6 for placebo group.	maximum dose 30 g/d, for five days (N = 21) vs. Placebo, identical taste and appearance to aminocaproic acid. (N = 13).		intraocular pressure elevation and visual acuity at the time of discharge / complications: (23% vs. none in aminocaproic acid group, p<0.05) / (12 vs. non in placebo group, p<0.001) / (similar between groups, p>0.3) / (aminocaproic acid group had a significant amount of complications vs. placebo, p<0.02).	suggest that aminocaproic acid significantly reduces (p<0.05) reduces the incidence of secondary hemorrhage following traumatic hyphema."	of 21 vs. 13. Data suggest efficacy of oral ACA.

Tranexamic Acid for Traumatic Hyphema

Recommended.

Medications (including topical creams)

Tranexamic acid is recommended for treatment of traumatic hyphema [500].

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Non-penetrating traumatic hyphema.
Benefits:	Reduced risk of re-bleeding
Harms:	Negligible.
Frequency/Dose/Duration:	Tranexamic acid 25mg/kg orally three times a day [500].
Indications for Discontinuation:	When visual acuity is restored.
Rationale:	One moderate quality trial suggested efficacy of oral tranexamic acid for treatment of hyphema and further suggested superiority to steroid [500]. Tranexamic acid is not invasive, has some adverse effects, is moderately costly, but is highly efficacious to preserve and/or recover visual acuity and thus is moderately recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: nonpenetrating, superficial, ocular, corneal, penetrating, foreign body, eye foreign bodies, “rust ring, eye, eyes, removal, extraction, leaving in the eye, mydriatics, cycloplegic, meidiatric effect, extraction size, extraction location, woods lamp, slit lamp, fibrin tissue adhesive, fibrin sealant, autologous fibrin tissue adhesive, fibrin klebe system immune, transglutine, crosseal, tisseel, tissel, tussucol, beriplast, seal fibrin, eye irrigation, irrigation, morgan lens, morgan lenses, patching, patch, treatment, eye magnet, eye burr, diamond burr, alger brush, ophthalmic burr, aaron burr, burr, contusion, Acuvail, acular LS, acular PF, acuvil, bromday, bromfenac ophthalmic, diclofenac ophthalmic, flurbiprophen ophthalmic, Ilevro, ketorolac ophthalmic, phenylephrine ophthalmic, nepafenac ophthalmic, nevanac, ocufen, omidria, prolensa, voltaren ophthalmic, ketoroloac tromethamine, topical NSAID, “Anti-Inflammatory Agents, Non-Steroidal", Gentamicin, tobramycin, besifloxacin, ciproflaxin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, azithromycin, erythromycin, bacitracin, polymyxin, natamycin, neomycin, gramicidin, trimethoprim, sulfacetamide, Neosporin, polytrim, natacyn, romycin, Azasite, ocuflox, vigamox, lquix, quixin, Zymar, Ciloxan, besivance, tobrex, Anti-Bacterial Agents, Anti-Bacterial, Agents, antibiotic ointment, antibacterial ointment, anesthetics, lidocaine, tetracaine,

proparacaine, fluress, topical anesthetic, prednisolone, fluorometholone, steroids, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 85 articles, and considered 13 for inclusion. In Scopus, we found and reviewed 10,342 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed 137 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 173 articles, and considered 0 for inclusion. We also considered for inclusion 4 articles from other sources. Of the 18 articles considered for inclusion, 1 randomized trial and 1 systematic study met the inclusion criteria.

Comments: N/A

Evidence for Tranexamic Acid

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rahmani 1999[120] (score = 5.5)	Tranexamic vs. other treatments	RCT	No mention of industry sponsorship or COI.	N = 238 who developed hyphema after blunt trauma. Mean±SD age: Acid group: 14.9±12.6 years. Prednisole 12.5±8.5 years. Placebo 14.8±1.7 years.	Oral tranexamic acid (TA) 75 mg/kg TID (N = 80) Vs. Placebo (N = 80) TID Vs. Oral prednisolone 0.375 mg/kg BID (N = 78). Each medication was prescribed for 5 days, and if no rebleeding occurred, then the medication was discontinued.	Follow-up for 15 days.	N (%) rebleeding Acid vs. Prednisole vs. Placebo: 8(80) vs. 14(78) vs. 21(26) p=0.028.	"[T]A is more effective than oral prednisolone or no oral treatment in preventing rebleeding among patients with traumatic hyphema."	Data suggest efficacy of Tranexamic Acid over prednisolone over placebo for secondary bleeding.

Evidence for Stabilization of the Intraocular Foreign Body Without Removal

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Azad 2004[104] (score = 4.5)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N = 28 men with retained intraocular foreign bodies. Age mean: 22.5 years (range: 17-30 years).	Placement of encircling 360° scleral buckle in addition to pars plana vitrectomy and foreign body removal (group I; N = 15) vs. Pars plana vitrectomy and foreign body removal (group II; N = 13).	Follow-up for 6-24 months (mean : 11.8 months).	Retinal detachment rate of group I vs. group II: 6.6% vs. 30.8% (p=0.24). Retinal detachment was reduced to 24% due to prophylactic scleral buckle.	“Based on our results we propose that prophylactic scleral buckle placement is an important additional manoeuvre during pars plana vitreous surgery for RIOFB removal and helps prevent subsequent retinal detachment.”	Prophylactic scleral buckling may decrease retinal detachment (6.6%) vs. patients not receiving a scleral buckle (30.8%).

Evidence for Glucocorticosteroids for Treatment of Traumatic Hyphema

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Crouch 1997 (score = 8.0)	Aminocaproic acid vs. Topical aminocaproic acid	RCT	Supported by the Lions Medical Eye Bank and Research Center. No mention of COI.	N = 64 with nonpenetrating traumatic hyphema; mean ages not reported.	Systemic aminocaproic acid 50 mg/kg every 4 hours with a maximum dose of 30 g/day, plus placebo topical gel, (N = 35) vs. Topical aminocaproic acid 30% aminocaproic acid in 2% carboxypolymethylene gel, 0.2 mL applied in the inferior fornix of the involved eye every 6 hours and an oral placebo (N = 29) vs. Control (N = 54). Both groups with + 30º of head elevation, metal eye shield and moderate ambulation.	Follow-ups were everyday for the first 5 days and then up to 6 years.	Final visual acuity ≥20/40: topical group: 30 patients (86%) vs. 23 patients (43%) in the control group (p<0.001). Final	"Topical aminocaproic acid appears to be a safe, effective treatment to prevent secondary hemorrhage in traumatic hyphema."	Variable follow-ups. Data suggest strong efficacy of topical aminocaproic acid.
Farber 1991[116] (score = 8.0)	Aminocaproic acid vs. Prednisone	[RCT, prospective, etc.]	Supported by a grant from the National Eye Institute and an unrestricted grant from Research to Prevent Blindness.	N = 112 who sustained hyphema after blunt trauma. Mean±SD age: Aminocaproic acid 23.8±13.8 years. Prednisone group 23.3±13.4 years.	Aminocaproic acid 50 mg/kg every 4 hours for 5 days with maximum dosage at 30 g daily (N = 56) vs. Prednisone, 40 mg daily (N = 56). Both groups with head elevated to 30º, no reading, a patch/shield applied to the involved eye, topical application of 1% atropine sulfate 4x/day to the involved eye, oral administration of	Follow-up over 5 days.	Visual acuity after 5 and 10 days / IOP at admission and discharge / rebleeds / initial hyphemas size: (21 vs. 26 in placebo, and 10 vs. 7 who had visual acuity of 20/200 or worse) / (17.8 vs. 17.7 mmHg, and 13.1 vs.	"Although it is not possible to determine whether aminocaproic acid or prednisone is the preferred treatment of traumatic hyphemas, our study suggests that both drugs are successful in reducing the incidence of rebleeds."	Data suggest oral aminocaproic acid is equivalent to prednisone for prevention of rebleed.

					acetaminophen as needed, no aspirin.		13.3 mmHg) / (4 in each group had rebleeds) / (43% vs. 75%, p=0.001).		
Pieramici 2003[114] (score = 7.0)	Aminocaproic acid vs. placebo	RCT	Sponsored by Orphan Medical Inc., Covance Inc., National Eye Institute, and an unrestricted research grant from Research to Prevent Blindness. No COI.	N = 51 with traumatic hyphema. Mean±SD age for topical aminocaproic acid was 24±4 years and 23±3 years for placebo.	Topical, 30% in 2% gel, aminocaproic acid (ACA) (N = 24) vs. Placebo gel that looked like the ACA gel (N = 27). All patients received 1 drop of proparacaine hydrochloride (0.05%) in the involved eye and then the gel was given every 6 hours for 5 days and 1 drop of homatropine 2% was given topically 3 times a day.	Follow-ups were daily for 7 days.	Rebleeding occurred in 30% of the placebo group 8 of 27; 95% CI = 14-50% vs. 8% of the treatment group (2 of 24; 95% CI = 1-27%) (95% CI = -3-38%, (p=0.08). Median days to rebleeding was 6 in the ACA gel group and 3.5 in the placebo group, (p=0.02). At the last follow-up a higher percentage of patients in the ACA gel group (46%) than in the placebo group (33%) showed improved visual acuity (p=0.03).	"[T]opical aminocaproic acid is safe and demonstrates trends towards reducing the rebleeding rate in the management of traumatic hyphema."	Study terminated due to slow enrollment. Suggest trend toward efficacy.
Karkhaneh 2003[118] (score = 6.5)	Cycloplegic drops	RCT	Study was conducted with the cooperation of	N = 132 with traumatic hyphema;	Group 1: received cycloplegic drops only (N = 52) vs. Group 2: received cycloplegic	Follow-up was at 2 weeks.	Rebleeding / clot absorption: (8 vs. 7 vs. 5	"Topical 25% ACA is not effective in reducing the incidence of	Somewhat different group sizes. Data suggest

			Sina Darou (an ophthalmic pharmaceutical company in Iran). No mention of COI.	mean ages not reported.	drops and 2% carboxy polymethylene (N = 39) Vs. Group 3: who was treated with cycloplegic drops and 25% aminocaproic acid (ACA) in CPM gel (N = 41).		patients in group 1, 2 and 3, respectively) / (11.1 vs. 9.3 vs. 9.5 days in groups 1, 2, and 3, respectively). Clots in the anterior chamber absorbed on average 2 days later in the group 3 (p<0.04).	rebleeding and lengthens the time needed for clot absorption."	lack of efficacy
Palmer 1986[115] (score = 6.0)		RCT	Sponsored by grants from the National Eye Institute, Sickle Cell Center, Heart and Lug Institute, and by an unrestricted grant from Research to Prevent Blindness.	N = 59 with hyphema sustained after blunt trauma. Mean age for the 50mg dose group was 20 years (range of 4-46), and 22.8 (rage 3-50) for 100mg dose group.	Aminocaproic acid 50 mg/kg (N = 26) vs. 100 mg/kg every 4 hours for 5 days, up to a maximum of 30 g/day,	Follow-up for 1 week.	Rebleeding / dizziness and hypotension / mean serum concentration: (statistically significant with hyphema level or p = 0.18 or visual acuity of less than 6/15 (20 / 50; p = 0.12) or injury to initial dose time interval, p = 0.19) / (0 vs. 5 patients in full dose group, p = 0.063) / (7.27 mg / 100 ml vs. 12.7 mg / 100 ml in full dose group, p = 0.0001).	"In a dose of 50 mg/kg for four hours, up to 30 g/day Amicar significantly reduces serious side effects, has no adverse consequence on recurrent hemorrhages, and is safer and more cost-effective when compared to the maximum dose recommended in the Physicians' Desk Reference."	No placebo control. Variable doses. Less rebleeding with ½ doses (4% v. 15.6%). Higher rebleed in black patients.

McGetrick 1983[117] (score = 6.0)		RCT	Sponsored by grants from the National Eye Institute and by an unrestricted grant from Research to Prevent Blindness. No mention of COI.	N = 49 with non-perforating traumatic hyphema; mean ages not reported.	Aminocaproic acid 100 mg/kg po every 4 hours up to a maximum dose of 30 g/day for 5 days (N = 28) vs. Oral placebo (N = 21).	Follow-up ranged from 0 to 9 months.	Drug related complications / clotted blood / rebelling / mean duration hospitalization: (6 vs. no complications in placebo, (p<0.05) / (mean of 4.5 days vs. 6.3 in placebo) / (1 vs. 7 rebelled in placebo, (p>0.01) / (5.7 vs. 7.3 in placebo).	"Aminocaproic acid, when used in a dosage of 100 mg/kg orally every four hours, up to a maximum dose of 30 g/24 hr, dramatically and significantly (p<.01) reduces the incidence of secondary hemorrhage."	Patients not well described. Variable follow-up. Data suggest efficacy.
Spoor 1980[119] (score = 5.5)	Prednisone vs. placebo	RCT	No mention of industry sponsorship or COI.	N = 43 with traumatic hyphema. Average age of prednisone group: 20.1, and 21.2 years for placebo group.	Prednisone (40 mg/day for adults and children older than 10 years; 15mg/day for children aged 4 to 10 years; and 10mg/day for those aged 18mos to 4 years) (N = 23) vs. Placebo (N = 20).	Patients with intraocular pressure greater than 24 mmHg were treated with 30 mg/kg of oral sodium acetazolamide in divided doses.	Final visual acuity were very similar between groups, (p=0.85). Secondary hemorrhage occurred in 23 vs. 20 placebo patients, (p=0.85).	"[P]rednisone given for systemic effect is of no significant value in the treatment of traumatic hyphema."	Follow up period unclear. Larger hyphema not associated with worse outcome. Data suggest lack of efficacy.
Rahmani 1999[120] (score = 5.5)	Tranexamic vs. other treatments	RCT	No mention of industry sponsorship or COI.	N = 238 who developed hyphema after blunt trauma. Mean±SD age: Acid group: 14.9±12.6 years. Prednisole 12.5±8.5 years. Placebo 14.8±1.7 years.	Oral tranexamic acid (TA) 25 mg/kg TID (N = 80) Vs. Placebo (N = 80) Vs. Oral prednisolone 0.375 mg/kg BID (N = 78).	Follow-up for 15 days.	N (%) rebleeding Acid vs. Prednisole vs. Placebo: 8(80) vs. 14(78) vs. 21(26) p=0.028.	"[T]A is more effective than oral prednisolone or no oral treatment in preventing rebleeding among patients with traumatic hyphema."	Data suggest efficacy of Tranexamic Acid over prednisolone over placebo for secondary bleeding.

Crouch 1976 (score = 5.0)	Aminocaproic acic vs Aromatic clixir vs Placebo	RCT	No mention of industry sponsorship or COI.	N = 59 with traumatic hyphemas. Mean ages not reported.	Aminocaproic acid 100 mg/kg of body weight) every four hours orally, for five days (N = 32) vs. Placebo. 200 ml of aromatic clixir per 1,000 ml of solution also given every four hours for five days (N = 27).	Follow-ups were at 1 week, 1/2/3/6/12/18/24 months.	Rebleed / clots: (9 placebo vs. 1 in ACA group. At the last follow-up 79% of the patients in the aminocaproic acid had 20/40 or better vision vs. 67% in the placebo group.	"Based on the statistically significant reduction (P < .01) in the incidence of rebleeding of traumatic hyphemas in our patients treated with aminocaproic acid, we think that aminocaproic acid can prevent secondary hemorrhage."	Variable follow-up. Patients not well described. Placebo somewhat better visual acuity at baseline. Data suggest efficacy.
Kutner 1987[113] (score = 5.0)	Aminocaproic acid (Amicar) vs Placebo	RCT	No mention of industry sponsorship or COI.	N = 34 with nonperforating ocular injury and traumatic hyphema. Mean age for aminocarproic acid group 18.9±7.7, and 22.8±7.6 for placebo group.	Aminocaproic acid Amicar, 100 mg/kg every four hours, maximum dose 30 g/d, for five days (N = 21) vs. Placebo, identical taste and appearance to aminocaproic acid. (N = 13).	Not specified.	Rebleeding / residual blood present/ intraocular pressure elevation and visual acuity at the time of discharge / complications: (23% vs. none in aminocaproic acid group, p<0.05) / (12 vs. non in placebo group, p<0.001) / (similar between groups, p>0.3) / (aminocaproic acid group had a significant amount of	"Our findings confirm and strongly suggest that aminocaproic acid significantly reduces (p<0.05) reduces the incidence of secondary hemorrhage following traumatic hyphema."	Computer randomization but group size of 21 vs. 13. Data suggest efficacy of oral ACA.

							complications vs. placebo, p<0.02).		
Vangsted 1983[121] (score = 4.0)	Tranexamic vs. other treatments	RCT	No mention of industry sponsorship or COI.	N = 112 with traumatic hyphema; mean age for the bed rest group was 23.5 years and for the tranexamic acid group was 23.5 years.	Bed rest 6 days, atropine (N = 53) vs. Peroral Tranexamic acid (Cyclokapron), 25 mg.kg, 3 times daily for 7 days (N = 59). All received 1% Atropine twice a day and Dexamethasone 3 times a day and monocular patching	Follow-up at weeks 1 and 2.	No patients had a secondary hemorrhage. Tranexamic: average length of stay in the hospital and period time off work were 6 and 17 days, respectively. Bed rest group: average length of hospitalization was 7 vs. 20 days.	"[A]ntifibrinolytics should replace the traditional treatment with bed rest."	Data suggest modest delayed resorption with tranexamic acid without sign of adverse effect. Data suggest equal efficacy in rebleed rate but with quicker return to work rates.
Marcus 1988[122] (score = 3.0)	Aspirin vs other nonaspirin treatments for traumatic hyphema	RCT	No mention of sponsorship or COI	N = 51 patients with traumatic hyphema. Average age: 20	All patients received 1% atropine, .1% drops dexamycin, and bedrest. Group A 500 mg aspirin three times a day for 5 days. (N = 23) Vs. Group B Control group (N = 28)	Follow up: 3 times daily for 5 days.	3 of 23 eyes in Group A and 2 of 28 eyes in Group B experienced rebleeding. The difference between groups was not statistically significant.	No significant findings in the relationship between aspirin and non-aspirin treatments in treatment of traumatic hyphema.	Data suggest comparable (in)efficacy.

Viral, Bacterial, and Fungal Infections and Corneal Ulcers

RELATED TERMS

- Viral conjunctivitis
- Bacterial conjunctivitis
- Fungal conjunctivitis
- Fungal keratitis
- Corneal ulcer
- Epithelial keratitis
- Nummular keratitis
- Interstitial keratitis
- Ulcerative keratitis

OVERVIEW

Most eye infections are diagnosed as viral conjunctivitis [501-507]. These infections are highly contagious [508-511]. Viral conjunctivitis normally does not require treatment other than instructions on careful handwashing, potentially isolating the patient/worker from others, avoiding touching the eye and any other object (contact precautions) [512]. Conjunctivitis caused by herpes simplex or herpes zoster may be resolved faster with treatments [513] [503-506, 514-516]. Herpetic and zoster corneal infections are considerably more complex than conjunctivitis caused by, e.g., adenovirus. Herpetic and zoster corneal infections may be vision-threatening and require prolonged treatment with anti-viral medications.

Bacterial infections are the second most common cause [501-503, 506, 507]. Bacterial infections may be self-limited and thus not require treatment [508], but they can also be more serious. Fungal infections are more serious and require treatment. One of the more serious conditions is ulcer(s) complicated by bacterial and fungal infection; these require treatment and more vigilant follow-up care. Fungal infections typically take at least a month to resolve [517]. Contact-lens related infections are caused by bacterial, fungal and Acanthamoeba infections and are beyond the scope of this guideline [518]. Simple infections are mostly treated by primary care, urgent care and other non-ophthalmological and non-optometric specialists [509].

Corneal ulcers are considered an ophthalmologic emergency. They may result in permanent visual impairment. They may be bacterial, viral, fungal, or parasitic in origin and may occur following corneal lacerations, abrasions, and intrusion of foreign bodies. They may result from poorly fitted or inadequately cleaned contact lenses. Patients with corneal ulcers present with complaints of changes in visual acuity, photophobia and/or eye pain, tearing, and a sensation that a foreign body is in the eye. The presence of corneal ulcers can be determined by direct visualization, but magnified viewing with fluorescein staining is needed to completely rule out their presence.

RISK AND CAUSATION

Risk Factors

Viral conjunctivitis is highly contagious. Thus in some circumstances, the source or index case may be apparent. In most cases, the case appears spontaneously and thus the source and location of the source is unknown.

Bacterial and fungal infections most commonly occur as complications of either acute injuries or contact lens use [519, 520]. Other cases may occur without apparent cause. Risk factors include poor hygiene, poor contact lens hygiene, immunocompromised states, dry eyes, rheumatological disorders with ocular effects, recent eye surgery, crowded living conditions, dry eyes, blepharitis, contaminated cosmetics, use of topical medications, and sexually transmitted disease (especially Neisseria).

Causation

Work-relatedness of ocular infections as direct complications of acute injury (e.g., work-related corneal abrasion with subsequent fungal infection) is not difficult as the mechanism of injury and acuity of symptom onset generally begets a straightforward determination of work-relatedness. Causation of infections that occur without a work-related injury is also relatively simple, as the lack of an association is usually apparent and in most jurisdictions simplifies a determination of non-work relatedness.

Prevalence/Incidence

Infections are estimated to cause approximately 6 million infections in the US annually [521]. The incidence of culture-proven microbial infection has been estimated as 0.26/10,000 overall with a rate of 1.8/10,000 among those using contact lenses [522]. Those estimates compare with presumed incidence rates of 0.36/10,000 and 2.44/10,000 respectfully [522]. The incidence of fungal eye infections is unknown (CDC).

Work Relatedness

A determination of work-relatedness is usually determined in most juridictions based on the presence of a work-related acute injury that precedes the infection. In some unusual cases, an epidemic of viral conjunctivitis may occur in an occupational setting and the probability of the acquisition of a case in that setting exceeds 50% making a case work-related.

SIGNS AND SYMPTOMS

Medical History

Symptoms of corneal infections commonly include:

- Red or pink eye
- Tearing
- Purulence
- Crusty eyelids, especially on awakening
- Mild pruritis is sometimes present
- Photophobia, especially if more severe

- Visual acuity is usually preserved unless visual axis affected, e.g., by corneal ulcer or corneal abrasion
- Corneal ulcers typically include a foreign body sensation

Onset

- Symptom onset is usually gradual. However, as onset is most often noticed on awakening with mattering of the eyelids, some patients may report this as sudden onset.
- Some infectious cases occur after acute onset of trauma to the cornea, e.g., corneal abrasion.
- Onset of corneal ulcers are similarly gradual, although the inciting event may have been an acute injury.

Current treatments used

- Usually none, although may have included flushing of the eye.
- Some cases will occur on a delayed basis after acute injury. Thus, some cases will have had prior corneal foreign body(ies) removed.

RED FLAGS

Corneal ulcers are considered ophthalmological emergencies and thus are red flags.

Other red flags for potentially more serious infections include:

- Reduced visual acuity
- Periocular swelling and inflammation
- History of penetrating trauma or high impact metalworking without eye protection
- Suspected penetration of the globe
- Impaired extraocular eye movements
- Photophobia
- Systemic symptoms or diseases, especially rheumatological
- Copious purulence

DIAGNOSIS

Initial Assessment

The most important clinical assessment is whether the infection is vision-threatening or not. In general, vision threatening infections involve corneal ulcers and/or corneal infections.

The patient evaluation should include assessment of temperature, visual acuity, observation, extraocular movements, type of discharge, corneal opacity, eyelid swelling, proptosis, shape and size of the pupil, and sensitivity to light [512]. Lymphadenopathy is more commonly associated with viral as compared to bacterial conjunctivitis [523].

Diagnostic Criteria

Infections are among the differential diagnoses for a red eye (See Table 1) and eye infections may be acute, subacute or chronic. Infections of the conjunctive or cornea are generally accompanied by mattering of the eyelids on awakening as well as either an absence of or minimal pruritis [523, 524]. Thus, a symptom of mattering is somewhat helpful to narrow the differential diagnosis to be more likely

an infectious etiology. Bilateral mattering is thought to be more likely bacterial [512]. However, mattering is not particularly helpful to distinguish the type of infection. Mattering also is a symptom of blepharitis (low level infection along the lid margins), as well as a few other conditions.

The diagnostic criteria for viral conjunctivitis are: (i) watery discharge (although it may also be mucopurulent), (ii) minimal or no purulent discharge, (iii) in an erythematous eye, (iv) with preserved visual acuity and (v) with no corneal opacities.

Diagnostic criteria for corneal viral infections (e.g., herpes simplex or zoster) are: (i) watery discharge, (ii) minimal or no purulent discharge, (iii) in an erythematous eye, (iv) with impaired visual acuity (or preserved visual acuity but impaired visual fields if the infected corneal area is out of the visual axis) and (v) with corneal opacities.

Diagnostic criteria for bacterial and fungal eye infections are: (i) the presence of purulent discharge [525, 526], (ii) in an erythematous eye [527, 528], (iii) with preserved visual acuity, (iv) lack of pruritis, (v) no history of conjunctivitis, and (vi) that may or may not be confirmed by culture [529, 530]. Bacterial and fungal Infections may be confirmed with gram stain, KOH (potassium hydroxide) preparation and bacterial and fungal cultures. Cultures are often not performed especially in milder cases where the condition may be self-limited and thus resolve with no or limited empiric treatment [512]. Cultures are necessary for cases with neonatal conjunctivitis, severe infections, recurrent infections, Neisserial infections, chlamydia infections, and cases that are difficulty to treat [512].

Particularly with acute infections, there usually is marked conjunctival injection. The main infectious etiologies in the differential diagnosis among immunocompetent individuals in the developed world are viral conjunctivitis, bacterial and fungal infection. In other parts of the world or elsewhere among select populations, other etiologies include mycobacterium, parasites, and trachoma. Infections due to chlamydia trachomatis or Neisseria gonorrhea are beyond the scope of this guideline, yet for completeness are noted to require treatment with a systemic antibiotic plus an ophthalmologic antibiotic preparation.

Bacterial or fungal infections may also accompany and/or complicate corneal ulcers. Diagnostic criteria for bacterial or fungal ulcers are the same as those for infection with the added finding of corneal defect(s) or ulcer(s) on slit lamp examination.

Table 1: Selected Differential Diagnosis of Red Eye (Adapted from Cronau 2010)

Condition	Signs	Symptoms	Causes
Conjunctivitis			
Viral	Normal vision, normal pupil size and reaction to light, diffuse conjunctival injections (redness), preauricular lymphadenopathy,	Mild to no pain, diffuse hyperemia, occasional gritty discomfort with mild itching, watery to serous discharge, photophobia	Adenovirus (most common), enterovirus, coxsackievirus, VZV, Epstein-Barr virus, HSV, influenza

	lymphoid follicle on the undersurface of the eyelid	(uncommon), often unilateral at onset with second eye involved within one or two days, severe cases may cause subepithelial corneal opacities and pseudomembranes	
Herpes zoster ophthalmicus	Vesicular rash, keratitis, uveitis	Pain and tingling sensation precedes rash and conjunctivitis, typically unilateral with dermatomal involvement (periocular vesicles)	Herpes zoster
Bacterial (acute and chronic)	Eyelid edema, preserved visual acuity, conjunctival injection, normal pupil reaction, no corneal involvement	Mild to moderate pain with stinging sensation, red eye with foreign body sensation, mild to moderate purulent discharge, mucopurulent secretions with bilateral glued eyes upon awakening (best predictor)	Common pathogens in children: Streptococcus pneumoniae, nontypeable Haemophilus influenzae Common pathogen in adults: Staphylococcus aureus Other pathogens: Staphylococcus species, Moraxella species, Neisseria gonorrhoeae, gram-negative organisms (e.g., Escherichia coli), Pseudomonas species
Bacterial (hyperacute)	Chemosis with possible corneal involvement	Severe pain; copious, purulent discharge; diminished vision	N. gonorrhoeae
Chlamydial (inclusion conjunctivitis)	Vision usually preserved, pupils reactive to light, conjunctival injections, no corneal involvement, preauricular lymph node swelling is sometimes present	Red, irritated eye; mucopurulent or purulent discharge; glued eyes upon awakening; blurred vision	Chlamydia trachomatis (serotypes D to K)
Allergic	Visual acuity preserved, pupils reactive to light, conjunctival injection, no corneal involvement, large cobblestone papillae under upper eyelid, chemosis	Bilateral eye involvement; painless tearing; intense itching; diffuse redness; stringy or ropy, watery discharge	Airborne pollens, dust mites, animal dander, feathers, other environmental antigens

Classification

Viral, bacterial and fungal eye infections are not commonly classified other than by the inciting organism when known.

History

Symptoms usually begin gradually. Mattering of the eyelid(s) and a red eye on awakening is often the first sign of an eye infection. Common symptoms of corneal infections include: red/pink eye, tearing, purulence, crusty eyelids, mild pruritis, photophobia (if more severe), and potentially a mild foreign body or irritation sensation. Visual acuity is generally preserved, although some viral infections, especially herpes or zoster, may involve the visual axis and reduce visual acuity.

DIAGNOSTIC RECOMMENDATIONS

Viral Screening

Adenovirus screening has been performed in clinical settings to diagnose viral conjunctivitis [531] as most cases of viral conjunctivitis are caused by adenovirus [523].

Adenovirus Screening, Select Patients

Recommended.

Adenovirus screening is selectively recommended for evaluation of infectious conjunctivitis where there is diagnostic uncertainty and a significant consideration for bacterial conjunctivitis. It is not recommended for routine evaluation of typical viral conjunctivitis cases.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Adenovirus screening is highly selectively recommended for evaluation of eye infections where there is diagnostic uncertainty and a significant consideration for bacterial conjunctivitis and the condition is more serious, thus there is contemplation of other treatment(s). The main purpose of this screening is to determine the cause and prevent unnecessary antibiotic use. Screening is not recommended for routine evaluation of typical viral conjunctivitis cases.
Indications for Discontinuation:	N/A
Benefits:	Potential to improve diagnostic accuracy and reduce use of antibiotics.
Harms:	May mislead especially with negative test results as assumptions may be incorrect that the agent is a bacterium. False positive results are also possible.
Comments:	
Rationale:	There is 1 high-quality study showing 89% sensitivity and 94% specificity [531]. The primary purpose of adenovirus screening is to rule out other infections and prevent excessive antibiotic usage for a condition that is usually self-limited. Yet, there are other viral causes, thus it is an imperfect test. As most cases resolve readily without treatment, routine screening is not recommended. Adenovirus

screening is not invasive, has negligible adverse effects, is low cost, has demonstrated efficacy and is thus indicated for selectively diagnosing viral conjunctivitis.

Adenovirus Screening, Routine

Not Recommended.

Routine adenovirus screening is not recommended for evaluation of infectious conjunctivitis.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – High

Indications:
Indications for Discontinuation:
Benefits:
Harms:
Comments:
Rationale: There is 1 high-quality study showing 89% sensitivity and 94% specificity [531]. The primary purpose of adenovirus screening is to rule out other infections and prevent excessive antibiotic usage for a condition that is usually self-limited. Yet, there are other viral causes, thus it is an imperfect test. As most cases resolve readily without treatment, routine screening is not recommended. Adenovirus screening is not invasive, has negligible adverse effects, is low cost, has demonstrated efficacy and is thus indicated for selectively diagnosing viral conjunctivitis.
Evidence:

Culture and Sensitivity

Gram Stain, Potassium Iodide (KOH) preparation, Culture and Sensitivity of Eye Infections (Select Patients)

Recommended.

Gram Stain, KOH preparation, culture and sensitivity of eye infections are selectively recommended, especially for moderate to severe and/or poorly responding and/or recurrent cases.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – High

Indications: Gram Stain, potassium iodide (KOH) preparation, culture and sensitivity of eye infections are selectively recommended, especially for evaluation of eye infections where there is a moderate to severe infection [532, 533]. These are also recommended if there is either poor clinical response to empiric treatment and/or a recurrent infection. The main purpose of this screening is to determine the most appropriate treatment.
Indications for Discontinuation:
Benefits: Potential to improve diagnostic accuracy and reduce use of inappropriate antibiotics.

Harms: Negligible. There is potential for misinterpretation if current antibiotic use produces a false negative test result.

Comments:

Gram Stain, Potassium Iodide (KOH) preparation, Culture and Sensitivity of Eye Infections (Routine)

Not Recommended.

Routine Gram Stain, KOH preparation, culture and sensitivity of eye infections is not recommended as many cases are able to be treated empirically.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Moderate

Indications:
Indications for Discontinuation:
Benefits:
Harms:
Comments:
Rationale: There is evidence suggesting antibiotic anti-fungal resistance correlates with worse outcomes [532, 533]. The primary purpose of Gram Stain, potassium iodide (KOH) preparation, culture and sensitivity of eye infections is to secure a diagnosis that allows for a specific, focused treatment regimen. This also helps prevent excessive antibiotic use and/or excessively broad spectrum use that may foster the development of resistant organisms. age for a condition that is usually self-limited. Yet, there are other viral causes, thus it is an imperfect test. As many cases of milder conjunctivitis resolve readily without treatment and others resolve readily with empiric treatment, routine Gram Stain, potassium iodide (KOH) preparation, culture and sensitivity of eye infections is not recommended. Gram Stain, potassium iodide (KOH) preparation, culture and sensitivity of eye infections is not invasive, have negligible adverse effects, are low cost, have demonstrated clinical efficacy and are thus indicated for selectively diagnosing bacterial and fungal eye infections.

Evidence:

Other Diagnostic Testing

Generally, other diagnostic testing is not needed for evaluating eye infections. Occasionally, there may be a need for other tests based on any other accompanying symptoms and/or injuries (e.g., sinus x-ray, sinus CT scan, CT of orbits, MRI of orbits).

TREATMENT

Initial Care

For presumptive viral conjunctivitis and mild bacterial conjunctivitis, there is no medication necessary. However, careful instructions about vigilant hand-eye hygiene is important to reduce risks of further

spread. For moderate to severe bacterial conjunctivitis, closer follow-up is required for progress and recovery. For corneal infections or corneal ulcers, medication(s) are necessary and close follow-up is required to minimize risk of visual loss.

TREATMENT RECOMMENDATIONS

Medications

No antibiotic treatment is required for common causes of viral conjunctivitis [534]. Herpes simplex and herpes zoster corneal infections require anti-viral treatment, but are beyond the scope of this guideline as they are not considered occupational conditions. In adults, the most common causes of bacterial conjunctivitis are *Streptococcus pneumoniae (51%), Pseudomonas (23%), Staphylococcus sp* and *Hemophilus influenzae* [535, 536]. Treatment of bacterial conjunctivitis shortens the clinical course [512, 537-540]. Yet, mild mucopurulent infections are not improved faster with antibiotics [541]. Ulcer severity is strongly correlated with outcome [542]. Fungal infections are generally more severe and require longer treatment times to resolve [543].

Antibiotics for Bacterial Conjunctivitis and Bacterial Infections Complicating Corneal Ulcers

Moderately Recommended.

Medications (including topical creams)

Antibiotics are recommended for select treatment of bacterial conjunctivitis and bacterial infections complicating corneal ulcers.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – Moderate

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Moderate to severe bacterial conjunctivitis to shorten the clinical course. May not be necessary for mild cases, as mild mucopurulent infections are not improved faster with antibiotics (Reitveld 05). Cases of Neisseria require both topical and systemic treatment and are beyond the scope of this guideline. Bacterial infections complicating corneal ulcers also require treatment with the additional indication of treatment until the corneal defect has also resolved. Baseline visual acuity is predictive of visual recovery [544].
Frequency/Dose/Duration:	There is quality evidence of comparable efficacy among all of the following ophthalmologic antibiotic preparations: ciprofloxacin 0.3%, gatifloxacin 0.3%, levofloxacin 0.5%, lomefloxacin 0.3%, moxifloxacin 0.5-1.0%, ofloxacin 0.3%, ofloxacin- benzalkonium chloride, tobramycin-cefazolin 1.33-1.5%/5-10%, cefazolin-amikacin, cefazolin-gentamicin, and thimerosal 0.005%. Thimerosal is not recommended due to a 5-fold rate of toxicity [545]. Tailoring the antibiotic selection to the estimated bacteria genus and specie as well as incorporating local antibiotic resistance profiles is advisable. Gram stain is not commonly performed but may assist in preliminary antibiotic tailoring,

and further adjustments of the selected antibiotic may be necessary based on culture and sensitivity results, if obtained, as there is evidence suggesting antibiotic resistance correlates with worse outcomes [533]. Length of treatment is for the duration of symptoms and for ulcers is typically for the duration of the ulcer until the corneal defect is resolved.

Antibiotic regimens used in the highest quality studies include:

- Amikacin/Cefazolin eye drops every 10 minutes during first 30 minutes of treatment and later decreased to hourly every 3 days [546]
- Ciprofloxacin 0.3% eye drops every 15 minutes for 1st 6 hours, 1 drop every hour 1st day, then hourly [547],
- Gatifloxacin 0.3% eye drops hourly [548]
- Levofloxacin 0.5% eye drops every 10 minutes during first 30 minutes of treatment and later decreased to hourly every 3 days [546]
- Lomefloxacin ophthalmic solution 0.3% 1 drop every 15 minutes for 1st 6 hours, 1 drop every hour 1st day, then hourly the following days [547]
- Moxifloxacin 1 drop every hour for 48 hours, day 3 every hour by day and 2 hours by night, days 4 and 5, 1 drop every 2 hours and 4 by night, days 6 and 7, 1 drop every 4 hours and after every 6 hours [549]
- Ofloxacin 0.3% every ½ hr on study day 1, every hour on days 2 - 4, and every 2 hours on days 5 – 21 [550]
- Ofloxacin 0.3% eye drops every 30 minutes for 6 hours, hourly on days 1-3, 2-hourly on days 4-5 and 4 hours until 1 week [551]
- Azithromycin 1% 1 drop twice daily for 3 days [552-554]
- Tobramycin 1.33% / Cefazolin 5% group received 1 drop every hour for 48 hours, day 3 every hour by day and 2 hours by night, days 4 and 5, 1 drop every 2 hours and 4 by night, days 6 and 7, 1 drop every 4 hours and after every 6 hours [549]
- Tobramycin/Cefazolin 1.5%/5% solution 0.3% 1 drop every 30 minutes for 6 hours, hourly on days 1-3, 2-hourly on days 4-5 and 4 hours until 1 week [551]

Indications for Discontinuation: Resolution of infection, resolution of all corneal defects. In case of allergy, discontinuation of an antibiotic and initiation of a second from a different antibiotic class is indicated.

Benefits: Shortened clinical course. Likely improved visual acuity compared with non-treatment in those with baseline visual field defects. Improve ulcer healing if bacterial infection complicating an ulcer.

Harms: Risks of antibiotic use, mostly allergies and increased bacterial resistance.

Comments:

Rationale: There are many quality comparative trials evaluating treatment of bacterial infections with keratitis or complicating corneal ulcers. There are several placebo-controlled trials, all showing earlier clinical resolution with antibiotic treatment [537-540]. There is no quality evidence that any antibiotic is superior to another for treatment of these infections and all of the following have quality evidence of comparable efficacy: besifloxacin [537, 538, 555, 556], ciprofloxacin [547, 548, 550, 557-559], gatifloxacin [548, 560-563], levofloxacin [546, 564] lomefloxacin [547, 565, 566], moxifloxacin [549, 560, 562, 567,

568] [569], ofloxacin [549-551, 564, 570, 571], ofloxacin- benzalkonium chloride [545], tobramycin-cefazolin [549, 551, 557, 560, 570-572], cefazolin-amikacin [546], cefazolin-gentamicin [558, 565], azithromycin [552-554], and thimerosal [545]. However, thimerosal is not recommended due to a 5-fold rate of adverse effects [545]. Topical ophthalmological antibiotic preparations are not invasive, have low adverse effects, are low cost, and are effective for treatment of moderate to severe bacterial eye infections and ulcers complicated by bacterial infections. Thus, they are recommended.

Evidence:

Adjuvant Glucocorticosteroids for Bacterial Conjunctivitis and Bacterial Infections Complicating Corneal Ulcers

Not Recommended.

Medications (including topical creams)

Adjuvant glucocorticosteroids are not recommended for treatment of bacterial conjunctivitis and bacterial Infections complicating corneal ulcers.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:
Frequency/Dose/Duration:
Indications for Discontinuation:
Benefits:
Harms:
Comments:
Rationale: Adjuvant glucocorticosteroid use for bacterial corneal ulcers has been widespread with a strong belief in efficacy at improving visual outcomes [573]. There are quality trials evaluating adjuvant glucocorticosteroid use for treatment of bacterial keratitis after initial treatment with an antibiotic and failing to show significant differences in outcomes over intermediate to longer terms [544, 567, 574, 575]. Another trial suggested delayed epithelialization with glucocorticosteroid compared with placebo [574]. It has also been suggested steroids may not be helpful for nocardial infections [544, 567, 574-576]. Topical ophthalmological preparations of glucocorticosteroids are not invasive, and are low cost. These medications do not have significant demonstrated efficacy [544, 561, 567, 574, 575], appear to have the adverse effect of delaying healing, and are thus not recommended.

Evidence:

Antibiotics for Viral Conjunctivitis

Not Recommended.

Medications (including topical creams)

Antibiotics are not recommended for routine treatment of viral conjunctivitis.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:
Frequency/Dose/Duration:
Indications for Discontinuation:
Benefits:
Harms:
Rationale: There are is one moderate quality trial of antibiotics for treatment of viral conjunctivitis that showed minimal shortening of symptom duration with empiric antibiotic treatment [534]. Topical ophthalmological antibiotics are not invasive, have few adverse effects, are low cost, but do not have a sound rationale for use in viral conjunctivitis and are thus generally not recommended. However, the threshold for treatment with antibiotics is fairly low as they have low rates of adverse effects. Additionally, it can be difficult to separate some viral from bacterial infections, thus there are many cases that are treated with antibiotics. Severe infections or those thought to be bacterial are obvious candidates for treatment. Herpes simplex and herpes zoster corneal infections do require anti-viral treatment but are beyond the scope of this guideline.

Evidence:
Comments:

Non-steroidal Anti-inflammatory Drugs for Symptoms of Viral Conjunctivitis

Not Recommended.

Medications (including topical creams)

NSAIDs are not recommended for treatment of viral conjunctivitis.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:
Frequency/Dose/Duration:
Indications for Discontinuation:
Benefits:

Harms:
Comments:
Rationale: Two quality articles failed to find superiority of an NSAID to artificial tears [577] [578], thus there is no demonstrable efficacy. NSAIDs are not invasive, have low adverse effects especially for short-term use, are low cost, but are not effective and thus are not recommended.
Evidence:

Glucocorticosteroids for Symptoms of Viral Conjunctivitis

No Recommendation.

Medications (including topical creams)

There is no recommendation for or against glucocorticosteroid for treatment of viral conjunctivitis.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:
Frequency/Dose/Duration:
Indications for Discontinuation:
Benefits:
Harms:
Comments:
Rationale: There is one trial that had methodological issues including protocol deviation which was interpreted as suggesting reduced symptoms [579]. Glucocorticosteroids are not invasive, have low adverse effects, are low cost, but effectiveness is unclear and thus there is no recommendation.

Evidence:

Antifungal Medications for Fungal Conjunctivitis and Fungal Infections Complicating Corneal Ulcers

Recommended.

Medications (including topical creams)

Antifungal medications are recommended for treatment of fungal conjunctivitis and fungal infections complicating corneal ulcers.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications: Fungal conjunctivitis. Fungal infections complicating corneal ulcers also require treatment with the additional indication of treatment until the corneal defect has also resolved.

Frequency/Dose/Duration: There is quality evidence of comparable efficacy among most of the following ophthalmologic antibiotic preparations: econazole 2%, natamycin 5%, voriconazole 1%, and Amphotericin B. Metanalysis of multiple trials suggests natamycin is superior to voriconazole [543], thus voriconazole is not recommended. One trial suggested superiority of chlorhexidine gluconate compared with natamycin 5% [580]. One trial found superiority of Amphotericin B drops plus subconjunctival injections of fluconazole to topical treatment alone [581]. Potassium iodide (KOH) is not always performed but may assist in preliminary antifungal regimen tailoring, and further adjustments in the medication(s) used may be necessary based on culture and sensitivity results. Length of treatment is until resolution of the ulcers, which varies widely and is commonly 4-6 weeks.

Antifungal regimens used in the highest quality studies include:

- Econazole 2% drops on hourly basis between 7 am to 9 pm [582].
- Natamycin 5% every hour while awake until reepithelialization, then 4 times daily for at least 3 weeks [542, 580, 582-584].
- Amphotericin B 0.2 mg/ml Q2hrs for 21 days [581]
- Amphotericin B 0.2 mg/ml Q2hrs for 21 days plus subconjunctival injections of fluconazole 2mg/mL daily for 10 days [585]
- Chlorhexidine gluconate 0.2%, 1/2-hourly to 2-hourly for up to 5 days, then with reduced frequency, and all patients re-assessed at 21 days. [580]

Indications for Discontinuation: Resolution of infection, resolution of all corneal defects. In case of allergy, discontinuation of an antifungal and initiation of a second may be indicated.

Benefits: Improve ulcer healing if fungal infection complicating an ulcer. Likely improved visual acuity compared with non-treatment in those with baseline visual field defects.

Harms: Risks of antifungal use, mostly allergies and increased fungal resistance.

Rationale: There are multiple quality comparative trials evaluating treatment of fungal infections with keratitis or complicating corneal ulcers. There are no placebo-controlled trials. There is limited quality evidence that one antifungal may be superior to another, as multiple trials suggest natamycin is superior to voriconazole [543]. One moderate quality trial found Amphotericin B drops plus subconjunctival injections of fluconazole superior to topical treatment alone [585]. There is also limited evidence the chlorhexidine gluconate may be superior to natamycin drops [580]. All of the following have been assessed in quality trials: Amphotericin B [581], econazole [582], natamycin [542, 580, 582-584, 586], voriconazole [542, 580, 582-584, 586]. Topical ophthalmological antifungal preparations are not invasive, have low

adverse effects, are low cost and are likely effective for treatment of fungal eye infections and ulcers complicated by fungal infections. Thus, they are recommended. Adjuvant antifungal injections in addition to topical treatment may be effective and may be best for severe cases, but evidence is currently insufficient to conclude an evidence-based recommendation [581].

Evidence for Glucocorticosteroids

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Lyra 2014 (Score = 7.5)	Glucocorticosteroids	RCT	No sponsorship or COI.	N = 50 with acute viral conjunctivitis;	mean age of 31.6±10.7 years.	Group 0: artificial tears (N = 26) vs. Group 1: 0.45% ketorolac tromethamine + carboxymethylcellulose (N = 24). In both the groups, The patients were instructed to use the medication 4 times daily.	Follow-up on 3rd and 7th days of treatment.	There was no significant difference in symptom and sign scores between Group 0 and Group 1 in the study visits (p>0.05). The frequency of side effects during treatment was similar between groups (p>0.05).	"…0.45% ketorolac tromethamine was not superior to artificial tears in relieving the signs and symptoms of viral conjunctivitis. Further research studies to evaluate safe and effective therapies for this common eye disease are required."	Comparable efficacy between the 2 treatment groups.
Shiuey 2000 (Score = 7.0)	Glucocorticosteroids	RCT	Sponsored by an unrestricted grant from Allergan Pharmeceuticals, Irvine, California. No COI.	N = 117 with unilateral or bilateral conjunctivitis of less than 2 weeks;	mean age of 31 for both groups.	Ketorolac 0.5% ophthalmic solution 1 drop in each symptomatic eye 4 times / day for 7 days (N = 57) vs. Artificial tears 1 drop in each symptomatic eye 4 times / day for 7 days (N = 48).	Follow up at 3 to 4 days.	Redness classified as worse / no change / better for artificial tears was 0 (0.0%) / 5 (10.4%) / 43 (89.6%) vs. ketorolac group 6 (10.5%) / 12 (21.1 %) / 39 (68.4%), (p=0.012). Adverse events at stinging / headache / photophobia for artificial tears 9 (18.8%) / 0 (0%) / 0 (0%) vs. ketorolac group 34 (59.6%) / 1 (1.7%) /1 (1.7%), (p<0.001).	"Topical ketorolac 0.5% used four times daily is no better than artificial tears at relieving the symptoms or signs of viral conjunctivitis and produces more stinging than artificial tears."	Data suggest lack of efficacy.

Everitt 2006 (Score = 6.5)	Glucocorticosteroids	RCT	Sponsored by the Medical Research Council of a clinical training fellowship awarded to Dr. Everitt. No COI.	N = 307 with acute infective conjunctivitis adults and children;	mean age 27.2±27.6 for no antibiotics, 27.2±25.1 for immediate antibiotics and 28.2±25.9 for delayed antibiotics.	Immediate antibiotics for 3.3 days (N = 104) vs. Delayed antibiotics for 3.9 days (N = 109) vs. No antibiotic or controls for 4.8 days (N = 94).	Follow up?	Antibiotic use / belief in antibiotic effectiveness / intention to reattend for eye infections: (99% vs. 53% vs. 30% in control group / (47% vs. 55% vs. 47% in controls) / (68% vs. 41% vs. 40% in controls).	"Compared with no initial offer of antibiotics delayed prescribing had the advantage of reduced antibiotic use (almost 50%), no evidence of medicalisation, similar symptom control to immediate prescribing, and reduced attendance for eye infections."	No blinding. Intervention process poorly described.
Wilkins 2011 (Score = 6.0)	Glucocorticosteroids	RCT	Sponsored by the UK department of Health's NIHR BRC at Moorfields Eye Hospital and the UCL Institute of Ophthalmology. No COI.	N = 111 with acute follicular conjunctivitis, presumed viral in origin;	mean age for group 1 was 39 years and group 2 was 38 years.	Group 1: dexamethasone drops, 0.1% (N=56) vs. Group 2: hypromellose lubricant drops, 0.3% (N= 55). Both groups were prescribed those drops for four times daily for 1 week.	No follow-up time reported.	Most patients (39/45 (87%) receiving dexamethasone and most of those receiving hypromellose 30/43 (70%) felt that the treatment helped. Analysis of all responses showed a significant difference between treatments (p=0.0248).	"[T]his trial provides evidence to support the use of a short course of topical dexamethasone for patients presenting with acute follicular conjunctivitis without keratitis signs or pseudomembrane. Where topical dexamethasone is prescribed we have not found it to be harmful, although it is important to remember that the trial was not powered to find a difference in side effects between the two arms. The lack of harm matches previous experience where topical steroids have been used for this condition."	Protocol states deviation to achieve statistical significance after recruitment failure. Data suggest some efficacy for use of topical steroid.

Toker 2006 (Score = 2.5)	Glucocorticosteroids	RCT	No mention of sponsorship or COI.	N = 62 with measles conjunctivitis;	age range of 20 to 22.	Ketorolac 0.5% in the right eye, artificial tears in the left eye (N = 31) vs. Indomethacin 0.1% in the right eye, artificial tears in the left eye (N = 31).	Follow up at baseline, 7 and 14 days.	Conjunctival injection score at days 7 and 14 was significantly lower in ketorolac treated group compared to indomethacin treated eye ($p<0.05$).	"In patients with measles during the first two weeks of infection, ketorolac and indomethacin were more effective than artificial tears in decreasing conjunctival hyperemia, but burning sensations, foreign body sensation, and photophobia were unaffected."	Study labeled double masked but all left eyes placebo. Most measures did not differ.
Srinivasan a 2012	Steroid	RCT Multicenter Double-blind	Sponsored by National Eye Institute grant, Dr. Acharya is supported by National Eye Institute grant, and a Research to Prevent Blindness Award, and a core grand from the National Eye Institute. No COI.	N = 500 with bacterial keratitis.	The median age was 53.0 (40.0 – 61.0).	Entry criteria were at least 48 hours of moxifloxacin treatment. Then either: Topical prednisolone sodium phosphate 1.0% 1 drop 4 times daily for 1 week, then 2 a day for 1 week, then once a day for 1 week (N = 250) vs Placebo adjunctive Therapy the same dosing as topical prednisolone sodium group (N = 250).	Follow-up at 3 months.	Significantly different infiltrate/scar size at 3 weeks, 0.05 mm; 95% CI, –0.09 to 0.15, (p = 0.60) or 3 months, 0.06 mm; −0.07 to 0.17, (p = 0.40). At 3-month BSCVA (−0.009 logarithm of the minimum angle of resolution; 95% CI, −0.085-0.068, (p = 0.82) / infiltrate /scar size (p = 0.40) / time to reepithelialization, (p = 0.44) / or corneal perforation (p > 0.99). Significant effect of corticosteroids seen in subgroups of baseline BSCVA,	"[N]o overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers."	All treated with moxifloxacin for at least 2 days prior to RCT with steroid. Comparable efficacy at 3 months, but at 3 weeks, data suggest poorer healing with steroid.

								(p = 0.03) / ulcer location, (p = 0.04).		
Srinivasan b 2012 (Score = 6.0)	Steroid	RCT Multicenter Double-blind	Sponsored by the National Eye Institute grant, Dr. Acharya is supported by National Eye Institute grant, and a Research to Prevent Blindness Award.	N = 500 with bacterial keratitis.	The median age was 53 (40-61).	Topical moxifloxacin 0.5% drop 4 times daily for 1 week, then twice a day for 1 week, and then once per day for 1 week (N = NA) vs Topical prednisolone phosphate 1% or placebo drops were given according the same schedule as treatment group (N = NA).	Follow-up at 3 months.	Median baseline visual acuity was 0.84 logMAR, IQ range 0.36-1.7, (p = 0.55). Baseline visual acuity was not significantly different between the United States and India. Ulcers in India had larger infiltrate/scar sizes, (p = 0.04) and deeper infiltrates, (p = 0.04) and were more likely to be localized centrally, (p = 0.002) than ulcers	"The Steroids for Corneal Ulcers Trial will compare the use of a topical corticosteroid with placebo as adjunctive therapy for bacterial corneal ulcers."	Methods paper for SCUT studies. Some baseline comparability differences between the study and placebo groups.

								enrolled in the United States.		

Evidence for Topical Glucocorticosteroids

Blair 2011 (Score = 8.5)	**Topical glucocorticosteroids**	RCT, prospective	**Supported by The Physicians' Services Incorporation Foundation. No COI.**	N = 30 with bilateral corneal ulcer confirmed by culture;	**mean age of 40.7±21.12 for antibiotic only group, and 48.7±19.88 for antibiotic and steroid group.**	Gatifloxacin (Zymar) and a masked placebo (N = 15) vs Gatiflozacin and masked dexamethasone, 0.1% Maxidex (N = 15). Patients were instructed to take the antibiotic every hour they were awake for days 1 and 2; reduce dose to every 2 hours and begin steroid/placebo 4 times a day; on day 7, patients reduced the antibiotic to 4 times a day.		Mean residual ulcer size at 10 weeks compared with baseline: antibiotic only vs. antibiotic plus steroid: -0.789mm squared vs. -4.206mm squared, (p = 0.05).	"No benefit was demonstrated in our primary outcome for using steroids in combination with antibiotic therapy in treatment of corneal ulcers. This study suggests that the early addition of steroids to the antibiotic treatment of corneal ulcers does not seem to be harmful when employed in a closely monitored clinical setting."	Very small sample sizes. Some baseline comparability discrepancies. Data suggest no benefit of adjuvant steroid to antimicrobial versus antimicrobial alone for corneal ulcers. Likely underpowered for either efficacy or adverse effects.

Srinivasan 2009 (Score = 7.0)	Topical glucocorticosteroids	RCT Double-blinded	Sponsored from That Man May See and the South Asia Research Fund, a core grant from the National Eye Institute, Eye Institute Grant, and T M Lietman is supported by a National Eye Institute grant. No COI.	N = 42 with bacterial keratitis.	The mean age for steroid / placebo was: 44.1 (17.0) / 49.9 (13.0).	Topical prednisolone phosphate 1% 4 times a week for 1 week, then every 2 hours and 4 times a day until 3 weeks (N = 20) vs Placebo 0.9% sodium chloride 4 times a day for 1 week, every 2 hours and 4 times a day until 3 weeks (N = 22).	Follow-up at 3 months.	Compared with placebo treatment, steroid treatment was associated with 0.19 lower (better) logMAR acuity at 3 weeks or 95% CI 20.52-0.15, (p = 0.26) / 0.09 lower logMAR acuity at 3 months, 95% CI 20.41-0.24, (p = 0.60). At 3 months, steroid treatment was associated with 0.33 mm smaller infiltrate / scar size diameter or 95% CI 1.4 mm smaller to 0.75 mm larger vs placebo, (p = 0.53).	"In this trial, although the steroid-treated group had a significant delay in re-epithelialisation, steroids were not associated with a statistically significant difference in BSCVA or infiltrate/scar size."	Pilot study of steroid versus placebo suggesting slower re-epithelialisation but visual acuity similar in both groups.

Srinivasan a 2012 (Score = 6.5)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by National Eye Institute grant, Dr. Acharya is supported by National Eye Institute grant, and a Research to Prevent Blindness Award, and a core grand from the National Eye Institute. No COI.	N = 500 with bacterial keratitis.	The median age was 53.0 (40.0 – 61.0).	Topical prednisolone sodium phosphate 1.0% 1 drop 4 times daily for 1 week, then 2 a day for 1 week, then once a day for 1 week (N = 250) vs Placebo adjunctive Therapy the same dosing as topical prednisolone sodium group (N = 250).	Follow-up at 3 months.	Significantly different infiltrate/scar size at 3 weeks, 0.05 mm; 95% CI, –0.09 to 0.15, (p = 0.60) or 3 months, 0.06 mm; −0.07 to 0.17, (p = 0.40). At 3-month BSCVA (−0.009 logarithm of the minimum angle of resolution; 95% CI, −0.085-0.068, (p = 0.82) / infiltrate /scar size (p = 0.40) / time to reepithelialization, (p = 0.44) / or corneal perforation (p > 0.99). A significant effect of corticosteroids was observed in subgroups of baseline BSCVA, (p = 0.03) / ulcer location, (p = 0.04).	"[N]o overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers."	Comparable efficacy at 3 months. However, data at 3 weeks suggest delay

Lalitha 2012 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by Grant from the National Eye Institute, National Institutes of Health. The Department of Ophthalmology U.C. sponsored by Core Grant from the National Eye Institute, unrestricted grant from Research to Prevent Blindness, Inc, and by That Man May See, Inc, C.A. COI, Dr. Acharya sponsored by Grant from the National Eye Institute, and Research to Prevent	N = 55 with bacterial corneal ulcers or Nocardia corneal ulcer.	The median age was 48 years or age range, 40 – 60 years.	Topical prednisolone phosphate 1 drop topically 4 times daily for 1 week, then twice daily for 1 week, and then once daily for 1 week (N = NA) vs Placebo received at least 48 hours of topical moxifloxacin 0.9% 1 drop applied topically every hour while awake for the first 48 hours, then 1 drop every 2 hours until reepithelialization and then 4 times daily until 3 weeks (N = NA).	Follow-up at 3 months.	Best spectacle corrected visual acuity (BSCVA) / infiltrate or scar size at 3 months: median BSCVA was worse in patients receiving amikacin 0.54 logMAR vs 0.09 log- MAR, (p = 0.01) / on average 0.40-mm larger infiltrate or scar size in Nocardia keratitis cases, with enrollment scar size and addition of amikacin as covariates, 0.40 mm, 95% CI, 0.03-0.77 mm, (p = 0.03).	"Nocardia ulcers responded well to treatment. They showed less overall improvement in visual acuity than non-Nocardia ulcers, but had better presentation acuity."	Post-hoc subset study from original SCUT to look at Nocardia Keratitis versus other bacterial keratitis and how these respond to steroids showed less improvement but may be due to Nocardia patients having better baseline visual acuity.

			Blindness Award, N.Y.							
Srinivasan 2014 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by the National Eye Institute, Dr. Lietman is also supported by a Research to Prevent Blindness Physician Scientist Award. Dr. Acharya is supported by a National Eye Institute and a Research to Prevent Blindness	N = 500 with bacterial corneal ulcers.	The mean age for placebo / steroid group; 50 (40-60) / 52 (40-61).	Moxifloxacin 0.5% 1 drop every hour for the first 48 hours, then every 2 hours until re-epithelialization, and then 4 times a day until 3 weeks (N = 250) vs Topical prednisolone Phosphate 1.0% or topical placebo 1 drop 4 times per day for 1 week, then twice a day for 1 week, and then once per day for 1week (N = 250).	Follow-up at 12 months.	No significant differences in BSCVA or scar size between treatment arms, (p = 0.39 or 0.69) or at 12 months among Nocardia ulcer, (p = 0.16) or scar size, (p = 0.02). No statistical difference for non-Nocardia ulcers, (p = 0.46).	"Adjunctive topical corticosteroid therapy may be associated with improved long term clinical outcomes in bacterial corneal ulcers not caused by Nocardia species."	12 month SCUT follow-up study. Topical steroids may be beneficial from non Nocardia ulcers.

			Award. NO COI.							
McClintic 2014 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by 3 National Eye Institute Grants, a Research to Prevent Blindness Award (NRA), Alcon/Novartis AG, and Core Grant. No COI.	N = 50 with bacterial keratitis.	The median age was 45 years (38-60).	Topical prednisolone phosphate (1%) tapered over 3 weeks (N = 24) vs Topical placebo tapered over 3 weeks (N = 26).	Follow-up at 3 weeks, 3 months, 12 months and 4 years.	Visual acuity or VA (logMAR) at 4 year visit: *28* or 59.6% had VA better than 20/40, *15* or 31.9% had VA from 20/40 up to 20/200, *1* or 2.1% had VA from 20/ 200 to 20/800, and *3* (or 6.4% had VA of counting fingers or worse. Best spectacle-corrected visual acuity (BSCVA) at 4 years was not statistically different between groups, (p = 0.53).	"Cases of bacterial keratitis may continue to demonstrate improvements in visual acuity up to 12 months following diagnosis, but further improvements are unlikely."	4 year post-hoc subset analyses of original SCUT study. Visual acuity did not improve after 12 months although 60% of the 4 year subset population still had 20/20 vision and the remainder of vision problems was largely attributable to corneal scaring and cataracts.

Ray 2013 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by grant from the National Eye Institute (Dr. Lietman). Dr. Acharya is supported by grant from the National Eye Institute and a Research to Prevent Blindness Award. Alcon provided moxifloxacin (Vigamox) for the trial.	N = 480 with bacterial keratitis.	The median age was 50 years, ranging from 39 – 60.	Prednisolone phosphate 1% (N = NA) vs Topical placebo group of sodium chloride 0.9%, and preservative (N = NA).	Follow-up not specified.	Patients reporting fluoroquinolone were 2.01-fold–higher minimum inhibitory concentration (MICs) at (95% CI, 1.39-fold to 2.91-fold; P <.001). Patients reported using different fluoroquinolones, including ciprofloxacin hydrochloride (N=26), ofloxacin (N=24), gatifloxacin (N=18), and moxifloxacin (N=16). No significant results when comparing patients reporting 3rd generation fluoroquinolone (with levofloxacin) baseline at (95% CI, 0.35-fold to 8.11-fold; P = .51)	"This study provides evidence that prior use of fluoroquinolones is associated with antibiotic resistance."	Subset SCUT study to demonstrate prior fluoroquinolones treatment and how the MIC increased (i.e. antimicrobial resistance was induced).

Sy 2012 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blinded	Sponsored by National Eye Institute Grants and Core Grant: a Research to Prevent Blindness Award, The Proctor Foundation, A Dean's Research Fellow-ship from the UCSF School of Medicine, a Pathways to Careers in Clinical and Translational Research Fellowship; an restricted gran from Research to Prevent Blindness; and That Man May See. No COI.	N = 500 with bacterial keratitis.	The age median, for those with P. aeruginosa / all other bacteria: 43 (30-54) / 55 (42.5-63).	Those with P. aeruginosa Corneal Ulcers randomized to: Topical prednisolone phosphate 1% (N = 59) vs Topical placebo NaCl 0.9% and preservative (N = 51).	Follow-up at 3 months.	At baseline, those with P. aeruginosa (N = 110) ulcers presented with significantly worse visual acuities than did patients with other bacterial ulcers, (p = 0.001). At 3 months, P. aeruginosa ulcers to show significantly greater improvement in visual acuity than other bacterial ulcers (N = 384) of similar presentation severity, (p = 0.004). The median visual acuity, 1.12 (0.46-1.7) in treatment vs 1.50 (0.46-1.8) in placebo group, (p = 0.10). The median infiltrate/scar size in mm, 3.75 (2.4-5.5) vs 3.75 (2.7-5.5) control group, (p = 0.29).	"Although P. aeruginosa corneal ulcers have a more severe presentation, they appear to respond better to treatment than other bacterial ulcers. The authors did not find a significant benefit with corticosteroid treatment, but they also did not find any increase in adverse events."	Post-hoc, subset of SCUT study for pseudomonas aeruginosa Keratitis showed this group showed greater improvement at 3 months than other types of bacterial ulcers. This may have been due to baseline acuity being greater in pseudomonas patients.

Srinivasan b 2012 (Score = 6.0)	Topical glucocorticosteroids	RCT Multicenter Double-blind	Sponsored by the National Eye Institute grant, Dr. Acharya is supported by National Eye Institute grant, and a Research to Prevent Blindness Award.	N = 500 with bacterial keratitis.	The median age was 53 (40-61).	Topical moxifloxacin 0.5% drop 4 times daily for 1 week, then twice a day for 1 week, and then once per day for 1 week (N = NA) vs Topical prednisolone phosphate 1% or placebo drops were given according the same schedule as treatment group (N = NA).	Follow-up at 3 months.	Median baseline visual acuity was 0.84 logMAR, IQ range 0.36-1.7, (p = 0.55). Baseline visual acuity was not significantly different between the United States and India. Ulcers in India had larger infiltrate/scar sizes, (p = 0.04) and deeper infiltrates, (p = 0.04) and were more likely to be localized centrally, (p = 0.002) than ulcers enrolled in the United States.	"The Steroids for Corneal Ulcers Trial will compare the use of a topical corticosteroid with placebo as adjunctive therapy for bacterial corneal ulcers."	Methods paper for SCUT studies. Some baseline comparability differences between the study and lacebo groups.
Ray 2014 (Score = 6.0)	Corticosteroids	RCT	Sponsored by Grants from the National Eye Institute, and a Research to Prevent Blindness Award (Dr. Acharya). The Department of Ophthalmology at the U.C., is supported by core grant from	N = 492 with bacterial keratitis.	The mean age and range in Earlier Addition / Later Addition Corticosteroids; 54.5 and 40-62 / 51 and 40-61.	Earlier Addition of Corticosteroids or Placebo 2 to 3 days (N = 340) vs Later Addition of Corticosteroids or Placebo 4 or more days of topical antibiotics (N = 152).	Follow-up for 3 months.	At 3 months, antibiotic therapy for 2-3 days had approximately 1-line better visual acuity, (p = 0.01). At 3 months, antibiotic therapy for 4 or more days had approximately 1-line worse visual acuity, (p = 0.14).	"There may be a benefit with adjunctive topical corticosteroids if application occurs earlier in the course of bacterial corneal ulcers."	Original SCUT study at 3 months suggest possible benefit of addition of topical steroids if added early to other treatments.

			the National Eye Institute. Alcon provided moxifloxacin (Vigamox).							

Evidence for Ciprofloxacin

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Booranapong 2004 (Score = 7.0)	Ciprofloxacin	RCT Double-blind	No mention of sponsorship or COI.	N = 46 eyes with bacterial corneal ulcers.	The mean age for Lomefloxacin / Ciprofloxacin; 26.74 ± 10.86 / 29.72 ± 11.01.	Lomefloxacin ophthalmic solution 0.3% 1 drop every 15 minutes for 1st 6 hours, 1 drop every hour 1st day, then hourly the following days (N = 24) vs Ciprofloxacin ophthalmic solution 0.3%, dosing frequency the same as Lomefloxacin group (N = 22).	Follow-up every 3 days until recovery, 17.22 ± 3.97 vs 18.67 ± 6.05 days in Ciprofloxacin group.	Clinical efficacy / time to cure / clinical symptoms and signs / safety and adverse events: Epithelial defect and stromal inflammations, (p = 0.716 and 0.922) / 17.22 ± 3.97 vs 18.67 ± 6.05 days, (p < 0.05) / no statistically significant differences, (p > 0.05).	"Lomefloxacin ophthalmic solution (0.3%) is equivalent clinically and statistically to ciprofloxacin ophthalmic solution (0.3%) for the treatment of mild severity of bacterial corneal ulcers without statistically significant differences in the adverse effects and discomfort."	Equivalent efficacy. Sparse methodological details. Small sample size.

Parmar 2006 RCT	Ciprofloxacin	RCT	No mention of sponsorship or COI.	N = 104 with bacterial keratitis.	The mean age for Gatifloxacin / Ciprofloxacin; 41.5 ± 18.3 / 41.5 ± 16.3.	Gatifloxacin 0.3% eye drops or GAT group hourly until the ulcer had begun to heal (N = 50) vs Ciprofloxacin 0.3% eye drops or CIP group hourly (N = 54).	Follow-up until healing reported at 13.9 ± 10.2 mean days in Gatifloxacin and 16.8 ± 15.3.	GAT group exhibited complete healing vs the CIP group; 39 eyes or 95.1% vs 38 or 80.9%, (p = 0.042).	"Gatifloxacin had a significantly better action against gram-positive cocci both in vitro and in vivo when compared with ciprofloxacin."	Comparable efficacy between groups in terms of healing but Gatifloxacin showed better activity against gram positive organisms.
Prajna 2001 (Score = 7.0)	Ciprofloxacin	RCT Double-blinded	Sponsored by an unrestricted educational grant from Allergan Labs, Inc., Irvine, CA. No mention of COI.	N = 217 with bacterial keratitis.	Age ranging from ≤ 29 – ≥ 60.	Ofloxacin 0.3% every ½ hr on study day 1, every hour on days 2 - 4, and every 2 hours on days 5 - 21 (N = 112) vs Ciprofloxacin 0.3% every 1/2 on study day 1, every hour on days 2 - 4, and every 2 hours on days 5 - 21 (N = 105).	Follow-up for 21 days.	Corneal healing rates was observed in 6% (7 of 112) of ofloxacin- and 10% (10 of 105) of ciprofloxacin-treated patients, (p not reported). The average time to corneal healing in ofloxacin or ciprofloxacin, 13.7 ± 0.7 days and 14.4 ± 0.8 days, respectively, (p = 0.80). Time to corneal ulcer healing was 13.7 days in those treated with ofloxacin and 14.4 days in those treated with ciprofloxacin.	"Ofloxacin 0.3% and ciprofloxacin 0.3% ophthalmic solutions are effective and safe in the treatment of patients with culture-positive bacterial keratitis."	Comparable efficacy.

Hyndiuk 1996 (Score = 6.5)	Ciprofloxacin	RCT Parallel group Double-blind Multicenter	Sponsored in part by an unrestricted grant from Research to Prevent Blindness, New York, and by Alcon Laboratories, Inc, Fort Worth, Texas. No mention of COI.	N = 324 with bacterial keratitis, (2 children).	The mean ages of the Ciprofloxacin / standard therapy were; 45.8 ± 18.9 / 44.6 ± 21.4.	Ciprofloxacin group for 1 to 2 drops of the first medication every 30 minutes for 6 hours then hourly, days 2 and 3 for 1 to 2 drops hourly, days 4 and 5 for 1 to 2 drops every 2 hours, days 6 and 14 for 1-2 drops every 4 hours (N = 82) vs Standard therapy or fortified tobramycin-cefazolin, dosing schedule the same as Ciprofloxacin group (N = 94).	Follow-up at days 2, 4, 7, 14, and >16.	No statistical differences between treatments in times of overall clinical efficacy / resolution of clinical signs and symptoms / or timing to cure: (p = 0.034) / (p > 0.08) or / (p = 0.55). Fewer patients experienced discomfort in Ciprofloxacin group, (p = 0.01).	"Ciprofloxacin solution is equivalent clinically and statistically to standard therapy (fortified tobramycin-cefazolin) for treatment of bacterial corneal ulcers and procedures significantly less ocular discomfort."	Comparable efficacy between treatments although Ciprofloxacin group experienced less discomfort. Unclear baseline comparability.

Kosrirukvongs 2000 (Score = 3.5)	Ciprofloxacin		No mention of sponsorship or COI.	N = 41 with moderate bacterial corneal ulcers (2-6 mm in diameter), diagnosed clinically.	The mean age for ciprofloxacin / control groups; 39.9 ± 21.5 / 55.2 ± 16.9.	Ciprofloxacin 0.3% group or cefazolin (50 mg/ml) and fortified gentamicin (14 mg/ml) every 15 minutes for the 1st 6 hours, every ½ hour on the 1st day, plus every hour while awake till midnight until complete recovery, plus atropine sulfate 1% twice daily (N = 17) vs Control group received topical cefazolin (50 mg/ml) and fortified gentamicin 14 mg/ml, plus atropine sulfate 1% twice daily (N = 24).	Follow-up until recovey or 14.6 days in the control and 15.6 days in the ciprofloxacin group.	Main outcomes were the success rate / mean duration of the healing of the ulcer after treatment of each group: 12 or 70.6% patients in ciprofloxacin group were therapeutically successful vs 62.5% patients in control group showed similar outcome, (p = 0.839) / 14.6 ± 5.8 compared to 15.6 ± 8.6 control group, (p = 0.726). Visual improvements in ciprofloxacin was 66.7% vs 46.7% in control group, (p = 0.516). No statistical differences at baseline or demographics.	"Treatment with topical ciprofloxacin in suspected bacterial corneal ulcer should be considered as an alternative to standard therapy."	Slightly better outcomes with Ciprofloxacin but not statistically significant.

Weyenberg 2004 (Score = 3.5)	Ciprofloxacin	RCT Crossover	Sponsored by a grant from the Funds for Research in Ophthalmology (FRO), Belgium. No COI.	N = 6 with bacterial keratitis.	The age range between 20 and 30 years.	1 drop of a 0.3% (wt/vol) ciprofloxacin solution (N = NA) vs A sterilized minitablet containing 3% (wt/wt) ciprofloxacin (N = NA).	Follow-up for 5 days.	The mean tear concentration of ciprofloxacin was 33.0, 135.2, and 33.7 µg/g at 30, 300, and 480 minutes after application of the minitablet. Mean tear levels of 84.7, 45.6, and 8.4 µg/g were obtained at 5, 30, and 60 minutes after application of an eye drop.	"Due to their prolonged drug release properties, the ocular minitablets containing ciprofloxacin can be considered as a promising drug delivery system to be used in the treatment of ulcerative bacterial keratitis."	Pilot study only with small sample size. Sparse methodological details. Two way crossover trial.

Evidence for Gatifloxacin

Parmar 2006 (Score = 7.0)	Gatifloxacin	RCT	No mention of sponsorship or COI.	N = 104 with bacterial keratitis.	The mean age for Gatifloxacin / Ciprofloxacin; 41.5 ± 18.3 / 41.5 ± 16.3.	Gatifloxacin 0.3% eye drops or GAT group hourly until the ulcer had begun to heal (N = 50) vs Ciprofloxacin 0.3% eye drops or CIP group hourly (N = 54).	Follow-up until healing reported at 13.9 ± 10.2 mean days in Gatifloxacin and 16.8 ± 15.3.	GAT group exhibited complete healing vs the CIP group; 39 eyes or 95.1% vs 38 or 80.9%, (p = 0.042).	"Gatifloxacin had a significantly better action against gram-positive cocci both in vitro and in vivo when compared with ciprofloxacin."	Comparable efficacy between groups in terms of healing but Gatifloxacin showed better activity against gram positive organisms.
Price 2005 (Score = 5.0)	Gatifloxacin	RCT, prospective	Supported by an unrestricted educational grant from Allergan, Inc., and by the Cornea Research Foundation of America. COI, Dr. Maclellan is employed by	N = 44 healthy subjects who followed distinct antibiotic dosing regimens;	mean age of 40±9.7 years with a range of 24 to 59 years, and 35±11 years with a range of 23 to 61 years	Gatifloxacin 0.3% ophthalmic solution in one eye and moxiflaxcin 0.5% ophthalmic solution in the other eye, 4 times a day for 10 days (N = 20) vs Gatifloxacin 0.3% in one eye and moxifloxacin the other eye, hourly	No follow up.	Mean±SD for increase in hyperemia: gatifloxacin hourly for 10 hrs vs. gatifloxacin 4 times daily for 7 days: .28±.58, (p = 0.029) vs. -.025±.30, (p = 0.72).	"This study suggests that 4 times a day/7-day dosing or hourly/10-hour dosing regimens with 2 commercially available fourth-generation fluoroquinolone ophthalmic solutions causes little toxicity to	Comparable efficacy and toxicity in both groups.

			Nidel, which sells the Confoscan 3 confocal microscope.			for 10 hours (N = 24). Pre and post testing.			healthy human corneas with intact epithelium and no active surface disease."	

Evidence for Moxifloxacin

Constantinou 2007 (Score = 5.0)	Moxifloxacin	RCT	Sponsored by an unrestricted grant from Alcon Australia, Frenchs Forest, Australia. No COI.	N = 229 with bacterial keratitis.	The mean age for Fortified Tobramycin / Moxifloxacin / Moxifloxacin; 64.9 ± 20.5 / 65.9 ± 19.6 / 66.0 ± 20.8.	Fortified Tobramycin 1.33% / Cefazolin 5% group received 1 drop every hour for 48 hours, day 3 every hour by day and 2 hours by night, days 4 and 5, 1 drop every 2 hours and 4 by night, days 6 and 7, 1 drop every 4 hours and after every 6 hours (N = 78) vs Moxifloxacin 1.0%, intervention the same as fortified Tobramycin group (N = 77) vs Ofloxacin 0.3%, intervention the same as fortified tobramycin group (N = 74).	Final follow-up scheduled for between 2 and 3 months.	Primary objective to assess treatment failure: healing of ulcer in 175 or 94% of nonexiting patients, with no differences between 3 treatment groups, (p = 0.25). Second objective: total duration to cure and mean time discharge without any statistical difference, (p = 0.27 and 0.25, respectively). No statistical differences at baseline or demographics.	"[N]o significant difference in healing rate, cure rate, or complications between traditional fortified Cephazolin and tobramycin, ofloxacin alone, or moxifloxacin alone was seen in this study."	

Sharma 2013a (Score =)	Moxifloxacin	RCT Equivalence clinical trial Double-blinded	Sponsored by the All India Institute of Medical Sciences, New Delhi, India. No COI.	N = 225 with bacterial keratitis.	Age ranged from < 29 – 90.	Group A received fortified cefazolin sodium 5% and tobramycin sulfate) for 72 hours hourly, and every 2 hours for next 7 days (N = 110) vs Group B received Moxifloxacin for 72 hours hourly, and every 2 hours for next 7 days (N = 108).	Follow-up at 3 months.	Healing of ulcer occurred in 178 or 81.6%, of those 90 or 81.8% vs 88 or 81.4%. Percentage healing difference was 0.33, 95% CI, -10.04 to 10.7 and adjusted for socioeconomic status, pre-study pathologic features, and presence of systemic factor was found to be 1.58, 95% CI, -9.66 to 12.83, at 3 months.	"Corneal healing using 0.5% moxifloxacin monotherapy is equivalent to that of combination therapy using fortified cefazolin and tobramycin in the treatment of moderate bacterial corneal ulcers."	

Evidence for Ofloxacin Solution

Khokhar 2000 (Score = 7.0)	Ofloxacin solution	RCT	No mention of sponsorship or COI.	N = 30 eyes with bacterial corneal ulcers	and with age ranging for Ofloxacin / Tobramycin and Cefazolin group; 15 – 70 / 14 – 72.	Group 1 or Ofloxacin solution 0.3% 1 drop every 30 minutes for 6 hours, hourly on days 1-3, 2-hourly on days 4-5 and 4 hours until 1 week (N = 15) vs Group 2 or Tobramycin 1.5% and Cefazolin 5% group, the same dosing as Group 1 (N = 15).	Follow-up (until relief) maximum reported at 26 days.	The mean duration of symptomatic relief and / epithelial healing; 7.8 ± 1.54 in Group 1 vs 8.33 ± 1.44 Group 2, (p = 0.13) / 15.0 ± 3.86 in Group 1 vs 15.46 ± 3.86 days in Group 2, (p = 0.46).	"Both Ofloxacin 0.3% and combined fortified Tobramycin 1.5% and Cefazolin 5% topical drops were comparable for treating cases of bacterial corneal ulcer of moderate severity."	Small sample size. Comparable efficacy. Monotherapeutic advantage of Ofloxacin over combination therapy.

O'Brien 1995 (Score = 7.0)	Ofloxacin solution	RCT Multicenter Double-blind	Sponsored by Pharmaceutical Sciences Operations, Allergan Inc. No mention of COI.	N = 140 with suspected bacterial acute keratitis.	Age range in years from ≤ 29 – 90.	Ofloxacin 0.3% solution 2 bottles 1 drop from bottle 1 and 2 on the hour, plus 2 times during the night at 2 and 4 AM until second follow-up at days 3 and 5, then from bottle 1 and 2 every 2 hours, after 4 times daily (N = 73) vs Combination of the fortified antibiotics tobramycin 1.5% 1 bottle and 1 bottle of cefazolin solutions 10.0% dosing the same as Ofloxacin group (N = 67).	Follow-up examinations occurred on days 2, 3, 6, 7, to 11, 12, 18, and 19 to 28.	At 7 days after study entry, the keratitis in 37% of the ofloxacin group vs 38% of the fortified antibiotics group had healed, (p not provided). At 28 days, keratitis in 89% of the ofloxacin vs 86% of the fortified antibiotics group had healed, (p not provided). Those receiving ofloxacin reported substantially less burning/stinging on instillation than those receiving fortified antibiotics, (p < 0.001).	"The efficacy of ofloxacin solution in treating bacterial keratitis is equivalent to that of the fortified cefazolin and tobramycin solutions."	Comparable efficacy.
Prajna 2001 (Score = 7.0)	Ofloxacin solution	RCT Double-blinded	Sponsored by an unrestricted educational grant from Allergan Labs, Inc., Irvine, CA. No mention of COI.	N = 217 with bacterial keratitis.	Age ranging from ≤ 29 – ≥ 60.	Ofloxacin 0.3% every 1/2 on study day 1, every hour on days 2 - 4, and every 2 hours on days 5 - 21 (N = 112) vs Ciprofloxacin 0.3% every 1/2 on study day 1, every hour on days 2 - 4, and every 2 hours on days 5 - 21 (N = 105).	Follow-up for 21 days.	Corneal healing rates was observed in 6% (7 of 112) of ofloxacin- and 10% (10 of 105) of ciprofloxacin-treated patients, (p not reported). The average time to corneal healing in ofloxacin or ciprofloxacin, 13.7 ± 0.7 days and 14.4 ± 0.8 days, respectively, (p = 0.80). Time to	"Ofloxacin 0.3% and ciprofloxacin 0.3% ophthalmic solutions are effective and safe in the treatment of patients with culture-positive bacterial keratitis."	Comparable efficacy.

								corneal ulcer healing was 13.7 days in those treated with ofloxacin and 14.4 days in those treated with ciprofloxacin.		
Panda 1999 (Score = 6.5)	Ofloxacin solution	RCT Multicenter Double-blind	No mention of sponsorship or COI.	N = 30 eyes with bacterial keratitis.	Age range for Ofloxacin / Control group: 15 – 70 / 14 – 72.	Ofloxacin 0.3% 1 bottle 1 drop of every 30 minutes, 1 hour on days 2-3, 2 drops hourly on days 4-5, and 4 hourly until 1 week (N = 15) vs Control group received 1 bottle of normal saline solution (1+2) or 1 bottle of 1.5% tobramycin solution ad 5% cefazolin solution (3+4) 1 drop of each every 30 minutes, 1 hour on days 2-3, 2 drops hourly on days 4-5, and 4 hourly until 1 week (N = 15).	Follow-up for up to 10 days.	Time required for symptomatic relief was 7.8 ± 1.54 or range 6-10 days in the ofloxacin vs 8.33 ± 1.54 or range 5-10 days in the control group, (p = 0.05). The duration of healing in the ofloxacin was 15.0 ± 3.86 or range 10-26 days vs 15.46 ± 3.86 or range 11-26 days in the control group, (p = 0.46).	"In summary, monotherapy with 0.3% ofloxacin drops for treating bacterial keratitis should be encouraged and can be tried as a first-line drug for all cases of bacterial keratitis."	Small sample size. Comparable efficacy.

Pavesio 1997 (Ofloxacin Study Group) (Score = 4.5)	Ofloxacin solution	RCT		122 patients with a clinical diagnosis of microbial keratitis.	Mean±SD age: 48.53±21.0 years.	Ofloxacin drops (3mg/ml, benzalkonium chloride 0.005%) vs. conventional treatment group (sodium chloride 0.43%, thimerosal 0.005%)	14 day follow up.	No difference in the treatment success between both groups. Toxicity encountered: conventional treatment group vs ofloxacin group: 50.8% vs. 10.2%; p<0.0001.	"[T]reatment outcomes with ofloxacin monotherapy compared favorably with their conventional therapy and were associated with less toxicity."	Some patients blinded, some not. Similar efficacy between both treatments but more toxicity in conventional treatment group.
Evidence for Tobramycin-Cefazolin										
Khokhar 2000 (Score = 7.0)	Tobramycin=-Cefazolin	RCT	No mention of sponsorship or COI.	N = 30 eyes with bacterial corneal ulcers	and with age ranging for Ofloxacin / Tobramycin and Cefazolin group; 15 – 70 / 14 – 72.	Group 1 or Ofloxacin solution 0.3% 1 drop every 30 minutes for 6 hours, hourly on days 1-3, 2-hourly on days 4-5 and 4 hours until 1 week (N = 15) vs Group 2 or Tobramycin 1.5% and Cefazolin 5% group, the same dosing as Group 1 (N = 15).	Follow-up (until relief) maximum reported at 26 days.	The mean duration of symptomatic relief and / epithelial healing; 7.8 ± 1.54 in Group 1 vs 8.33 ± 1.44 Group 2, (p = 0.13) / 15.0 ± 3.86 in Group 1 vs 15.46 ± 3.86 days in Group 2, (p = 0.46).	"Both Ofloxacin 0.3% and combined fortified Tobramycin 1.5% and Cefazolin 5% topical drops were comparable for treating cases of bacterial corneal ulcer of moderate severity."	Small sample size. Comparable efficacy. Monotherapeutic advantage of Ofloxacin over combination therapy.

O'Brien 1995 (Score = 7.0)	Tobramycin=-Cefazolin		Multicenter Double-blind Sponsored by Pharmaceutical Sciences Operations, Allergan Inc. No mention of COI.	N = 140 with suspected bacterial acute keratitis.	Age range in years from ≤ 29 – 90.	Ofloxacin 0.3% solution 2 bottles 1 drop from bottle 1 and 2 on the hour, plus 2 times during the night at 2 and 4 AM until second follow-up at days 3 and 5, then from bottle 1 and 2 every 2 hours, after 4 times daily (N = 73) vs Combination of the fortified antibiotics tobramycin 1.5% 1 bottle and 1 bottle of cefazolin solutions 10.0% dosing the same as Ofloxacin group (N = 67).	Follow-up on days 2, 3, 6, 7, to 11, 12, 18, and 19 to 28.	At 7 days after study entry, the keratitis in 37% of the ofloxacin group vs 38% of the fortified antibiotics group had healed, (p not provided). At 28 days, keratitis in 89% of the ofloxacin vs 86% of the fortified antibiotics group had healed, (p not provided). Those receiving ofloxacin reported substantially less burning/stinging on instillation than those receiving fortified antibiotics, (p < 0.001).	"The efficacy of ofloxacin solution in treating bacterial keratitis is equivalent to that of the fortified cefazolin and tobramycin solutions."	Comparable efficacy.
Hyndiuk 1996 (Score = 6.5)	Tobramycin=-Cefazolin	RCT	Parallel group Double-blind Multicenter Sponsored in part by an unrestricted grant from Research to Prevent Blindness, New York, and by Alcon Laboratories, Inc, Fort Worth, Texas. No	N = 324 with bacterial keratitis, (2 children).	The mean ages of the Ciprofloxacin / standard therapy were; 45.8 ± 18.9 / 44.6 ± 21.4.	Ciprofloxacin group for 1 to 2 drops of the first medication every 30 minutes for 6 hours then hourly, days 2 and 3 for 1 to 2 drops hourly, days 4 and 5 for 1 to 2 drops every 2 hours, days 6 and 14 for 1-2 drops every 4 hours (N = 82) vs Standard therapy or fortified	Follow-up at days 2, 4, 7, 14, and >16.	No statistical differences between treatments in times of overall clinical efficacy / resolution of clinical signs and symptoms / or timing to cure: (p = 0.034) / (p > 0.08) or / (p = 0.55). Fewer patients experienced discomfort in	"Ciprofloxacin solution is equivalent clinically and statistically to standard therapy (fortified tobramycin-cefazolin) for treatment of bacterial corneal ulcers and procedures significantly less ocular discomfort."	Comparable efficacy between treatments although Ciprofloxacin group experienced less discomfort. Unclear baseline comparability.

			mention of COI.			tobramycin-cefazolin, dosing schedule the same as Ciprofloxacin group (N = 94).		Ciprofloxacin group, (p = 0.01).		
Panda 1999 (Score = 6.5)	Tobramycin=-Cefazolin	RCT	Multicenter Double-blind No mention of sponsorship or COI.	N = 30 eyes with bacterial keratitis.	Age range for Ofloxacin / Control group: 15 – 70 / 14 – 72.	Ofloxacin 0.3% 1 bottle 1 drop of every 30 minutes, 1 hour on days 2-3, 2 drops hourly on days 4-5, and 4 hourly until 1 week (N = 15) vs Control group received 1 bottle of normal saline solution (1+2) or 1 bottle of 1.5% tobramycin solution ad 5% cefazolin solution (3+4) 1 drop of each every 30 minutes, 1 hour on days 2-3, 2 drops hourly on days 4-5, and 4 hourly until 1 week (N = 15).	Follow-up for up to 10 days.	Time required for symptomatic relief was 7.8 ± 1.54 or range 6-10 days in the ofloxacin vs 8.33 ± 1.54 or range 5-10 days in the control group, (p = 0.05). The duration of healing in the ofloxacin was 15.0 ± 3.86 or range 10-26 days vs 15.46 ± 3.86 or range 11-26 days in the control group, (p = 0.46).	"In summary, monotherapy with 0.3% ofloxacin drops for treating bacterial keratitis should be encouraged and can be tried as a first-line drug for all cases of bacterial keratitis."	Small sample size. Comparable efficacy.

Shah 2010 (Score = 6.0)	Tobramycin=-Cefazolin	RCT	No sponsorship or COI.	N = 61 with bacterial keratitis.	The median age or range for Cef + Tob / Gat / and Mox groups: 33 or 12-36 / 40 or 13-70 / and 46 or 11-68.	Group A received combination therapy with fortified antibiotics with Cefazolin 5% + Tobramycin 1.3% (N = 20) vs Group B received monotherapy with Gatifloxacin 0.3% (N = 21) vs Group C received monotherapy with moxifloxacin 0.5% (N = 20).	Follow-up at least 3 weeks.	57 healed on treatment there were no significant differences among the treatment groups for the mean time to heal, (p = 0.98) / final vision acuity, (p = 0.97) / or final corneal opacity size, (p = 0.85).	The study failed to find a difference in the efficacy of monotherapy with fourth-generation fluoroquinolones in the treatment of bacterial corneal ulcers of 2–8 mm size when compared with combination therapy of fortified antibiotics."	Relatively small sample size in each group. Comparable efficacy.
Constantinou 2007 (Score = 5.0)	Tobramycin=-Cefazolin	RCT	Sponsored by an unrestricted grant from Alcon Australia, Frenchs Forest, Australia. No COI.	N = 229 with bacterial keratitis.	The mean age for Fortified Tobramycin / Moxifloxacin / Moxifloxacin; 64.9 ± 20.5 / 65.9 ± 19.6 / 66.0 ± 20.8.	Fortified Tobramycin 1.33% / Cefazolin 5% group received 1 drop every hour for 48 hours, day 3 every hour by day and 2 hours by night, days 4 and 5, 1 drop every 2 hours and 4 by night, days 6 and 7, 1 drop every 4 hours and after every 6 hours (N = 78) vs Moxifloxacin 1.0%, intervention the same as fortified Tobramycin group (N = 77) vs Ofloxacin 0.3%, intervention the same as fortified	Final follow-up scheduled for between 2 and 3 months.	Primary objective to assess treatment failure: healing of ulcer in 175 or 94% of nonexiting patients, with no differences between 3 treatment groups, (p = 0.25). Second objective: total duration to cure and mean time discharge without any statistical difference, (p = 0.27 and 0.25, respectively). No statistical differences at baseline or demographics.	"In conclusion, no significant difference in healing rate, cure rate, or complications between traditional fortified Cephazolin and tobramycin, ofloxacin alone, or moxifloxacin alone was seen in this study."	No significant differences between 3 treatments in terms of healing rate, cure rate or adverse events.

						tobramycin group (N = 74).				
Sharma 2013a (Score =)	**Tobramycin=-Cefazolin**	RCT	Equivalence clinical trial Double-blinded Sponsored by the All India Institute of Medical Sciences, New Delhi, India. No COI.	N = 225 with bacterial keratitis.	Age ranged from < 29 – 90.	Group A received fortified cefazolin sodium 5% and tobramycin sulfate) for 72 hours hourly, and every 2 hours for next 7 days (N = 110) vs Group B received Moxifloxacin for 72 hours hourly, and every 2 hours for next 7 days (N = 108).	Follow-up at 3 months.	Healing of ulcer occurred in 178 or 81.6%, of those 90 or 81.8% vs 88 or 81.4%. Percentage healing difference was 0.33, 95% CI, -10.04 to 10.7 and adjusted for socioeconomic status, pre-study pathologic features, and presence of systemic factor was found to be 1.58, 95% CI, -9.66 to 12.83, at 3 months.	"Corneal healing using 0.5% moxifloxacin monotherapy is equivalent to that of combination therapy using fortified cefazolin and tobramycin in the treatment of moderate bacterial corneal ulcers."	

Evidence for Lomefloxacin Ophthalmic Solution

Booranapong 2004 (Score = 7.0)	**Lomefloxacin ophthalmic solution**	RCT Double-blind	No mention of sponsorship or COI.	N = 46 eyes with bacterial corneal ulcers.	The mean age for Lomefloxacin / Ciprofloxacin; 26.74 ± 10.86 / 29.72 ± 11.01.	Lomefloxacin ophthalmic solution 0.3% 1 drop every 15 minutes for 1st 6 hours, 1 drop every hour 1st day, then hourly the following days (N = 24) vs Ciprofloxacin ophthalmic solution 0.3%, dosing the same as Lomefloxacin group (N = 22).	Follow-up every 3 days until recovery, 17.22 ± 3.97 vs 18.67 ± 6.05 days in Ciprofloxacin group.	Clinical efficacy / time to cure / clinical symptoms and signs / safety and adverse events: Epithelial defect and stromal inflammations, (p = 0.716 and 0.922) / 17.22 ± 3.97 vs 18.67 ± 6.05 days, (p < 0.05) / no statistically significant differences, (p > 0.05).	"Lomefloxacin ophthalmic solution (0.3%) is equivalent clinically and statistically to ciprofloxacin ophthalmic solution (0.3%) for the treatment of mild severity of bacterial corneal ulcers without statistically significant differences in the adverse effects and discomfort."	Equivalent efficacy. Sparse methodological details. Small sample size.

Erjongmanee S 2004 (Score = 6.0)	Lomefloxacin ophthalmic solution	RCT	No mention of sponsorship or COI.	N= 40 with acute bacterial keratitis.	The mean age of lomefloxacin and standard therapy treated patients were 25.95 years and 28.0 years respectively.	Lomefloxacin group received lomefloxacin 0.3% solution and one placebo (0.9% normal saline) (N=20) vs. Standard therapy group received one bottle of fortified cefazolin solution (50 mg/ml) and one bottle of fortified gentamicin (14mg/ml)	Follow up examinations are scheduled on days 2, 4, 7, 14, 21 and 28.	Positive results of bacterial corneal cultures were obtained in 27.5%. there was no statistically significant difference in time to complete re epitheliazation in all types of bacterial keratitis (p=0.251) By day 7, keratitis was healed: 44% in lomefloxacin group and 33% in fortified antibiotic group.	"[I]n conclusion, ophthalmic lomefloxacin 0.3% may be recommended as initial monotherapy in the treatment of all grades of severity of acute bacterial keratitis at a dose of one drop, once every hour, in order to maximize the therapeutic effect until the corneal ulcer starts to improve."	Comparative efficacy with some benefit of lomofloxacin group in terms of clinical improvement. Small sample size.
Evidence for Levofloxacin										
Kasetsuwan 2011 (Score = 6.0)	Levofloxacin	RCT Double-blind	Sponsored in part by Daiichi, Thailand. No COI.	N = 71 eyes with mild or moderate bacterial keratitis.	The mean ages of Levofloxacin / Fortified Cefazolin & Amikacin; 34.6 ± 18.1 / 34.4 ± 15.4.	Levofloxacin 0.5% eye drops every 10 minutes during the first 30 minutes of and later decreased in increments of 1 hour every 3 days (N = 34) vs Fortified Cefazolin and Amikacin, dosing schedule the same as levofloxacin group (N = 37).	Follow-up on days 2, 7, 14, and 21.	61 out of 71 eyes completely healed and mean time to heal, (p = 0.81) and (p = 0.92). No statistical differences between both groups for clinical signs and symptom score, (p = 0.99) and (p = 0.85	"[T]opical Levofloxacin monotherapy can be used for the treatment of mild to moderate bacterial corneal ulcers as an alternative treatment without developing any serious complications."	Comparable efficacy but patient compliance may be increased due to monotherapy of Levofloxacin.

Evidence for Tarsorrhaphy

Khokhar 2005 (Score = 3.5)	**Tarsorrhaphy**	RCT		N = 30 with neurotrophic corneal ulcers of varying etiology, which failed to respond to medical management for at least 4 weeks and which were sterile on microbiologic examination.		Group 1, N = 15 Received conventional management with tarsorrhaphy (N=11) or bandage contact lens (N=3). Group 2, N = 15 were treated with a single or multilayer Amniotic Membrane Transplantation (AMT).		No significant difference between groups with respect to complete epithelialization (p=0.96) and healing of corneal ulcer, epithelialization time, and visual improvement.	"We conclude that both the conventional management and amniotic membrane transplantation are effective for the treatment of neurotrophic corneal ulcers refractory to medical management. "	Data sparse.

Evidence for Cefazolin

Carmichael 1990 (Score = 2.5)	Cefazolin	RCT, prospective	No mention of sponsorship or COI.	N = 40 patients with bacterial corneal ulcers;	mean age of 51.6 for steroid group and 51.4 for non-steroidal group.	Kerfzol eye drops (cefazolin, fortified, 32 g/l), and gentamicin eye drops (fortified, 14 g/l) hourly, Atropine eye drops 1% twice daily, chloromycetin eye ointment at night and twice daily multivitamin tablets, plus sub-conjunctival cefazolin, 125 mg and gentamicin, 20 mg. (N = 21) vs Sub-conjunctival cefazolin, 125 mg and gentamicin, 20 mg only (N = 19). Maxidex eye drops (0.1% dexamethasone) were also added to both groups, four times a day, minimum of two weeks.	Follow up at baseline and 4 weeks.	No statistically significant differences to report between groups.	"No adverse effects were encountered with topical steroids in the dosage shown above. To demonstrate benefits from steroids a larger study would be needed and perhaps some refinements in assessment techniques."	Small sample size. Baseline comparability unclear. Comparable efficacy.

Said 2014	PACK-CXL	RCT, prospective	No mention of sponsorship. COI, Dr. Hafezi was the co-inventor of the ultraviolet light source.	N = 40 with infective corneal ulcer with a possible bacterial, fungal, or mixed origin with evident corneal melting;	mean age of 37.3 years for the PACK-CXL group and 49.8 years for the control group.	PACK-CXL within 48 hours, 0.4% benoxinate hydrochloride drops (topical anesthesia) and medical treatment (N = 21) vs Control group and medical treatment (N = 19). Antimicrobial treatment for both groups: fortified vancomycin eye drops 50 mg/ml, fortified ceftazidime eye drops 50 mg/ml hourly, and the antifungal agent itraconazole 100 mg orally twice daily.	No follow-up.	Mean±SD X Mean±SD for size of ulcer: PACK-CXLvs. Control: 5.62±1.88 X 6.22±1.98mm, (p = 0.004) vs. 3.97±2.5 X 4.22±2.18mm, (p = 0.007).	"Our results demonstrated the beneficial effect of PACKCXL in cases of infectious keratitis with corneal melting. In the management of infectious keratitis with corneal melting, PACK-CXL could serve as valuable adjuvant therapy. This treatment may minimize or avoid severe complications, such as corneal perforation, recurrence of the infection, or both."	CXL did not decrease the healing time but did have fewer complications compared to the control group.

Evidence for Neomycin

Reddy 1988 (Score = 1.5)	Neomycin	RCT	No mention of sponsorship or COI.	N = 82 adult patients suffering from corneal ulcer;	age ranged between 10 and 60 years.	Framycetin sulphate 0.5% (N = N/A) vs Gentamicin 3mg/ml (N = N/A) vs Chloramphenicol 0.4% (N = N/A) vs Neomycin combination containing polymixin B sulphate 1700u and gramicidin 0.02 5 mg/ml (N = N/A)	Follow ups at pre-treatment, and days 2, 7, and 14.	Mean±SD score progress: pre-treatment vs. 14th day: framycetin: 2.43±0.2 vs. 0.29±0.04, ($p < 0.05$); gentamicin: 2.41±0.2 vs. 0.73±0.05, ($p < 0.05$); chloramphenicol: 2.36±0.2 vs. 0.97±0.08, ($p < 0.05$); neomycin+: 2.38±0.2 vs. 0.84±0.07, ($p < 0.05$).	"It can thus be concluded that framycetin has a better profile of antibacterial activity and clinical efficacy than some other commonly used topical antibiotics in the treatment of corneal ulcer."	Sparse methodological details.

Evidence for Chlorhexidine Gluconate

Geffen 2009 (Score = 3.5)	Chlorhexidine gluconate	RCT Double-blind	No mention of sponsorship or COI.	N = 28 with corneal ulcers, clinically diagnosed	with age ranging from 22 – 70.	Group A or treatment group received chlorhexidine gluconate 0.02% diluted in sterile buffered diluent for injection, 6 times a day for 7 days and after stopped at once (N = 14) vs Group B or control group had placebo drops, the same sterile buffered diluent, 6 times a day for 7 days and after stopped at once (N = 14).	Follow-up at days 2, 5, 11, 18 and 28.	No significant differences between the 2 groups were found in the risk factors for corneal infections, ($p = 0.391$). No statistical differences of corneal infection / risk factors for corneal infections / lens-related ulcers: ($p = 1.000$) / ($p = 0.391$) / ($p = 1.000$).	"Chlorhexidine gluconate 0.02% may improve the clinical course of corneal ulcers."	Differences in baseline comparability potentially leading to randomization failure. Study group had higher baseline ulcer severity compared to control group ($p=0.033$).

Evidence for Acanthamoeba Keratitis

Lim 2008 (Score = 5.5)	Acantha moeba keratitis	RCT Double-blind	No sponsorship or COI.	N = 56 eyes with a clinical diagnosis of Acanthamoeba keratitis.	The median age was 31 years.	Chlorhexidine 0.02% hourly day and night for the first 2 days, then reduced hourly for the next 5 days, then for 4 times daily until recovery (N = 30) vs Polyhexamethylene biguanide or PHMB 0.02% dosing schedule the same as Chlorhexidine group (N = 26).	Follow-up until recovery, the median 83 days vs 92 days in PHMB group.	Treatment was successful in 18 or 78.3% those receiving PHMB vs 85.7%, (p = 0.49). The secondary outcome was improvement in visual acuity (VA) in 13 eyes or 56.5% receiving PHMB vs 20 eyes or 71.4%, (p = 0.91)	"Outcomes were similar when using PHMB and chlorhexidine as monotherapy agents in treating Acanthamoeba keratitis."	Baseline comparability differences in duration of diagnosis and treatment duration. Comparable efficacy.

Evidence for Fungal Keratitis

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Agarwal 2001 (Score = 2.0)	Itraconazole	RCT Two-period Crossover	No mention of sponsorship or COI.	N = 54 with fungal corneal ulcer;	age range was 21-40 years old.	Patients were divided into Group I: new patients (N = 22) and Group II: patients who had already received treatment with another agent (N = 32). Topical itraconazole (1%) (N = 27) vs. Oral Itraconazole (100 mg twice daily for 3 weeks) and topical	Follow-up for 6 months.	85.2% of patients came from rural areas and 72.2% had history of trauma or a corneal foreign body. Culture was positive on 81.5% cases and half of them showed Aspergillus species. Of 54 patients treated with topical itraconazole or both systematic and topical	"Itraconazole, given either topically or systemically, is effective in treating mycotic corneal ulcers."	Crossover study. Sparse methodological details.

						iatraconazole every hour (N = 27). After three weeks, oral itraconazole was discontinued, but topical 1% itraconazole was continued for 6 weeks after keratitis was resolved.		itraconazole, 42 (77.78%) responded to the treatment, 16 (29.63) in Group-I and 26 (48.15) in Group-II. 12 (22.22%) patients did not respond.		
Arora 2011 (Score = 7.0)	Natamycin	RCT Double-masked	No mention of sponsorship or COI.	N = 30 with fungal keratitis;	mean age was 37.93 ± 15.14 years in group A and 48.47 ± 13.53 years in group B.	Group A: topical 5% Natamycin (N = 15). vs. Group B: topical 1% voriconazole (N = 15).	Follow-up for 1, 2, 4 and 8 weeks.	21 (70%) patients had Hypopyon ranging from 0.5 to 4 mm (p = 0.465). All ulcers healed completely in group A. In group B, one patient did not respond to the treatment. In group A, average time of complete resolution of corneal infiltrate was 24.33 days vs. 27.42 days in group B. In the last follow-up, the mean LogMAR visual acuity in group A was 1.368 ± 0.887 vs. 1.775 ± 1.036 in group B (p = 0.227).	"Topical 1% voriconazole was found to be safe and effective drug in primary management of fungal keratitis, its efficacy matching conventional natamycin. There was no added advantage of using topical 1% voriconazole over topical natamycin as primary treatment in fungal keratitis."	Pilot study showing comparable efficacy between groups.

Prajna 2010 (Score = 6.5)	Natamycin	RCT	Sponsored by That Man May See and the South Asia Research Fund, the National Eye Institute (Department of Ophthalmology at University of California, San Francisco), That Man May See Foundation at University of California, Alcon Inc, and Pfizer Inc. No COI.	N = 120 with fungal keratitis; age mean (SD) of Natamycin group was 49.8 (11.9) in scraping and 45.9 (13.1) in no scraping.	Age mean (SD) of Voriconazole 47.0 (14.5) in scraping and 45.0 (14.5) in no scraping.	Topical natamycin (N = 60). vs. Topical voriconazole (N = 60). Each group received scraping or no scraping.	Follow-up for 3 months.	Visual acuity improved in both groups. The mean (SD) BSCVA in natamycin and voriconazole at baseline/ 3 weeks/ 3 months was: 0.91 (0.63)/ 0.73 (0.72)/ 0.69 (0.80) and 0.95 (0.65)/ 0.73 (0.75)/ 0.63 (0.76) logMAR, (p<0.001).	"Overall, there were no significant differences in visual acuity, scar size, and perforations between voriconazole-andnatamycin-treated patients. There was a trend toward scraping being associated with worse outcomes."	Comparable efficacy.
Prajna 2013 (Score = 6.5)	Natamycin	RCT comparator–controlled, double-masked, multicenter	Sponsored by National Eye Institute, That Man May See, the Harper/Inglis Trust, the South Asia Research Foundation, and Research to Prevent Blindness. No COI.	N = 323 with filamentous fungal keratitis;	Age median 47 (38–56).	Topical 1% Voriconazole (N = 161). vs Topical 5% Natamycin (N = 162). Treatments were applied every hour while awake until reepithelialization, then 4 times daily for at least 3 weeks.	Follow-up for 3 weeks and 3 months.	The most common microorganisms were *Fusarium* species (128 patients [40%]) and *Aspergillus* species (54 patients [17%]). The median treatment of treatment was 31 days in the natamycin group vs. 39	"Natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to	Phase III trial natamycin group had improved visual acuity at 3 months while Voriconazole group experienced fewer perforations or required keratoplasty.

								days in the voriconazole group (p = 0.006). At 3 weeks, the mean BSCVA in the voriconazole group was poorer vs. the natamycin group (regression coefficient = −0.11 logMAR; 95% CI: −0.21 to −0.01), (p = 0.03). At 3 months, the mean BSCVA in the voriconazole group was worse vs. natamycin group (regression coefficient = −0.18 logMAR; 95% CI: −0.30 to −0.05), (p = 0.006). Patients with *Fusarium* species in the natamycin group, the mean BSCVA was better vs. the voriconazole group (regression coefficient = −0.41 logMAR; 95% CI: −0.61 to	improved results in Fusarium cases."	

								−0.20) (p<0.001).		
Prajna 2012 (Score = 6.5)	Natamycin	Subgroup analysis of RCT	Sponsored by That Man May See and the South Asia Research Fund, the National Eye Institute (Department of Ophthalmology at University of California, San Francisco), That Man May See Foundation at University of California, Alcon Inc, and Pfizer Inc. No COI.	N = 120 with smear-positive fungal keratitis.		Topical voriconazole 1% (N = 60). vs. Topical natamycin 5% (N = 60). Each group received scraping or no scraping.	Follow-up for 3 months.	101 cases were found to have a positive growth on culture (84%). There was found 44(44%) cases of *Fusarium* species: 21 were randomized to natamycin (48%) and 23 to voriconazole (52%). There was found 17(17%) cases of *Aspergillus* species: 10 were randomised to natamycin (59%) and 7 to voriconazole (41%). Voriconazole was associated with an increase in perforation in Fusarium cases [OR 33.4 (95% CI: 1.16 to 962.9)], (p = 0.041).	"This study found no difference in 3-month BSCVA or scar size between voriconazole- and natamycin-treated patients in Fusarium or Aspergillus keratitis."	Subgroup analyses from previous RCT. No differences between treatments at 3 months.
Rahman 1997 (Score = 5.5)	Natamycin	RCT	Sponsored by the British Council for Prevention of Blindness. No mention of COI.	N = 58 with fungal corneal ulcers;	mean age of 44.3 ± 17.3.	Natamycin 5% drops (N = 16). vs. 0.05% chlorhexidine gluconate (N = 17). vs. 0.1% chlorhexidine gluconate (N =	Follow-up for 5 and 21 days.	At 5 days, 0.2% chlorhexidine group had more favorable response vs. natamycin 5% group (p = 0.043) after	"This preliminary study justifies further trials of chlorhexidine as a primary treatment for fungal corneal ulcers in circumstances where	At 3 weeks twice as many non-severe ulcers were healed in CHG group compared to natamycin.

						17). vs. 0.2% chlorhexidine gluconate (N = 8).		excluding any patient that had prior antifungal treatment. At 21 days, 0.2% chlorhexidine group appeared to have more favorable outcomes in contrast to the other groups; however, there was no statistically significant differences.	specific antifungal are not available."	
Prajna 2003 (Score = 4.0)	Natamycin	RCT	Sponsored by Aravind Medical Research Foundation, Madurai. No COI.	N = 116 with fungal keratitis with ulcer areas of at least 2 mm^2 and no more than 60 mm^2;	age range was 7-84 years (mean age 37.0 ± 13.8 years).	2% econazole eye drops (N = 61). vs. 5% natamycin eye drops (N = 55). Eye drops were applied on hourly basis between 7 am to 9 pm. 4 patients were lost in the follow-ups.	Follow-up for week 2, 3, and 4.	There was no significant difference between the two groups for improvement (log rank 0.52, p = 0.47). There was no significant difference in the time to heal based on baseline size of epithelial defects (log rank 0.82, p = 0.37).	"2% Econazole appears to be as effective as 5% natamycin for the management of fungal keratitis."	Comparable efficacy between study groups.
Rahman 1998 (Score = 3.5)	Natamycin	RCT Masked	Sponsored by the British Council for the Prevention of Blindness. No	N = 71 with fungal keratitis;	age group: 10–39 (31.4%), 40–49 (42.9%),	0.2% chlorhexidine gluconate drops (N = 35). vs. 2.5% natamycin drops (N = 36).	Follow-up for 5 days and 21 days.	At 5 days, the chlorhexidine group had more favorable response with 31/35 (88.6%) efficacy vs. 18/35 (51.4%) in	"Chlorhexidine may have potential as an inexpensive topical agent for fungal keratitis and warrants further assessment as a first line treatment in	Baseline characteristics unequally distributed. Patients were allowed to crossover if treatment failed.

			mention of COI.		and 50–75 (25.7%).			the natamycin group. The relative efficacy (RE) was 1.72 (95% CL: 1.24–2.63), (p <0.001). At 21 days, 14/21 (66.7%) patients in chlorhexidine group had more favorable response vs. 9/25 (36.0%) in natamycin group, the RE was 1.85 (95% CL: 1.01–3.39), (p = 0.04).	situations where microbiological facilities and a range of antifungal agents are not available."	
Sharma 2013b the American Academy of Ophthalmology pages 677–681 (Score = 3.5)	Natamycin	RCT	Sponsored by the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, India. No COI	N = 40 with fungal keratitis;	mean age was 40.85 ± 14.6 in group I and 47.7 ± 16.62 in group II.	Group I: topical 1% voriconazole therapy (N = 20). vs. Group II: intrastromal injections of voriconazole 50 µg/0.1 ml (N = 20). Both groups continued topical natamycin 5% every 4 hours until the ulcer healed.	Follow-up for 3, 7, 14, and 28 days after 2 months and 3 months.	The mean BSCVA was 1.295 ± 0.5 logMAR in group I vs. 1.692 ± 0.29 logMAR in group II. The visual acuity after treatment was significantly better in group I (p = 0.008).	"Topical voriconazole seems to be a useful adjunct to natamycin in fungal keratitis not responding to topical natamycin. Intrastromal injections did not offer any beneficial effect over topical therapy."	Intrastromal delivery not superior to topical voriconazole at 3 months.
Mahdy 2010 Journal of ocular pharmacology and therapeuti	Amphotericin B	RCT Prospective	No mention of sponsorship. No COI.	N = 48 with fungal keratitis;	age range was 15 to 69 years (mean age, 44 years).	Group 1: combination therapy of topical amphotericin B (0.5 mg/mL) eye drops (used every 2 hours)	Follow-up weekly for 3 months.	Group 1 showed statically significant healing of corneal ulcers in 20 eyes (83%) (p<0.05). Also, the mean	"Combination therapy of topical amphotericin B eye drops with subconjunctival injection of fluconazole was more efficient (according	Combination therapy was more effective than topical therapy alone.

cs (Score = 4.0)						with subconjunctival injection of fluconazole (2 mg/mL) (used every 48 hours) (N = 24). vs. Group 2: topical amphotericin B (0.5 mg/mL) eye drops only (N = 24).		duration of healing was 31 ± 3 days (p<0.05). Group 2 showed healing of corneal ulcers in 16 eyes (67%), the mean duration of healing was 37 ± 2 days.	to the percentage and the duration of healing of the ulcers) than the use of topical amphotericin B eye drops alone in dealing with cases of fungal keratitis—it may be contributed to the broad spectrum of the antifungal agents of the combination therapy than the monotherapy."	
Mahdy 2010 Cutaneous and Ocular Toxicology (Score = 3.5)	Amphotericin B	RCT Prospective	No mention of sponsorship. No COI.	N = 12 with fungal keratitis;	age range was 17 to 66 years (mean age of 49 years).	Combination therapy of topical amphotericin B (0.2 mg/mL) eye drops (applied every 2 hrs. for 21 days) together with subconjunctival injections of fluconazole (2 mg/mL) (injected daily for 10 injections).	Follow-up weekly for 3 months.	After treatment, the study showed that corneal healing occurred in 9 patients (75%) (p<0.05). Seven of these patients had positive cultures: 5 *Candida* (100%) cases, and one case each of Aspergillus and *Penicillium*. Three cases (25%) showed no improvement. The duration of healing ranged from 4 to 6 weeks.	"The use of a combination of topical amphotericin B eye drops at a concentration of 0.2 mg/mL in dextrose 5% with subconjunctival injection of fluconazole 2 mg/mL had the advantage of a lower incidence of the complications of local use of amphotericin B and a broader spectrum of antifungal coverage. This study reports a relatively high success rate of healing of fungal keratitis, with a significant reduction of the potential side effects of the local use of antifungal agents."	Small sample size. Pilot study.

Mohan 1988 (Score = 3.5)	Miconazole ointment	RCT Double-masked	No mention of sponsorship or COI.	N = 40 fungal corneal ulcers;	age range was 14 to 68 years.	Group I: 1% miconazole ointment (N = 20). vs. Group II: 1% silver sulphadiazine ointment (N = 20). Patients applied the ointment 5 times a day.		1% silver sulphadiazine showed to be effective in 16 eyes (80%) vs. 11 (55%) eyes in 1% miconazole ($p<0.05$).	"[S]ilver sulphadiazine is a safe and effective broad spectrum antifungal agent which can be used for the treatment of human keratomycosis."	Study allowed for some crossover. Sparse methodological details.

Evidence for Bacterial Conjunctivitis

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
McDonald 2009 (Score = 8.5)	Bacterial Conjunctivitis: Besifloxacin ophthalmic suspension	RCT	Sponsored by Baush & Lomb, Inc. COI, McDonald is consultant for Allergan, Bausch & Lomb, Santen, and AMO; Protzko is consultant for Ista Vision, Inspire, and Santen, Brunner, Morris, Haas, Paterno, Comstock, and Usner are employees	N = 1161 with clinical manifestations or culture-confirmed bacterial conjunctivitis,	mean age, besifloxacin 31.6±26.2 years, Moxifloxacin 38.3±27.7 years.	Besifloxacin suspension 0.6% one drop in the infected eye 3 times daily for 5 days (N = 555) vs. Moxifloxacin solution instilled in the infected eye(s) 3 times daily for 5 days + participation in study visits on days (N = 579). Assessments on days 1, 5, and 8.		There were no significant differences between groups for clinical (p=0.6520) or microbial eradication (0.1238) at day 5 or day 8 (p=0.5014 and p=0.0608 respectively).	"[T]reatment of bacterial conjunctivitis with besifloxacin ophthalmic suspension 0.6% produces safety and efficacy outcomes that are clinically similar to those seen with Moxifloxacin ophthalmic solution."	Minimal differences observed between groups. No assessment of blinding success. Selected patient's eye to include in study to assess maximal difference between treatments.

			of Bausch & Lomb, Inc.							
Karpecki 2009 (Score = 7.5)	Bacterial Conjunctivitis: Besifloxacin ophthalmic suspension	RCT	Sponsored by Bausch & Lomb Global Clinical Programs which also designed and conducted the study. COI, Karpecki is consultant for Bausch & Lomb and received consulting fees/payment for advisory board participation from Bausch & Lomb Advanced Medical Optics, Inc, OCuSOFT,	N = 269 with diagnosed with acute bacterial conjunctivitis.	Mean age 32.4 years	Besifloxacin ophthalmic suspension 0.6% TID for 5 days (N = 137) vs. Control vehicle administered TID for 5 days (N = 132). Assessments at day 1 (visit 1), day 4, (visit 2) and day 8 or 9 (visit 3).		Clinical resolution (%): day 4 besifloxacin 33.3% vs. vehicle 17.2% (p=0.069); day 8, 73.3% vs. 43.1% (p<0.001). Eradication of bacterial infection (%): day 4 besifloxacin 90.0% vs. vehicle 46.6% (p<0.001); day 8, 88.3% vs. 60.3% (p<0.001).	"In these patients with bacterial conjunctivitis, treatment with besifloxacin opthalmic suspension 0.6% administered 3 times daily for 5 days was both efficacious and well tolerated compared with vehicle."	Besifloxacin superior to vehicle for resolution of infection and was well tolerated.

			Inc, Odyssey Medical, Inc, Rapid Pathogen Screening Inc, and Allergan, Inc; Dr. DePaolis has received consulting fees/payment for advisory board participation and lecture fees from Bausch & Lomb.							
Silverstein 2011 (Score = 7.0)	Bacterial Conjunctivitis: Besifloxacin ophthalmic suspension	RCT	Sponsored by Bausch & Lomb. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 202 with a clinical diagnosis of acute bacterial conjunctivitis;	mean age of 25.2±24.3 years.	Besifloxacin ophthalmic suspension 0.6% (N = 97) vs. Vehicle, the solution without besifloxacin (N = 105). All patients: one drop in infected eye(s) twice daily at 8 hour intervals during waking hour for 3 days.	Follow up at baseline, visit 1 (day 1), visit 2 (day 4 or 5) and visit 3 (day 7±1).	Rate of Clinical Resolution of conjunctivitis: visit 2: besifloxacin ophthalmic vs vehicle: 37/53(69.8%) vs 21/56(37.5%), (p<0.001); visit 3: 46/53(86.8%) vs 39/56(69.6), (p=0.038); eradication of bacterial infection: besifloxacin vs vehicle: visit 2: 46/53(86.8%) vs 32/56(57.1%),	"In this study in adults and children with bacterial conjunctivitis, besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days was associated with significantly higher rates of clinical resolution and bacterial eradication compared with vehicle and was well tolerated."	Only 54% had positive culture. Of these, data suggest more clinically improved at day 3. No differences on day 7.

								(p<0.001); visit 3: 39/53(73.6%) vs 37/56(66.1%), not significant, no p-value to report.		
Tepedino 2009 (Score = 3.5)	Bacterial Conjunctivitis: Besifloxacin ophthalmic suspension	RCT	Sponsored by Bausch & Lomb.	N = 957 with clinical symptoms of acute bacterial conjunctivitis in at least one eye;	mean age of 27.3 years	Besifloxacin ophthalmic suspension, 0.6% (N = 473) vs. Vehicle, applied topically three times daily for 5 days. (N = 484). (**There were misrandomizations) Patients presented for Day 1 (Visit 1), Day 5 (1 day; Visit 2), and Day 8 or 9 (Visit 3).		390 patients had Culture-confirmed bacterial conjunctivitis. Clinical resolution and microbial eradication were significantly greater with Besifloxacin ophthalmic suspension than with vehicle at Visit 2 (45.2% vs. 33.0%, p = 0.0084; and 91.5% vs. 59.7%, p<0.0001, respectively) and Visit 3 (84.4% vs. 69.1%, p=0.0011; and 88.4% vs.	"Besifloxacin ophthalmic suspension produces clinical resolution and microbial eradication rates significantly better than vehicle and is safe for the treatment of bacterial conjunctivitis."	Phase III clinical trial. Lack of study details for allocation, blinding, control of cointervention, sparse baseline comparisons. Sixty percent of randomized patients based on clinical diagnosis were dropped after baseline cultures were negative. Data insufficient to recommend use of study drug.

								71.7%, p<0.0001, respectively).		
Rietveld 2005 (Score = 7.5)	Fusidic acid gel	RCT		N = 181 with red eye and either (muco)-purulent discharge or sticking of the eyelids.		Fusidic acid gel one drop four times daily + daily diary (N = 81) vs. Placebo ne drop four times daily + daily diary (N = 100).		Primary outcome, difference in recovery rate: 62% vs. 59% in the placebo group. Secondary outcome, difference in bacterial eradication rates: after 7 days, 76% vs. 41%.	"[A]t 7 days, cure rates in both the fusidic acid gel and placebo group were similar, although the trial lacked power to demonstrate equivalence conclusively."	No meaningful differences between groups. Intervention had significantly more adverse events than control arm.

Tauber 2010 (Score = 7.0)	MOXI AF	RCT	Sponsored by by Alcon Research, Ltd. Shachar Tauber's wife is an employee of Alcon Laboratories, Inc. Gale Cupp, Richard Garber, Firoz Vohra, John Bartell and David Stroman are employees of Alcon Research, Ltd. Alcon Research, Ltd. designed the study and performed the data analysis.	N = 1179 with a clinical diagnosis of bacterial conjunctivitis in one or both eyes;	age range of 30 days to 92 years.	Treated with MOXI-AF, one drop in each eye (N = 593) vs. Vehicle, one drop in each eye (N = 586).		In the MBITT dataset, 74.5% of the patients treated BID for 3 days with MOXI-AF were microbiological successes, compared with 56.0% for patients treated with vehicle (p<0.0001). MOXI-AF was significantly more effective than vehicle in eradicating the three principle conjunctivitis pathogens, *H. influenzae* (98.5% vs. 59.6%, respectively), *S. pneumoniae* (86.4% vs. 50.0%, respectively), and *S. aureus* (94.1% vs. 80.0%, respectively) (p<0.001).	"These microbiological eradication data demonstrated that MOXI-AF provided effective eradication of bacterial pathogens following 3 days of treatment for bacterial conjunctivitis. The convenience of the simplified BID dosing regimen and the rapid eradication of the most common causative pathogens may be expected to allow earlier return to daycare or school for children as young as 1 month old, without risk of spreading the infection to others."	Phase III clinical trial. Lack of details for allocation, compliance, control for cointerventions. Age span of population was 30 days to 90 years. Data suggest microbial eradication of drug superior to vehicle.
Schwab 2002 (Score = 6.0)	Levofloxacin	RCT	Sponsored by Santen, Inc. No COI.	N = 423 with bacterial conjunctivitis;	mean age not reported.	0.5% levofloxacin (N = 211) vs. 0.3% ofloxacin (N = 212). Both the drops were assigned for 5 days (every 2 hours on		Microbial eradication rates were significantly greater in the 0.5% levofloxacin treatment group compared with the 0.3% ofloxacin group at both the final visit (89% vs. 80%,	Although clinical cure rates in the 0.5% levofloxacin and 0.3% ofloxacin treatment groups were similar, a 5-day treatment regimen with 0.5% levofloxacin achieved microbial eradication rates that were statistically superior	Details sparse or absent for allocation method, baseline comparability, compliance, cointervention control. Fifty percent of randomized patients based on clinical diagnosis were dropped after baseline cultures were negative. Data suggest clinical equivalency in cure rates.

						days 1 and 2 and every 4 hours on days 3–5) Ocular signs and symptoms were evaluated on day 1 (baseline), days 3 to 5 (interim), and days 6 to 10 (final).		p=0.034) and at end point (90% vs. 81%; p=0.038). Treatment with 0.5% levofloxacin was significantly more effective in resolving photophobia than was 0.3% ofloxacin treatment (94% vs. 73%, p=0.006).	to those attained with 0.3% ofloxacin. Despite the higher concentration of active drug in 0.5% levofloxacin versus 0.3% ofloxacin, there was no difference between treatment groups in the incidence of treatment-related adverse events.	0.5% solution significantly better in children. However, no other differences were reported.
Szaflik, 2009 (Score = 3.5)	Levofloxacin	RCT	Sponsored by Santen Oy, Niittyhaankatu. No mention of COI.	N = 120 with bacterial conjunctivitis symptoms ;	mean age of 43.3±15.1 years.	Group A (experimental dosage group) 1-2 eye drops of levofloxacin 0.5% to each infected eye three times daily for 5 days. (N = 41) vs. Group B (classic dosage group) 1-2 eye drops of levofloxacin 0.5% to each infected eye every 2 hours (up to 8 times daily) for the first 2 days and every 4 hours (up to		No difference between the groups in frequency of patients with clinical outcome resolved (85.4% in experimental vs 93.3% in classic dosage group, p=0.3). The microbial eradication rates did not differ statistically between the groups (92.7% vs 95.6%, respectively, p=0.67).	"There was no statistically significant difference in the efficacy or safety between the two methods of drug administration. Analysis of the results of compliance supported our conclusion that the less frequent method of dosing of 0.5% levofloxacin eye drops was more convenient for patients and resulted in better adherence to the drug-dosing scheme."	Lack of study details for allocation, blinding, randomization efficacy. Twenty-two percent of patients enrolled on clinical diagnosis were dropped after negative baseline culture. Data suggest similar outcomes between dosing schedules. Lack of study details and high dropout limit conclusions. Possible failed randomization.

						four times daily) for the next 3 days. (N = 45). The second visit was performed 3 to 4 days after; the final visit (V3) took place 7 ± 1 days from visit 1.				
Hwang 2003 (Score = 3.5)	Levofloxacin	RCT	Sponsored by Santen Inc that also designed the protocol. No mention of COI.	N = 249 with bacterial conjunctivitis.	Mean age levofloxacin 31.4±22.3 years, placebo 31.6±23.0 years.	0.5% levofloxacin (N = 126) vs. Placebo (N = 123). One to 2 drips into affected eye every 2 hours while awake on days 1 and 2 and then every 4 hours on days 3-5.	Follow-up at days 3-5 and 6-10.	Efficacy, microbial eradication / clinical efficacy or cure rates / ocular signs of conjunctival discharge, bulbar and palpebral conjunctival injection, burning, itching, and photophobia: ($p < 0.001$, in favor of treatment group at all visits; and for subgroups microbial eradication rates in children 88% vs. 24 in placebo group and in adults 90% vs. 65% in placebo)	"In summary, the present study demonstrates that a 5 day treatment regimen with 0.5% levofloxacin ophthalmic solution is safe and effective for treatment group of bacterial conjunctivitis in both children and adults."	No ITT analysis. Data suggest levofloxacin better than placebo for treatment of bacterial conjunctivitis.

								/(in favor of treatment group, p = 0.020; and subgroup analysis rates were 88% vs. 53%, p = 0.034) / (p = 0.027, p =0.029 and 0.018, p = 0.008, p = 0.037 and p = 0.023).		
Protzko 2007 (Score = 5.5)	Azithromycin	RCT	No mention of sponsorship. COI, Bowman and Abelson affiliated with the Insite Vision.	N = 743 with a clinical diagnosis of bacterial conjunctivitis < 3 days.	Mean age azithromycin 26.2±21.48 years, tobramycin 27.9±21.73 years.	1% azithromycin twice a day on days 1 & 2 and daily on 3 to 5 + masked medication four time a day for 5 days (N = 365) vs. 0.3% tobramycin + masked medication four times a day for 5 days (N = 378).	No mention of follow-up time.	Adverse events / visual acuity / biomicroscopy and ophthalmoscopy: (no statistical significance in frequency of adverse events between the groups) / (96% of patients had no change in visual acuity) / (most treatment-emergent outcome was swelling of the eyelid, 3.3% in each group).	"Azithromycin 1% in DuraSite is safe and can be administrated in a regimen of less frequent doses than can tobramycin, while producing an equivalent clinical outcome."	Similar efficacy but azithromycin can be given less frequently to achieve similar results when compared to tobramycin. Blinding success questionable. No ITT analysis. Intervention poorly described.

Abelson 2008 (Score = 4.5)	Azithromycin	RCT	Sponsored by Insite Vision. No COI.	N = 685 with positive clinical diagnosis of acute bacterial conjunctivitis;	mean age of 31.0 years.	1% azithromycin in DuraSite (active drug) for five days (N = 335) vs. Vehicle, for five days (N = 350). Signs of bacterial conjunctivitis were measured at each visit: visit 1 (day 1, study entry), visit 2 (day 3 or 4), and visit 3 (day 6 or 7).	Both follow-up visits occurred at least 12 hours after the previous dose of study medication.	Clinical resolution with azithromycin ophthalmic solution was statistically significant compared with that of vehicle (p=0.030) at visit 3. Bacterial eradication rates with azithromycin ophthalmic solution reached 88.5% at visit 3 (p<0.001) and included some pathogens resistant to azithromycin in vitro.	"[A]zithromycin 1% ophthalmic solution in DuraSite showed statistically significant differences in clinical resolution and bacterial eradication rates when compared with vehicle in children and adults. Because it was well tolerated in this population, it may be a viable treatment option for bacterial conjunctivitis."	Phase III trial. Sparse or absent details for randomization method, baseline comparability, compliance, ITT analysis. Sixty percent of randomized patients based on clinical diagnosis were dropped after baseline cultures were negative. Data suggest superiority of clinical cure of drug vs. vehicle.
Denis 2008 (Score = 4.5)	Azithromycin	RCT	RCT Sponsored by Laboratoreies Théa, Clermont-Ferrand, France. No COI.	N = 1043 with purulent bacterial conjunctivitis.	Mean age 39.0±20.7 years.	Azithromycin 1.5% (AZT) 1 gtt BID for 3 days (N = 524) vs. Tobramycin 0.3% (TOB) 1 gtt hourly while awake NTE 8xD for 2D + 1 gtt QID for 5D. Conjunctival testing at baseline + 3 (except those > 3 years), and 9 days post - treatment, optional	Follow-up at day 3, day 9, and optional at day 28.	There were no significant differences between groups for bacteriologic resolution on days 3 (exacted 2-sided 5% CI on difference, -5.3%; 8.3%) and 9 (exacted 2-sided 5% CI on difference, -6.6%; 3.0%).	"The microbiologic findings support the conclusion that topical therapy with azithromycin 1.5% BID 3 days effectively eradicates most pathogenic bacteria associated with bacterial conjunctivitis."	Short follow-up. Data suggest comparable efficacy.

						swabbing at 28 days post treatment (N = 519) Bacteriologic control specimens were randomized into lab analysis, under blinded conditions. Presence of pathogenic bacteria was determined via Cagle's microbiologic criteria.				
Gallenga 1999 (Score = 5.0)	Lomefloxacin	RCT		N = 99 with conjunctival hyperemia.		Lomefloxacin 0.3% eye drops twice daily (N = 50) vs. Tobramycin 0.3% 4 times daily (N = 49).		Total score of all signs and symptoms decreased significanlty in both groups on day 3-4 as compared to base line, $p < 0.0001$. No differences were found between groups for bacterial count.	"Both lomefloxacin 0.3% twice daily and tobramycin 0.3% administered 4 times daily were well tolerated and showed a high degree of clinical and microbiological efficacy in the treatment of acute bacterial conjunctivitis."	Blinding success questionable. Intervention procedure poorly described.

Yee 2005 (Score = 5.0)	Gatifloxacin	RCT	RCT Sponsored by Allergan, Inc. COI, Bernstein, Jensen, Schiffmaan, and Whitcup affiliated with Allergan, Inc.	N = 104 with acute bacterial conjunctivitis.	Mean age 42.4 years.	Gatifloxacin 0.3% BID twice daily for 5 days (N = 52) vs. Gatifloxacin 0.3% QID four times daily for 5 days (N = 52).	Follow-up at day 3 and day 5.	No statistical differences between groups for adverse events / age / sex / race: (p > 0.999) / (p = 0.727) / (p = 0.840) / (p = 0.407). On day 5 86.5 % vs. 71.2% in QID group achieved clinical cure.	"[Gatifloxacin] 0.3% administered BID was as effective and as safe as gatifloxacin 0.3% administrated QID for 5 days for the treatment of bacterial conjunctivitis."	Intervention process poorly described. No statistical significant difference between groups observed. Investigator blinding questionable.
Kernt 2005 (Score = 2.5)	Tobramycin	RCT	No mention of sponsorship. No COI	N = 276 with bacterial conjunctivitis based on clinical observation,	min. age of 1 year and max. of 91.	One drop of tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution BID instructed to dose 4 times daily for the first day and twice daily for the rest of the treatment (N = 137) vs. Tobramycin 0.3% (3 mg/mL) ophthalmic solution QID in the affected eye for (± 1) 7 days (N = 139). Study duration, 12 days.	Study duration, 12 days.	Efficacy / safety / microbiological susceptibility testing: (no statistical difference between treatments for the final clinical judgment at the test-of-cure visit, p = 0.6037) / (spectrum of bacteria isolated from severe case was similar to that in non-severe cases p value=not reported) / (no clinical relevant, treatment related change in visual acuity or statistical significance between groups p value= not reported).	"In conclusion, the results of this study indicate that tobramycin 0.3% (3 mg/mL) enhanced viscosity ophthalmic solution provides an alternative treatment for acute bacterial conjunctivitis that may help to improve patient compliance and satisfaction with therapy."	Failed randomization. Methodological details sparse. No difference observed between treatment arms.

Papa 2002 (Score = 1.5)	Netilmicin	RCT	Sponsored by SIFI Spa, Catania, Italy.Netilmicin ophthalmic solution Is manufactured by SIFI SpA. No mention of COI.	N = 209 with bacterial conjunctivitis.	Mean age 49±19 years.	0.3% netilmicin one to two drops applied to the affected eyes 4 times daily (N = 106) vs. 0.3% gentamicin one to two drops applied to the affected eyes 4 times daily (N = 103). Treatment for up to 10 days.	Follow-up at days 3, 5, and 10.	Percentage of eradicated infections over time / clinical results / safety and tolerance: (day 5 and 10; p = 0.001 and 0.037) / (amelioration of clinical symptoms favors netilmicin at day 3, 5 and 10 statistically significant difference, p = 0.037, 0.001 and 0.001, respectively) / (96.6% vs. 70.9% in gentamicin group).	"In conclusion, the current study indicates that netilmicin is safe, effective, and well tolerated in the treatment of acute bacterial conjunctivitis."	Methodological details sparse. Blinding success questionable. Study suggests netilmicin better than gentamicin in treatment of acute bacterial conjunctivitis and had better efficacy in gram positive organism eradication.

PROGNOSIS

The prognosis of most eye infections is quite good, as most resolve with minimal difficulty. The prognosis may be more guarded for those with immunodeficiencies, severe infections, certain types of infections, or complicating ulcers.

Corneal ulcers are ophthalmological emergencies. The clinical results are dependent on many factors including age, immunocompetence, extent, involvement of visual axis, speed of diagnosis and treatment.

DIFFERENTIAL DIAGNOSIS

A list of potential differential diagnoses of a red eye is found in Table 1.

COMPLICATIONS / COMORBIDITIES

Complications and comorbidities include:

- Increasing age
- Retained foreign body(ies)
- Dry eyes
- Rheumatological disorders (e.g., Sicca syndrome, Reiter's syndrome)
- Immunodeficiency states

FOLLOW-UP CARE

There are no quality studies comparing the frequency and/or intensiveness of follow-up of patients with eye infections with or without ulcers. There are also no quality studies evaluating education in conjunction with care for these infections. In general, follow-up is every few days for more severe infections and then less frequently until complete resolution. Follow-up intensity initially may also be more frequent for concerns about retained foreign bodies complicating the condition, as additional treatment may be required to remove foreign matter that is otherwise delaying recovery [587].

For bacterial or fungal infections, different frequencies of follow-up visits have been utilized in the randomized controlled clinical trials with most starting follow-up visits at least twice a week. Follow-up may be more or less frequently depending on the patient's age, severity of the infection, compliance with treatment, immunocompetency of the patient, and the clinical judgment as to the risk(s) of complications. Bacterial infections are expected to resolve in 1 to 2 weeks [512, 526]. Ulcers can take longer to heal and are recovery time is proportional to the size and depth of the ulcer.
Examples of specific follow-up visit frequencies include visits: (i) every 3 days [547, 548]; (ii) days 2, 4, 7, 14 and then longer if needed [557]; and (iii) days 2-3, 6-7, 11-12, 18-19 and 28, [570]. Fungal infections usually require longer follow-up due to longer healing times that have averaged 4-5 weeks in clinical trials [585].

JOB ANALYSIS

Generally not indicated. If the inciting event was an acute traumatic event, then protective eye programs, eye gear, engineering, and education may be indicated (see above)

MULTIMEDIA

Blepharoconjunctivitis

OVERVIEW

Blepharoconjunctivitis is a chronic inflammation of the eyelid along the base of the eyelashes. This results in irritation, itchy eyes, watery eyes, mattering, frequent blinking and may result in photophobia. It may be caused by insufficient oil gland production, bacterial infection, allergies, rosacea and other conditions. Staphylococcal infection is a common cause of blepharoconjunctivitis. Overall quality of the literature on this subject is notably poor [588]. Although It is generally considered a non-occupational condition, it is commonly identified on clinical evaluation, and is included in the guideline for completeness.

The most common treatment is lid hygiene, which involves daily washing of the eyelid with a cotton tip applicator, baby shampoo and water. Lid hygiene suffices for the majority of people. Artificial tears and warm compresses may be helpful. Thus treatment is also nearly always non-prescription self-care.

TREATMENT RECOMMENDATIONS

Daily Lid Hygiene for Blepharoconjunctivitis

Recommended.

Activity Modification and Exercise

Daily Lid Hygiene is recommended for treatment of blepharoconjunctivitis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Nearly all cases of blepharoconjunctivitis
Frequency/Dose/Duration:	Daily eyelid and eyelash scrubbing with tepid water, baby shampoo and using a cotton tip applicator.
Indications for Discontinuation:	Resolution of the symptoms. Reduction in scrubbing frequency may be possible when the condition is under control.
Benefits:	Self-management of the condition and symptoms, but with negligible cost.
Harms:	Negligible
Comments:	
Rationale:	There are a few trials of various disorders, especially for dry eyes that suggest efficacy of is evidence to suggest lid hygiene is helpful for managing lipid deficient dry eyes [589]. A thermodynamic lipid device has also been reportedly successful for Meibomian gland dysfunction [590]. Lid hygiene is not invasive, has few adverse effects, is low cost, appears clinically effective and thus is recommended.
Evidence:	

Antibiotics for Blepharoconjunctivitis

Recommended.

Medications (including topical creams)

Topical antibiotics are recommended for treatment of anterior blepharoconjunctivitis.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic
☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Anterior blepharoconjunctivitis. Generally, lid hygiene is instituted and antibiotics are used for clinical failures. Initial prescriptions of topical antibiotics may be particularly prescribed for treatment of more severe presentations.
Frequency/Dose/Duration:	Per manufacturer's recommendation
Indications for Discontinuation:	Completion of a clinical course or sufficient management of symptoms without need of further antibiotic treatment.
Benefits:	May help eradicate bacteria from lid margin. Symptom reduction
Harms:	Antibiotic resistance. Adverse reactions.
Comments:	
Evidence:	
Rationale:	There are trials of topical antibiotics for treatment of anterior blepharitis. Some trials do not clearly specify anterior blepharitis, providing a potential confounder. Most trials appear to show efficacy for reductions in symptoms. Topical antibiotics are not invasive, have few adverse effects, are low cost for short courses, appear effective and are thus recommended for anterior blepharitis.
Evidence:	

Evidence for Antibiotics for Blepharoconjunctivitis

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Yactayo-Miranda 2009	Levofloxacin	RCT		N = 60 with chronic blepharoconjunctivitis or CBC.		No treatment group received no antibiotics (N = 20) vs. Levofloxacin only group treated with 0.5% topical levofloxacin in both eyes four times a day for seven days (N = 20) vs. Combined group received levofloxacin + scrub eyelid margins with a moistened cotton tip in (N = 20).		94% of patients with CBC had positive thioglycolate broth cultures vs. 58% in patients without CBC, p < 0.0001. Treated eyes resulted in significant reduction p < 0.05, in number of thioglycolate compared to non-treated eyes, ≥ 88%.	"CBC eyes have a significantly higher number of positive cultures than eyes without CBC."	Failed randomization. Methodological details sparse.
Rhee 2007 (Score = 3.0)	Tobramycin	RCT		N = 40 eyes of 40 patients with blepharo - keratoconjunctivitis.		Group 1: Tobramycin 0.3% + dexamethasone 0.1% + ophthalmic solution of one drop twice daily for 3 to 5 days (N = 20) vs. Group 2: Tobramycin 0.3% + loteprednol 0.5% ophthalmic solution one drop twice daily for 3 to 5 days (N = 20).		Treatment outcome for group 1 were statistically significant in post treatment signs of blepharitis / conjunctivitis / ocular discharge: (p = 0.017) / (p = 0.013) / (p = 0.025). Mean keratitis scores with group one were lower in comparison to group 2, but not statistically significant, p = 0.065.	"Overall, Tobramycin 0.3% / dexamethasone 0.1% significantly decreased clinical signs of ocular inflammation (i.e., blepharitis, discharge, conjunctivitis) and total ocular inflammation scores when compared with Tobramycin 0.3% / loteprednol 0.5% in patients with moderate BKC."	Methodological details sparse. Patient blinding questionable.

Allergic Disorders: Seasonal Allergic Conjunctivitis, Perennial Allergic Conjunctivitis, and Vernal Conjunctivitis

RELATED TERMS

- Itchy eye
- Seasonal allergic conjunctivitis (SAC)
- Allergic rhinoconjunctivitis
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (VKC)
- Contact dermatoconjunctivitis
- Giant papillary conjunctivitis
- Pink eye (often this infectious not allergic conjunctivitis)

OVERVIEW

Allergic conjunctivitis (the inflammatory response of the conjunctiva to allergens) is estimated to affect up to 40% of the general population [591]. It encompasses a spectrum of severity and chronicity including seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC) [592]. SAC and PAC are considered the most common forms of ocular allergies and affect 15-20% of the population [592] [593]. Some cases of allergic eye disease are largely confined to the eyes, while most also involve the upper respiratory tract. More severe cases usually involve asthma (see Occupational/Work-Related Asthma Guideline).

RISK AND CAUSATION

Risk Factors

While allergies may occur at any age, children and young adults are at greatest risk. A past history of atopy, whether upper respiratory tract or asthma, is a risk for subsequent development of additional allergies, including those to workplace allergens. There are many studies supporting a lower risk of atopy if the person is raised in a building and in close proximity with animals (Hygiene Hypothesis) [594-598] and more recent data support relationships with microflora [599-603]. A family history of allergies is also a risk factor. Among those with pre-existing allergies, high exposures to allergens (e.g., dust mites, tree pollen, mold) are risks for allergy exacerbations. Allergic conjunctivitis may also develop in response to various occupational exposures (e.g., flour) and chemicals (e.g., thimerosal, specific perfumes). Work-related cases general involve exposure(s) to airborne allergens. See also Work-related Asthma Guideline.

Causation

Determinations of causation range from relatively simple with a high degree of certainty to those with a high degree of complexity and low certainty. Simpler causal associations involve limited or no non-occupational symptoms, exposure to a well-known sensitizer, symptoms occurring at work and complete resolution on nights and weekends. More complex cases have pre-existing atopic problems, perennial, largely unremitting symptoms that are worse at work and exposure to a known or potential allergen(s). Because more severe cases tend to involve asthma, see also Work-related Asthma Guideline.

Prevalence/Incidence

The prevalence of allergic conjunctivitis is steadily increasing with estimates approximating 40% of the U.S. population being affected. Seasonal allergic conjunctivitis (SAC) constitutes 90% of all allergic conjunctivitis. [591] Typically, all allergies are more common in younger persons and it is substantially less common for serious allergies to develop in an older adult.

Work Relatedness

A determination of work-relatedness is usually determined in most jurisdictions based on the presence of a work-related exposure to a known allergen, which precedes the allergic response. Generally, it is helpful for the causal assessment that there should be complete recovery from symptoms of allergic conjunctivitis after prolonged removal from exposure. Exceptions to complete recovery most commonly include those with ongoing exposure(s) and/or those susceptible to non-occupational allergens.

SIGNS AND SYMPTOMS

Symptoms of allergic conjunctivitis may include:

- Bilateral itchy eyes (pruritis)
- Bilateral watery eyes
- Bilateral swollen eyelids (ocular edema)
- Bilateral erythematous eyes
- Bilateral eye pain (usually not severe)
- Bilateral eye inflammation
- Rhinorrhea (runny nose)
- Itchy nose, itchy roof of mouth
- Sneezing

Symptom onset in an occupational setting may be rapid or gradual. In general, the higher the dose of exposure, the faster and more intense the symptom development tends to be. Still there is a wide range. Subsequent symptom experiences tend to parallel frequency, intensity and duration of the exposure(s). Typically, both eyes are equally affected in allergic conjunctivitis. Eyes may be unequally affected if there is differential introduction of the allergen into the eyes (e.g., flour dust rubbed into one eye).

RED FLAGS

If symptoms worsen or persist (swelling, inflammation, etc.) there may be something more serious than allergic conjunctivitis.

If visual acuity worsens, it is probably not allergic in etiology.

- Acquired abnormal visual fields
- Purulence
- Systemic diseases, especially auto-immune

DIAGNOSIS

Initial Assessment

The initial assessment consists of a careful history and limited testing to rule out other conditions. The history focuses on symptoms, patterns of symptoms and probable allergens.

Diagnostic Criteria

Proposed criteria from the American Optometric Association for allergic conjunctivitis include symptoms, signs and limited testing [604]. A clinical history and assessment of environmental factors are considered to be the first step in diagnosing allergic conjunctivitis [604]. Following the initial assessment, an allergy workup based on skin tests and determination of serum specific IgE is generally recommended. Occasionally, a conjunctival challenge is performed. [604, 605]. Increased conjunctival sickle cells, frequent eosinophils in corneal scrapings and a high total serum IgE are indicators of allergic conjunctivitis [604].

Allergic eye diseases present with episodic bilateral pruritic, watery, erythematous eyes, and photophobia [604]. Symptoms most often wax and wane based on exposure, although persistent symptoms may be present if exposures are ongoing. For those with intermittent symptoms, a pattern of symptom development, or aggravation after exposures is present that is often quite helpful in assessing the causative allergen(s). The degree of pruritis is highly helpful diagnostically to increase the probability of allergic disease, although infectious diseases may present with some pruritis. Confirmatory testing of atopy is possible for some specific allergens (see Occupational/Work-Related Asthma Guideline).

Some patients also have systemic symptoms, such as asthma. All patients with allergic eye disease should be assessed for systemic manifestations as those with asthma and ongoing exposure may incur progressive pulmonary impairments that may become permanent (See Occupational/Work-Related Asthma Guideline). Occupational asthma also increases the potential for a fatal outcome (See Occupational/Work-Related Asthma Guideline).).

Classification

The consensus classification for allergic conjunctivitis (AC) takes into account the frequency and severity of ocular signs and symptoms [604]. AC generally affects both eyes and is considered *intermittent* when it involves ocular signs and symptoms (conjunctival pruritus, tearing, a burning sensation, blurred vision, photophobia, and hyperemia) for up to 4 days a week or up to 4 consecutive days. AC is considered

persistent when the ocular signs and symptoms have been present more than 4 days per week or more than 4 consecutive days [604].

The severity of AC is classified as *mild* when signs and symptoms are 1) not bothersome, 2) do not effect vision, 3) there are no interferences with activities of daily living, and 4) no interferences with school or work tasks. It is considered *moderate* when 1-3 items are met and *severe* when all conditions are met. [604].

History

The history consists of a search for both positive responses to identify a probable allergic disease process. The history also consists of a search for pertinent negatives, e.g., to rule out other conditions such as other immunological disorders. Exposure to likely allergens is of critical interest in a history for allergic conjunctivitis. A search through occupational exposures to identify potential allergens is another important part of the history. Timing of both the onset of symptoms and relief of symptoms is key in ascertaining the probability of allergic conjunctivitis.

Medical History Questionnaire

- Do you have a history of allergies? If so, which ones? At what age of onset?
- Do you have itchy eyes (pruritis)? Bilateral?
- Are your eyes watery or teary?
- Do you get pink or red eyes? Bilateral?
- Do you have any eye pain? Bilateral? How severe?
- Is there any eye inflammation?
- Does your nose run (rhinorrhea)?
- Do you have an itchy nose, itchy roof of mouth?
- Do you have sneezing?
- Do these symptoms come on during spring or fall pollen seasons?
- Are the symptoms timed with anything you do or are exposed to at work?
- Are symptoms perennial (year round)?
- Are both eyes affected equally?
- Have you ever been diagnosed with pink eye?
- Are you allergic to certain animals like cats?
- Do you have any known food allergies?
- Do your eyes tear when wearing certain perfumes, or cosmetics?
- Do you need to use decongestants or antihistamines to control sneezing coughing and congestion?
- Has your visual acuity been affected?
- Is your peripheral vision normal?
- Have you had discharge from your eyes? Mucous? Purulence?
- Do you have systemic diseases, especially auto-immune such as Reumatoid arthritis, Lupus, Reiter's Sicca Syndrome?
- Do you have glaucoma?

Physical Exam

The physical examination includes testing of visual acuity and vision fields. Slit lamp examination is often performed. Tonometry is helpful to rule out glaucoma. Other physical examination components may

include evaluations of joints and mucous membranes, particularly if there are symptoms suggestive of autoimmune diseases.

For initial evaluations, slit lamp examination is not always required, as a preliminary diagnosis and treatment plan is possible in some situations, such as mild cases.

DIAGNOSTIC RECOMMENDATIONS

High Molecular Weight Specific Antigens

Strongly Recommended.

Specific immunological testing (IgE) is strongly recommended for workers with symptoms consistent with occupational asthma to certain high molecular weight specific allergens and when standardized antigens and assay protocols exist. The specificity and sensitivity of the allergens should have been evaluated in quality studies using validated test methods that are commercially available. High molecular weight allergens for which there is sufficient evidence in quality studies include flour dusts, bovine danders, laboratory, and other animal allergens. Natural rubber latex (NRL) allergy can be confirmed by serum IgE testing, but the assay does not include all potential NRL allergens, such that a negative result does not necessarily exclude the diagnosis of NRL allergy.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

Level of Confidence – High

IgG Specific Immunological Testing for High Molecular Weight Specific Antigens

Not Recommended.

Specific immunological testing (IgG) is not recommended as a diagnostic tool for select workers with symptoms consistent with occupational asthma to high molecular weight specific allergens. It can be used for a marker of exposure to certain allergens, but in and of itself does not diagnose disease.

Strength of Evidence **– Not Recommended, Evidence (C)**

Level of Confidence – High

Low Molecular Weight Specific Antigens

Not Recommended.

Specific immunological testing (IgE) is not recommended for workers with symptoms consistent with occupational asthma to low molecular weight specific allergens due to low sensitivity and specificity and lack of method validation.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**

Level of Confidence – Moderate

TREATMENT

Initial Care

Initial treatment generally consists of identification of the probable allergen. Subsequently, reduction or elimination of exposure is the preferred initial management. Many cases involve environmental exposures that may not be readily reduced or controlled. In such cases, hygiene to reduce exposure, medications are implemented. Immunotherapy may be attempted for select cases with moderate to severe disease and inability to sufficiently modify exposures.

All of the following are common treatments used:

- Avoidance of known antigen
- Antihistamines
- Eye drops
- Decongestants (vasoconstrictors)
- Mast cell stabilizers
- NSAIDS
- Steroids
- Immunotherapy if severe (consult an allergist)

TREATMENT RECOMMENDATIONS

Medical removal is usually based on pulmonary symptoms and development of asthma, particularly if progressive loss is determined by spirometry (see above). Medical removal solely for ocular symptoms is relatively rare, and typically only occurs after education, institution of exposure reduction, exposure controls, and persistence of symptoms beyond a tolerable level.

Management of Allergic Eye Symptoms without Asthma (Reduction of Exposure)

Recommended.

Activity Modification and Exercise

For allergic eye symptoms, it is recommended that exposure reduction and medical monitoring to assess the presence or worsening of asthma should be performed to ensure ocular symptoms are acceptably reduced as well as to provide early identification of asthma.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

☒ Acute ☒ Subacute ☒ Chronic

☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	All patients with moderate to severe symptoms of allergic conjunctivitis. Exposure reduction is also indicated for mild allergic conjunctivitis cases where feasible.
Frequency/Dose/Duration:	

Indications for Discontinuation:

Benefits: Potential to eliminate the need for medical treatment. Otherwise, potential to reduce the intensity of other medical treatment(s) required.

Harms: May be problematic in some settings. May not be possible and worker may need to accept the symptoms due to economic issues. As noted in the Work-related Asthma guideline, "The clinical benefit of removal from exposure or exposure reduction should be balanced against the increased risk of unemployment."[606]"

Comments:

Rationale: There are quality studies for evaluation of removal from work exposures in the settings of occupational asthma.

This approach is not always effective, and from the Work-Related Asthma guideline, "The guidelines of the BOHRF and ACCP stated that reduction of exposure "is not always effective"[607] and that "there is little evidence for using this approach."[608]" Still there are patients who appear to benefit significantly from reductions in exposure. Exposure reduction is not invasive, has low to high adverse effects, could be high cost and thus selective removal from exposure is indicated, especially for those with severe symptoms.

Evidence:

Education for Allergic Conditions

Recommended.

Activity Modification and Exercise

Education is recommended for assisting patients to better manage their allergic condition.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic

☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications: All patients with ocular eye manifestations, particularly those without the ability to avoid future exposure. Education includes exposure reduction, exposure elimination, hand hygiene to avoid contaminating the eyes, and medication management.

Frequency/Dose/Duration: One appointment for education may suffice. An occasional, additional visit may be indicated, especially for reinforcement, complex cases, or if the disease substantially worsens.

Indications for Discontinuation:

Benefits:	Better ability to avoid symptoms from introducing allergens from the hands to the eyes. More informed medical removal decision-making for severe cases.
Harms:	Negligible
Comments:	
Rationale:	There are no quality studies evaluating efficacy of education for ocular allergic diseases. However, clinically, education is helpful in improving management of the patient's condition and for avoiding and/or reducing exposures to allergens. Education is not invasive, has no adverse effects, is low cost, is clinically effective and is thus recommended.
Evidence:	

Medications for Ocular Allergies

There are multiple medications in several medication classes that are used for allergic ocular symptoms. These different classes of medications have different strengths and weaknesses that may be utilized to optimize treatment and/or treatment compliance. Classes of medications include non-selective histamine receptor blockers, selective histamine receptor blockers, non-steroidal anti-inflammatory medications (NSAIDs), mast cell stabilizers, glucocorticosteroids, oral anti-histamines, and others. Normally, one medication suffices. Occasionally, moderate to severe symptoms may be addressed with combinations of agents, usually utilizing one medication from each of two different classes with different mechanisms of action.

Medications administered by ocular drops are cleared via the lacrimal ducts. These medications also tend to treat allergic nasal symptoms. Some evidence suggests ocular drops treat nasal symptoms better than ocular symptoms [609].

Antihistamine and/or Mast Cell Stabilization Medications for Allergic Diseases

Strongly Recommended.

Medications (including topical creams)

Antihistamine and/or mast cell stabilization medications are strongly recommended for treatment of ocular symptoms from allergic diseases.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic

☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Ocular eye symptoms from presumptive or proven allergic disease. Exposure elimination is the preferred initial treatment before medication. However, many cases benefit from prompt medical treatment.
Frequency/Dose/Duration:	Medications used follow. Dose, Frequency, Duration is as per manufacturer's recommendations.

Histamine blockers:

- Alcaftadine 0.25% 1 drop QD
- Azelastine 0.05% 1 drop BID
- Emadastine 0.05% 1 drop up to QID

Anti-histamine/mast cell stabilizer

- Bepotastine 1.5% 1 drop BID
- Epinastine 0.05% 1 drop BID
- Olopatadine 0.1% 1 drop BID (or longer preparation QD use)

Mast Cell Stabilizer

- Cromolyn 1 drop 4-6 times/day
- Ketotifen 1 drop Q8-12 hrs
- Lodoxamine 1-2 drops QID
- Nedocromil 1-2 drops BID
- Pemirolast 1-2 drops QID

Indications for Discontinuation: Resolution of symptoms, removal from exposure, intolerance, adverse effects.

Benefits: Reduction in pruritus, watering eyes. May also reduce allergic nasal symptoms.

Harms: May briefly burn, sting and/or cause dry eyes.

Comments:

Rationale: Antihistamines are typically used as the first line medication. Both antihistamines and mast cell stabilizers have strong evidence of efficacy. While there is efficacy, there is less evidence of efficacy for ketorolac.

Antihistamine eye drops and/or mast cell stabilizing medication eye drops are not invasive, have low adverse effects, are low to moderate cost depending on length of treatment, have proven efficacy and are thus recommended for treatment of allergic eye diseases.

There are dozens of moderate and high-quality RCTs. Nearly all have documented efficacy. All of the following medications have been assessed in quality studies: Bepotastine esilate 1.0-1.5% [609-613]; Alcaftadine [614, 615]; Epinastine HCl [616-620]; Emedastine HCl [621-626], Ketotifen fumorate [622, 627-634], Azelastine HCl [627, 635-643], Olopatadine HCl [614, 617, 619, 621, 628, 631, 632, 634, 644-656], Fluorometholone [621, 656, 657], Levobastine [618, 649], Levocabastine [630] [658] [659] [660] [661] [624], Cromolyn sodium [633, 649, 662-664], Sodium cromoglycate [638, 658, 660] [665-668], Nedocromil [650, 661, 665, 669-675], Pranoprofen [657] Ketorolac [651, 654, 676]; [677-679], Diclofenac [677], [680], Loteprednol etabonate [652, 681], Pentigetide [682], Oxymetazoline [683], and Mequitazine [684].

Oral medications assessed in trials for eye symptoms include Loratadine [620, 655], desloratadine [685] Cyclosporin A has been shown to be ineffective [686].

Comparative trials have mostly found comparable efficacy among more recent medications. For example, more trials suggested Olopatadine is superior to Ketotifen [634, 651, 655] but one found the opposite [632].

NSAID Eye Drops for Allergic Diseases

Moderately Recommended.

Medications (including topical creams)

NSAID eye drops are moderately recommended for treatment of ocular symptoms from allergic diseases.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – Moderate

☒ Acute ☒ Subacute ☒ Chronic

☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Ocular eye symptoms from presumptive or proven allergic disease. Exposure elimination is the preferred initial treatment before medication. However, many cases benefit from prompt medical treatment.
Frequency/Dose/Duration:	Medications used follow. Dose, Frequency, Duration is as per manufacturer's recommendations. Ketorolac 0.5% 1 drop QID
Indications for Discontinuation:	Resolution of symptoms, removal from exposure, intolerance, adverse effects.
Benefits:	Reduction in pruritus, watering eyes. May also reduce allergic nasal symptoms.
Harms:	May briefly burn, sting and/or cause dry eyes.
Rationale:	NSAIDs drops are not invasive, have low adverse effects, are low to moderate cost depending on length of treatment, have proven efficacy and are thus recommended for treatment of allergic eye diseases. There are dozens of moderate and high-quality RCTs. Nearly all have documented efficacy. All of the following medications have been assessed in quality studies: Bepotastine esilate 1.0-1.5% [609-613]; Alcaftadine [614, 615]; Epinastine HCl [615]; Abelsopn 04 [618-620, 687]; Emedastine HCl [621, 622, 624-626, 659], Ketotifen fumorate [622, 627-634], Azelastine HCl [627, 635-643], Olopatadine HCl [614, 617, 619, 621, 628, 631, 632, 634, 644-656], Fluorometholone [621, 656, 657] Levobastine [618, 649], Levocabastine [624, 630, 658-661], Cromolyn sodium [633, 649, 662-664], Sodium cromoglycate [638, 658] [660, 665-668], Nedocromil [650, 661, 665, 669-675], Pranoprofen [657] Ketorolac [651, 654, 676-679], Diclofenac [677, 680], Loteprednol etabonate [652, 681], Pentigetide [682], Oxymetazoline [683], and Mequitazine [684].

Glucocorticosteroid Eye Drops

Sometimes Recommended.

Medications (including topical creams)

Glucocorticosteroid eye drops are selectively recommended for short term treatment of severe ocular symptoms from allergic diseases.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☐ Acute ☐ Subacute ☐ Chronic

☒ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Acute, severe ocular eye symptoms from presumptive or proven allergic disease. Exposure elimination is the preferred initial treatment before medication. However, many cases benefit from prompt medical treatment. Not indicated for mild to moderate disease due to adverse effects potentially outweighing potential benefits.
Frequency/Dose/Duration:	Medications used follow. Dose, Frequency, Duration is as per manufacturer's recommendations. Loteprednol 0.2% 1 drop up to QID Loteprednol 0.5% 1-2 drops QID
Indications for Discontinuation:	Resolution of symptoms, removal from exposure, intolerance, adverse effects.
Benefits:	Reduction in pruritus, watering eyes. May also reduce allergic nasal symptoms.
Harms:	May briefly burn, sting and/or cause dry eyes.
Rationale:	Glucocorticosteroid drops have concerns about significant adverse effects, including cataracts and aggravating glaucoma. Thus, they are recommended for more limited use to treat short courses of severe symptoms. There are dozens of moderate and high-quality RCTs. Nearly all have documented efficacy. All of the following medications have been assessed in quality studies: Bepotastine esilate 1.0-1.5% [609-613]; Alcaftadine [614, 615]; Epinastine HCl [616-620] Emedastine HCl [621, 622, 624-626, 659], Ketotifen fumorate [622, 627, 629-634, 688], Azelastine HCl [616, 635-643], Olopatadine HCl [621] [614, 617, 619, 631, 632, 634, 644-656, 688], Fluorometholone [621, 656, 657]), Levobastine [618, 649], Levocabastine [624, 630, 658-661], Cromolyn sodium [633, 649, 662-664], Sodium cromoglycate [638, 658, 660, 665-668], Nedocromil [650, 661, 665, 669-675], Pranoprofen [657] Ketorolac [651, 654, 676-679], Diclofenac [677, 680], Loteprednol etabonate [652, 681], Pentigetide [682], Oxymetazoline [683], and Mequitazine [684].

Evidence for Antihistamine and/or Mast Cell Stabilization Medications

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Glucocorticosteroid Eye Drops – Bepatastine										
Meier 2012 (Score = 8.5	Bepotastine Besilate Solution vs. Placebo	RCT Double-Masked	No mention of sponsorship or COI.	N = 157 with allergic conjunctivitis (AC).	Mean age of 37.5±11.9 years.	Conjunctival allergen challenge (CAC): Bepotastine besilate ophthalmic solution (BBOS), one drop per eye (N = 78) vs. Placebo, one drop per eye (N = 79).	Follow-up at baseline, 15 min and 8 hours.	Mean±SD o\cular itching scores: BBOS vs placebo: onset of action (15 minutes): 3 min: 0.46±0.70 vs 1.87±0.93, (p<0.0001); 5 min: 0.60±0.75 vs 2.08±0.95, (p<0.0001), 7 min: 0.61±0.78 vs 1.95±1.00, (p<0.0001); duration of action (8 hours): 3 min: 0.85±0.87 vs 2.11±0.89, (p<0.0001), 5 min: 0.93±0.87 vs. 2.29±0.92, (p<0.0001), 7 min: 0.90±0.96 vs 2.16±0.98, (p<0.0001).	"BBOS 1.5% is safe and effective in the treatment of ocular itching associated with allergic conjunctivitis within 3 minutes of a CAC and with a sustained duration of action of at least 8 hours."	2 integrated Phase II trials comparing Bepotastine besilate to placebo suggests BBOS significantly better in reducing ocular itching.
Torkildsen 2010 (Score = 8.0)	Bepotastine Besilate Solution vs. Placebo	RCT Single-Center Double-Masked	No mention of sponsorship. COI, one or more authors have received or will receive benefits for	N = 71 with a history of allergic conjunctivitis (AC).	Mean age in placebo group 40.9±11.4 years and 44.3±16.0 years in the bepotastine	Bepotastine besilate 1.5%, one drop per eye (N = 35) vs. Placebo, one drop per eye (N = 36).	Follow-up at visit 1 (day 0), visit 2 (day 7), visit 3 (day 21), visit 4 (day 35),	No statistically significant differences between the two groups in any of the primary outcomes. Differences were seen in nonocular symptoms at all timepoints (reduced rhinorrhea, nasal congestion; p<0.05).	"The 1.5% bepotastine besilate formulation produced statistically significant reductions after a CAC in individual nonocular symptoms and NOCS scores at onset of allergic response and for at least 8 hours after instillation, with the greatest reduction seen for nasal	Symptoms of allergic conjunctivitis were significantly reduced in treatment group compared to placebo at 8 hours in both rhinorrhea and nasal congestion.

			personal or professional use.		besilate group.		and visit 5 (day 49).		congestion and rhinorrhea."	
Abelson 2009 (Score = 7.5)	Bepotastine Besilate Solution vs. Placebo	RCT Single-center Double-Masked	Sponsored by ISTA Pharmeceuticals, Inc. No COI.	N = 107 with a positive skin test reaction to a common allergen.	Mean age for bepotasine besilate 1.0% was 39.9±15.2 years and 44.3±16.0 years for bepotastine besilate 1.5%, and 40.9±11.4 years for placebo.	Bepotastine besilate 1.0% (N = 36) vs. Bepotastine besilate 1.5% (N = 35) vs. Placebo, inactive vehicle (N = 36). All participants: one drop per eye. 7 week treatment period.	Follow-up at baseline, and visit 1 (-21±3), visit 2 (-14±3), day 0 and 1 (3A and 3B), 14 and 28.	Mean ocular itching scores: bepotastine besilate 1.0%: 15 minute onset of action challenge: 3min vs. 5min vs. 7min: 1.4 vs 1.5 vs 1.4, ($p<0.001$); 8 hour duration of action challenge: 1.0 vs 1.2 vs. 1.1, ($p<0.001$); bepotastine besilate 1.5%: 15 minute: 1.5 vs 1.6 vs 1.4, ($p<0.001$); 8 hour: 1.3 vs 1.6 vs 1.4, ($p<0.001$). All results are comparing bepotastine to placebo.	"In this CAC model of allergic conjunctivitis in adults and children, bepotastine besilate ophthalmic solutions 1.0% and 1.5% were associated with clinically and statistically significant reductions in ocular itching, but not in conjunctival hyperemia, within 15 minutes and maintained for ≥8 hours after administration. Both solutions were well tolerated."	Data suggest treatment superior to placebo.

Macejko 2010 (Score = 7.5)	Bepotastine Besilate Solution various doses	RCT Double-Masked	Sponsored by ISTA Pharamaceuticals Inc. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 130 with allergic conjunctivitis (AC).	Mean age of 32±14.3 years.	Bepotastine besilate ophthalmic solution 1.0%, one droop per eye (N = 44) vs. Bepotastine besilate ophthalmic solution 1.5%, one drop per eye (N = 43) vs. Placebo one drop per eye (N = 43).	Follow-up at baseline, visit 1 (day 21), visit 2 (day 14), visit 3 (day 0), visit 4 (day 14±3), and visit 5 (day 28).	Mean ocular itching scores: bepotastine besilate solution 1.0% vs. 1.5%: onset of action: 3 min: 1.4 vs 1.5, 5 min: 1.5 vs 1.6, 7 min: 1.3 vs 1.4, ($p < 0.001$); 16 hour duration of action: 3 min: 0.6 vs. 0.6, 5 min: 0.7 vs 0.7, 7 min: 0.8 vs 0.8, ($p<0.001$).	"Bepotastine besilate ophthalmic solutions 1.0% and 1.5% both substantially decreased CAC induced ocular itching for at least 8 hours after dosing. Reductions in conjunctival hyperemia after a CAC, although statistically significant for bepotastine besilate ophthalmic solutions 1.0% and 1.5% compared with placebo when assessed at 15 minutes after dosing, were modest."	3 arms to study including placebo. At 8 hours, both solutions decreased ocular itching compared to placebo.

Williams 2011 (Score = 6.0)	Bepotastine Besilate Solution various doses	RCT Single-Center	Sponsored by a grant from ISTA Pharmeceuticals, Inc. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 107 with a history of allergic conjunctivitis (AC).	Mean age 39.9±15.2 years for bepotastine besilate 1.0%; 44.3±16.0 years for bepotastine besilate 1.5% and 40.9±11.4 years for placebo.	Bepotastine besilate ophthalmic solution 1.0%, one drop (N = 36) vs. Bepotastine besilate ophthalmic solution 1.5%, one drop (N = 35) vs. Placebo, one drop (N = 36).	Follow-up at baseline, visit 1 (day -21±3), visit 2 (day -14±3), visit 3A (day 0), visit 3B (day 1), visit 4 (day 14±3), and visit 5 (day 28).	Mean itching scores: bepotastine besilate 1.0 vs. bepotastine besilate 1.5%: PP (per protocol) population: 3 min: 0.7 vs. 1.0, (p<0.001); 5 min: 0.9 vs 1.1, (p<0.001); 7 min: 0.9 vs. 1.1, (p<0.001); ITT (intention to treat) with LOCF (last observation carried forward): 3 min: 0.7 vs 0.9, (p<0.001); 5 min: 0.8 vs 0.9, (p<0.001); 7 min: 0.9 vs 0.8, (p<0.01).	"Bepotastine besilate ophthalmic solution 1.5% produced predefined clinically meaningful reduction in CAC-induced ocular itching and tearing in a single-site trial and was more effective than bepotastine besilate ophthalmic solution 1.0% and placebo for reducing ocular itching in a CAC test 16 h after dosing."	Bepotastine is superior to placebo. However, there were minimal differences between bepotastine 1.0% and 1.5% solutions.
Alcaftadine										
Greiner 2011 (Score = 7.0)	Alcaftadine various doses	RCT Single-Center Double-Masked	Sponsored by Vistakon Pharmeceuticals LLC. No mention of COI.	N = 170 with a history of allergic conjunctivitis (AC).	Mean age of 41.5±11.5 years.	Alcaftadine 0.05%, one drop per eye (N = 34) Alcaftadine 0.1%, one drop per eye (N = 34) vs. Alcaftadine 0.25%, one drop per eye (N = 34) vs. Olopatadine 0.1%, one drop per eye (N = 34) vs. Placebo,	Follow-up at visit 1 (day -21), visit 2 (day -14±3), visit 3 (day 0±3),	Mean ocular itching score: 15 min onset action: placebo vs alca 0.05% vs alca 0.1% vs alca 0.25%vs olopatadine: 3 min: 2.22 vs 0.53 vs 0.56 vs 0.27 vs 0.33, (p<0.05); 5 min: 2.33 vs 0.72 vs 0.60 vs 0.41 vs 0.49, (p<0.05); 7 min: 2.14 vs 0.69 vs 0.55 vs 0.37 vs 0..48, (p<0.05); 16 hour	"Treatment with alcaftadine 0.25% ophthalmic solution resulted in mean differences of 0.1 unit (ocular itching) and approximately .1 unit (conjunctival redness), which was significant (p<0.001) compared with placebo treatment. All	5 groups including 1 placebo showed Alcaftadine 0.25%, significantly decreased redness and itching compared to placebo.

						vehicle of the alcaftadine ophthalmic solutions, one drop per eye (N = 34).	and visit 4 (day 14±3)	duration: 3 min: 1.75 vs 0.40 vs 0.31 vs 0.27 vs 0.63, (p<0.05); 5 min: 1.88 vs 0.52 vs 0.47 vs 0.40 vs 0.79, (p<0.05); 7 min: 1.83 vs 0.56 vs 0.48 vs 0.43 vs 0.85, (p<0.05). Conjunctival redness: 15 min onset of action challenge: alcaftadine 0.05 vs placebo: 7 min: 1.13 vs 1.85, (p<0.05); alcaftadine 0.1 vs placebo: 1.14 vs 1.85, (p<0.05); alcaftadine 0.25 vs placebo: 0.50 vs 1.85, (p<0.05); olopatadine 0.1 vs placebo: 1.15 vs 1.85, (p<0.05); 15 min: 1.09 vs 1.96, (p<0.05); 20 min: 1.15 vs 1.80, (p<0.05); 16 hour duration of action: alcaftadine 0.05 vs placebo: 1.22 vs 1.77, (p<0.05), alcaftadine 0.1 vs placebo: 1.18 vs 1.77, (p<0.05); 15 min: 1.44 vs 2.02, (p<0.05); alcaftadine 0.25 vs placebo: 7 min: 0.77 vs 1.77, (p<0.05), 15 min: 1.01 vs 2.02, (p<0.05); olopatadine 0.1 vs placebo: 7 min: 0.89 vs 1.77, (p<0.05); 15 min: 1.12 vs 2.02, (p<0.05); 20 min: 0.99 vs 1.91, (p<0.05).	doses of alcaftadine were safe and well tolerated in the population studied."	

Torkildsen 2011 (Score = 3.5)	Alcaftadine vs. placebo	RCT 2-Arm Single-Center Double-Masked	Sponsored by Johnson & Johnson Vision Care, Inc., the parent of Vistakon Pharmaceuticals, LLC. COI, Dr. Shedden is an employee of Vistakon Division of Johnson & Johnson Vision Car Inc.	N = 60 with a history of allergic conjunctivitis (AC).	Mean age of 35.9±14.9 years.	Vehicle, placebo (N = 30) vs. Alcaftadine 0,.25% ophthalmic solution bilaterally (N = 30).	Follow-up at visit 1 (day 21), visit 2 (day 14), visit 3 (day 0), and visit 4 (day 15).	Difference of >1 unit in mean ocular itching score: alcaftadine-treated eyes vs vehicle: visit 3: 16 hours: 3 min vs. 5 min vs. 7 min: -1.731 vs. -1.687 vs. -1.576, (p<0.001); visit 4: 15 min: 3 min vs 5 min vs 7 min: -1.500 vs. -1.491 vs. -1.474, (p<0.001). Differences are mean vehicle score subtracted from the mean alcaftadine score. Differences in mean conjunctival redness scores: visit 3: duration of action: visit 3: 7 min vs. 15 min vs 20 min: -0.952 vs.-0.542 vs. -0.542, (p<0.001); visit 4: onset of action: -0.875 vs, -0.612 vs. -0.578, (p<0.001).	"With an onset of action within 3 minutes and a duration of action of at least 16 hours, the statistically and clinically significant effect of alcaftadine 0.25% on itching makes it an important addition to therapy for ocular allergy. Additional studies are warranted to better understand the mechanisms affording a fast onset and prolonged duration of action."	Methodological details sparse. Data suggest Alcaftadine superior to placebo.
Epinastine										
Torkildsen 2008 (Score = 8.5)	Epinastine hydrochloride	RCT/Crossover	Sponsored by Inspire Pharmeceuticals, Inc., and ORA Clinical Research &	N = 40 with a history of allergic conjunctivitis (AC).	mean age of 39.58.	Epinastine HCl 0.05% ophthalmic solution in one eye (N = 40 eyes) vs. Ketotifen Fumarate 0.025% in second eye (N = 20 eyes) vs. Azelastine HCl 0.05% 1 single drops one drug per	Follow up at baseline, weeks 1, 2 and 3.	Mean comfort scores between treatment scores (0.5/1/2/5 min): epinastine vs. azelastine (2.90/1.85/1.35/0.63), (p<0.001, 0.001, p=0.001, and p=0.014); epinastine vs. ketotifen right after instillation (1.2), p=0.014; Ketotifen vs. azelastine	"[E]pinastine was rated as more comfortable than azelastine and ketotifen. None of the tested medications were associated with statistically significant ocular drying effects."	Suggest very short term, advantage but only 1-2 minutes. Otherwise equal efficacy. Lack of placebo control limits conclusions of efficacy.

			Development. No mention of COI.			eye then switching after 7 days in second eye (N = 20 eyes).		(0.5: 2.35 /1: 1.35 / 2: 1.10), (p=0.001, p=0.023, and p=0.028). NS between groups for ocular drying and tear-film stability.		
Borazan 2009 (Score = 6.5)	Epinastine hydrochloride	RCT	No mention of sponsorship or COI.	N = 100 with seasonal allergic conjunctivitis (SAC) for at least 2 years, a history of active allergic conjunctivitis, and a positive diagnostic test for allergic hypersensitivity;	mean age of 26.9±10 6 for olopatadine group, 26.1±7.9 for ketotifen group, 29.3±12. 8 for epinastine group and 22.05±8. 7 for fluorometholone group.	Group 1: Olopatadine hydrochloride 0.1% or Patanol, in one eye (N = 20) vs. Group 2: Ketotifen Fumarate 0.025% or Zaditen, in one eye (N = 20) vs. Group 3: Epinastine hydrochloride 0.05% or Relestat, in one eye (N = 20) vs. Group 4: Emedastine Difumarate 0.05% or Emadine, in one eye (N = 20) vs. Group 5: Fluorometholone acetate 0.1% or Flarex BID for 14 days, in one eye (N = 20). Placebo (vehicle ophthalmic solution) in the other eye.	Follow up at baseline, and weeks 1 and 2.	At all visits and all groups scores for ocular itching / conjunctival redness / tearing / chemosis and eyelid swelling were significant with placebo treated eye, (p<0.001). At the end of treatment conjunctival impression cytology scores were significantly lower for drug-treated eyes than for placebo-treated eyes, (p<0.01).	"In patients with SAC, olopatadine, ketotifen, epinastine, and emedastine are more efficacious than fluorometholone acetate in preventing itching and redness. All the antiallergic agents gave similar results in terms of reducing tearing, chemosis and eyelid swelling. Our data showed that impression cytology parameters improved after treatment with antiallergic agents in patients with SAC."	Many treatment groups (N=5) and many outcomes. Data suggest all treatments superior to placebo.

Abelson 2004 (Score = 6.0)	Epinastine hydrochloride	RCT Single-center Double-Masked	No mention of sponsorship or COI.	N = 67 patients who had a history of allergic conjunctivitis (AC) with ≥1 allergy to cat hair, cat dander; dust mites; or ragweed, tree, or grass pollens.	Mean age of 38.4 and range from 12 to 67 years.	Epinastine hydrochloride 0.05% ophthalmic solution, (N = n/a) vs. Vehicle of epinastine (sodium phosphate monobasic, sodium chloride, edetate sodium, benzalkonium chloride and purified water) (N = n/a). All patients: one drop per eye on two separate occasions, weeks 3 and 5.	Follow-up at baseline, and weeks 1, 3, and 5.	Mean±SD for ocular itching score: 3 min after onset challenge: epinastine vs vehicle: 0.45±0.77 vs. 1.99±1.03, (p<0.001). Mean±SD for ocular itching score: 3 min after duration challenge: epinastine vs vehicle: 0.92±0.93 vs. 1.86±0.93, (p<0.001). Mean±SD for conjunctival hyperemia score: 5 min after onset challenge: epinastine vs. vehicle: 1.28±0.86 vs. 2.03±0.78, (p<0.001). Mean±SD for hyperemia score: 5 min after duration challenge: epinastine vs. vehicle: 1.37±0.78 vs. 1.93±0.77, (p<0.001).	"In this CAC model, multiple signs and symptoms of allergic conjunctivitis were significantly reduced by topical administration of epinastine compared with vehicle. Epinastine showed prompt onset (3 minutes) and long duration of action (28 hours). The tolerability of epinastine was similar to that of vehicle."	Missing group populations groups. Patient data sparse. Data suggest Epinastine superior to placebo for antigen challenge.
Whitcup 2004 (Score = 6.0)	Epinastine hydrochloride	RCT	No mention of sponsorship or COI.	N = 298 with allergen sensitive and history of seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis	Mean age of 33.6±15.3 for epinastine, 32.5±13.6 for levocabastine and 31.5±15.2 for vehicle.	Epinastine Hydrochloride 0.05% (N = 118) vs. Levocabastine Hydrochloride 0.05% (N = 118) vs. Vehicle of Epinastine 1 drop/eye BID (morning and afternoon) for 8 weeks. (N = 62).	Follow ups at week 0, 2, 4, 6, and 8.	Worst daily ocular itching scores mean: epinastine 0.77±0.86 vs. levocabastine 0.86±0.86 vs. vehicle 0.93±0.76, (p=0.045) (epinastine vs. vehicle). No significance between group for mean worst daily ocular hyperemia, ciliary, conjunctival, episcleral hyperemia, chemosis, ocular mucous discharge, eyelid swelling, or tearing throughout the study.	"[O]phthalmic epinastine instilled twice daily was more effective than vehicle for the control of ocular itching and was similar in efficacy to levocabastine for control of ocular itching and hyperemia."	Sparse on blinding. Data with modest efficacy vs. Placebo.

Mah 2007 (Score = 6.0)	Epinastine hydrochloride	RCT Double-Masked	Sponsored by an unrestricted grant from Alcon Laboratories, Inc. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 92 with allergic conjunctivitis (AC).	Mean age of 40.9±12.8 years.	Olopatadine 0.2% in one eye (left or right) and epinastine 0.05% in the contralateral eye (N = 28) vs. Olopatadine 0.2% in one eye and placebo in the fellow eye (N = 27) vs. Epinastine 0.05% in one eye and placebo in the fellow eye (N= 28) vs. Placebo in both eyes (N = 9). 7 week treatment period.	Follow-up at baseline, visit 2 (day -28±3), visit 3 (day 0), and visit 4 (day 14).	Olopatadine 0.2% treated eye exhibited significantly lower mean ocular itching scores compared to epinastine 0.05% treated eyes at 5 min (p=0.024), and 7min (p=0.003). Mean redness scores: olopatadine vs epinastine: 7 min: 0.94 vs 1.50, (p=0.0010), 15 min: 1.23 vs. 1.68, (p= 0.0150), 20 min: 1.25 vs. 1.68, (p=0.0125)	"Olopatadine 0.2% was superior to epinastine 0.05% in preventing ocular itching and redness at onset when induced by the CAC model."	Likely unequal control size (N=9). Probable randomization failure.
Ousler 2007 (Score = 4.0)	Epinastine hydrochloride	RCT Investigator-masked Crossover	Sponsored by an unrestricted grant from Inspire Pharmaceuticals, Inc., Durham, North Carolina. No COI.	N = 18 healthy individuals with a history of seasonal allergic conjunctivitis (SAC).	Aged >18 years.	Topical epinastine 0.05% administered as 1 drop per eye twice daily (N = NA) vs. Systemic loratadine 10 mg 4 days once daily, with a 10-day washout between treatments. (N = NA).	Follow-up for 4 days.	After week 4 systematic loratadine was associated with the mean decrease in tear volume / tear flow / and increase in global fluorescein straining, (all, p<0.05).	"In this small study in healthy adult volunteers with seasonal allergic conjunctivitis, 4 days of twice-daily treatment with topical epinastine was associated with no clinical signs of ocular drying, whereas 4 days of once-daily dosing with systemic loratadine was associated with signs of ocular dryness that included decreased tear volume and tear flow."	Missing group populations. Open label crossover study. Loratadine associated with increased drying effects vs. Epinastine.

Lanier 2004 (Score = 3.0)	Epinastine hydrochloride	RCT	Sponsored by unrestricted grant from Alcon Laboratories, Inc, Fort Worth, Texas. No mention of COI.	N = 66 with a history of allergic conjunctivitis (AC).	Mean age of 44.4 years.	Olopatadine eye drops, 1 drop each eye. (N = N/A) vs. Epinastine eye drops, 1 drop each eye (N = N/A).	Follow up on (day 7±2) and (day 21±3).	Olopatadine treated eyes exhibited significantly lower mean itching and conjunctival redness scores than the contralateral Epinastine treated eyes, –0.19 (p=0.003) and –0.52 (p<0.001), respectively. Olopatadine treated eyes also exhibited significantly less chemosis: –0.24 (*p* < 0.001), ciliary redness: –0.55 (p<0.001), and episcleral redness: -0.58 (p<0.001) than Epinastine treated eyes.	"In this study it was demonstrated that Olopatadine, with its antihistaminic and mast cell stabilizing effects against a broad range of pro-inflammatory mediators, is more effective than Epinastine in controlling itching, redness and chemosis associated with allergic conjunctivitis."	Missing group population. Methodological details sparse. Data suggest Epinastine may be superior to Olopatadine.
Nichols 2009 (Score = 2.5)	Epinastine hydrochloride	RCT	Sponsored by Inspire Pharmaceuticals, Inc. No mention of COI.	N = 146 with symptomatic during allergy season, used daily-wear soft contacts for at least 1 month, and currently complaining of contact lens discomfort due to allergic conjunctivitis (AC).	mean age 34.3.	Epinastine 0.05% ophthalmic solution (Elestat) twice a day + rewetting drops as needed (N = 75) vs. Rewetting drops alone, as needed, at least twice a day for 5-7 days (N = 71).		The epinastine group has significant increases from baseline in comfortable wearing time vs. the control group, day 2 (epinastine 1.35 ± 4.11 vs. control 0.26 ± 3.49, p=0.042) day 7 (2.31±4.57 vs. 0.50±3.25, p=0.020). Average increase in comfortable wear time over study period was greater for epinastine group (1.33±2.89 hr) vs. control (0.43±2.28 hr), (p=0.012). Mean increase from baseline in total contact lens wearing time or duration of study: epinastine 0.35±1.87 hr	"Epinastine 0.05% may be useful for the treatment of seasonal allergic conjunctivitis in contact lens wearers."	Methodological details sparse.

								vs. control -0.32±1.81, (p=0.008). Reduction in ocular itch on all treatment days from baseline: epinastine -0.54±0.73 vs. control -0.07±0.64, (p<0.001). Rewetting drop usage was less in the epinastine group vs. control on day 5 (p=0.007), day 6 (p=0.015), and for mean usage over treatment period (epinastine -0.55±1.32 vs. control 0.06±1.38), (p=0.012). Epinastine had significantly greater improvement in overall eye comfort from baseline (1.43±0.82) vs. control (1.87±0.92), (p=0.001).		
Ketotifen										

Abelson 2003 (Score = 8.0)	Ketotifen Fumarate vs. placebo	RCT	Sponsored by Novartis Ophthalmics, Inc. No mention of COI.	N = 89 with a history of allergic hypersensitivity to animal dander, grass, or tree, or ragweed pollen;	mean age ?	At visit 1 and 2 participants received Ketotifen 0.025% in one eye (N = N/A) vs. Placebo. (N =N/A) At visit 3, 4 and 5 participants received either placebo in the contralateral eye 1 drop 15 minutes, 6 hours, and 8 hours before allergen challenge or , allergen concentration eliciting in the other eye at each visit (N = 89, 83, 72).	Follow up?	Ocular itching / Hyperemia / Safety: (between group differences favoring ketotifen-treated eyes at all-time points, p<0.001, and eyes with no itching compared to placebo was also significantly higher, (p<0.001) / (ketotifen-treated eyes had significantly lower mean scores compared to placebo, (p<0.05) / (no statistical significant differences between groups).	"Ketotifen 0.025% ophthalmic solution had a statistically significant effect in reducing ocular itching and hyperemia related to allergic conjunctivitis."	Experimental study. Suggest efficacy.
Greiner 2003 (Score= 6.0)	Ketotifen Fumarate vs. placebo	RCT	No mention of sponsorship or COI.	N = 87 and 85 with a history of type I hypersensitivity to selected environmental allergens and a positive diagnostic test for allergic disease or a positive conjunctival allergen	mean age of 38.7 years.	Study 1: single dose Ketotifen Fumarate, 0.025% in one eye (N = 87) vs. Placebo in the other eye with a conjunctival provocation test (CPT) 15 minutes, 6 hours, and 8 hours later (N = 87). Study 2: Multiple dose (N = 85) vs. Ketotifen Fumarate, 0.025% in one eye vs. Placebo in the other eye twice daily for 4 weeks (N = 85).	Follow up?	Study 1: Ketotifen superior to placebo for reducing ocular itching (p<0.0001) and ocular injection in all vessel beds, (p<0.001) at all-time points. Study 2: all between treatment differences were statistically significant in favor of ketotifen, mean itching at all-time points, (p<0.001).	"[K]etotifen fumarate 0.025% ophthalmic solution was safe, well-tolerated, and statistically effective in preventing the signs and symptoms of allergic conjunctivitis at 15 minutes, 6 hours, and 8 hours after the first dose and 8 hours after the final dose of a 4-week treatment regimen in the allergen challenge model of allergic conjunctivitis."	Experimental study. Data suggest efficacy.

				challenge in the past 2 years;						
Torkildsen 2008 (Score = 5.0)	Ketotifen Fumarate vs. placebo	RCT Double-Masked	No mention of sponsorship or COI.	N = 108 with a history of allergic conjunctivitis (AC).	Mean age 41.45 years for test + test, 44.42 years for test + placebo, 40.83 for reference + reference, and 42.86 for reference + placebo.	Test + Test, ketotifen fumarate ophthalmic solution 0.025% (N = 33) vs. Test + Placebo, inactive vehicle (N = 24) vs. Reference + Reference, Zatidor (N = 30) vs. Reference + Placebo, inactive vehicle (N = 21). Follow-up at baseline, vist1 (day -21±3), visit 2 (day -14±3), visit 3 (day 0±3), and visit 4 (day 14±3). The study lasted 2 weeks	The study lasted 2 weeks	Mean (95% CI) for itching scores: test vs reference: 3 min: -1.2 (-1.5 to -0.9) vs. -1.2 (-1.5 to -0.8), (p<0.001); 5 min: -1.3 (-1.6 to -1.0) vs -1.3 (-1.6 to -0.9), (p<0.001); 7 min: -1.3 (-1.6 to -1.0) vs.-1.30(-1.6 to -1.0), (p<0.001). Onset of action: 3 min:-1.6 (-1.9 to 1.4) vs. -1.5 (-1.7 to -1.2), (p<0.001); 5 min: -1.7 (-1.9 to -1.4) vs. -1.6 (-1.9 to -1.4), (p<0.001); 7 min: -1.6 (-1.9 to 1.3) vs. -1.6 (-1.8 to -1.3), (p<0.001).	"In this population of patients with AC, the test formulation of ketotifen fumarate ophthalmic solution 0.025% met criteria for bioequivalence to the reference formulation, as established by the protocol. The test and reference formulations were well tolerated in the population studied."	Ketotifen better than placebo for itching but no difference between test and reference ketotifen dosage.

Horak 2003 (Score = 9.0)	Ketotifen Fumarate vs. Other solution	RCT/ Crossover	Sponsored by Novartis Ophthalmics. No mention of COI.	N = 37 with a history of seasonal allergic conjunctivitis (SAC) of at least 2 years with no current symptom;	mean age of 27.30±4.8, range of 20 to 43.	Ketotifen Fumarate 0.025%, first eye (N = 37) vs. Emedastine Difumarate 0.05% eye drops single dose 1 drop in each eye with a 6 day washout period before crossover (N = 37).	Follow up a baseline, and visits one and two.	Ketotifen was significantly superior to emedastine for time to onset for 15 vs. 30 minutes, p=0.048. Ocular and nasal symptom scores 0-2 hours post dose for redness / ocular symptoms / total symptom complex: (1.97±1.10 vs. 2.25±0.87, (p=0.046) / (8.06±2.46 vs. 6.97±3.19, (p=0.026) / (10.93±3.53 vs. 9.18, (p=0.014).	"[K]etotifen fumarate 0.025% and emedastine difumarate 0.05% both effectively alleviated ocular symptoms of SAC for a period of at least 8 hours after single-dose administration."	Crossover. Experimental study across aerosol chamber. Data suggest comparable efficacy with modestly faster onset with ketotifen.
Torkildsen 2008 (Score = 8.5)	Ketotifen Fumarate vs. Other solution	RCT/ Crossover	Sponsored by Inspire Pharmeceuticals, Inc., and ORA Clinical Research & Development. No mention of COI.	N = 40 with a history of allergic conjunctivitis (AC);	mean age of 39.58.	Epinastine HCl 0.05% ophthalmic solution in one eye (N = 40 eyes) vs. Ketotifen Fumarate 0.025% in second eye (N = 20 eyes) vs. Azelastine HCl 0.05% 1 single drops one drug per eye then switching after 7 days in second eye (N = 20 eyes).	Follow up at baseline, weeks 1, 2 and 3.	Mean comfort scores between treatment scores (0.5/1/2/5 min): epinastine vs. azelastine (2.90/1.85/1.35/0.63), (p<0.001, 0.001, p=0.001, and p=0.014); epinastine vs. ketotifen right after instillation (1.2), p=0.014; Ketotifen vs. azelastine (0.5: 2.35 /1: 1.35 / 2: 1.10), (p=0.001, p=0.023, and p=0.028). NS between groups for ocular drying and tear-film stability.	"[E]pinastine was rated as more comfortable than azelastine and ketotifen. None of the tested medications were associated with statistically significant ocular drying effects."	Suggest very short term, advantage but only 1-2 minutes. Otherwise equal efficacy. Lack of placebo control limits conclusions of efficacy.

Abelson 2003 (Score = 8.0)	Ketotifen Fumarate vs. Other solution	RCT	Sponsored by Novartis Ophthalmics, Inc. No mention of COI.	N = 89 with a history of allergic hypersensitivity to animal dander, grass, or tree, or ragweed pollen;	mean age ?	At visit 1 and 2 participants received Ketotifen 0.025% in one eye (N = N/A) vs. Placebo. (N =N/A) At visit 3, 4 and 5 participants received either placebo in the contralateral eye 1 drop 15 minutes, 6 hours, and 8 hours before allergen challenge or , allergen concentration eliciting in the other eye at each visit (N = 89, 83, 72).	Follow up?	Ocular itching / Hyperemia / Safety: (between group differences favoring ketotifen-treated eyes at all-time points, p<0.001, and eyes with no itching compared to placebo was also significantly higher, (p<0.001) / (ketotifen-treated eyes had significantly lower mean scores compared to placebo, (p<0.05) / (no statistical significant differences between groups).	"Ketotifen 0.025% ophthalmic solution had a statistically significant effect in reducing ocular itching and hyperemia related to allergic conjunctivitis."	Experimental study. Suggest efficacy.
Kidd 2003 (Score = 7.5)	Ketotifen Fumarate vs. Other solution	RCT	Sponsored by Novartis Ophthalmics AG, Bülach, Switzerland. No mention of COI.	N = 519 suffering from seasonal allergic conjunctivitis (SAC);	mean age for Ketotifen group 46.3±17.0, for placebo 47.9±16.5, and for Levocabastine was 49.5±17.4.	Ketotifen Fumarate 0.025% ophthalmic solution (N = 172) vs. Placebo, vehicle ophthalmic solution (N = 173) vs. Levocabastine ophthalmic suspension HCl 0.05% (N = 174). Twice daily in each eye for 4 weeks.	Follow up at baseline, and days 5-8 and 25-31.	Redness/ itching / tearing / chemosis, lid swelling, discharge: (0.08 vs. 0.93 vs. 0.92 in levocabastine group, p=0.03, and ketotifen vs. placebo, (p=0.04) / (0.64 vs. 0.84 vs. 0.89, p=0.02, and ketotifen vs. placebo, (p=0.02) / (0.64 vs. 0.84 vs. 0.89, p=0.02, and ketotifen vs. placebo, (p=0.02) / (3.54 vs. 4.15 vs. 4.18, p=0.03, and ketotifen vs. placebo, (p=0.03).	"[K]etotifen fumarate 0.025% ophthalmic solution is effective in reducing the signs and symptoms of SAC, and in preventing their recurrence."	Data suggest modest efficacy. High dropouts.

Borazan 2009 (Score = 6.5)	Ketotifen Fumarate vs. Other solution	RCT	No mention of sponsorship or COI.	N = 100 with seasonal allergic conjunctivitis (SAC) for at least 2 years, a history of active allergic conjunctivitis, and a positive diagnostic test for allergic hypersensitivity;	mean age of 26.9±10.6 for olopatadine group, 26.1±7.9 for ketotifen group, 29.3±12.8 for epinastine group and 22.05±8.7 for fluorometholone group.	Group 1: Olopatadine hydrochloride 0.1% or Patanol, in one eye (N = 20) vs. Group 2: Ketotifen Fumarate 0.025% or Zaditen, in one eye (N = 20) vs. Group 3: Epinastine hydrochloride 0.05% or Relestat, in one eye (N = 20) vs. Group 4: Emedastine Difumarate 0.05% or Emadine, in one eye (N = 20) vs. Group 5: Fluorometholone acetate 0.1% or Flarex BID for 14 days, in one eye (N = 20). Placebo (vehicle ophthalmic solution) in the other eye.	Follow up at baseline, and weeks 1 and 2.	At all visits and all groups scores for ocular itching / conjunctival redness / tearing / chemosis and eyelid swelling were significant with placebo treated eye, ($p<0.001$). At the end of treatment conjunctival impression cytology scores were significantly lower for drug-treated eyes than for placebo-treated eyes, ($p<0.01$).	"In patients with SAC, olopatadine, ketotifen, epinastine, and emedastine are more efficacious than fluorometholone acetate in preventing itching and redness. All the antiallergic agents gave similar results in terms of reducing tearing, chemosis and eyelid swelling. Our data showed that impression cytology parameters improved after treatment with antiallergic agents in patients with SAC."	Many treatment groups (N=5) and many outcomes. Data suggest all treatments superior to placebo.

Avunduk 2005 (Score = 6.0)	Ketotifen Fumarate vs. Other solution	RCT	No mention of sponsorship or COI.	N = 49 with signs and symptoms of seasonal allergic conjunctivitis (SAC), at least 18 years old, and had a history of seasonal allergic conjunctivitis (SAC) in the last 2 years;	ages range from 18 to 61.	Ketotifen Fumarate 0.025% solution (N = 12) vs. Olopatadine HCl 0.1% solution (N = 13) vs. Preservative free artificial tear substitute or ATS control group, 2 drops in each eye BID for 30 days (N = 14). 30-day treatment period.	Follow up?	Mean itching scores (day 0 / day 15 / day 30): ketotifen (2.08 / 1.08 / 0.75), olopatadine (1.84 / 1.08 / 0.76), ATS (2.00 / 1.85 / 1.71).	"[K]etotifen and olopatadine were associated with effective decreases in the expression of CAMs an inflammatory markers on the conjunctival surface cells. Both active treatments were found to be more efficacious compared with ATS. We did not find significant differences between the 2 active treatments."	Patients not well described. Data suggest active treatment of comparable efficacy and superior to placebo. 1 month study.

Ganz 2003 (Score = 5.0)	Ketotifen Fumarate vs. Other solution	RCT Double-Masked	No mention of sponsorship or COI.	N = 66 were suffering from seasonal allergic conjunctivitis (SAC).	Mean age of 37.47±16.8 years for ketotifen and 35.2±14.4 years.	Ketotifen Fumarate 0.025% (N = 32) vs. Olopatadin hydrochloride 0.1% as an active control (N = 34). All patients: one drop per eye twice daily (8 hours between doses). 3 week treatment period. Follow-up at baseline, days 5 through 8, and 21 to 24. This study lasted 3 weeks.	Follow-up at baseline, days 5 through 8, and 21 to 24. This study lasted 3 weeks.	Responder rate (%): ketotifen vs. control: 88% vs. 55%, (p<0.0001). Mean±SD for conjunctival hyperemia: ketotifen vs. olopatadine: day 5: right: 0.016±0.88 vs. 0.227±0.397, (p=0.048); left 0.016±0.88 vs. 0.273±0.435, (p=0.032); day 21: right: 0.016±0.088 vs. 0.339±0.651, (p=0.003); left: 0.016±0.088 vs. 0.387±0.715, (p=0.003). Itching: day 5: right: 0.234±0.458 vs. 0.652±0.897, (p=0.007); left: 0.219±0.457 vs. 0.621±0.884, (p=0.008); day 21: right: 0.156±0.296 vs. 0.823±0.909, (p<0.0001); left: 0.156±0.296 vs. 0.839±0.916, (p<0.0001).	"In a 3-week study under actual-use conditions during fall allergy season, ketotifen fumarate 0.025% ophthalmic solution was superior to olopatadine hydrochloride 0.1% ophthalmic solution in relieving the signs and symptoms of allergic conjunctivitis. No differences in comfort, tolerability, or safety were noted between groups over the course of the study. The superior efficacy and sustained inhibition of the allergic response make ketotifen an ideal treatment option for allergic conjunctivitis."	Data suggest Ketotifen superior to Olopatadin.

Greiner 2002 (Score = 4.0)	Ketotifen Fumarate vs. Other solution	RCT Single-Masked	Sponsored by Novartis Ophthalmics. No mention of COI.	N = 47 with a history of allergy to environmental allergens not currently in season.	Mean age of 40 years.	Ketotifen fumarate vehicle solution, placebo (glycerol, sodium hydroxide/hydrochloric acid, and purified water) 0.025% ophthalmic solution, one dose only (N = 47 eyes, l/r) vs. Cromolyn sodium 4% ophthalmic solution, 4 times daily (N = 47 eyes, l/r). 2 week treatment period. Follow-up at baseline, and visits 1 through 3. This study lasted 2 weeks.	Follow-up at baseline, and visits 1 through 3. This study lasted 2 weeks.	Mean efficacy scores for itching: ketotifen vs cromolyn: 15 min: -2.09±0.87 vs. -0.43±1.20, (p<0.001); 4 hours: -2.26±0.61 vs. -1.43±1.08, (p<0.001); Conjunctival redness: 15 min: -1.05±0.75 vs. -0.45±0.64, (p<0.001).	"A single dose of ketotifen was superior to a 2-week four-times-daily regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the conjunctival allergen-challenge model."	Data suggest Ketotifen superior to Cromolyn. Methodological details sparse.
Azelastine										
Torkildsen 2008 (Score = 8.5)	Azelastine drops vs. placebo	RCT/Crossover	Sponsored by Inspire Pharmeceuticals, Inc., and ORA Clinical Research & Development. No mention of COI.	N = 40 with a history of allergic conjunctivitis (AC);	mean age of 39.58.	Epinastine HCl 0.05% ophthalmic solution in one eye (N = 40 eyes) vs. Ketotifen Fumarate 0.025% in second eye (N = 20 eyes) vs. Azelastine HCl 0.05% 1 single drops one drug per eye then switching after 7 days in second eye (N = 20 eyes).	Follow up at baseline, weeks 1, 2 and 3.	Mean comfort scores between treatment scores (0.5/1/2/5 min): epinastine vs. azelastine (2.90/1.85/1.35/0.63), (p<0.001, 0.001, p=0.001, and p=0.014); epinastine vs. ketotifen right after instillation (1.2), p=0.014; Ketotifen vs. azelastine (0.5: 2.35 /1: 1.35 / 2: 1.10), (p=0.001, p=0.023, and p=0.028). NS between	"[E]pinastine was rated as more comfortable than azelastine and ketotifen. None of the tested medications were associated with statistically significant ocular drying effects."	Suggest very short term, advantage but only 1-2 minutes. Otherwise equal efficacy. Lack of placebo control limits conclusions of efficacy.

								groups for ocular drying and tear-film stability.		
Horak 1998 (Score = 8.0)	Azelastine drops vs. placebo	RCT/Crossover	Sponsored by ASTA Medica AG, Frankfurt /Main, Germany. No mention of COI.	N = 24 with history of seasonal allergic conjunctivitis (SAC)/rhinoconjunctivitis for at least 1 year;	mean age of 13.8 years.	Single dose of Azelastine eye drops 0.025% + 0.05% + 0.1% in one eye (N = 23, 22) vs. Placebo, each separated with a 14 day washout period in the following eye (N = 24).	No follow up time reported.	VAS for itching at each time point before or 15 minutes after conjunctival allergen provocation / lacrimation at each time point before or 15 minutes after provocation: (51, 32.0, 47.5, (p<0.01), 0.05, and 0.05 for azelastine 0.025/0.05/0.1%, or 15 min after, 19.0, 4.5, 6.5, (p<0.01) for all vs. placebo 107.0 or 15 min after 24.0, not significant) / (19.0, 19.0, 18.5, p < 0.01, (p<0.05), 0.05, and 2.0, 1.0, 1.0, p = not significant, (p<0.05), 0.05 vs. 28.5 and 2.5, p = not significant).	"Azelastine eye drops extend the spectrum of effective topical anti-inflammatory agents for the treatment of allergic conjunctivitis and can be recommended at a dose of 0.05%."	Crossover. Dose ranging. Data suggest efficacy and little differences between. Experimental study using challenge chamber.

Friedlaender 2000 (Score = 7.0)	Azelastine drops vs. placebo	RCT Double-Blind	Sponsored by a grant from Muro Pharmeceutical an ASTA Medica Company. No COI	N = 80 with a history of allergic conjunctivitis (AC) (≥ 2 years).	Mean age of 37 years.	AZE (0.03 ml containing 0.015mg of azelastine hydrochloride) in one eye (N = 40 eyes, l/r) vs. one drop of placebo (0.03ml of vehicle) in the other eye (N = 40 eyes, l/r).	Follow-up at visits 1 through 4.	Mean itching scores: azelastine vs. placebo: 3min: 0.55 vs. 1.50, (p<0.001); 5 min: 0.60 vs. 1.80, (p<0.001); 10 min: 0.60 vs. 2.0, (p<0.01). Mean redness scores: azelastine vs. placebo: 3 min: 1.50 vs. 2.00, (p < 0.001); 5 min: 1.60 vs.2.10, (p<0.001); 10 min: 1.90 vs. 1.50, (p<0.001).	"Therapy of experimentally induced allergic conjunctivitis with AZE was highly effective, with an onset of action seen within 3 minutes and a duration of effect of at least 8 to 10 hours."	Compared to placebo, ocular itching and redness were significantly lower in azelastine group from 3 min to 10 hours.
Sabbah 1998 (Score = 6.0)	Azelastine drops vs. placebo	RCT Double-Blind	Sponsored by ASTA Medica. No mention of COI.	N = 107 children suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 8.3±2.4 years for placebo, 8.6±2.3 years for azelastine, and 8.2±2.5 years for levocabastine.	Azelastine 0.05% (0.015mg), one drop per eye twice daily (N = 47) vs. Levocabastine 0.05% (0.015mg), one drop per eye twice daily (N = 32) vs. Placebo, identical to the azelastine eye drops except for the active drug, one drop per eye twice daily (N = 28). 14 day treatment period.	Follow-up at baseline, and after 3 and 14 days of treatment.	Responder rates (%) for three main eye symptoms: itching, lacrimation, and conjunctival redness: day 3: yes vs no: azelastine: 74% vs 26%, (p<0.01). Compared with placebo group: yes vs no: 39 vs. 61.	"In conclusion, azelastine eye drops are effective in the rapid relief of symptoms in young children with seasonal allergic conjunctivitis/rhinoconjunctivitis and show comparable safety to that of levocabastine eye drops. Azelastine eye drops offer an effective and safe alternative to levocabastine eye drops in the treatment of pediatric allergic conjunctivitis."	Study non-specific to working population.

James 2003 (Score = 6.0)	Azelastine drops vs. placebo	RCT Double-Blind	Supported by ASTA Medica AG. No mention of COI.	N = 144 participants with a two-season history of conjunctivitis/ rhinoconjunctivitis;	mean age for azelastine 0.05% 37.1, 35.5 years for sodium cromoglycate 2% and 36.1 years for placebo.	Azelastine 0.05% (N = 45) vs. Sodium Cromoglycate (SCG) 2% (N = 50) vs. Placebo (N = 49). All participants: one drop per eye, twice daily.	Follow-up at baseline and after 3, 7 and 14 days of treatment.	Responder rates (%) for three main eye symptoms: itching, tearing and conjunctival redness: day 3: no vs yes: azelastine: 14.6% vs. 85.4%, (p=0.005); SCG: 17.0% vs. 83.0, (p=0.007)	"The results of this study indicate that the therapeutic use of azelastine eye drops in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis can be recommended."	Lack of study details for randomization, allocation and compliance.
Nazarov 2003 (Score = 5.5)	Azelastine drops vs. placebo	RCT Double-Blind	No mention of sponsorship or COI.	N = 116 with perennial conjunctivitis for at least one year.	Mean age of 33.7±11.3 years.	Azelastine drops (approximately 0.03ml solution to each eye twice daily) (N = 58) vs. Placebo (approximately 0.03ml solution to each eye twice daily) (N = 58) **Patients could increase the dose to 3 to 4 administrations per day if symptoms were severe during both the baseline and the 6-week treatment period.	Follow-up on day 7, 21, and 42.	Azelastine significantly improved itching and redness compared to placebo treatment. Main eye symptom score (range 0-6) mean values ± SD (Day 0: absolute 3.9±0.7, Azelastine); placebo (Day 0: absolute 3.9±0.7) Day 7, p<0.001.	"Azelastine eye drops are well- tolerated and effectively relieve the hallmark symptoms of itching and conjunctival redness in patients suffering from perennial allergic conjunctivitis."	Data suggest Azelastine drops superior to placebo.

Lenhard 1997 (Score = 5.5)	Azelastine drops vs. placebo	RCT Double-Blind	Sponsored by ASTA Medica. No mention of COI.	N = 278 participants suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age for azelastine 0.025% group 31.6±10.6 years, 31.7±11.7 years for azelastine 0.05%, and 33.9±11.9 years for placebo.	Azelastine 0.025% (0.008mg) (N = 92) vs. Azelastine 0.05% (0.015mg) (N = 92) vs. Placebo, identical composition of azelastine without the active substance (N = 94). All participants: one drop per eye, twice daily at an interval of 10 to 12 hours in the morning and evening. 14 day treatment period. This study lasted 14 days.	Follow-up at baseline, and days 7 and 14.	Responder rates (%) for three main eye symptoms: itching, lacrimation, and conjunctival redness: day 7: responders vs. non-responders: 98% vs. 2%, (p=0.0015).	"The results of this present study show that azelastine eye drops are well tolerated and exert a concentration-dependent therapeutic effect in the treatment of seasonal allergic conjunctivitis. For further investigations, the high concentration of 0.05% azelastine eye drops is recommended."	Sparse details for randomization, allocation blinding and compliance. Data suggest no immediate efficacy until 7 days compared with placebo.
Giede-Tuch 1998 (Score = 5.5)	Azelastine drops vs. placebo	RCT Double-Blind	Sponsored by ASTA Medica. No mention of COI.	N = 151 patients suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 35.4±11.4 years for azelastine 0.025%, 35.2±10 7 years for azelastine 0.05%, and 35.9±11.5 years for placebo.	Azelastine 0.025% (0.008 mg) (N = 47) vs. Azelastine 0.05% (0.015 mg) (N = 52) vs. Placebo, Benzalkonium chloride and sodium Edetate (N = 52). All participants: one drop per eye, twice daily at intervals of 10 to 12 hours in the morning and evening.	Follow-up at baseline, and after 3, 7, and 14 days of treatment.	Responder rate (%) for main eye symptoms itching, lacrimation, and conjunctival redness: day 3: no vs. yes: 18% vs 82%, (p=0.011).	"The results of this double-blind study show that azelastine eye-drops provide rapid, dose-dependent relief from ocular symptoms in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis."	Author conclusion not supported by statistical presentation as neither treatment reached statistical significance.

Giede 2000 (Score = 5.0)	Azelastine drops vs. placebo	RCT	Sponsored by ASTA Medica AG, Frankfurt / Main, Germany. No mention of COI.	N = 307 with seasonal allergic conjunctivitis (SAC), for at least 1 year.	Aged 17 to 69 years.	Azelastine 0.05% eye drops twice daily (N = 101) vs Levocabastine 0.05% eye drops twice daily (N = 103) vs. Placebo eye drops identical to the treatment eye drops except for the active ingredient twice daily (N = 103).	Follow-up after 3, 7, and 14 days.	68.2% defined as responders in azelastine group vs 59.1% of levocabastine vs 51.1% in placebo. Only those in azelastine group had higher the responder rate vs placebo, (p=0.022). In terms of soreness / swollen eyelids / azelastine treatment was superior to levocabastine, 60.2% and 58.4% improvement, by day 3.	"[The results of this study confirms the therapeutic potential of 0.05% azelastine eye drops in the treatment of allergic conjunctivitis / rhino conjunctivitis and indicate that the product possesses a more rapid onset of action and a slightly superior extent of efficacy as compared to levocabastine eye drops."	Poor response rate and variable response rates. Study cannot be double blinded as packaging was different between treatment groups. Also, Azelastine is known for causing significant taste changes.
Sodhi 2003 (Score = 2.5)	Azelastine drops vs. placebo	RCT	No mention of sponsorship or COI.	N = 63 with allergic conjunctivitis (AC).	Mean age of 34.8±17.3 years.	Azelastine 0.02%, four times daily (N = 32) vs. Mitomycin C (MMC) 0.02 mg/ml, four times daily (N = 31). 3 month treatment period.	Follow-up at baseline, and weeks 2 and 4. This study lasted 3 months.	N (%) for Outcome measure: redness: MMC vs. azelastine: 25 (80.7%) vs. 19 (55.9%), (p=0.033); follicles: 31 (100.0%) vs 6 (17.7), (p=0.0001); papillae: 29 (93.6%) vs. 4 (11.8), (p=0.0001); changes in agent: 0 (0%) vs. 30 (88.2), (p=0.0001).	"Though this was a short-term study, we found topical MMC to be more effective than topical azelastine in the treatment of allergic conjunctivitis both in terms of relief of symptoms and resolution of signs. The use of topical MMC in low doses does not cause any significant adverse effect."	Methodological details sparse.
Levocabastine										
Kidd 2003 (Score = 7.5)	Levocabastine vs. Other solution	RCT	Sponsored by Novartis Ophthalmics AG, Bülach,	N = 519 suffering from seasonal allergic	mean age for Ketotifen group 46.3±17.0, for	Ketotifen Fumarate 0.025% ophthalmic solution (N = 172) vs. Placebo, vehicle ophthalmic solution (N = 173) vs.	Follow up at baseline, and days	Redness/ itching / tearing / chemosis, lid swelling, discharge: (0.08 vs. 0.93 vs. 0.92 in levocabastine group, p=0.03, and ketotifen vs. placebo,	"[K]etotifen fumarate 0.025% ophthalmic solution is effective in reducing the signs and symptoms of SAC, and in	Data suggest modest efficacy. High dropouts.

			Switzerland. No mention of COI.	conjunctivitis (SAC);	placebo 47.9±16.5, and for Levocabastine was 49.5±17.4.	Levocabastine ophthalmic suspension HCl 0.05% (N = 174). Twice daily in each eye for 4 weeks.	5-8 and 25-31.	(p=0.04) / (0.64 vs. 0.84 vs. 0.89, p=0.02, and ketotifen vs. placebo, (p=0.02) / (0.64 vs. 0.84 vs. 0.89, p=0.02, and ketotifen vs. placebo, (p=0.02) / (3.54 vs. 4.15 vs. 4.18, p=0.03, and ketotifen vs. placebo, (p=0.03).	preventing their recurrence."	
Donshik 2000 (Score = 7.5)	Levocabastine vs. Other solution	RCT	Sponsored by an unrestricted educational grant from Allergan Labs, Inc., Irvine, California. No mention of COI.	N = 224 with a history of seasonal allergic conjunctivitis (SAC) during ragweed season and a positive skin test for ragweed in the last 2 years;	mean of 37 years, range from 14 to 73 years.	Acular, 5 ml Ketorolac Tromethamine 0.5% eye drops (N = 73) vs. Livostin, Levocabastine hydrochloride 0.05% eye drops (N = 75) vs. Placebo, 1 drop in each eye 4 times daily for 6 weeks (N = 75).	Follow up at baseline, and weeks 1 and 3.	Ketorolac more effective than vehicle reducing itching scores, palpebral hyperemia, bulbar hyperemia, and edema, (p<0.05). Levocabastine treated eye showed significant reduction in bulbar hyperemia, (p=0.008). No significant differences among treatment groups in safety or tolerability.	"[K]etorolac 0.5% ophthalmic solution is well tolerated and effective in relieving the signs and symptoms of seasonal allergic conjunctivitis."	Data suggest modest efficacy.
Davies 1993 (Score = 6.5)	Levocabastine vs. Other solution	RCT	No mention of sponsorship or COI.	N = 95 patients over 5 years of age with a history of allergic conjunctivitis (AC) during a previous hay fever season with ≥ typical symptom of	age range 5 to 69 years.	Topical levocabastine 0.5 mg/ml (N = 28) vs. Topical sodium cromoglycate 20 mg/ml (N = 32) vs. Matching placebo eye-drops (N = 29) one in each eye four times daily for 28 days. Oral terfenadine and beclomethasone or	No follow-up time.	NS between sodium cromoglycate group and placebo for treatment efficacy (no p-value reported). End of study intergroup differences: levocabastine superior to sodium cromoglycate for **severest ocular symptom** (p<0.05), lacrimation (p<0.01), and red eyes (p<0.05); sodium cromoglycate vs. placebo,	“[T]opical levocabastine is more effective than sodium cromoglycate and placebo for the prophylaxis and treatment of seasonal allergic conjunctivitis,”	Therapeutic efficacy at 4 weeks was 87% in Levocabastine and 68% in sodium cromoglycate and placebo groups respectively.

				allergic conjunctivitis (ocular irritation, burning sensation, itch, redness, photophobia, lacrimation, lid oedemia, conjunctival oedema) needing treatment;		budesonide nasal spray were allowed as rescue medications. Assessments at baseline, 2 weeks, and 4 weeks.		NS for same outcomes. Pain free for at least 75% of study: levocabastine 37% vs. sodium cromoglycate 6% (p<0.01) vs. placebo 4% (p<0.01).		
Verin 2001 (Score = 6.5)	Levocabastine vs. Other solution	RCT	Sponsored by Alcon Research, Ltd, Fort Worth, Texas. No mention of COI.	N = 202 with a history of allergic conjunctivitis (AC) and signs and symptoms characteristic of the disease;	mean age of 30 years, range of 4 to 76 years.	Emedastine 0.05% eye drops (N = 97) vs. Levocabastine 0.05% eye drops one drop in each eye twice daily (morning and evening) for 6 weeks (N =105).	Follow ups on days 3, 7 14, 30, 42, and 7 to 10 days after the cessation of therapy.	Primary outcome itching / redness at days 3, 7, 14, 30, and 42: (p=0.245, 0.0016, 0.0002, 0.0001 and p=0.0001) / (p=0.145, 0.0009, 0.0002, 0.0002, and 0.0001). Secondary; Chemosis / swelling at days 3, 7, 14, 30, and 42: (p=0.0559, p=0.0050, 0.0005, 0.0046, and 0.0001)/ (p=0.0672, 0.0023, 0.0001, 0.0061, and 0.0009).	"[E]medastine 0.05% eye drops administered twice daily were more efficacious than levocabastine 0.05% eye drops in the prevention and treatment of the signs and symptoms of allergic conjunctivitis in adults and children of 4 years and above."	Baseline comparability not well described. Both groups showed improvements in symptom relief at 6 weeks but at 7 days, Emedastine was significantly better than Levocabastine in symptom alleviation.

Azevedo 1991 (Score = 6.0)	Levocabastine vs. Other solution	RCT Double-blind Parallel-groups	No mention of sponsorship or COI.	N = 60 with symptoms of allergic conjunctivitis (AC) during the previous hayfever season, skin and/or RAST tests that were positive for pollen, and presented with at least one typical symptom of allergic conjunctivitis evaluated as moderate or severe;	median age; 27 years / 26 years/ 34 years.	Levocabastine 0.5 mg/ml 1 drop in each eye (N = 18) vs. Cromoglycate 20 mg/ml 1 drop in each eye (N = 21) vs. Placebo received eye drops 1 drop in each eye (N = 21).	Follow-up at baseline, 2 and 4 weeks.	Levocabastine-treated patients responded better vs both the cromoglycate, (p=0.03) und the placebo, (p=0.007). There was no significant difference between cromoglycate vs placebo, (p=0.42). Levocabastine have a faster onset of action than 77% of the previous medications taken in this group vs 44%, and 33% in the cromoglyeate and placebo group, (p<0.005).	"[L]evocabastine is efficacious in the management of allergic conjunctivitis, producing better symptomatic relief than cromoglycate."	4 week arms parallel design. High dropout rate in 2 of 3 groups.
Hammann 1996 (Score = 5.5)	Levocabastine vs. Other solution	Cross over trial, randomized, Double-Blind	Sponsored by a grant from Janssen Research Foundation. No mention of COI.	N = 24 volunteers with a history of grass pollen conjunctivitis.	Mean age of 25.4±4.8 years.	Topical levocabastine, 0.5 mg/ml, one drop per eye (N = n/a) vs. Topical Nedocromil, 20 mg/ml, one drop per eye (N = n/a). Erythma and severity of pruritus were recorded before provocation, 15 minutes after instillation of medication 10 minutes after the instillation of the		Both drugs allowed a significant increase in the tolerated dose of allergen expressed as shift in allergen concentration, (p<0.001). The number of shifts in allergen concentration was significantly greater after levocabastine treatment than after nedocromil treatment, (p=0.019).	"In a provocation test with allergen, levocabastine and nedocromil were both effective in increasing the conjunctival tolerance to allergen, with better protection provided by levocabastine."	Missing group populations. Small sample size. Data suggest levocabastine superior to nedocromil.

						dilutent and 10 minutes after provocation with each allergen concentration.				
Secchi 2000 (Score = 4.5)	Levocabastine vs. Other solution	RCT	No mention of sponsorship or COI.	N = 202 with redness of the eye graded at least a 2 and an itching score of at least 4.		Emedastine 0.05% BID solution (N = 97) vs. Levocabastine 0.05% BID in both eyes for 42 days with follow-up 7-10 after therapy (N = 105).	Follow-up at days 0, 3, 7, 14, 30 and 42. 7-10 days post therapy.	Chemosis / eyelid swelling at baseline and follow-up / itching, redness at days 7, 14, 30, 42: (1.27±1.13 and 0.36 ± 0.56 vs. levocabastine, 1.29±1.10 and 0.68±0.89, (p=0.0064) / (1.26±1.11 and 0.28±0.47 vs. 1.28±1.09 and 0.61±0.84, (p=0.0014) / (p<0.05).	"Emedastine is more efficacious than levocabastine in reducing chemosis, eyelid swelling and other efficacy variable associated with seasonal allergic conjunctivitis."	Groups not well described. No placebo group. Fig 2.
Olopatadine										

Leonardi 2003 (Score = 5.5)	Olopatadine vs. placebo	RCT	Sponsored by an unrestricted grant from Alcon Laboratories. No mention of COI.	N = 10 with a clinical history of seasonal allergic conjunctivitis (SAC);	mean age of 31.5±11.3 years.	Olopatadine, one drop (left or right eye) vs. placebo (artificial tears) in the contralateral eye. Symptoms were evaluated 5, 10, 15, 20, 30 minutes and 5 hours after CAC.		Itching and redness were significantly reduced in the olopatadine group compared with the placebo group ($p<0.01$ and $p<0.03$, respectively).	"In the present study, olopatadine significantly reduced the levels of histamine, cellular infiltrate, and ICAM expression compared with placebo after CAC, suggesting that it reduced the release of mast cell–derived mediators in humans. This inhibition of mediator release correlated with reduction of itching and redness."	Small sample size (n=10). Results suggest Olopatadine decreased mast cell mediators resulting in decreased itching and redness.
Mah 2007 (Score = 5.0)	Olopatadine various doses	RCT Double-Masked	Sponsored by an unrestricted grant from Alcon Laboratories, Inc. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 92 with allergic conjunctivitis (AC).	Mean age of 40.9±12.8 years.	Olopatadine 0.2% in one eye (left or right) and epinastine 0.05% in the contralateral eye (N = 28) vs. Olopatadine 0.2% in one eye and placebo in the fellow eye (N = 27) vs. Epinastine 0.05% in one eye and placebo in the fellow eye (N= 28) vs. Placebo in both eyes (N = 9). 7 week treatment period.	Follow-up at baseline, visit 2 (day -28±3), visit 3 (day 0), and visit 4 (day 14).	Olopatadine 0.2% treated eye exhibited significantly lower mean ocular itching scores compared to epinastine 0.05% treated eyes at 5 min (p=0.024), and 7min (p=0.003). Mean redness scores: olopatadine vs epinastine: 7 min: 0.94 vs 1.50, (p=0.0010), 15 min: 1.23 vs. 1.68, (p= 0.0150), 20 min: 1.25 vs. 1.68, (p=0.0125)	"Olopatadine 0.2% was superior to epinastine 0.05% in preventing ocular itching and redness at onset when induced by the CAC model."	Likely unequal control size (N=9). Probable randomization failure.

Mah 2008 (Score = 5.0)	Olopatadine various doses	RCT	Sponsored by an unrestricted grant from Alcon Laboratories. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 52 with a history of conjunctivitis and dry eye.	Mean age of 55.5 years.	Olopatadine 0.2%, one drop per eye (N = 25) vs. Tear saline, one drop per eye (N = 27). 1 week treatment period.	Follow-up at baseline, visit 1 (day -3±1), visit 2 (day 0), visit 3 (day 7±1). This study lasted 1 week.	There were no statistically significant values to report between the two groups in any of the outcomes. No p-values to report.	"As there were no significant changes in the signs and symptoms of dry eye, olopatadine hydrochloride 0.2% is safe to use in ocular allergy patients with mild-to-moderate dry eye."	Sparse baseline comparability. Similar efficacy between groups.

Abelson 2003 (Score = 8.5)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by a grant from Alcon Laboratories, Inc., Fort Worth, Texas.	N = 56 with a positive skin test, history of allergic conjunctivitis (AC) or rhinoconjunctivitis with eyelid swelling, and prior conjunctival allergen challenge (CAC) titration within the past year;	mean age of 44.7 years, age range of 19 to 72.	1 drop of Olopatadine hydrochloride 0.1% into one eye (N = 56) vs. 1 drop of placebo into the contralateral eye for a one time visit (N = 56).	Follow up?	The olopatadine group had significantly less eyelid swelling at both 15 and 30 minutes, (p<0.001 and 0.017) minutes vs. placebo. Olopatadine group show significantly greater relief from itching / prevention of ocular redness / chemosis / vessel beds / mean conjunctival redness scores / mean episcleral redness scores / mean chemosis score vs. placebo, (p<0.001).	"[E]yelid swelling - an indicator of allergic changes to the tissues surrounding the eyes - was quantifiably measured with 3D imaging technology as well as subjective rating scales."	Experimental study. High dropout rate. Data suggest efficacy.
Katelaris 2002 (Score = 8.0)	Olopatadine hydrochloride vs. other solutions	RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 188 with a history of allergic conjunctivitis (AC) for at least 1 allergy season, reacted positively to 21 common local pollen on a skin test at screening or in the previous 12 months.	Ages ranged from 4 to 77 years.	One group instilled olopatadine 0.1% ophthalmic solution in the morning and afternoon and placebo BID at noon and afternoon (N = 91) vs. Instilled cromolyn 2% ophthalmic solution QID the same 4 time dosing as group one (N = 94).	Follow-up for 42 days.	Days 14-42 (itching) and on day 42 (redness), the upper 95% CI was 10 unit, olopatadine was statistically superior to cromolyn for both variables, (p<0.05). Days 30 and 42 for itching and on day 42 for redness, (all, p<0.05).	“The signs and symptoms of SAC improved progressively with 6 weeks’ instillation of olopatadine 0.1% ophthalmic solution BID and cromolyn 2% ophthalmic solution QID.”	At 6 weeks, olopatadine significantly reduced itchiness and redness as compared to cromolyn although both treatments produced significant reductions in SAC symptoms from baseline.

Ciprandi 2004 (Score = 7.0)	Olopatadine hydrochloride vs. other solutions	RCT	No mention of sponsorship or COI.	N = 30 children with seasonal allergic conjunctivitis (SAC) (study I). N = 22 children with seasonal allergic conjunctivitis (SAC) (study II).	aged 4 to 11 years.	*Study I* Cromolyn sodium ophthalmic solution 2% and levocabastine ophthalmic solution 0.05% 4 times daily (N = 13) vs. Placebo or Olopatadine ophthalmic solution 0.1% at noon and afternoon (N = 17). *Study II* Levocabastine ophthalmic suspension twice daily (N = 10) vs. Placebo or Olopatadine ophthalmic solution 0.1% at noon and afternoon (N = 12).	Follow-up for 6 weeks.	Study I: Ocular itching and conjunctival redness were significantly less with olopatadine than with cromolyn sodium, (p=0.010 and p=0.003, respectively). All symptoms decreased significantly relative to baseline values with both treatments during both the peak and declining pollen periods, (all, p<0.05). Study II: During the peak pollen period, conjunctival redness was significantly lower with olopatadine vs levocabastine 0.05%, (p=0.040). All symptoms except eyelid swelling decreased significantly from baseline values during both the peak and declining pollen periods, (all, p<0.05).	"Olopatadine hydrochloride ophthalmic solution 0.1% was more effective than both cromolyn sodium 2% and levocabastine 0.05% ophthalmic preparations in controlling ocular signs and symptoms of SAC in children and was well tolerated when administered twice daily for 6 weeks."	In children, Olopatadine appears more effective than either Cromolyn or levocabastine in decreasing ocular SAC changes. Nasal symptoms did not change.
Abelson 1998 (Score = 7.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by Alcon Laboratories, Fort Worth, Texas. No mention of COI.	N = 169 with a history of active allergic conjunctivitis (AC) within the previous 2 seasons and not receiving current treatment;	mean age of 39 for olopatadine 0.05% and 38 for olopatadine 0.10%.	Olopatadine 0.05% in one eye + Olopatadine 0.1% (N = 84) vs. 0.1% Olopatadine in one eye placebo in contralateral eye for 3 visits total; at days 1, 14, and 28 (N = 85). Assessments were completed 3, 10,	Assessments were completed 3, 10, and 20 minutes after conjunctival	Both 0.5% and 0.1% treated eyes were significantly more effective than placebo, (p<0.05). Mean itching and redness significantly lower in treated eyes compared to placebo, (p<0.05) (at 3, 10, and 20 minutes, after the 27-minute and 8-hours challenges).	"[O]lopatadine is an effective ocular anti-allergic agent with a rapid onset and prolonged duration of action with excellent tolerability. A 0.05% of 0.1% concentration of olopatadine administered twice daily was shown to be	2 RCTs. Experimental study. Suggest efficacy.

						and 20 minutes after conjunctival allergen challenge.	allergen challenge.		effective for treatment of allergic conjunctivitis."	
Greiner 2011 (Score = 7.0)	Olopatadine hydrochloride vs. other solutions	RCT Single-Center Double-Masked	Sponsored by Vistakon Pharmeceuticals LLC. No mention of COI.	N = 170 with a history of allergic conjunctivitis (AC).	Mean age of 41.5±11.5 years.	Alcaftadine 0.05%, one drop per eye (N = 34) vs. Alcaftadine 0.1%, one drop per eye (N = 34) vs. Alcaftadine 0.25%, one drop per eye (N = 34) vs. Olopatadine 0.1%, one drop per eye (N = 34) vs. Placebo, vehicle of the alcaftadine ophthalmic solutions, one drop per eye (N = 34). Follow-up at visit 1 (day -21), visit 2 (day -14±3), visit 3 (day 0±3), and visit 4 (day 14±3)	Follow-up at visit 1 (day -21), visit 2 (day -14±3), visit 3 (day 0±3), and visit 4 (day 14±3)	Mean ocular itching score: 15 min onset action: placebo vs alca 0.05% vs alca 0.1% vs alca 0.25%vs olopatadine: 3 min: 2.22 vs 0.53 vs 0.56 vs 0.27 vs 0.33, (p<0.05); 5 min: 2.33 vs 0.72 vs 0.60 vs 0.41 vs 0.49, (p<0.05); 7 min: 2.14 vs 0.69 vs 0.55 vs 0.37 vs 0..48, (p<0.05); 16 hour duration: 3 min: 1.75 vs 0.40 vs 0.31 vs 0.27 vs 0.63, (p<0.05); 5 min: 1.88 vs 0.52 vs 0.47 vs 0.40 vs 0.79, (p<0.05); 7 min: 1.83 vs 0.56 vs 0.48 vs 0.43 vs 0.85, (p<0.05). Conjunctival redness: 15 min onset of action challenge: alcaftadine 0.05 vs placebo: 7 min: 1.13 vs 1.85, (p<0.05); alcaftadine 0.1 vs placebo: 1.14 vs 1.85, (p<0.05); alcaftadine 0.25 vs placebo: 0.50 vs 1.85, (p<0.05); olopatadine 0.1 vs placebo: 1.15 vs 1.85, (p<0.05); 15 min: 1.09 vs 1.96, (p<0.05); 20 min: 1.15 vs 1.80, (p<0.05); 16 hour duration of action: alcaftadine 0.05 vs	"Treatment with alcaftadine 0.25% ophthalmic solution resulted in mean differences of 0.1 unit (ocular itching) and approximately .1 unit (conjunctival redness), which was significant (p<0.001) compared with placebo treatment. All doses of alcaftadine were safe and well tolerated in the population studied."	5 groups including 1 placebo showed Alcaftadine 0.25%, significantly decreased redness and itching compared to placebo.

								placebo: 1.22 vs 1.77, (p<0.05), alcaftadine 0.1 vs placebo: 1.18 vs 1.77, (p<0.05); 15 min: 1.44 vs 2.02, (p<0.05); alcaftadine 0.25 vs placebo: 7 min: 0.77 vs 1.77, (p<0.05), 15 min: 1.01 vs 2.02, (p<0.05); olopatadine 0.1 vs placebo: 7 min: 0.89 vs 1.77, (p<0.05); 15 min: 1.12 vs 2.02, (p<0.05); 20 min: 0.99 vs 1.91, (p<0.05).		
Butrus 2000 (Score = 6.5)	Olopatadine hydrochloride vs. other solutions	RCT Double-blind	Sponsored by a grant from Alcon Laboratories, Inc, Fort Worth, Texas. Dr. Greiner was compensated for his role as principal investigator. No mention of COI.	N = 49 with a history of allergic conjunctivitis (AC).	Mean age of 44.2 years / 42.0 years / 47.5 years.	Olopatadine included baseline screening, confirmatory visit and at visit 3, efficiency and comfort assessment 1 drop from the left-bottle in left eye and from the right-bottle in right eye (N = 20) vs. Nedocromil the same 3 visits and scheduling as Olopatadine group (N = 18) vs. Placebo the same 3 visits and scheduling as Olopatadine group (N = 11).	Follow-up for 14 days.	Olopatadine-treated eyes or 40 eyes had itching scores >2 units lower than placebo or 22 eyes, a clinically/statistically significant difference, (p<0.001). The comparison between nedocromil treated 36 eyes or vs 22 placebo exhibited a much smaller treatment effect vs the olopatadine placebo comparison. There was statistically significant difference in favor of nedocromil group in relief of itching at 3 minutes, (p=0.045).	"In the conjunctival allergen challenge model, olopatadine was more efficacious and comfortable than nedocromil in reducing the itching associated with allergic conjunctivitis."	One drop of Olopatadine was more effective than Nedocromil bid in decreasing itching associated with allergic conjunctivitis.

Borazan 2009 (Score = 6.5)	Olopatadine hydrochloride vs. other solutions	RCT Double-blind	No mention of sponsorship or COI.	N = 100 with seasonal allergic conjunctivitis (SAC) for at least 2 years, a history of active allergic conjunctivitis, and a positive diagnostic test for allergic hypersensitivity;	mean age of 26.9±10 6 for olopatadine group, 26.1±7.9 for ketotifen group, 29.3±12. 8 for epinastine group and 22.05±8. 7 for fluorometholone group.	Group 1: Olopatadine hydrochloride 0.1% or Patanol, in one eye (N = 20) vs. Group 2: Ketotifen Fumarate 0.025% or Zaditen, in one eye (N = 20) vs. Group 3: Epinastine hydrochloride 0.05% or Relestat, in one eye (N = 20) vs. Group 4: Emedastine Difumarate 0.05% or Emadine, in one eye (N = 20) vs. Group 5: Fluorometholone acetate 0.1% or Flarex BID for 14 days, in one eye (N = 20). Placebo (vehicle ophthalmic solution) in the other eye.	Follow up at baseline, and weeks 1 and 2.	At all visits and all groups scores for ocular itching / conjunctival redness / tearing / chemosis and eyelid swelling were significant with placebo treated eye, (p<0.001). At the end of treatment conjunctival impression cytology scores were significantly lower for drug-treated eyes than for placebo-treated eyes, (p<0.01).	"In patients with SAC, olopatadine, ketotifen, epinastine, and emedastine are more efficacious than fluorometholone acetate in preventing itching and redness. All the antiallergic agents gave similar results in terms of reducing tearing, chemosis and eyelid swelling. Our data showed that impression cytology parameters improved after treatment with antiallergic agents in patients with SAC."	Many treatment groups (N=5) and many outcomes. Data suggest all treatments superior to placebo.
Deschenes 1999 (Score = 6.5)	Olopatadine hydrochloride vs. other solutions	RCT/ crossover	No mention of sponsorship or COI.	N = 36 with a history of seasonal allergic conjunctivitis (SAC) within 2 seasons and a positive diagnostic test for	mean age of 36 years, age range of 19 to 68.	Olopatadine 0.1% ophthalmic solution in one eye and placebo in the contralateral eye (N = 36) vs. Ketorolac 0.5% ophthalmic solution in one eye and placebo in the contralateral eye (N = 36). Patients		Itching mean difference olopatadine vs. placebo (3 min / 10 min / 20 min): -1.47 / -1.51 / -1.18, (p<0.0001). Olopatadine vs. ketorolac: NS. Olopatadine was significantly different for reduction in hyperemia scores compared to placebo redness scores at	"[O]lopatadine is effective and safe in preventing and treating ocular itching and hyperemia associated with acute allergic conjunctivitis and is more effective and more comfortable than ketorolac."	Patients not well described. Crossover. Experimental model. Data suggest olopatadine is superior to ketorolac. No long term results.

				allergic disease within the past 24 months;		received an allergen challenge 27 minutes after treatment. Crossover at least 14 days in between. Evaluation 3, 10, and 20 minutes after challenge.		3, 10, and 20 minutes after challenge, ($p<0.0001$). Olopatadine was more comforatable vs. ketorolac ($p<0.05$).		

Greiner 2005 (Score = 6.5)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by Pfizer Consumer Healthcare, Pfizer Inc. No COI.	N = 83 with a history of allergic conjunctivitis (AC); age range of 20 to 70 years,	mean age of 42.5 years.	Pheniramine maleate 0.3%/naphazoline hydrochloride 0.025% and olopatadine hydrochloride 0.1% (N = n/a) vs. Pheniramine maleate 0.3% /naphazoline hydrochloride and placebo (N = n/a) vs. Olopatadine hydrochloride 0.1% and placebo (N = n/a). Signs and symptoms were evaluated at 7, 12 and 20 minutes after the conjunctival allergen model was completed.		Mean±SD for ocular allergy index scores for itching: pheniramine/naphazoline and placebo vs olopatadine and placebo vs pheniramine/naphazoline and olopatadine: 7 min: -1.39±60.3 vs. -1.69±73.4 vs 0.30±49.3, (p<0.001, p<0.001, p=0.029, respectively); 20 min: -1.08±-70.4 vs -1.17±-76.1 vs 0.09±23.9, (p<0.001, p<0.001, p=0.437, respectively); chemosis: 7 min: -0.63±-71.5 vs -0.48±-54.6 vs -0.15±-36.4, (p<0.001, p<0.001, p=0.065, respectively); 20 min: -0.72±-64.3 vs -0.48±-43.1 vs -0.24±-37.2, (p<0.001, p<0.001, p=0.009, respectively); eyelid swelling: 7 min: -0.47±-71.5 vs -0.49±-73.6, (p<0.001, p<0.001, respectively); 20 min: -0.51±-70.0 vs -0.42±-57.6, (p<0.001, p<0.001, respectively).	"In this patient sample, studied in a CAC model of onset of action, prophylactic pheniramine/ naphazoline was more effective than olopatadine and placebo in alleviating the signs and symptoms of the acute ocular allergic reaction, as measured by the OAI."	Missing group population. Both groups better than placebo in reducing OAI scores with Pheniramine group better than olopatadine group.

Berdy 2000 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by a grant from Alcon Laboratories, Inc. No mention of COI.	N = 32 with symptoms of ocular allergy;	mean age not reported.	Group A: one drop of olopatadine hydrochloride 0.1% ophthalmic solution in the right eye, one drop of ketotifen fumigate 0.025% ophthalmic solution in the left eye (N = n/a) vs. Group B: one drop of olopatadine hydrochloride 0.1% in the left eye, and one drop of ketotifen fumarate 0.025% in the right eye (N = n/a).	Follow-up at visit 1 (day 0), visit 2 (day 7±2), and visit 3 (day 21±3).	Mean efficacy scores: olopatadine vs ketotifen: 3 min: 1.84 vs 1.25, (p<0.05); 5 min: 1.75 vs 1.34, (p<0.05). Mean comfort scores: olopatadine vs ketotifen: 1.25 vs 2.09, (p<0.05)	"Both olopatadine and ketotifen are approved for the relief of ocular itching associated with allergic conjunctivitis. In this study, olopatadine was shown to be more effective and cause less ocular discomfort than ketotifen in the conjunctival antigen challenge model of allergic conjunctivitis, as measured by subjective ratings of efficacy and comfort."	Missing group populations. Baseline comparability sparse. At 12 hours, olopatadine was better than ketotifen in reducing ocular discomfort.
Brodsky 2003 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by Alcon Laboratories, Fort Worth, Texas.. No mention of COI.	N = 20 wearing contacts participating in a conjunctival allergen challenge with no active allergic conjunctivitis (AC);	mean age of 35.3 for olopatadine and 32.3 for placebo.	Olopatadine Hydrochloride 0.1% ophthalmic solution (N = 10) vs. Placebo received 1 drop bilaterally + contacts 15 minutes later + conjunctival allergen challenge was performed bilaterally 10 minutes after (N = 10). Follow up immediately after challenge, every minute up to and including 10 minutes, and every 5 minutes up and	Follow up immediately after challenge, every minute up to and including 10 minutes, and every 5 minutes up	Olopatadine was superior to placebo for improvement in itching at 3 and 7 minutes (p<0.05) and for reduction in redness at 5 and 10 minutes for ciliary, conjunctival, and episcleral vessel beds (p<0.05).	"Olopatadine was clinically and significantly superior to placebo in improving the ocular comfort of contact lens wearers suffering from the signs and symptoms of seasonal allergic conjunctivitis, as induced by the conjunctival allergen-challenge model."	Small sample size. Data suggest efficacy.

						including 60 minutes.	and including 60 minutes.			
Abelson 2007 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by an unrestricted grant from Alcon Laboratories. No COI.	N = 23 participating in a conjunctival allergen challenge with no active allergic conjunctivitis (AC);	mean age of 41.	Olopatadine 0.2% vs. Olopatadine 0.1% + a 2nd dose of medication 8 hours + conjunctival allergen 24 hours after first dose (N = n/a) vs. Placebo each eye randomized separately + a 2nd dose of medication 8 hours after the first + conjunctival allergen challenged 24 hours after first dose (N = n/a). Assessments were completed 3, 5, 7, minutes following allergen challenge; and 7, 15, and 20		At 24 hours, olopatadine 0.1% reduced itching scores vs. placebo (p=0.002) and 1 dose of olopatadine 0.2% reduced itching scores vs. placebo, (p=0.0007). NS between the olopatadine 0.1% and 0.2% for itching scores.	"[A]t the end of a 24-hour period, one dose of olopatadine 0.2% was comparable to two doses (separated by 8 hours) of olopatadine 0.1% in the prevention of ocular itching. Olopatadine 0.2% has therefore demonstrated once-daily efficacy in the prevention of ocular itching associated with allergic conjunctivitis."	Small sample size. Contralateral Control either placebo or active treatment. Experimental challenge study suggests efficacy.

						minutes post-challenge.				
Avunduk 2005 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT	No mention of sponsorship or COI.	N = 49 with signs and symptoms of seasonal allergic conjunctivitis (SAC), at least 18 years old, and had a history of seasonal allergic conjunctivitis (SAC) in the last 2 years;	ages range from 18 to 61.	Ketotifen Fumarate 0.025% solution (N = 12) vs. Olopatadine HCl 0.1% solution (N = 13) vs. Preservative free artificial tear substitute or ATS control group, 2 drops in each eye BID for 30 days (N = 14). 30-day treatment period.	Follow up?	Mean itching scores (day 0 / day 15 / day 30): ketotifen (2.08 / 1.08 / 0.75), olopatadine (1.84 / 1.08 / 0.76), ATS (2.00 / 1.85 / 1.71).	"[K]etotifen and olopatadine were associated with effective decreases in the expression of CAMs an inflammatory markers on the conjunctival surface cells. Both active treatments were found to be more efficacious compared with ATS. We did not find significant differences between the 2 active treatments."	Patients not well described. Data suggest active treatment of comparable efficacy and superior to placebo. 1 month study.

Yaylali 2003 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	2 RCTs	No mention of sponsorship. No COI.	N = 40 with signs and symptoms of seasonal allergic conjunctivitis (SAC); average age of 19 years,	age range of 15 to 25 years.	Group 1: 0.1% Olopatadine in one eye and placebo in the other twice daily (N = 20) vs. Group 2: 0.5% Ketorolac in one eye and placebo in the other 4 times daily (N = 20).	Follow-up for 15 days.	Itching, hyperemia improved in the olopatadine eyes vs. placebo eyes, ($p<0.05$). Ketorolac eyes showed a reduction in signs, symptoms compared to placebo eyes, ($p<0.05$). Itching scores lower in olopatadine group vs. ketorolac at 2,7, and 15 days: ($p=0.018$), ($p=0.007$), and ($p=0.036$).	"[B]oth olopatadine and ketorolac ophthalmic solutions were found to be effective in alleviating the clinical signs and symptoms of SAC compared to placebo."	2 RCTs. Patients not well described. Analysis comparing drugs seem questionable as patients did not crossover to other drug. Suggest both effective.
Abelson 2007 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT	No mention of sponsorship or COI.	N = 92 with a history allergic conjunctivitis (AC);	at least 18 years of age.	Olopatadine 0.2% bilaterally (N = 23) vs. Olopatadine 0.2% in right eye and placebo in left eye (N = 23) vs. Placebo in right eye and Olopatadine 0.2% in left eye (N = 23) vs. Placebo bilaterally (N = 23). Instillation of mediation followed 16 hours later by conjunctival allergen challenge with assessment at 3, 5, and 7 minutes post challenge. Assessment again 14 days later with gap between medication and challenge of 27 minutes.	Follow up?	Ocular itching / conjunctival redness / chemosis / eyelid swelling; (0.2% vs. placebo at all-time points, ($p<0.001$) / (0.2% significant efficacy in olopatadine group at all times, ($p<0.01$) / (significant improvement in eye swelling in olopatadine vs. placebo group, ($p<0.01$).	"The use of the olopatadine molecule as a safe, effective, and well-tolerated once-daily antiallergy eye drop is supported by the data from this population of ocular allergy subjects."	Patients not well described between groups. Experimental study. Equal efficacy and superiority to placebo.

Abelson 2004 (Score = 6.0)	Olopatadine hydrochloride vs. other solutions	RCT Double-Masked	No mention of sponsorship or COI.	N = 260 with a history of seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 36.8±14.8 years for olopatadine group and 36.0±13.2 years for placebo.	Self-administer olopatadine 0.2%, one drop per day (N = 129) vs. Placebo, Olopatadine 0.2% vehicle (dibasic sodium phosphate, sodium chloride, disodium EDTA, Povidone and BAC), one drop per day (N = 131).	Follow-up at baseline, weeks 1 through 9, and exit (week 10).	Mean frequency scores for ocular itching and redness were significantly lower in the opolatadine group compared with the placebo group (p<0.05). Mean severity scores for itching and redness was statistically significant for opolatadine 0.2% compared to placebo on 57 of 70 study days, (p<0.05).	"In the patients enrolled in this trial, olopatadine 0.2% appeared to be effective and well tolerated when administered once daily for the treatment of the ocular signs and symptoms of allergic conjunctivitis or rhinoconjunctivitis."	Baseline data for outcome not well described. Lack of details for blinding, control of co-interventions and compliance.
Berdy 2002 (Score = 5.5)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by a grant from Alcon Laboratories, Inc, Fort Worth, Texas. No mention of COI.	N = 50 with allergic conjunctivitis (AC);	age range of 21 to 71 years.	Olopatadine Hydrochloride 0.1% ophthalmic solution (N = 20) vs. Loteprednol Etabonate 0.2% ophthalmic suspension (N = 20) vs. Placebo 56 drops, plus Olopatadine 1 drop (N =10). Assessments were completed at 3, 5, 10, 15 and 20 minutes after allergen challenge.		Itching relief at 3, 5, and 10 min / and redness at 10,15 and 20 mins was significantly greater in olopatadine compared to loteprednol: (1.875 vs. 0.388, (p=0.001); (2.275 vs. 0.425, (p<0.001); and (2.263 vs. 0.588, (p<0.001) / (1.300 vs. 0.638, (p=0.003), and (1.075 vs. 0.525, (p=0.011), (1.00 vs. 0.550, (p=0.027).	"In the population studied, the efficacy and tolerability of olopatadine were significantly superior to those of loteprednol in treating the acute-phase signs and symptoms of the ocular allergic reaction."	Short trial. Experimental study. Experimental study on challenge testing.

Lanier 2001 (Score = 5.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by Alcon Laboratories. No mention of COI.	N = 94 with moderate to severe signs and symptoms of seasonal allergic conjunctivitis (SAC).	Mean age of 38, range from 9 to 74 years.	Olopatadine ophthalmic solution0.1%, one drop per eye twice daily, plus loratadine 10 mg , once daily (N = 45) vs. Control drug, loratadine 10 mg, once daily (N = 49).	Follow-up at baseline, day 3 and 7.	Mean itching score: olopatadine+loratadine vs loratadine: day 0: 3.96 vs 4.0, not significant; day 7: 2.21 vs 2.74, (p<0.05). Mean patient impression: day 3: 1.82 vs 2.17, not significant; day 7: 1.49 vs 2.15, (p=0.0022). The improvement in overall quality of life was significantly greater in the olopatadine plus loratadine group versus the loratadine only group (p<0.05).	"Compared with loratadine alone, olopatadine adjunctive to loratadine provides greater relief of ocular itching and redness, a better quality of life, and is well tolerated in patients with seasonal allergic conjunctivitis."	Olopatadine better than loratadine for SAC symptoms alleviation, faster action in relieving symptoms and improvement in quality of life scores.
Abelson 2003 (Score = 5.0)	Olopatadine hydrochloride vs. other solutions	RCT Double-Blind Multi-Center	Sponsored by Alcon Laboratories, Inc. No mention of COI.	N = 131 with a history of seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 38.53±11.61 years for olopatadine and 38.16±11.31 years for placebo.	Olopatadine 0.1% ophthalmic solution (N = 64) vs. Placebo eye drops, over-the-counter artificial tear product (N = 67). All participants: one drop per eye, twice daily, for 10 weeks.	Follow-up at baseline, and days 7, 14, 28, 35, 42, 56, and 70.	Mean scores for ocular itching: day 7: olopatadine vs. placebo: 1.06 vs. 1.58, (p<0.04); day 14: 1.19 vs. 1.60, (p<0.04); day 35: 0.88 vs. 1.43, (p<0.006); day 63: 0.69 vs. 1.15), (p<0.021); day 70: 0.55 vs. 1.00, (p<0.024). Mean scores for ocular hyperemia: day 14: 0.75 vs 1.22, p<0.011); day 28: 0.67 vs. 1.07, (p<0.030); day 42: 0.63 vs. 1.16, (p<0.004); day 63: 0.42 vs. 0.82, (p<0.03). Mean scores for tearing (rated): day 14: 0.61 vs. 1.01, (p<0.020).	"In the population studied, olopatadine 0.1% ophthalmic solution controlled ocular and nasal symptoms of allergic conjunctivitis and rhinoconjunctivitis and was well tolerated when administered twice daily for 10 weeks."	Lack of study details for allocation, blinding, control for co-interventions, and compliance. Data suggest efficacy of treatment.

Ganz 2003 (Score = 5.0)	Olopatadine hydrochloride vs. other solutions	RCT Double-Masked	No mention of sponsorship or COI.	N = 66 were suffering from seasonal allergic conjunctivitis (SAC).	Mean age of 37.47±16.8 years for ketotifen and 35.2±14.4 years.	Ketotifen Fumarate 0.025% (N = 32) vs. Olopatadin hydrochloride 0.1% as an active control (N = 34). All patients: one drop per eye twice daily (8 hours between doses). 3 week treatment period.	Follow-up at baseline, days 5 through 8, and 21 to 24. This study lasted 3 weeks.	Responder rate (%): ketotifen vs. control: 88% vs. 55%, (p<0.0001). Mean±SD for conjunctival hyperemia: ketotifen vs. olopatadine: day 5: right: 0.016±0.88 vs. 0.227±0.397, (p=0.048); left 0.016±0.88 vs. 0.273±0.435, (p=0.032); day 21: right: 0.016±0.088 vs. 0.339±0.651, (p=0.003); left: 0.016±0.088 vs. 0.387±0.715, (p=0.003). Itching: day 5: right: 0.234±0.458 vs. 0.652±0.897, (p=0.007); left: 0.219±0.457 vs. 0.621±0.884, (p=0.008); day 21: right: 0.156±0.296 vs. 0.823±0.909, (p<0.0001); left: 0.156±0.296 vs. 0.839±0.916, (p<0.0001).	"In a 3-week study under actual-use conditions during fall allergy season, ketotifen fumarate 0.025% ophthalmic solution was superior to olopatadine hydrochloride 0.1% ophthalmic solution in relieving the signs and symptoms of allergic conjunctivitis. No differences in comfort, tolerability, or safety were noted between groups over the course of the study. The superior efficacy and sustained inhibition of the allergic response make ketotifen an ideal treatment option for allergic conjunctivitis."	Data suggest Ketotifen superior to Olopatadin.

Alexander 2000 (Score = 3.5)	Olopatadine hydrochloride vs. other solutions	Randomized, Cross-over	Sponsored in part by an unrestricted grant from Allergan, Inc. No COI.	N = 28 with symptoms of allergic conjunctivitis (AC) during each month of the year.	Mean age of 33, range of 14 to 58 years.	Ophthalmic solutions of nedocromil sodium 2% , for minimum of 5 days of Olopatadine therapy prior to baseline visit (N = 27) vs. Olopatadine hydrochloride 0.1% for 150 days 6 months prior to study (N = 1).		After 1 week of treatment, there was a trend for greater patient acceptance of nedocromil, although the differences between medications were not statistically significant 16 of the 28 patients (57.1%) would request a prescription for nedocromil, while 10 (35.7%) reported that they would request a prescription for Olopatadine (p=0.157). Similarly, 22 patients (78.6%) would recommend nedocromil to other allergy sufferers, while 18 (64.3%) would recommend olopatadine (p=0.480). Fifteen patients (53.6%) would be willing to use nedocromil for the entire allergy season, and 12 (42.9%) would be willing to use olopatadine (p=0.617)	"[N]edocromil sodium 2% ophthalmic solution is an effective and well accepted treatment of allergic conjunctivitis. Switching patients from olopatadine to nedocromil sodium produced no loss in efficacy or patient satisfaction yet lowered the cost of treatment. Nedocromil sodium 2% ophthalmic solution has great potential as a cost-effective, patient-satisfying treatment for allergic conjunctivitis"	Methodological details sparse. Study included some pediatric participants. Minimal differences between treatment arms.

Celik 2014 (Score = 3.5)	Olopatadine hydrochloride vs. other solutions	RCT	No mention of sponsorship. No COI.	N = 104 eyes of 52 patients with the signs and the symptoms of seasonal allergic conjunctivitis (SAC);	mean age of 30.1 years/ 32.3 years.	Olopatadine 0.01% And Fluorometholone 0.1% Treatment in one eye (N = NA) vs. Placebo or Olopatadine 0.01% Combined Ketorolac 0.4% in the second eye (N = NA).	Follow-up for 10 days.	Both drugs were similar in alleviating the: symptoms itching / burning / and tearing, (p=0.074) / (p=0.064) / and (p=0.072). Fluorometholone was superior to ketorolac in: reducing redness / mucus secretion / chemosis and / eyelid edema: (p=0.032) / (p=0.028) / (p=0.030) / and (p=0.042).	"Fluorometholone was better than ketorolac in relieving redness, chemosis, mucus secretion and eyelid edema when concomitantly used with olopatadine, however, these two drugs were found equal in attenuating the symptoms itching, burning and tearing."	Missing group population. Sparse methodological details. Two drugs equal in efficacy for itching, burning and tearing but Fluorometholone was better than Olopatadinefor decreasing redness, chemosis, edema and mucus secretion. Effects most significant on 10th day.
Rosenwasser 2008 (Score = 3.0)	Olopatadine hydrochloride vs. other solutions	RCT Single-Center	Sponsored by Alcon Laboratories and Ophthalmic Research Associates. COI, one or more authors received of will receive benefits for personal or professional use.	N = 60 with a history of allergic conjunctivitis (AC).	Mean 45.75±11.60 years for olopatadine, 46.35±12.68 years for fluticasone fumarate, 43.60±9.85 years for tears natural, and 41.10±11.29 years for saline nasal spray.	Olopatadine 0.2% ophthalmic solution in both eyes, one drop (N = 20) vs. Fluticasone furoate nasal spray in both nostrils, one spray (N = 20) vs. Tears Naturale II in both eyes, one drop (N = 10) vs. Saline nasal spray in both nostrils, one spray (N = 10).	Follow-up at baseline, visit 1 (day 14±3), visit 2 (day 7±3), visit 3 (day 0), and visit 4 (day 7±3)	Olopatadine showed a greater reduction in ocular itching compared to all other treatment groups (p<0.0001) for both visits 3 and 4.	"This study showed the importance of treating topical disease topically. Specifically, when selecting the appropriate treatment option for allergic conjunctivitis, a topical eye drop would appear to provide the most efficacy. The ophthalmic solution, olopatadine 0.2%, was able to more effectively treat the signs and symptoms of allergic conjunctivitis compared with the nasal spray fluticasone furoate."	Methodological details sparse. Data suggest Olopatadine superior to Fluticasone and placebo.

Lanier 2004 (Score = 3.0)	Olopatadine hydrochloride vs. other solutions	RCT	Sponsored by unrestricted grant from Alcon Laboratories, Inc, Fort Worth, Texas. No mention of COI.	N = 66 with a history of allergic conjunctivitis (AC);	mean age of 44.4 years.	Olopatadine eye drops, 1 drop each eye. (N = N/A) vs. Epinastine eye drops, 1 drop each eye (N = N/A).	Follow up on (day 7±2) and (day 21±3).	Olopatadine treated eyes exhibited significantly lower mean itching and conjunctival redness scores than the contralateral Epinastine treated eyes, –0.19 (p=0.003) and –0.52 (p<0.001), respectively. Olopatadine treated eyes also exhibited significantly less chemosis: –0.24 (*p* < 0.001), ciliary redness: –0.55 (p<0.001), and episcleral redness: -0.58 (p<0.001) than Epinastine treated eyes.	"In this study it was demonstrated that Olopatadine, with its antihistaminic and mast cell stabilizing effects against a broad range of pro-inflammatory mediators, is more effective than Epinastine in controlling itching, redness and chemosis associated with allergic conjunctivitis."	Missing group population. Methodological details sparse. Data suggest Epinastine may be superior to Olopatadine.
Cromolyn Sodium										
Liu 2011 (Score = 8.0)	Cromolyn Sodium vs. Other	RCT Double-Masked	Sponsored by the Chi Fu Trading Co., Ltd. No mention of COI.	N = 33 patients who had seasonal or perennial allergic conjunctivitis (AC).	Mean age of 39.2±13.5 years.	Cromolyn sodium 2% ophthalmic solution, one drop with 0.01% benzalkonium chloride (BAK) (right or left eye) (N = 33 eyes) vs. Cromolyn sodium 2% ophthalmic solution, one drop without 0.01% benzalkonium chloride (BAK) one drop (right or left	Follow-up at baseline, visits 1, 2 and 3.	There were no statistically significant values to report in any of the primary variables. Conjunctival redness: visit 2: treatment vs control: (p=0.743); visit 3: (p=0.676); visit 4: (p=0.343)	"Cromolyn 2 % ophthalmic solution was effective and safe to treat allergic conjunctivitis. A short-term use of cromolyn 2 % ophthalmic solution with 0.01% BAK would not cause any significant toxicity in patients with allergic conjunctivitis. Preservative-free cromolyn may be beneficial to the compromised eyes or	No difference between groups.

						eye) (N = 33 eyes). 4 week treatment period.			eyes required of long-term medication."	
Nizami 1981 (Score = 7.0)	Cromolyn Sodium vs. Other	RCT/ Crossover	No mention of sponsorship or COI.	N = 26 with symptoms of allergic conjunctivitis (AC) induced by ragweed pollen;	mean age not reported.	2% Cromolyn sodium (N = 13) vs. Those who preferred placebo received 1 tube 4 times a day (N = 13). Two 1 week periods with a 3 day washout before crossover.	Follow up?	84.6% of all patients preferred the active drug compared to placebo, (p<0.001).	"These drops were equally effective for those patients who could continue to wear their contact lenses through the ragweed season."	Data suggest efficacy.
Greiner 2002 (Score = 4.0)	Cromolyn Sodium vs. Other	RCT Single-Masked	Sponsored by Novartis Ophthalmics. No mention of COI.	N = 47 with a history of allergy to environmental allergens not currently in season.	Mean age of 40 years.	Ketotifen fumarate vehicle solution, placebo (glycerol, sodium hydroxide/hydrochloric acid, and purified water) 0.025% ophthalmic solution, one dose only (N = 47 eyes, l/r) vs. Cromolyn sodium 4% ophthalmic solution, 4 times daily (N = 47 eyes, l/r). 2 week treatment period.	Follow-up at baseline, and visits 1 through 3. This study lasted 2 weeks.	Mean efficacy scores for itching: ketotifen vs cromolyn: 15 min: -2.09±0.87 vs. -0.43±1.20, (p<0.001); 4 hours: -2.26±0.61 vs. -1.43±1.08, (p<0.001); Conjunctival redness: 15 min: -1.05±0.75 vs. -0.45±0.64, (p<0.001).	"A single dose of ketotifen was superior to a 2-week four-times-daily regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the conjunctival allergen-challenge model."	Data suggest Ketotifen superior to Cromolyn. Methodological details sparse.
Kalpaxis 1990 (Score = 3.5)	Cromolyn Sodium vs. Other	RCT Double-Blind	Sponsored by a grant from Immunetech Pharmace	N = 50 with allergic conjunctivitis (AC).	Mean age 35.0 years for pentigetide and 33.6 years for	Pentigetide, 0.5% ophthalmic solution, one drop per eye four times daily (N = 25) vs. Cromolyn Sodium, 4% ophthalmic	Follow-up at days 1, 3, 8, and 15. This	Percent improvement: itching: pentigetide vs cromolyn sodium: day 3: 43 vs. 42; day 8: 43 vs 51; day 15: 49 vs 56, (p<0.05),	"[P]entigetide, 0.5%, ophthalmic solution is safe and effective in the treatment of allergic conjunctivitis."	Data suggest Pentigetide superior to Cromolyn.

			uticals. No mention of COI.		cromolyn sodium.	solution, one drop per eye four times daily (N = 25).	study lasted 2 weeks.	in favor of cromolyn sodium.		
Friday 1983 (Score = 3.0)	Cromolyn Sodium vs. placebo	RCT Double-Masked	Sponsored by grants to the Fight for Sight Children's Eye Clinic of the Eye and Ear Hospital from Fight of Sight Inc., and by a grant from the Fisons Corp. No mention of COI.	N = 34 with allergic ragweed allergic conjunctivitis (AC) severe enough to require symptomatic medication for at least two years.	Mean age for active treatment 19.4 years and 25.6 years for placebo.	Active drug: cromolyn sodium 4%, EDTA 0.01%, and 2 phenylethanol 0.4% (N = 18) vs. Placebo: sodium chloride 0.3%, EDTA 0.01%, benzalkonium chloride 0.01%, 2 phenylethanol 0.4%, and sodium acid phosphate and sodium phosphate (N = 16). All participants: 2 drops in each eye four times daily, total dose of 25.6 mg of cromolyn sodium per day. 45 day treatment period.	Follow-up on baseline and days 5, 10, 15, 20, 25, 30, 35, 44, 45, 50, 55, and 60.	Low Ragweed IgE subgroups shown statistically significant differences in favor of the active treatment group for itching eyes ($p<0.01$); ocular irritation ($0.05<p<0.10$); and total ocular symptoms ($p<0.05$).	"Our double-masked, placebo-controlled, parallel-group prospective study demonstrated that prophylactic use of cromolyn sodium 4% solution is safe and effective means of controlling the symptoms of ragweed allergic conjunctivitis in patients with significant, but low (less than 100mg/ml), serum I gE levels specific for ragweed."	Methodological details sparse
Pheniramine maleate										
Greiner 2005 (Score = 6.5)	Pheniramine maleate vs. placebo	RCT	Sponsored by Pfizer Consumer Healthcare, Pfizer	N = 83 with a history of allergic conjunctivitis (AC);	age range of 20 to 70 years, mean age of	Pheniramine maleate 0.3%/naphazoline hydrochloride 0.025% and olopatadine hydrochloride 0.1% (N = n/a) vs.		Mean±SD for ocular allergy index scores for itching: pheniramine/naphazoline and placebo vs olopatadine and placebo vs pheniramine/naphazoline	"In this patient sample, studied in a CAC model of onset of action, prophylactic pheniramine/ naphazoline was more effective than olopatadine and placebo	Missing group population. Both groups better than placebo in reducing OAI scores with Pheniramine group better than olopatadine group.

			Inc. No COI.		42.5 years.	Pheniramine maleate 0.3% /naphazoline hydrochloride and placebo (N = n/a) vs. Olopatadine hydrochloride 0.1% and placebo (N = n/a). Signs and symptoms were evaluated at 7, 12 and 20 minutes after the conjunctival allergen model was completed.		and olopatadine: 7 min: -1.39±60.3 vs. -1.69±73.4 vs 0.30±49.3, (p<0.001, p<0.001, p=0.029, respectively); 20 min: -1.08±-70.4 vs -1.17±-76.1 vs 0.09±23.9, (p<0.001, p<0.001, p=0.437, respectively); chemosis: 7 min: -0.63±-71.5 vs -0.48±-54.6 vs -0.15±-36.4, (p<0.001, p<0.001, p=0.065, respectively); 20 min: -0.72±-64.3 vs -0.48±-43.1 vs -0.24±-37.2, (p<0.001, p<0.001, p=0.009, respectively); eyelid swelling: 7 min: -0.47±-71.5 vs -0.49±-73.6, (p<0.001, p<0.001, respectively); 20 min: -0.51±-70.0 vs -0.42±-57.6, (p<0.001, p<0.001, respectively).	in alleviating the signs and symptoms of the acute ocular allergic reaction, as measured by the OAI."	
Nedocromil										
Alexander 1999 (Score = 7.5)	Nedocromil	RCT Double-blind Multicenter	Sponsored in part by Fisons Pharmaceuticals, Rochester, New York. No mention of COI.	N = 268 with diagnosis of seasonal allergic conjunctivitis (SAC), a positive skin-prick test to ragweed pollen (wheal ≥ 3	Mean age was 33 years (12 to 68).	Group one received nedocromil sodium 2% ophthalmic solution and inert tables (N = 89) vs. Group two received 60-mg terfenadine tables plus inert ophthalmic solution (N = 89) vs. Group 3 or placebo received inert ophthalmic	Follow-up for 4 weeks.	Onset of action / Tolerability; No significant difference in symptom relief between the first two groups / 90 patients experienced adverse events during the study; headache in 12 or 13.5% in nedocromil group / 12 or 13.5% terfenadine	"[A]ll 3 groups have comparable improvements in all efficacy end points and that all treatments were well tolerated."	A double placebo comparative study. Results suggest nedocromil sodium acted faster than either terfenadine or placebo.

				mm), and a history of requiring treatment for moderate to severe conjunctivitis after exposure to ragweed pollen.		solution and inert tablets (N = 90).		patients and / 18 or 20% placebo patients.		
Melamed 1994 (Score = 7.0)	Nedocromil	RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 86 with seasonal allergic conjunctivitis (SAC).	Age range from 12 to 60 years.	Nedocromil sodium 2% ophthalmic solution 1 drop 0.04 mL per eye bid twice daily (N = 43) vs. Placebo group 1 drop 0.04 mL per eye bid twice daily (N = 43).	Follow-up at 0, 1, 3, 5, and 8 weeks.	Those treated with placebo showed statistically higher level of eye symptoms vs those treated with nedocromil sodium at the peak pollen period, (p≤0.004). Reduction of all symptom scores from baseline were statistically significant during the peak pollen period for itching eyes / tearing / and overall eye condition in favor of nedocromil group; (p≤0.001)/ (p≤0.01/ and (p≤0.002). Those in nedocromil group had significantly less tearing / conjunctival injection / and conjunctival edema: (p≤0.03)/ (p≤0.02)/ and (p≤0.02).	"[N]edocromil sodium, 2% ophthalmic solution, administrated twice daily was well tolerated and effective in treating the symptoms of patients with seasonal allergic conjunctivitis."	Nedocromil sodium appears to have some efficacy over placebo. Both study groups report similar numbers of adverse events.

Blumenthal 1992 (Score= 7.0)	Nedocromil	RCT Double-blind Multicenter Group-parallel	Supported by a grant from Fisons Pharmaceuticals. No mention of COI.	N = 140 with a history of seasonal allergic conjunctivitis (SAC).	Ages of 12 and 62 years.	Nedocromil sodium 2% of 1 drop 0.04 ml of solution per eye twice daily (N = 69) vs. Placebo of 1 drop 0.04 ml of solution per eye twice daily (N = 71).	Follow-up for 8 weeks.	Those using nedocromil sodium had statistically significant reduction in conjunctival injection / overall disease sensitivity vs placebo group, (p≤0.001). 55% or 38 in nedocromil sodium group with symptoms mostly controlled vs 32% in placebo group statistically significant difference at, (p≤0.004). Between treatment groups; the mean placebo drops 1.27 per day, and 1.31 in sodium group, (p≤0.78).	"[N]edocromil sodium 2% ophthalmic solution administrated twice daily is effective in relieving major symptoms associated with seasonal allergic conjunctivitis."	Nedocromil vs. placebo showed significant efficacy in reducing eye itching and severity of symptoms. However, 86% of Nedocromil and 82% of placebo group reported an adverse event during the trial.
Leino 1992 (Score = 7.0)	Nedocromil	RCT	No mention of sponsorship or COI.	N = 195 with seasonal allergic conjunctivitis (SAC) to birch pollen;	mean age of 20.8 years in the nedocromil group, 19.3 years in the sodium cromolycate group, and 19.7 in the placebo group.	2% Nedocromil sodium twice a day (morning /late afternoon), plus placebo eye drops twice daily, noon/evening (N = 64) vs. 2% sodium Cromoglycate eye drops 4 times a day vs. placebo 4 times a day for 4 weeks (N = 62).	Follow ups after week 1 and 4 of treatment.	The treatment groups had less itching vs. placebo , (p<0.05) nedocromil and (p<0.001) sodium cromoglycate. There were no other significant differences between groups.	"Nedocromil sodium eye drops (b.d.) and sodium cromoglycate eye drops (q.i.d.) were both considered clinically more effective than placebo in controlling symptoms of SAC due to birch pollen."	Limited quantification of results. Data suggest strong placebo effect.

Shulman 2003 (Score = 6.5)	Nedocromil	RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 78 with seasonal allergic conjunctivitis (SAC). Ages ranging from 18 to 60+ years.		Pemirolast potassium 0.1% four times daily (N = 40) vs. Nedocromil sodium 2% twice daily (N = 40). Follow-up for 8 weeks.		No clinical statistical difference visit 2 vs visit 1 mean difference / 3 vs 1 / and 4 vs 1: (p=0.470) / (p=0.011) / (p=0.004).	"Twice-daily administration of the new antiallergy agent Pemirolast was as efficacious and safe as nedocromil sodium twice daily in the 8-week treatment of ragweed allergic conjunctivitis."	Both treatments showed similar efficacy.
Miglior 1993 (Score = 6..5)	Nedocromil	RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 200 with seasonal allergic conjunctivitis (SAC).	Mean age of 24 years (6 to 70).	Nedocromil sodium 2% one drop four times daily (N = 51) vs. Astemizole 10 mg one tablet daily (N = 51) vs. Nedocromil sodium 2% + Astemizole (N = 50) vs. Placebo four times daily eye drops (N = 55).	Follow-up at 1, 2 and 4 weeks.	Benefits of active therapy vs placebo, especially at week 2, (p=0.042). Overall opinion at the 2nd week showed active treatment significantly improved symptoms vs to placebo, (p<0.01 vs 0.05). At week 2, ocular symptoms significantly improved in treatment group vs placebo for: itching / redness: (p≤0.01) / (p<0.059).	"[W]e report the efficacy of nedocromil sodium eye drops in the treatment of seasonal allergic conjunctivitis."	Results suggest Nedocromil may perform better than placebo or astemizole but results not significant.
Melamed 2000 (Score = 6.0)	Nedocromil	RCT Double-blind Multicenter	Sponsored in part by Fisons Pharmaceuticals. No COI.	N = 189 with seasonal allergic conjunctivitis (SAC).	Age range from 12 to 65 years.	Nedocromil sodium 2% one drop (N = 94) vs. Vehicle b.i.d opaque bottle (placebo) (N = 95).	Follow-up for 8 weeks.	Mean scores at baseline were 4.48 for nedocromil group and 4.56 for vehicle, and mean score at the peak pollen period was 3.95 or 11.8% vs 4.92 or 6.0%. Nedocromil group had significantly greater reduction in mean score for itch / tearing / and overall eye condition: (p=0.005)/ (p=0.044)/ and (p<0.001).	"[N]edocromil sodium 2% ophthalmic solution was found to be effective and sage in the treatment of seasonal allergic conjunctivitis."	Combination analysis. Nedocromil compared to placebo showed efficacy in treatment of SAC symptoms.

Leino 1990 (Score = 6.0)	Nedocromil	RCT	No mention of sponsorship or COI.	N = 126 with seasonal allergic conjunctivitis (SAC);	mean age of 38.7 years, and ranged from 11 to 67 years; mean age was 22.4 years in the nedocromil sodium group, and 21.4 years in the placebo group.	Nedocromil sodium 2%, plus 0.01% benzalkonium chloride, plus 0.05% disodium edentate, plus0.55% NaCl, plus purified water 100% (N = 64) vs. Placebo 0.01% also received benzalkonium chloride, plus 0.05% disodium edentate in isotonic solution (N = 62).	Follow up at 2 and 4 or 6 weeks.	Clinical effectiveness for nedocromil was significantly different from placebo with totally, moderately, slight and no effectiveness; 18 vs. 6, 17 vs. 17, 8 vs. 9, and 12 vs. 18, Withdrawal duration to treatment failure and due to other reasons; 2 vs. 6 and 7 vs. 6, (p=0.0060).	"[N]edocromil sodium is beneficial in the treatment of seasonal allergic conjunctivitis."	Data suggest Nedocromil sodium superior to placebo. Blinding not well described or assessed.
Hamman 1996 (Score = 5.5)	Nedocromil	Crossover trial, randomized, Double-Blind	Sponsored by a grant from Janssen Research Foundation. No mention of COI.	N = 24 volunteers with a history of grass pollen conjunctivitis.	Mean age of 25.4±4.8 years.	Topical levocabastine, 0.5 mg/ml, one drop per eye (N = n/a) vs. Topical Nedocromil, 20 mg/ml, one drop per eye (N = n/a). Erythma and severity of pruritus were recorded before provocation, 15 minutes after instillation of medication 10 minutes after the		Both drugs allowed a significant increase in the tolerated dose of allergen expressed as shift in allergen concentration, (p<0.001). The number of shifts in allergen concentration was significantly greater after levocabastine treatment than after nedocromil treatment, (p=0.019).	“In a provocation test with allergen, levocabastine and nedocromil were both effective in increasing the conjunctival tolerance to allergen, with better protection provided by levocabastine.”	Missing group populations. Small sample size. Data suggest levocabastine superior to nedocromil.

						instillation of the dilutent and 10 minutes after provocation with each allergen concentration.				
Stockwell 1994 (Score = 4.5)	Nedocromil	NON-RCT Double-blind	No mention of sponsorship or COI.	N = 64 with seasonal allergic conjunctivitis (SAC).	Mean age not reported.	Nedocromil sodium 2%, benzalkonium chloride 0.01%, edetate sodium (EDTA) 0.05%, and sodium chloride 0.05% (N = NA) vs. Placebo with the same concentration with riboflavin concentration of 0.0005% as a yellow colourant (N = NA).	Follow-up for 4 weeks.	During the period described as high pollen count, dairy card symptoms or clinical symptoms showed no significant difference, ($p<0.05$). Overall opinion showed nedocromil group 40% of patients symptoms were fully controlled vs 36% were moderately controlled, 8% slightly controlled vs 36% fully controlled, 23% moderately, 10% slightly and 37% not controlled in placebo group.	"During a longer period of less high pollen count, a significant difference in favor of nedocromil sodium was show only for the symptom of soreness."	Missing group populations. Baseline comparability no described. High placebo response. Timing variation.
Emedastine										
Horak 2003 (Score = 9.0)	Emedastine	RCT/ Crossover	Sponsored by Novartis Ophthalmics. No mention of COI.	N = 37 with a history of seasonal allergic conjunctivitis (SAC) of at least 2 years with no current symptom;	mean age of 27.30±4.8, range of 20 to 43.	Ketotifen Fumarate 0.025%, first eye (N = 37) vs. Emedastine Difumarate 0.05% eye drops single dose 1 drop in each eye with a 6 day washout period before crossover (N = 37).	Follow up a baseline, and visits one and two.	Ketotifen was significantly superior to emedastine for time to onset for 15 vs. 30 minutes, p=0.048. Ocular and nasal symptom scores 0-2 hours post dose for redness / ocular symptoms / total symptom complex: (1.97±1.10 vs. 2.25±0.87, (p=0.046) / (8.06±2.46 vs. 6.97±3.19, (p=0.026) /	"[K]etotifen fumarate 0.025% and emedastine difumarate 0.05% both effectively alleviated ocular symptoms of SAC for a period of at least 8 hours after single-dose administration."	Crossover. Experimental study across aerosol chamber. Data suggest comparable efficacy with modestly faster onset with ketotifen.

								(10.93±3.53 vs. 9.18, (p=0.014).		
Verin 2001 (Score = 6.5)	Emedastine	RCT	Sponsored by Alcon Research, Ltd, Fort Worth, Texas. No mention of COI.	N = 202 with a history of allergic conjunctivitis (AC) and signs and symptoms characteristic of the disease;	mean age of 30 years, range of 4 to 76 years.	Emedastine 0.05% eye drops (N = 97) vs. Levocabastine 0.05% eye drops one drop in each eye twice daily (morning and evening) for 6 weeks (N =105).	Follow ups on days 3, 7 14, 30, 42, and 7 to 10 days after the cessation of therapy.	Primary outcome itching / redness at days 3, 7, 14, 30, and 42: (p=0.245, 0.0016, 0.0002, 0.0001 and p=0.0001) / (p=0.145, 0.0009, 0.0002, 0.0002, and 0.0001). Secondary; Chemosis / swelling at days 3, 7, 14, 30, and 42: (p=0.0559, p=0.0050, 0.0005, 0.0046, and 0.0001)/ (p=0.0672, 0.0023, 0.0001, 0.0061, and 0.0009).	"[E]medastine 0.05% eye drops administered twice daily were more efficacious than levocabastine 0.05% eye drops in the prevention and treatment of the signs and symptoms of allergic conjunctivitis in adults and children of 4 years and above."	Baseline comparability not well described. Both groups showed improvements in symptom relief at 6 weeks but at 7 days, Emedastine was significantly better than Levocabastine in symptom alleviation.
Orfeo 2002 (Score = 5.5)	Emedastine	RCT/ Crossover	No mention of sponsorship or COI.	N = 30 with a history of active allergic conjunctivitis (AC);	mean age of 22 years, range of 7 to 38.	First visit: Emedastine 0.05% (2 drops) in one eye (N = 30) vs. Second visit: Nedocromil 2% (2 drops) in the second eye (N = 30) vs. Third visit: The same procedure as in previous two groups or placebo (2 drops) in the eye used as control during second visit with 1 week in between trials (N = 30).	Follow-up at 3, 10, and 20 minutes after instillation of allergen in eye.	Both treatments were more effective than placebo throughout the study period, (p<0.01). Emedastine relieved redness better vs. nedocromil throughout the study, (p<0.01). Emedastine reduced itching more effectively vs. nedocromil during the first 10 minutes, (p<0.01).	"[B]oth emedastine 0.05% and nedocromil 2% eye drops are effective and well tolerated in controlling the ocular allergic reaction induced by conjunctival challenge, but emedastine shows significantly greater efficacy. These findings confirm the superiority of H1-selective topical antihistamines in producing immediate relief when subjects with allergic conjunctivitis are exposed to offending allergens."	Data suggest efficacy. Experimental challenge study.

Discepola 1999 (Score = 4.5)	Emedastine	RCT/ Crossover	No mention of sponsorship or COI.	N = 36 with a positive diagnostic skin test and a history of allergic conjunctivitis (AC);	mean age not reported.	Emedastine ophthalmic solution 0.05% in one eye and placebo in the contralateral eye (N = 36) vs. Ketorolac ophthalmic solution 0.5% in one eye and placebo in the contralateral eye. 2 drops in each eye followed by an allergen challenge 10 minutes after drops were administered (N = 36).	Follow up 3, 10 and 20 minutes after challenge.	Itching scores emedastine vs. placebo eye, (p<0.05). Emedastine was superior to ketorolac for reducing ocular itching. Emedastine significantly reduced hyperemia, p < 0.5% (that's what the article presented). Ketorolac saw an increase in total redness score vs. placebo, (p<0.05). Emedastine was more comfortable vs. ketorolac, (p<0.05).	"Emedastine is superior to ketorolac in controlling itching and redness, the cardinal symptom and sign of allergic conjunctivitis."	Experimental crossover. Patients not well described.
Secchi 2000 (Score = 4.5)	Emedastine	RCT	No mention of sponsorship or COI.	N = 202 with redness of the eye graded at least a 2 and an itching score of at least 4.		Emedastine 0.05% BID solution (N = 97) vs. Levocabastine 0.05% BID in both eyes for 42 days with follow-up 7-10 after therapy (N = 105).	Follow-up at days 0, 3, 7, 14, 30 and 42. 7-10 days post therapy.	Chemosis / eyelid swelling at baseline and follow-up / itching, redness at days 7, 14, 30, 42: (1.27±1.13 and 0.36 ± 0.56 vs. levocabastine, 1.29±1.10 and 0.68±0.89, (p=0.0064) / (1.26±1.11 and 0.28±0.47 vs. 1.28±1.09 and 0.61±0.84, (p=0.0014) / (p<0.05).	"Emedastine is more efficacious than levocabastine in reducing chemosis, eyelid swelling and other efficacy variable associated with seasonal allergic conjunctivitis."	Groups not well described. No placebo group. Fig 2.
Opticrom										
Lindsay-Miller 1979 (Score = 6.5)	Opticrom	RCT Double-blind	No mention of sponsorship or COI.	N = 50 with history of severe eye symptoms.	Age range from 10 to 39 / 6 to 57 in years.	Opticrom eye drops contained 2% sodium cromoglycate with benzalkonium chloride 001% vs. phenylethanol 0 4%	Follow-up for 4 weeks.	90% receiving Opticrom found it successful, (p<0.02) vs of the 23 patients receiving placebo twelve or 52% found it successful, (p<0.02). 12 side effects complaints; 6	“The results of this trial indicate that Opticrom is an effective addition to the treatment of seasonal allergic conjunctivitis.”	Opticrom showed efficacy over placebo.

						(N = 20) vs. Placebo contained benzalkonium chloride 0 01% and phenylethanol 0 4% (N = 23).		from opticrom and 6 from placebo group.		
Oxymetazoline										
Duzman 1986 (Score = 5.5)	Oxymetazoline	RCT	No mention of sponsorship or COI.	N = 39 with bilateral allergic or environmental conjunctivitis;	mean age 33.6 for oxymetazoline and 33.2 for vehicle.	Oxymetazoline 0.025% group one drop in each eye at 8 AM and 8 PM for 7 days (N = 21) vs. Placebo received 1 drop in each eye at 8 am and again at 8 pm for the next 7 days (N = 18).	Follow up on 3 and 7 days.	Improvement in the oxymetazoline group was greater for Conjunctival hyperemia compared to placebo on day 3, (p=0.06). Treatment effectiveness on days 3 and mean scores; 7, 2.0 vs. 1.3 and 1.9 vs. 0.8, significantly better rating for oxymetazoline, (p=0.03).	"[A] solution of oxymetazoline 0.025% is safe and significantly relieves the signs and symptoms of allergic or environmental conjunctivitis."	Methodological details sparse.
Desloratadine (oral medication)										
Torkildsen 2009 (Score = 7.0)	Desloratadine	RCT/Crossover	Sponsored by Schering-Plough. No mention of COI.	N = 41 with at least a 2 year history of allergic conjunctivitis (AC) associated with seasonal allergic rhinitis (SAR);	mean age for placebo 39.1±12.95, and 39.5±11.31 for desloratadine.	Desloratadine 5 mg daily (N = 20) vs. Placebo once daily for 7 days with a 2 week washout period (N = 21). There was a 2-week washout period.	Follow up at baseline, day 7±2, day 15±3, day 21±3, day 36±3, and	Chemosis Scores / eyelid swelling / tearing scores: at 10, 15, and 20 min. (68, 0.71, and 0.67 vs.0.93, 0.96, and 0.98 placebo, (p=0.020, p=0.026, and p=0.003) / (0.031, 0.42, and 0.39 vs. 0.80, 0.76, and 0.86, (p=0.002, p=0.026, and p=0.004) / (0.37, 0.47, and 0.43 vs. 0.79, 0.98, and 0.93, (p=0.003, p<0.001, p=0.001).	"The non-sedating second-generation antihistamine desloratadine administered 5 mg once daily for 7 days reduced ocular redness and pruritus, chemosis, eyelid swelling, and tearing following a CAC in subjects with a history of seasonal AC and demonstrated an AE profile similar to that of placebo."	Crossover study. Data suggest efficacy at 7 days vs. placebo.

							day 42±3.			
Mequitazine										
Persi 1997 (Score = 7.0)	Mequitazine	RCT	Sponsored by Laboratoire Chauvin-France. No mention of COI.	N = 20 with a history of seasonal allergic conjunctivitis (SAC);	age range of 20 to 37.	0.05% Mequitazine in the first eye (N = 20) vs. Placebo in the other eye 4 times a day for 5 days (N = 20).	Follow up?	Mean scores during CPT after day 5 of treatment. Cumulative score: placebo 6.20±2.16 vs. treatment 1.37±1.34, (p=0.0001). Redness: 2.02±0.49 vs. 0.62±0.62, (p=0.0001). Itching: 2.10±0.59 vs. 0.37±0.64, (p=0.0001). Tearing: 0.87±0.55 vs. 0.20±0.37, (p=0.0001). Chemosis: 1.20±0.97 vs. 0.17±0.43, (p=0.0001).	"[M]equitazine appears to be an interesting alternative to existing topical antiallergic treatments and has to be fully evaluated."	Challenge study with each eye. Data suggest efficacy.
Patanol-systemic Claritin therapy										
Abelson 1999 (Score = 7.5)	Patanol - systemic Claritin therapy	RCT	No mention of sponsorship or COI.	N = 15 with a successful allergen challenge and history of symptoms of allergic conjunctivitis (AC);	mean age not reported.	Patanol group received 1 - 2 drops in one eye + 10 mg Claritin in tablet form (N = 15) vs. Placebo received 1 - 2 drops in the following eye, 2 times 14 days apart + 10 mg Claritin in tablet form (N = 15).	Follow up at baseline, day 7, 14, and 28.	An hour and 8 hours after drugs were administered; ocular itching was lower in the Patanol-Claritin group, at 3, 7, and 10 minutes post-challenge, (p<0.0002) and after 8 hours at 3 and 7 minutes post-challenge, (p<0.05).	"[T]he combination of local Patanol-systemic Claritin therapy was shown to be significantly superior to Claritin alone for the control of ocular itching, the primary symptom of allergic conjunctivitis."	Experimental challenge study. Small sample size. Suggest additive benefit.
Azelastine and Mitomycin C										
Sodhi 2003	Azelastine and	RCT	No mention of sponsors	N = 63 with allergic	Mean age of	Azelastine 0.02%, four times daily (N = 32) vs. Mitomycin C (MMC) 0.02 mg/ml,	Follow-up at baseline,	N (%) for Outcome measure: redness: MMC vs. azelastine: 25 (80.7%) vs. 19 (55.9%), (p=0.033);	"Though this was a short-term study, we found topical MMC to be more effective than topical	Methodological details sparse.

(Score = 2.5)	Mitomycin C		hip or COI.	conjunctivitis (AC).	34.8±17.3 years.	four times daily (N = 31). 3 month treatment period.	and weeks 2 and 4. This study lasted 3 months.	follicles: 31 (100.0%) vs 6 (17.7), (p=0.0001); papillae: 29 (93.6%) vs. 4 (11.8), (p=0.0001); changes in agent: 0 (0%) vs. 30 (88.2), (p=0.0001).	azelastine in the treatment of allergic conjunctivitis both in terms of relief of symptoms and resolution of signs. The use of topical MMC in low doses does not cause any significant adverse effect."	

Evidence for Immunosuppressive Medications

Daniell 2006 (Score = 4.5)	Cyclosporian vs. placebo	RCT Double-Masked	Sponsored by Allergan Australia. No mention of COI.	N = 40 with allergic conjunctivitis (AC).	Mean age of 26.2±18 years for CsA group and 26.2±16.3 years for placebo group.	0.05% topical Ciclosporian A (CsA) (N = 20) vs. Placebo, vehicle (N = 20). All patients: one drop per eye, four times daily. This study lasted 3 months. 3 month treatment period.	Follow-up at baseline, and weeks 1 and 2, and 3 months of treatment.	Significant reductions over time were seen in itching (p=0.04) and redness (p=0.01) for the CsA treatment group. The placebo group also experienced significant reduction over time in redness (p=0.01) and white discharge (p=0.01). There were no significant differences between groups (p=0.6)	“Topical ciclosporin A 0.05% was not shown to be of any benefit over placebo as a steroid sparing agent in steroid dependent allergic eye disease.”	No difference between groups suggest treatment not different from placebo. Data suggest lack of efficacy.

Evidence for Glucocorticosteroid Eye Drops

Leino 1992 (Score = 7.0)	Sodium Cromoglycate	RCT	No mention of sponsorship or COI.	N = 195 with seasonal allergic conjunctivitis (SAC) to birch pollen;	mean age of 20.8 years in the nedocromil group, 19.3 years in the sodium cromolycate group, and 19.7 in the placebo group.	2% Nedocromil sodium twice a day (morning /late afternoon), plus placebo eye drops twice daily, noon/evening (N = 64) vs. 2% sodium Cromoglycate eye drops 4 times a day vs. placebo 4 times a day for 4 weeks (N = 62).	Follow ups after week 1 and 4 of treatment.	The treatment groups had less itching vs. placebo , ($p<0.05$) nedocromil and ($p<0.001$) sodium cromoglycate. There were no other significant differences between groups.	"Nedocromil sodium eye drops (b.d.) and sodium cromoglycate eye drops (q.i.d.) were both considered clinically more effective than placebo in controlling symptoms of SAC due to birch pollen."	Limited quantification of results. Data suggest strong placebo effect.

Davies 1993 (Score = 6.5)	Sodium Cromoglycate	RCT	No mention of sponsorship or COI.	N = 95 patients over 5 years of age with a history of allergic conjunctivitis (AC) during a previous hay fever season with ≥ typical symptom of allergic conjunctivitis (ocular irritation, burning sensation, itch, redness, photophobia, lacrimation, lid oedemia, conjunctival oedema) needing treatment;	age range 5 to 69 years.	Topical levocabastine 0.5 mg/ml (N = 28) vs. Topical sodium cromoglycate 20 mg/ml (N = 32) vs. Matching placebo eye-drops (N = 29) one in each eye four times daily for 28 days. Oral terfenadine and beclomethasone or budesonide nasal spray were allowed as rescue medications. Assessments at baseline, 2 weeks, and 4 weeks.	No follow-up time.	NS between sodium cromoglycate group and placebo for treatment efficacy (no p-value reported). End of study intergroup differences: levocabastine superior to sodium cromoglycate for **severest ocular symptom** ($p<0.05$), lacrimation ($p<0.01$), and red eyes ($p<0.05$); sodium cromoglycate vs. placebo, NS for same outcomes. Pain free for at least 75% of study: levocabastine 37% vs. sodium cromoglycate 6% ($p<0.01$) vs. placebo 4% ($p<0.01$).	"[T]opical levocabastine is more effective than sodium cromoglycate and placebo for the prophylaxis and treatment of seasonal allergic conjunctivitis,"	Therapeutic efficacy at 4 weeks was 87% in Levocabastine and 68% in sodium cromoglycate and placebo groups respectively.
Leino 1994 (Score = 6.0)	Sodium Cromoglycate	RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 339 with seasonal allergic conjunctivitis (SAC) birch pollen.	Aged 11 to 78 years.	Cromoglycate 2% four times daily (N = 169) vs. Cromoglycate 4% four times daily, plus placebo eye drops twice daily (N = 170).	Follow-up for 4 weeks.	The only statistically significant treatment difference, ($p<0.05$) was for; soreness / pain in favor of 4% cromoglycate, after 2-3 weeks of treatment. Statistically significant treatment difference was for	"[T]he use of 4% sodium Cromoglycate eye-drops twice daily is as effective and well tolerated as 2% sodium Cromoglycate four times daily in the treatment of birch-pollen conjunctivitis."	Similar efficacy between the 2 treatments.

								chemosis after 4 weeks in favor of 4% group, (p=0.05). Overall, 60% rated treatment as “very effective”, most of the remaining rated “moderately effective”, at week 1, (p=0.67) and at week 4, (p=0.87).		
James 2003 (Score = 6.0)	Sodium Cromoglycate	RCT Double-Blind	Supported by ASTA Medica AG. No mention of COI.	N = 144 participants with a two-season history of conjunctivitis/ rhinoconjunctivitis;	mean age for azelastine 0.05% 37.1, 35.5 years for sodium cromoglycate 2% and 36.1 years for placebo.	Azelastine 0.05% (N = 45) vs. Sodium Cromoglycate (SCG) 2% (N = 50) vs. Placebo (N = 49). All participants: one drop per eye, twice daily.	Follow-up at baseline and after 3, 7 and 14 days of treatment.	Responder rates (%) for three main eye symptoms: itching, tearing and conjunctival redness: day 3: no vs yes: azelastine: 14.6% vs. 85.4%, (p=0.005); SCG: 17.0% vs. 83.0, (p=0.007)	“The results of this study indicate that the therapeutic use of azelastine eye drops in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis can be recommended.”	Lack of study details for randomization, allocation and compliance.

Abelson 1995 (Score = 5.5)	Sodium Cromoglycate	RCT	Supported by a grant from Johnson and Johnson, Skillman, New jersey, Iolab Pharmaceutical, Claremont, California and from the Harry, Evelyn, and John Axelsord Charitable Trust, Andover, Massachusetts. No mention of COI.	N = 50 with a positive history of allergic conjunctivitis (AC) and a positive diagnostic test;	mean age not reported.	4% sodium Cromolyn 4 times daily for 2 weeks, plus at day 18, 2 drops of 0.05% Levocabastine (N = 50) vs. Placebo 2 drops in each eye 4 times daily for 2 weeks (N = 50). Assessments were completed 3, 5, and 10 minutes after allergen challenge, and 3, 5, and 10 minutes after drug administration.		Mean itching score after initial and 4 hour challenge at 3, 5 and 10 mins: (0.41±0.67 vs. 1.91±1.05), (0.25±0.52 vs. 1.84±0.93), and (0.26±0.75 vs. 1.37±1.08), ($p<0.05$), and (0.42±0.56 vs. 1.13±0.73), (0.33±0.58 vs. 0.96±0.79), and (0.23±0.47 vs. 0.81±0.80), ($p<0.05$).	"[A] single dose of levocabastine was significantly more effective in inhibiting the signs and symptoms of allergen-induced conjunctivitis than treatment with cromolyn give four times daily for 14 days."	Data suggest levocabastine is superior to cromolyn.

Fujishima 2009 (Score = 5.5)	Sodium Cromoglycate	RCT	No mention of sponsorship or COI.	N = 86 with a history of seasonal allergic conjunctivitis (SAC) to Japanese cedar pollen with a positive skin prick, RAST, or MAST, and has itching and signs of ocular allergy	mean age 38.4±19.8 years.	Disodium Cromoglycate or DSCG 2.0% ophthalmic solution 4 times daily in both eyes from beginning of study (N = 86) vs. Bromfenac sodium or BF 0.1% concomitantly twice daily in 1 eye (N = 86) vs. Fluorometholone or FML 0.02% ophthalmic suspension concomitantly 4/daily in contralateral eye (N = ?). For 1 week.	Follow up?	There were no significant differences between groups, ($p<0.05$). From day 1 or 2; conjunctival itching, ($p<0.0001$), lacrimation day 2, ($p=0.0028$), conjunctival discharge from day 2, ($p=0.001$), foreign body sensation from day 1, ($p=0.0009$), and conjunctival injection from day 1, ($p=0.0009$).	"Bromfenac sodium for allergic conjunctivitis was effective, with efficacy equivalent to that of FML when used with DSCG."	Patients not well described.
Ciprandi 1991 (Score = 4.0)	Sodium Cromoglycate	RCT	No mention of sponsorship or COI.	N = 80 with allergic conjunctivitis (AC) from pollinosis; mean age of 37,	age range of 10 to 60.	Group 1: 4% Cromoglycate plus Chlorphenamine anti-H1 antihistamine in 0.2% solution (N = 20) vs. Group 2: 4% Cromoglycate plus Tetrizoline decongestive-imidazoline derivate in 5% solution (N = 20) vs. Group 3: 0.1% Nafazoline (anti-H1 antihistamine) plus imidazoline (decongestive) in	Follow ups at 2 and 4 weeks.	Score reductions after 2 and 4 weeks in groups 1, 2, and 3 were higher vs. group 4, ($p<0.01$).	"[C]romoglycate (preventive) associated with chlorphenamine (antihistamine) or tetrizoline (decongestive), as well as the association of nafazoline (antihistamine) plus imidazoline (decongestive), present effective treatments for allergic seasonal conjunctivitis, without side effects."	Data suggest all 3 active treatments efficacy.

						0.1% solution (N = 20) vs. Group 4: placebo 2 drops one in each eye for 4 weeks (N = 20).				
Collum 1992 (Score = 2.5)	Sodium Cromoglycate	RCT Multi-centered Double-blind	No mention of sponsorship or COI.	N = 159 with a history of seasonal allergic eye disease.	Mean age of 32.4 years.	Sodium Cromoglycate (SCG), 2%, four times a day (N = n/a) vs. Sodium Cromoglycate (SCG), 4%, two alternating occasions with placebo twice daily (N = n/a). 4 week treatment period.	Follow-up at baseline, and weeks 1, 2, 3, and 4.	There were no statistically significant values to report in any of the primary variables. Mean for itching: week 1: SCG 2% vs SCG 4%: 1.16 vs 1.12, (p=0.91); week 4: 0.62 vs 0.70, (p=0.81). redness: week1: 0.78 vs 0.85, (p=0.60); week 4: 0.32 vs 0.59, (p=0.02)	"This study concludes that 4% Sodium Cromoglycate used twice daily is at least as effective as 2% Sodium Cromoglycate used 4 times daily in patients with seasonal allergic conjunctivitis. Because of the problems of compliance, it is therefore suggested that the optimum treatment is 4% Sodium Cromoglycate used twice daily for seasonal allergic conjunctivitis. Only minimal adverse side effects are likely to occur with this medication."	Missing group populations. Methodological details sparse.

Abelson 2004 (Score = 6.0)	Epinastine hydrochloride	RCT Single-center Double-Masked	No mention of sponsorship or COI.	N = 67 patients who had a history of allergic conjunctivitis (AC) with ≥1 allergy to cat hair, cat dander; dust mites; or ragweed, tree, or grass pollens.	Mean age of 38.4 and range from 12 to 67 years.	Epinastine hydrochloride 0.05% ophthalmic solution, (N = n/a) vs. Vehicle of epinastine (sodium phosphate monobasic, sodium chloride, edetate sodium, benzalkonium chloride and purified water) (N = n/a). All patients: one drop per eye on two separate occasions, weeks 3 and 5.	Follow-up at baseline, and weeks 1, 3, and 5.	Mean±SD for ocular itching score: 3 min after onset challenge: epinastine vs vehicle: 0.45±0.77 vs. 1.99±1.03, (p<0.001). Mean±SD for ocular itching score: 3 min after duration challenge: epinastine vs vehicle: 0.92±0.93 vs. 1.86±0.93, (p<0.001). Mean±SD for conjunctival hyperemia score: 5 min after onset challenge: epinastine vs. vehicle: 1.28±0.86 vs. 2.03±0.78, (p<0.001). Mean±SD for hyperemia score: 5 min after duration challenge: epinastine vs. vehicle: 1.37±0.78 vs. 1.93±0.77, (p<0.001).	"In this CAC model, multiple signs and symptoms of allergic conjunctivitis were significantly reduced by topical administration of epinastine compared with vehicle. Epinastine showed prompt onset (3 minutes) and long duration of action (28 hours). The tolerability of epinastine was similar to that of vehicle."	Missing group populations groups. Patient data sparse. Data suggest Epinastine superior to placebo for antigen challenge.
Li 2013 (Score = 4.0)	Pranoprofen vs. Fluorometholone	RCT Investigator-Masked	No mention of sponsorship. No COI.	N = 75 with symptoms of chronic allergic conjunctivitis (AC) for more than six months.	Mean age not reported.	Pranoprofen, 0.1%, four times daily (N = n/a) vs. Fluorometholone, 0.1%, four times daily (N = n/a).	Follow-up at baseline, and days 3, 7, 14, 21, 28, 42 and 56.	The score ratio on day 3 was lower on day 3 in fluorometholone group compared to the pranoprofen group (p=0.005).	"Both fluorometholone and pranoprofen were effective for management of cases with chronic allergic conjunctivitis. Fluorometholone provided more rapid relief as compared with pranoprofen. The effect of fluorometholone was more pronounced in younger patients	Missing group populations. No meaningful differences between the groups were observed.

Donshik 2000 (Score = 7.5)	Ketorolac	RCT	Sponsored by an unrestricted educational grant from Allergan Labs, Inc., Irvine, California. No mention of COI.	N = 224 with a history of seasonal allergic conjunctivitis (SAC) during ragweed season and a positive skin test for ragweed in the last 2 years;	mean of 37 years, range from 14 to 73 years.	Acular, 5 ml Ketorolac Tromethamine 0.5% eye drops (N = 73) vs. Livostin, Levocabastine hydrochloride 0.05% eye drops (N = 75) vs. Placebo, 1 drop in each eye 4 times daily for 6 weeks (N = 75).	Follow up at baseline, and weeks 1 and 3.	Ketorolac more effective than vehicle reducing itching scores, palpebral hyperemia, bulbar hyperemia, and edema, ($p<0.05$). Levocabastine treated eye showed significant reduction in bulbar hyperemia, ($p=0.008$). No significant differences among treatment groups in safety or tolerability.	"[K]etorolac 0.5% ophthalmic solution is well tolerated and effective in relieving the signs and symptoms of seasonal allergic conjunctivitis."	Data suggest modest efficacy.

Evidence for NSAID Eye Drops

Kalpaxis 1990 (Score = 3.5)	Pentigetide	RCT Double-Blind	Sponsored by a grant from Immunetech Pharmaceuticals. No mention of COI.	N = 50 with allergic conjunctivitis (AC).	Mean age 35.0 years for pentigetide and 33.6 years for cromolyn sodium.	Pentigetide, 0.5% ophthalmic solution, one drop per eye four times daily (N = 25) vs. Cromolyn Sodium, 4% ophthalmic solution, one drop per eye four times daily (N = 25).	Follow-up at days 1, 3, 8, and 15. This study lasted 2 weeks.	Percent improvement: itching: pentigetide vs cromolyn sodium: day 3: 43 vs. 42; day 8: 43 vs 51; day 15: 49 vs 56, ($p<0.05$), in favor of cromolyn sodium.	"[P]entigetide, 0.5%, ophthalmic solution is safe and effective in the treatment of allergic conjunctivitis."	Data suggest Pentigetide superior to Cromolyn.
Li 2013 (Score = 4.0)	Pranoprofen vs. Fluorometholone	RCT Investigator-Masked	No mention of sponsorship. No COI.	N = 75 with symptoms of chronic allergic conjunctivitis (AC) for more than six months.	Mean age not reported.	Pranoprofen, 0.1%, four times daily (N = n/a) vs. Fluorometholone, 0.1%, four times daily (N = n/a).	Follow-up at baseline, and days 3, 7, 14, 21,	The score ratio on day 3 was lower on day 3 in fluorometholone group compared to the pranoprofen group ($p=0.005$).	"Both fluorometholone and pranoprofen were effective for management of cases with chronic allergic conjunctivitis. Fluorometholone provided more rapid	Missing group populations. No meaningful differences between the groups were observed.

							28, 42 and 56.		relief as compared with pranoprofen. The effect of fluorometholone was more pronounced in younger patients	
Tauber 1998 (Score = 7.5)	Ketorolac	RCT	Sponsored by CIBA Vision Ophthalmics. No mention of COI.	N = 60 with acute seasonal allergic conjunctivitis (SAC);	mean age of 39.8±12.1 for diclofenac and 41.3 for ketorolac.	Diclofenac or DS (N = 29) vs. Ketorolac or KT 1 drop 4 times a day for 14 days (N = 31).	Follow ups at baseline, 30 minutes and days 7 and 14.	No significant differences between groups for primary and secondary composite scores, (p=0.804 and 0.382) and individual parameters of itching and bulbar conjunctival injection, (p=0.323 and 0.218).	"[T]he use of either diclofenac sodium (Voltaren Ophthalmic 0.1% Solution) or ketorolac tromethamine (Acular 0.5% Ophthalmic Solution) 4 times daily produces prompt relief of many of the ocular symptoms of SAC within 30 minutes and provides continued relief of ocular symptoms for at least 14 days."	Data suggest DS is superior to KT. Some baseline differences of unclear significance.
Donshik 2000 (Score = 7.5)	Ketorolac	RCT	Sponsored by an unrestricted educational grant from Allergan Labs, Inc., Irvine, California. No mention of COI.	N = 224 with a history of seasonal allergic conjunctivitis (SAC) during ragweed season and a positive skin test for ragweed in the last 2 years;	mean of 37 years, range from 14 to 73 years.	Acular, 5 ml Ketorolac Tromethamine 0.5% eye drops (N = 73) vs. Livostin, Levocabastine hydrochloride 0.05% eye drops (N = 75) vs. Placebo, 1 drop in each eye 4 times daily for 6 weeks (N = 75).	Follow up at baseline, and weeks 1 and 3.	Ketorolac more effective than vehicle reducing itching scores, palpebral hyperemia, bulbar hyperemia, and edema, (p<0.05). Levocabastine treated eye showed significant reduction in bulbar hyperemia, (p=0.008). No significant differences among treatment groups in safety or tolerability.	"[K]etorolac 0.5% ophthalmic solution is well tolerated and effective in relieving the signs and symptoms of seasonal allergic conjunctivitis."	Data suggest modest efficacy.

Tinkelman 1993 (Score = 7.0)	Ketorolac	RCT	Sponsored in part by a grant from Syntex Research, Palo Alto, California. No mention of COI.	N = 93 with bilateral signs and symptoms of acute seasonal allergic conjunctivitis (SAC) and history of positive skin test to pollen;	mean age of 34.4.	Ketorolac 0.5% in one eye (N = 93) vs. Placebo in the fellow eye, one drop 4 times a day for 7 says (N = 93).	Follow up at 3-4 days and 7-8 days.	Conjunctival inflammation (baseline, midweek, final): ketorolac 2.16, 1.58, 1.21 vs. placebo 2.16, 1.81, 1.57, (p=1.000 / 0.051 / 0.003). Ocular itching: 3.00, 1.45, 1.20 vs. 3.00, 1.75 , 1.56, (p=1.00 / 0.074 / 0.020). Burning or stinging / Discharge or tearing / Foreign body sensation: (p=0.157, 0.486, 0.233) / (p=0.414, 0.380, 0.091) / (p=1.000, 0.484, 0.109). / 0.052.	"[K]etorolac 0.5% ophthalmic solution is an effective and well-tolerated treatment in alleviating the signs and symptoms associated with seasonal allergic conjunctivitis."	Crossover. High dropouts. Suggest efficacy.
Ballas 1993 (Score = 6.5)	Ketorolac	RCT/Crossover	Sponsored by a grant from Syntex Research, Palo Alto, California. No COI.	N = 148 with bilateral ocular itching and a history or seasonal allergic conjunctivitis (SAC);	mean age of 32.9±9.6.	Ketorolac 0.5% ophthalmic solution four times / day for seven days (N = 58) vs. Placebo solution, 1 drop in eye 4 times a day for 7 days. One eye served as the placebo (N = 28).	Follow up at 3-4 days and after 7 days.	At baseline ketorolac-treated eye showed statistically significant decrease in ocular itching / Conjunctival inflammation / allergic symptoms at mid-week and final visits: (p<0.001 and <0.001) / (p<0.001 vs. 0.005) / (allergies, p=0.004). At completion of the trial treated eye had significant treatment responses vs. vehicle for conjunctival inflammation / ocular itching / swollen eye / discharge - tearing / foreign body sensation: (p=0.010) / (p=0.006) / (p=0.002) / (p=0.021) / (p=0.035).	"[K]etorolac 0.5% ophthalmic solution applied topically is an effective therapy for the alleviation of the signs and symptoms of allergic conjunctivitis."	Crossover. Suggests efficacy.

Deschenes 1999 (Score = 6.5)	Ketorolac	RCT/Crossover	No mention of sponsorship or COI.	N = 36 with a history of seasonal allergic conjunctivitis (SAC) within 2 seasons and a positive diagnostic test for allergic disease within the past 24 months;	mean age of 36 years, age range of 19 to 68.	Olopatadine 0.1% ophthalmic solution in one eye and placebo in the contralateral eye (N = 36) vs. Ketorolac 0.5% ophthalmic solution in one eye and placebo in the contralateral eye (N = 36). Patients received an allergen challenge 27 minutes after treatment. Crossover at least 14 days in between. Evaluation 3, 10, and 20 minutes after challenge.		Itching mean difference olopatadine vs. placebo (3 min / 10 min / 20 min): -1.47 / -1.51 / -1.18, ($p<0.0001$). Olopatadine vs. ketorolac: NS. Olopatadine was significantly different for reduction in hyperemia scores compared to placebo redness scores at 3, 10, and 20 minutes after challenge, ($p<0.0001$). Olopatadine was more comforatable vs. ketorolac ($p<0.05$).	"[O]lopatadine is effective and safe in preventing and treating ocular itching and hyperemia associated with acute allergic conjunctivitis and is more effective and more comfortable than ketorolac."	Patients not well described. Crossover. Experimental model. Data suggest ophthalmic solution is superior to ketorolac. No long term results.
Tauber 1998 (Score = 7.5)	Diclofenac Sodium	RCT	Sponsored by CIBA Vision Ophthalmics. No mention of COI.	N = 60 with acute seasonal allergic conjunctivitis (SAC);	mean age of 39.8±12.1 for diclofenac and 41.3 for ketorolac.	Diclofenac or DS (N = 29) vs. Ketorolac or KT 1 drop 4 times a day for 14 days (N = 31).	Follow ups at baseline, 30 minutes and days 7 and 14.	No significant differences between groups for primary and secondary composite scores, ($p=0.804$ and 0.382) and individual parameters of itching and bulbar conjunctival injection, ($p=0.323$ and 0.218).	"[T]he use of either diclofenac sodium (Voltaren Ophthalmic 0.1% Solution) or ketorolac tromethamine (Acular 0.5% Ophthalmic Solution) 4 times daily produces prompt relief of many of the ocular symptoms of SAC within 30 minutes and provides continued relief of ocular symptoms for at least 14 days."	Data suggest DS is superior to KT. Some baseline changes of unclear significance.

Laibovitz 1995 (Score = 5.0)	Diclofenac Sodium	RCT	Sponsored by CIBA Vision Ophthalmics of Atlanta, Georgia. No mention of COI.	N = 20 with acute seasonal allergic conjunctivitis (SAC);	between the ages of 18 to 65.	DSOS, diclofenac sodium 0.1% ophthalmic solution (N = 10) vs. Placebo 1 drop in each eye 4 times daily for 2 weeks (N = 10).	Follow up at baseline, day 0, 3, 8 and 15.	There were no significant differences between groups from baseline-end of the study for itching / tearing / discomfort / burning / stinging, photophobia / foreign body sensation / pain/soreness / bulbar conjunctival injection / and palpebral conjunctival injection. Investigator's global assessment was significant in favor of DSOS, p=0.030.	"This study demonstrated the efficacy of DSOS in relieving the ocular signs and symptoms associated with acute SAC."	Small sample size. Suggest efficacy.

Evidence for Other Medications

Artificial tears

Bilkhu 2014 (Score = 4.0)	Artificial tears	RCT Double-blind	No mention of sponsorship or COI.	N = 18 with positive skin prick test and conjunctival challenge test results and proven sensitivity to grass pollen.	Mean age of 29.5±11.0 years (20 to 65 years).	Controlled exposure to grass pollen, followed, in random order by application of; Artificial tears, (ATs) (N = NA) vs. 5 minutes of cold compress (CC), or ATs combined with CC (N = NA) and Placebo or no treatment (N = NA).	Follow-up at baseline line and 1 hour.	Ocular symptom scores were similar at baseline at each visit, x = 6.091, (p=0.107), and post exposure effect, x = 2.729, (p=0.435). After treatment at 1 hour, ocular symptoms scores decreased: CC / ATs / ATS+CC, (p<0.001). A significant difference in ocular surface temperature between each of the treatments, and conjunctival hyperemia, (p<0.001).	"After controlled exposure to grass pollen, CC and AT treatment showed a therapeutic effect on the signs and symptoms of allergic conjunctivitis."	Group total not provided. Sparse baseline comparability and methodology.
Gous 2004 (Score = 5.5)	Unknown	RCT	Sponsored by Santen Oy, Finland. No mention of COI.	N = 169 children with a positive skin prick test, 12 itching and hyperemia.	Age range in years: 7 to 72 / 6 to 76 years.	2 times daily or BID group 1 drop according to the randomization schedule (N = 81) vs. 4 times daily or QID group 1 drop (N = 82).	Follow-up for 4 weeks.	The mean b.i.d. minus q.i.d. treatment difference was 0.17 with the 95% CI. Itching: 0.03; 95% CI (-0.27; 0.34) / Hyperemia: 0.26 with a 95% CI (0.02; 0.5). Week 4 mean difference: Itching: 5 0.17; 95% CI (-0.13; 0.47) / Hyperemia: 0.27; 95% CI (0.01; 0.52), based upon 4-point scoring standard for itching and hyperemia per protocol.	"B.i.d. dosing was statistically noninferior to q.i.d. dosing with respect to itching and hyperemia. Both regimens were similarly well tolerated in allergic conjunctivitis patients."	Comparable adverse events in both groups. Data suggest BID vs. QID dosing results in similar efficacy.
Other – Patanol-systemic Claritin therapy										

Abelson 1999 (Score = 7.5)	Patanol - systemic Claritin therapy	RCT	No mention of sponsorship or COI.	N = 15 with a successful allergen challenge and history of symptoms of allergic conjunctivitis (AC);	mean age not reported.	Patanol group received 1 - 2 drops in one eye + 10 mg Claritin in tablet form (N = 15) vs. Placebo received 1 - 2 drops in the following eye, 2 times 14 days apart + 10 mg Claritin in tablet form (N = 15).	Follow up at baseline, day 7, 14, and 28.	An hour and 8 hours after drugs were administered; ocular itching was lower in the Patanol-Claritin group, at 3, 7, and 10 minutes post-challenge, ($p<0.0002$) and after 8 hours at 3 and 7 minutes post-challenge, ($p<0.05$).	"[T]he combination of local Patanol-systemic Claritin therapy was shown to be significantly superior to Claritin alone for the control of ocular itching, the primary symptom of allergic conjunctivitis."	Experimental challenge study. Small sample size. Suggest additive benefit.
Other – Azelastine and Mitomycin C										
Sodhi 2003 (Score = 2.5)	Azelastine and Mitomycin C	RCT	No mention of sponsorship or COI.	N = 63 with allergic conjunctivitis (AC).	Mean age of 34.8±17.3 years.	Azelastine 0.02%, four times daily (N = 32) vs. Mitomycin C (MMC) 0.02 mg/ml, four times daily (N = 31). 3 month treatment period.	Follow-up at baseline, and weeks 2 and 4. This study lasted 3 months.	N (%) for Outcome measure: redness: MMC vs. azelastine: 25 (80.7%) vs. 19 (55.9%), (p=0.033); follicles: 31 (100.0%) vs 6 (17.7), (p=0.0001); papillae: 29 (93.6%) vs. 4 (11.8), (p=0.0001); changes in agent: 0 (0%) vs. 30 (88.2), (p=0.0001).	"Though this was a short-term study, we found topical MMC to be more effective than topical azelastine in the treatment of allergic conjunctivitis both in terms of relief of symptoms and resolution of signs. The use of topical MMC in low doses does not cause any significant adverse effect."	Methodological details sparse.
Other – Naphazoline and Antazoline phosphate										

Miller 1975 (Score = 5.5)	Unknown	RCT	No mention of sponsorship or COI.	N = 51 with allergic conjunctivitis (AC);	age range of 12 to 67.	Participants received study medication; either, Naphazoline hydrochloride 0.05%, or Antazoline phosphate 0.5% (N = 51) vs. Placebo single dose + 2 drops in one eye (N = 51).	Follow-up at 24-72 hours after allergen challenge.	The combination medication was significant at the post challenge evaluations for conjunctival inflammation (p<0.01) and photophobia (p<0.05).	"[T]he combination product offers a significant superiority over either of the components administered singly, thus supporting the rationale of the combination."	Patients not well described.
Other – Loteprednol Etabonate drops										
Dell 1998 (Score = 6.5)	Loteprednol Etabonate	RCT	Sponsored by Pharmos Corp and Bausch and Lomb Pharmaceuticals. No mention of COI.	N = 133 with signs and symptoms of environmental seasonal allergic conjunctivitis.	Mean age was 41 years.	Loteprednol Etabonate 0.2%, one drop bilaterally (N = 66) vs. Placebo, one drop bilaterally (N = 67).	Follow-up at baseline, and days 2, 3, 7, 14, 28, and 42.	Mean score for bulbar conjunctival injection: loteprednol etabonate vs placebo: first 2 hours: -0.78 vs -0.38, (p<0.001); first 2 weeks: -1.32 vs -0.79, (p<0.001); day 2-3: -1.1 vs -0.7, (p<0.001); day 7: -1.3 vs -0.7, (p<0.001); day 14: -1.3 vs -0.9, (p=0.006); day 28: -1.2 vs -0.7, (p=0.030). Mean score for itching: first two weeks: -3.36 vs -2.75, (p<0.001); day 2-3: -3.2 vs -2.6, (p<0.001); day 7: -3.4 vs -2.7, (p<0.001); day 14: -3.5 vs -3.1, (p=0.034).	"Loteprednol etabonate (0.2%) was more effective than placebo in the treatment of seasonal allergic conjunctivitis. Loteprednol etabonate (0.2%) had a safety profile comparable to placebo during this 6-week trial."	Sparse baseline comparability. At 6 weeks loteprednol better than placebo in treatment of SAC symptoms.

PROGNOSIS

The prognosis of ocular allergies is generally good. The prognosis is progressively worse with increasingly worse symptoms, especially with systemic symptoms such as occupational asthma. If symptoms include anaphylactic symptoms, then complete removal from exposure is indicated (see Work-related Asthma Guideline).

DIFFERENTIAL DIAGNOSIS

While the diagnosis is generally straightforward, the differential diagnosis includes:

- Blepharitis
- Chemical irritation
- Mechanical irritation (e.g., small particulates)
- Infections, including viral and bacterial conjunctivitis
- Giant papillary conjunctivitis
- Angle closure glaucoma
- Superior limbic keratoconjunctivitis
- Dry eyes
- Auto-immune disorders
- Sicca syndrome
- Ocular rosacea
- Keratitis
- Episcleritis/scleritis
- Vernal keratoconjunctivitis
- Atopic keratoconjunctivitis

COMPLICATIONS / COMORBIDITIES

The main complication is systemic allergic diseases, particularly work-related asthma (see Work-Related Asthma guideline). Anaphylaxis is also a rare potential among those with severe allergies, especially when combined with a high exposure.

FOLLOW-UP CARE

Follow-up care is highly variable and based primarily on severity of the case and response(s) to treatment. In mild cases, infrequent followup is indicated. In others, work-up and evaluation for concomitant asthma and consideration of exposure modification and/or removal from work is indicated. In others, immunotherapy is indicated, in which case treatments every 1-2 weeks for a period of many months to up to approximately 2 years may be indicated.

JOB ANALYSIS

A review of the workplace chemicals, products and agents is indicated to help identify likely allergen(s). In some cases, measurements of those agent(s) may be indicated to help quantify the exposure and guide treatment. Occasionally, the exposures may be reduced and following the measured exposure levels may be of assistance. In others settings (e.g., ragweed or other environmental allergens), measurement of the agent is not indicated.

Evidence for Rhinoconjunctivitis

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Weiser 1999 (Score = 9.0)		RCT	Sponsored by Heel GmbH. No mention of COI.	N = 146 outpatients with seasonal allergic rhinitis (SAR) as diagnosed by RAST, ages 18-60 years.	Mean age: homeopathic group 36.8±9.6 years and cromolyn group 34.7±11.6 years.	Cromolyn sodium (one spray, ~0.14ml, administered 4 times daily/naris) (N = 74) vs. Homeopathic treatment sodium (one spray, ~0.14ml, administered 4 times daily/naris) (N = 72). Treatment duration was 6 weeks.	Follow-up at baseline (visit 1), and after 7 ± 1, 14 ± 2, 28 ± 3 and 42 ± 3 consecutive days of treatment (visits 2 to 5).	Mean±SD values for Rhinoconjunctivitis Quality of Life Questionnaire comparing homeopathic vs. cromolyn: Visit 1: 1.87±1.50 vs. 2.12±1.53 (p=0.55). Visit 5: 1.26±1.34 vs. 1.10±0.98 (p=0.5).	"[T]he homeopathic nasal spray proved as effective, safe, and well-tolerated a therapy for seasonal allergic rhinitis as the conventional cromolyn sodium nasal spray in this study."	Similar efficacy between treatment groups.
Berger 2006 RCT		RCT	Sponsored by MedPointe Pharmaceuticals. COI, Sacks affiliated with MedPointe Pharmaceuticals.	N = 360 patients 12 years and older with a history of seasonal allergic rhinitis (SAR) for at least 2 years and a positive skin test reaction to ambient pollen aeroallergen in the past year.	Mean age 35 years.	Azelastine nasal spray 30 mL 2 sprays per nostril twice daily in morning and evening and placebo capsules filled with lactose for 2 weeks (N = 179) vs. 10 mg cetirizine tablets enclosed in placebo-matching capsule overfilled with lactose once a day in the morning and placebo nasal spray containing 30	No follow-up time.	Change from baseline to day 14 in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores: azelastine improved each domain (p≤0.05) and overall score (p=0.002) vs. cetirizine, no mean values reported.	"[A]zelastine nasal spray significantly improved QoL compared with cetirizine oral tablets in the overall RQLQ score and for each individual RQLQ domain."	Multicenter 2 week trial with similar efficacy in treatment groups.

						mL vehicle solution 2 sprays twice a day in the morning and evening for 2 weeks (N = 175). Assessments at baseline and 2 weeks.				
Corren 2005 (Score = 8.5)		RCT	No mention of sponsorship. COI, Sacks affiliated with MedPointe Pharmaceuticals, Wheeler D'Andrea (neither authors) are employees of MedPointe Pharmaceuticals. Wheeler contributed to the design of the study and preparation of the manuscript and	N = 307 patients ≥12 years of age with ≥2 year history of SAR indicated by a positive allergy skin test during the previous year.	Age range 12 to 74 years.	Azelastine nasal spray 2 sprays per nostril twice daily (morning and evening) and placebo tablets once daily in the morning (N = 152) vs. cetirizine 10 mg tablets once daily (morning) and placebo saline nasal spray 2 sprays per nostril twice daily (morning and evening) (N = 155). 2 week study. Assessments at baseline and 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after first dose of study medication.	No follow-up time.	Least squares mean±SD change from baseline Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ): Overall – azelastine 1.41±1.25 vs. cetirizine 1.11±1.18 (p=0.049); eye symptoms – NS between groups (p=0.251).	"[A]zelastine nasal spray was well tolerated and produced significantly greater improvements in TNSS and total RQLQ scores compared with cetirizine over 2 weeks of treatment."	Azelastine led to significant improvement in TNSS compared to cetirizine at 2 weeks.

			D'Andrea contributed to the clinical trial management.							
Meltzer 2012 (Score = 7.5)		Double-Blind RCT	Sponsorship, funded by a research grant from Meda Pharmaceuticals, Somerset, New Jersey. COI, Drs. Meltzer, La Force, Ratner, and Carr have consulted for and received research support from Meda Pharmaceuticals Inc., Dr. Price has consulted for Meda Pharma, Dr. Ginsberg is	N = 779 with moderate to severe symptoms of seasonal allergic rhinitis (SAR).	Mean age of 37.8 years.	MP29-02 Nasal Spray group (N = 195) vs. Azelastine Nasal Spray (N = 194) vs. Fluticasone Nasal Spray (N = 189) vs. Placebo (N = 201)	Follow-up at 12 hours and 14 days.	All active treatment groups improved significantly in total ocular symptom score at 12 hours compared to placebo ($p<0.05$). MP29-02 showed significant improvement in mean change compared with Fluticasone (-3.56 vs. -2.68, ($p=0.009$)) and approached significance compared with the Azelastine group (-3.56 vs. -2.96, ($p=0.069$)).	"Based on the evidence form this study, MP29-02 is a potentially valuable addition for pharmacotherapy of patients with moderate to severe SAR and addresses the unmet medical need for a more effective treatment for these patients.	MP29-02 significantly improved allergic rhinitis symptoms compared to placebo. Significant number of patients in Azelastine group with distorted taste may have biased patient blinding.

			an employee of Meda Pharmaceuticals Inc							
Meltzer 2013 (Score = 7.5)		RCT	Sponsored by MedaPharma. No mention of COI.	N = 610 with moderate to severe seasonal allergic rhinitis (SAR);	age: ≥12 years old.	MP29-02 nasal spray, which is a novel intra nasal formulation of 137µg of azelastine hydrochloride (AZE) and 50µg fluticasone propionate (FP) for 14 days (N = 153) vs. 137µg of commercially available AZE nasal spray (N = 152) vs. 50µg of commercially available FP nasal spray (N = 151) vs. placebo nasal spray (N = 151).	Outcomes assessed on days 1, 7 and 14.	Mean±SD overall LS change from baseline to day 14 for reflective total ocular symptom score (rTOSS) for MP29-02 vs. AZE vs. FP vs. placebo: 12.31±4.03 vs. 11.80±4.21 vs. 11.77±4.27 vs. 12.16±4.35 (MP29-02 vs. FP: p=0.0022; MP29-02 vs. AZE: p<0.0706; MP29-02 vs. placebo: p<0.0001). Mean±SD overall LS change from baseline to day 14 for ocular itching MP29-02 vs. AZE vs. FP vs. placebo: 4.48±1.36 vs. 4.42±1.28 vs. 4.31±1.40 vs. 4.46±1.42 (MP29-02 vs. FP: p=0.0001; MP29-02 vs. AZE: p=0.0127; MP29-02 vs. placebo: p<0.0001). Mean±SD overall LS change from baseline to day 14 for ocular watering MP29-02 vs. AZE vs. FP vs. placebo: 4.09±1.50 vs.	"MP29-02 provided faster and more complete symptom control than first-line therapies. It was consistently superior irrespective of severity, response criteria or patient-type, and may be considered the drug of choice for moderate-to-severe AR. These measures define a new standard for assessing relevance in AR."	1:1:1:1 14 day treatment post hoc analyses. MP29-02 showed quicker and more symptom relief compared to FP or AZE alone or placebo.

								3.98±1.57 vs. 3.91±1.56 vs. 4.01±1.56 (MP29-02 vs. FP: p=0.0218; MP29-02 vs. AZE: p=0.2923; MP29-02 vs. placebo: p<0.0001). Mean±SD overall LS change from baseline to day 14 for ocular redness MP29-02 vs. AZE vs. FP vs. placebo: 3.74±1.72 vs. 3.40±1.79 vs. 3.54±1.66 vs. 3.69±1.79 (MP29-02 vs. FP: p=0.0044; MP29-02 vs. AZE: p=0.0372; MP29-02 vs. placebo: p<0.0001).		
Buscaglia 1996 (Score = 1996)		RCT/Crossover	Sponsored by a PF CNR FATMA SP2 grant, CNR Target project 'Ingegneria genetica' PF, Associazione Ricerca Malattie Allergiche e Immunologiche and Janssen.	N = 10 sensitive to parietaria judaica (wall parietary) with allergic rhinoconjunctivitis;	mean age not reported.	Levocabastine 0.5 mg/ml eye drops, first week (N = 10) vs. Placebo 30 minutes before allergen-specific conjunctival challenge or ASCC, second week (N = 10). Crossover over after 1 week. Evaluations at baseline, 15 min, 30 min, and 6 hours after challenge.		30 minutes after the challenge, total symptom scores and single signs and symptoms were less severe in the treatment group vs. placebo, (p<0.002).	"Levocabastine exerts anti-allergic activity, in that it reduces in vivo inflammatory cell infiltration due to ASCC, and also adhesion molecule expression on conjunctival epithelium."	Crossover experimental trial. Small sample size. Data suggest efficacy.

			COI, one or more authors have received or will receive benefits for personal or professional use.							
Weiler 1997 (Score = 7.0)		RCT	Sponsored by Wallace Laboratories. No mention of COI.	N = 233 patients ≥12 years had a history and diagnosis of seasonal allergic rhinitis (SAR), were symptomatic to allergens.	Mean age in years: 27.4 years for Azelastine, and 30.5 years for placebo nasal spray.	Azelastine nasal spray (2 sprays each nostril bid, total daily dose 1.10 mg) (N = 116) vs. placebo (saline) nasal spray (2 sprays each nostril bid) (N = 117). Study conducted over 2 days.		Overall improvements for itchy eyes in the Azelastine group were superior to the placebo group ($p<0.05$). No additional data reported on individual symptom outcomes.	"Azelastine nasal spray can be effectively administered as adjunctive therapy, in an outdoor environment in which subjects are exposed to pollen and other aeroallergens."	Table 3 depicts taste perversion in treatment group showing why true patient blinding was not possible. Nasal spray plus tablet groups achieved statistically significant improvement in symptom relief up to 2 days over placebo plus tablet group.
LaForce 1996 (Score = 7.0)		RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 206 with history and diagnoses of seasonal allergic rhinitis (SAR). Age 12 years and older.		Azelastine 2 sprays per nostril qd daily dose of 0.52 mg (N = 66) vs. Azelastine nasal 2 sprays per nostril bid, daily dose of 1.04 mg (N = 66) vs. Oral chlorpheniramine maleate 12 mg bid		For the azelastine 2 spray qd group the improvements in itchy eyes / ears / throat / palate and cough were clinically significant vs placebo, ($p=0.05$ vs $p\leq0.05$ placebo). For the azelastine 2 spray bid group the	"Azelastine nasal spray demonstrated broad clinical antirhinitis activity that for the 2 spray/nostril bid dosage regimen was consistently clinically and statistically significant."	At 4 weeks, Azelastine efficacy persisted but true patient blinding is not possible due to taste differences in study drug vs. placebo.

						(N = 65) vs. Placebo matching the nasal spray given twice daily (N = 67). Follow-up for 4 weeks.		improvements in itchy eyes / ears / throat / palate and cough were clinically significant, (p≤0.042) vs placebo.		
Handelman 1976 (Score = 7.0)		RCT Double-blind	No mention of sponsorship or COI.	N = 104 with a history of ragweed hay fever severe enough to have required medications.	Age range: 5 to 51 / 4 to 51.	Cromolyn sodium included (N = 53) vs. Placebo (N = 51).	Follow-up for 9 weeks.	Cromolyn sodium is highly effective in reducing ocular irritation in ragweed hay fever patients, (p statistics not reported).	"The efficacy of the drug was notable despite the fact that patients used an average of 52 mg instead of the recommended 62.4 mg daily."	Cromolyn sodium was effective in reducing seasonal allergic rhinitis symptoms.
Hampel 2010 (Score = 7.0)		RCT Double-blind Multicenter	Sponsored by MedPointe Pharmaceuticals. No mention of COI.	N = 610 with moderate to severe nasal symptoms.	Mean age: 39.3 years.	Azelastine 0.1% and fluticasone 1 spray per nostril twice daily (N = 153) vs. Azelastine 0.1% 1spray per nostril twice daily (N = 152) vs. Fluticasone 1spray per nostril twice daily (N = 151) vs. Placebo 1spray per nostril twice daily (N = 151).	Follow-up for 14 days.	Combination therapy significantly improved all individual ocular symptoms compared with azelastine, fluticasone, or placebo, (p<0.05). Each component of the combination was better than placebo for each individual symptom for total ocular symptoms scores (TOSS), (p<0.05).	"The combination azelastine-fluticasone nasal spray provided statistically significant improvement in the TNSS and additive clinical benefit compared with either agent alone in patients with moderate-to-severe seasonal allergic rhinitis."	4 groups showed combination of Azelastine-Fluticasone groups had significant nasal symptom improvement at 14 days compared to other groups. Azelastine groups report taste changes.
Gastpar 1994 (Score = 7.0)		RCT	Sponsored by ASTA Medica AG. No mention of COI.	*Study I.* N = 167 patients with a history of seasonal allergic rhinitis (SAR) for ≥3 years confirmed	mean age of 30.5 years.	Azelastine nasal spray one puff per nostril (0.14 mg per nostril) (N = 81, Study I, N = 25 Study II) vs. terfenadine 60 mg morning and evening (N = 86	No follow-up time.	Study I. There were no significant differences between groups for ocular symptoms (no p-value reported). Study II. There were no significant differences between groups for	"[A]zelastine nasal spray with the dosage used is an effective treatment for both seasonal and perennial rhinitis."	6 week parallel group study. Similar efficacy in both treatment groups.

				by a skin prick test; mean age of 29.5 years. *Study II.* N = 52 patients with perennial allergic rhinitis with symptoms for ≥3 years confirmed by skin prick test;		Study I, N = 27 Study II) for 6 weeks. Assessments at baseline, days 8, 22, and 43 (end of treatment).		ocular symptoms (no p-value reported).		
Kray 1985 (Score = 6.5)		RCT	No mention of sponsorship or COI.	N = 58 with weed season allergic rhinoconjunctivitis and a history allergic ocular and nasal symptoms during late summer and fall for at least 2 years;	mean age of 24 and a range of 9 to 42 for the cromolyn sodium group, and a mean of 24 and a range of 9 to 54 for the placebo group.	2% Cromolyn sodium (CS) ophthalmic solution preserved with 0.01% Ethylenediamine Tetraacetic acid, plus 0.01% Benzalkonium chloride or CS (N = 25) vs. Placebo solution 1 drop in each eye 6 times a day for 5 weeks (N = 33).	Patients were followed up weekly.	The CS group experience less ocular symptoms during all treatment weeks and was significant at weeks 2, 4, and 5, ($p<0.02$). Less eye medication was used in the CS group except at week three and only week 2 was significant, ($p<0.05$). No significance between groups for nasal symptoms.	"Use of 2% CS ophthalmic solution without the preservative, 2-phenylethanol, resulted in a significant reduction in eye symptoms during 2 of the 3 weeks with the highest weed-pollen counts and a favorable trend throughout the treatment period."	Suggest efficacy.
Storms 1994 (Score = 6.5)		RCT	No mention of sponsorship or COI.	N = 247 patients (≥12 years) with symptomatic seasonal allergic	Mean age ranged from 31-34 years.	Azelastine 2 sprays per nostril bid (daily dose=1.1mg) (N = 63) vs. Azelastine 2 sprays per nostril qid (daily	Follow-up at week 1 and 2. Study duration was 2 weeks.	Changes in individual symptom severity scores from baseline: watery eyes improved in Chlorpheniramine ($p\leq0.01$) and Azelastine bid ($p=0.01$). No data	"[A]zelastine nasal solution administered once or twice daily is clinically effective in treating the symptoms of SAR."	Azelastine decreased seasonal allergy symptoms with increased effect in the BID treatment group.

				rhinitis (SAR).		dose=0.55mg) (N = 61) vs. Chlorpheniramine 12 mg bid (N = 62) vs. Placebo using a double-dummy technique (N = 61).		on symptom changes are reported.		Abstracts states "single blinded" while study design states "double blinded".
Horak 2006 (Score = 6.5)		RCT	Sponsored by VIATRIS GmbH & Co. KG. No mention of COI.	N = 46 with history of seasonal allergic rhinitis (SAR);	mean age: 23 / 22 / 26 / and 24 years.	Placebo (PLA) / Azelastine (AZE) / Desloratadine (DES) one puff of either one of the three tables (N = 15) vs. AZE / DES / PLA dosing the same as the first group (N = 16) vs. DES / PLA / AZE dosing the same as previous groups (N = 15).	Follow-up for at least 12 days.	The decrease of eye itching / eye tearing was comparable for azelastine and desloratadine, (p statistics not provided).	"This study confirms the usefulness of azelastine nasal spray for the symptomatic treatment of seasonal allergic rhinitis."	Crossover study, small group sample size.
Lurie 1992 (Score = 6.5)		RCT/crossover	No mention of sponsorship or COI.	N = 16 with allergic rhinitis;	mean age of 26.4±1.1 years.	Azelastine 2 mg for 10 days (N = 16) vs. Placebo (N = 16). Outcomes assessed at baseline and after treatment (day 10).	Outcomes assessed at baseline and after treatment (day 10).	The cumulative dose of allergen required to cause a twofold increase in nasal resistance was increased on the azelastine group ($p<0.05$), also in the number of sneezes ($p<0.05$); while there was a decrease on weight of nasal secretion ($p<0.02$). There was a multiple correlation between analogue scale and	"In conclusion, azelastine has been shown to reduce allergen-induced nasal responses. As an objective method posterior active rhinomanometry appears to be useful for assessing drug effects in allergic rhinitis."	Crossover trial. Small sample size (n=16). High dropout rate. Study shows Azelastine efficacy compared to placebo.

								nasal resistance, weight nasal secretion and number of sneezes (n=225, r=0.49, p<0.001).		
Orgel 1991 RCT (Score = 6.5)		RCT	No mention of sponsorship or COI.	N = 79 with symptoms of allergic rhinitis;	age range of 12 to 70 years.	Active cromolyn sodium nasal solution 4%, 5.2 mg/spray, in each nostril QID and placebo terfenadine tablet (N = 39) vs. Active terfenadine 1 tablet BID (60mg) and placebo cromolyn sodium spray (N = 40). Outcomes assessed weekly for 4 weeks.	Follow-up at 1 week post-treatment.	There was difference on between treatments for mean sneezing frequency, mean duration of nasal itching in favor of terfenadine (p=0.07 and p=0.08, respectively).	"[B]oth intranasal cromolyn, 4% QID, and oral terfenadine, 60 mg BIS, were effective for the treatment of patients symptomatic with allergic rhinitis with no significant differences between them. Relief was maintained throughout the 4-week treatment period with reoccurrence of symptoms within a week of stopping treatment. There were few adverse effects."	Comparable efficacy between groups.
Newson-Smith 1997 (Score = 6.0)		RCT	No mention of sponsorship or COI.	N = 291 with a 3-year history of seasonal allergic rhinitis (SAR), ages ranged from 18 to 65 years.	Median age was 35 years.	Azelastine nasal spray (total daily dose 0.14mg) (N = 83) vs. Beclomethasone (total daily dose 0.4mg nasal spray) (N = 83) vs. Placebo (N = 77). Medication taken twice daily.	Follow up after 7 and 14 days.	Azelastine was better than placebo for reduction in eye irritation (p<0.05). No detailed data are reported for individual eye symptoms.	"[B]oth intranasal azelastine and intranasal beclomethasone are effective drugs for the treatment of seasonal allergic rhinitis." .	Azelastine and Beclomethasone more effective than placebo in treatment of seasonal rhinitis symptoms at 2 weeks. Patient blinding not possible due to taste variations in nasally administered drugs.

Kremer 1999 (Score = 6.0)		RCT Double-blind Multicenter	No mention of sponsorship or COI.	N = 330 with seasonal allergic rhinitis (SAR).	Age range: 18 to 58 / 18 to 61 years.	Azelastine 0.05% one tablet at night and nasal spray twice daily (N = 129) vs. Placebo received nasal spray and placebo tablet (N = 133).	Follow-up for 14 days.	Statistically significant symptoms of comfort, (p<0.0001). Nasal scores reduced on day 0 vs 14: 6.1 ± 2.1 for combination and 6.2 ± 2.3 for spray, (p=0.7629) vs 2.8 ± 2.3 and 3.6 ± 2.5, (p=0.00289). No statistically significant reduction between groups in terms of symptoms reduction, (p=002671). There is no tendency favoring one group in terms of total group, (p=0.8382).	"[I]t seems sensible to combine oral and topical therapy in the crucial early phase of treatment, while later on topical therapy would be sufficient."	Both treatments tolerated well and had similar efficacy.
Pelucchi 1995 (Score = 6.0)		RCT	No mention of sponsorship or COI.	N = 45 with history of rhinitis and conjunctivitis during grass pollen season for at least 3 consecutive years;	age range of 17 to 49 years.	Nasal azelastine, 0.56 mg/day, 1 spray (0.14 mg) in each nostril (N = 15) vs. Nasal beclomethasone dipropionate (BDP), 200µG/day, 1 spray (50µg) in each nostril (N = 15) vs. Placebo (N = 15). All treatments were self-administered twice daily (at awakening and bed time) for 6 weeks.	Outcomes assessed at week 1, 2, 3, 4, and 5.	Nasal symptoms for the azelastine group were lower compared to placebo (p<0.05). BDP group had lower nasal symptoms compared to placebo (p<0.05 at week 4, and 5). No significant difference between active treatments.	"[O]ur study provides further evidence that topical azelastine and BDP are effective treatments for seasonal allergic rhinitis. BDP, but not k, likely achieves its efficacy by controlling allergic nasal inflammation. In addition, our results do not clearly support an effect of nasal treatment in the reduction of the increase in bronchial responsiveness occurring during pollen season in subjects with allergic rhinitis."	6 week follow-up study with 3 arms showed similar efficacy at week four for both study drugs compared to placebo for decreasing nasal symptoms.

Ciprandi 2003 (Score = 6.0)		RCT	Sponsored by a grant from Asta Medica Italia. No mention of COI.	N = 20 with seasonal allergic rhinoconjunctivitis for at least two previous seasons;	mean age of 29 years.	Azelastine hydrochloride, one drop in left eye (N = 10) vs. Placebo, blinded physiologic salt solution, one drop in left eye (N = 10).	Follow-up at baseline, 30 minutes after ASCC, 30 minutes and 6 hours after administration of azelastine.	Hyperemia, lacrimation, itching and total symptom score (TSS) scores were significantly lower in the azelastine group versus the placebo group (3 min: p<0.005 for all comparisons, 6 hours: p<0.05 for all comparisons).	"The ability of azelastine to reduce symptoms and inflammation during an ongoing allergic reaction can be considered concrete and convincing proof of a clinically relevant anti-inflammatory activity."	Experimental study design. 6 hour duration. Azelastine compared to placebo had efficacy in reducing symptoms both at 30 minutes and after 6 hours after administration.
Abelson 2004 (Score = 6.0)		RCT	No mention of sponsorship or COI.	N = 260 with a history of seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 36.8±14.8 years for olopatadine group and 36.0±13.2 years for placebo.	Self-administer olopatadine 0.2%, one drop per day (N = 129) vs. Placebo, Olopatadine 0.2% vehicle (dibasic sodium phosphate, sodium chloride, disodium EDTA, Povidone and BAC), one drop per day (N = 131).	Follow-up at baseline, weeks 1 through 9, and exit (week 10).	Mean frequency scores for ocular itching and redness were significantly lower in the opolatadine group compared with the placebo group (p<0.05). Mean severity scores for itching and redness was statistically significant for opolatadine 0.2% compared to placebo on 57 of 70 study days, (p<0.05).	"In the patients enrolled in this trial, olopatadine 0.2% appeared to be effective and well tolerated when administered once daily for the treatment of the ocular signs and symptoms of allergic conjunctivitis or rhinoconjunctivitis."	Baseline data for outcome not well described. Lack of details for blinding, control of co-interventions and compliance.
James 2003 (Score = 6.0)		RCT	Supported by ASTA Medica AG. No mention of COI.	N = 144 participants with a two-season history of conjunctivitis/	mean age for azelastine 0.05% 37.1, 35.5 years for sodium cromoglycate 2% and	Azelastine 0.05% (N = 45) vs. Sodium Cromoglycate (SCG) 2% (N = 50) vs. Placebo (N = 49). All participants: one	Follow-up at baseline and after 3, 7 and 14 days of treatment.	Responder rates (%) for three main eye symptoms: itching, tearing and conjunctival redness: day 3: no vs yes: azelastine: 14.6% vs. 85.4%, (p=0.005); SCG:	"The results of this study indicate that the therapeutic use of azelastine eye drops in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis can be recommended."	Lack of study details for randomization, allocation and compliance.

				rhinoconjunctivitis;	36.1 years for placebo.	drop per eye, twice daily.		17.0% vs. 83.0, (p=0.007)		
Sabbah 1998 (Score = 6.0)		RCT	Sponsored by ASTA Medica. No mention of COI.	N = 107 children suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age of 8.3±2.4 years for placebo, 8.6±2.3 years for azelastine, and 8.2±2.5 years for levocabastine.	Azelastine 0.05% (0.015mg), one drop per eye twice daily (N = 47) vs. Levocabastine 0.05% (0.015mg), one drop per eye twice daily (N = 32) vs. Placebo, identical to the azelastine eye drops except for the active drug, one drop per eye twice daily (N = 28). 14 day treatment period.	Follow-up at baseline, and after 3 and 14 days of treatment.	Responder rates (%) for three main eye symptoms: itching, lacrimation, and conjunctival redness: day 3: yes vs no: azelastine: 74% vs 26%, (p<0.01). Compared with placebo group: yes vs no: 39 vs. 61.	"In conclusion, azelastine eye drops are effective in the rapid relief of symptoms in young children with seasonal allergic conjunctivitis/rhinoconjunctivitis and show comparable safety to that of levocabastine eye drops. Azelastine eye drops offer an effective and safe alternative to levocabastine eye drops in the treatment of pediatric allergic conjunctivitis."	Study non-specific to working population.
Spangler 2003 (Score = 5.5)		RCT	Sponsored by an unrestricted grant from Alcon Laboratories, Inc. No COI.	N = 73 with a history of allergic rhinoconjunctivitis;	mean age 45.26, age range of 21-73.	Group A: received conjunctival allergen challenge or CAC included clinically significant signs and symptoms (> 1 unit difference) (N = 34) vs. Group B: Nasal allergen challenge or NAC Included clinically significant signs and symptoms (N = 39). All randomized to treat, to one of the three solutions:		There was a greater reduction in ocular itching with the olopatadine vs. mometasone (p=0.003) and fexofenafine (p=0.008) at 3 minutes and 5 minutes (p=0.007 and (p=0.013), respectively, post challenge.	"[T]he most effective way to treat ocular allergic symptoms is with a topical ophthalmic medication."	Experimental study. Patients not well described. Data suggest olopatedine much greater efficacy than other two arms. Short term follow-up.

						olopatadine 0.1% eye drops, plus placebo nasal spray, plus placebo tablets; or mometasone furoate monohydrate 50 ug nasal spray, plusplacebo eye drops,plus placebo tablets; or, fexofenadine hydrochloride 180 mg tablets, plusplacebo topical solution, plus placebo nasal spray, total of 3 visits. 1 tablet once daily, plus 2 sprays of nasal spray once daily for 1 week.				
Baroody 2008 (Score = 5.5)		Crossover Trial	Sponsored by GlaxoSmithKline and the McHugh Otolaryngology Research Fund. COI, Dr. Naclerio is on the scientific advisory	N = 20 with seasonal allergic rhinitis (SAR);	age range of 20 to 42 years.	Azelastine hydrochloride (274µg) intravenously, and ten minutes after treatment, nasal challenge with dose of allergen that caused ocular reflex place (N = 20) vs. Placebo (N = 20).	No follow-up reported.	Allergen and diluent challenges were lower after azelastine pretreatment vs. placebo pretreatment: 4.25 mg; -3 to 24 mg vs. 6.65 mg; -10.4 to 34.2 mg (p=0.18) on ipsilateral eye; And 2.4 mg; -3.7 to 26.4 mg vs. 8.8 mg; -17.9 to 28.4 mg (p=0.2) on contralateral eye. On the side ipsilateral to the nasal challenge,	"Nasal allergen challenge releases histamine at the site of the challenge, which probably initiates a nasonasal and a nasal ocular reflex. This reflex is reduced by an H1-receptor antagonist applied at the site of the challenge. The eye symptoms associated with allergic rhinitis probably arise, in part, from a naso-ocular reflex."	Data suggest pre-treatment with study medication reduces symptoms to allergic challenge in persons with positive skin test for those.

			boards of Schering-Plough, GlaxoSmithKline, Allux, and Merck and has received research grants from GlaxoSmithKline, Merck, Schering-Plough, and Novartis.					allergen challenge resulted in increase in ocular albumin levels vs. diluent challenge after pretreatment with placebo: 10.4 µg; 0.5 to 62.1 µg vs. 3.6 µg; 0.1 to 28.4 µg (p=0.03)		
Gambardella 1993 RCT No mention of sponsorship or COI.		RCT	No mention of sponsorship or COI.	N = 30 patients with a history of seasonal allergic rhinitis (SAR).	Age range 2 to 31 years.	Azelastine hydrochloride nasal spray at a metered dose of 0.14 mg/nostril twice a day (N = 15) vs. oral loratidine one 10 mg tablet once daily (N = 15). 6 week study period. Assessments at baseline, weeks 2, 4, and 6. Follow-up 1 week after study medication finished.		No significant differences between groups for any study outcomes (no p-value reported).	"The improvement in scores for both nasal and ocular symptoms during this study have confirmed that both azelastine and loratidine are effective treatments of seasonal rhinitis.	Sparse baseline comparability. Small overall sample size (N=30). No significant differences between both treatment groups.
Giede-Tuch		RCT Doubl	Sponsored by ASTA	N = 151 patients	mean age of	Azelastine 0.025% (0.008 mg) (N = 47)	Follow-up at baseline,	Responder rate (%) for main eye symptoms	"The results of this double-blind study show that azelastine eye-	Author conclusion not

1998 (Score = 5.5)		e-Blind	Medica. No mention of COI.	suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	35.4±11.4 years for azelastine 0.025%, 35.2±107 years for azelastine 0.05%, and 35.9±11.5 years for placebo.	vs. Azelastine 0.05% (0.015 mg) (N = 52) vs. Placebo, Benzalkonium chloride and sodium Edetate (N = 52). All participants: one drop per eye, twice daily at intervals of 10 to 12 hours in the morning and evening.	and after 3, 7, and 14 days of treatment.	itching, lacrimation, and conjunctival redness: day 3: no vs. yes: 18% vs 82%, (p=0.011).	drops provide rapid, dose-dependent relief from ocular symptoms in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis."	supported by statistical presentation as neither treatment reached statistical significance.
Lenhard 1997 (Score = 5.5)		RCT Double-Blind	Sponsored by ASTA Medica. No mention of COI.	N = 278 participants suffering from seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis;	mean age for azelastine 0.025% group 31.6±10.6 years, 31.7±11.7 years for azelastine 0.05%, and 33.9±11.9 years for placebo.	Azelastine 0.025% (0.008mg) (N = 92) vs. Azelastine 0.05% (0.015mg) (N = 92) vs. Placebo, identical composition of azelastine without the active substance (N = 94). All participants: one drop per eye, twice daily at an interval of 10 to 12 hours in the morning and evening. 14 day treatment period.	Follow-up at baseline, and days 7 and 14. This study lasted 14 days.	Responder rates (%) for three main eye symptoms: itching, lacrimation, and conjunctival redness: day 7: responders vs. non-responders: 98% vs. 2%, (p=0.0015).	"The results of this present study show that azelastine eye drops are well tolerated and exert a concentration-dependent therapeutic effect in the treatment of seasonal allergic conjunctivitis. For further investigations, the high concentration of 0.05% azelastine eye drops is recommended."	Sparse details for randomization, allocation blinding and compliance. Data suggest no immediate efficacy until 7 days compared with placebo.
Kyrein 1996 (Score = 5.0)		RCT	No mention of sponsorship or COI.	N = 12 with seasonal allergic rhinitis (SAR).	Ages 18 to 40 years.	Dimethindene (DMM) 0.025% once daily (N = N/A) vs. DMM 0.1% once daily (N =	Follow-up for 2 weeks.	The sight decrease between 120 and 60 min, during the third and fourth hour after score increase from 5.8	"0.1% DMM as nasal spray, is an efficient and safe galenical formulation for nasal spray application for patients suffering	Missing group populations. Small sample size (N=12). Crossover pilot study.

						N/A) vs. Placebo and azelastine 0.1% once daily (N = N/A).		to 6.3 could be detected. Visual analog scale showed a trend of increase values between 80 and 140 minutes for 0.025% DMM, and increase at lower level with smaller score peaks of 18.8 and 17.3 after 140 minutes, for 0.1% DMM and 0.1% azelastine, (p=0.076).	from seasonal allergic rhinitis (SAR)."	Similar efficacy between groups.
Meltzer, 1994 (Score = 5.0)		Double-Blind RCT	No mention of industry sponsorship or of COI.	N = 294 men and women with symptoms consistent with seasonal allergic rhinitis (SAR), who had required pharmacologic therapy at some point during the 2 years prior.	Mean age of 27.3 years.	Azelastine qd group, two sprays daily. (N = 71) vs. Azelastine q12h group, two sprays every 12 hours. (N = 76) vs. Chlorpheniramine Maleate 12 mg group-Once every 12 hours. (N = 72) vs. Placebo group (N = 75)	Follow-up time was hourly from baseline to 30 hours after.	The two Azelastine treatment groups showed significant improvement compared to placebo for the total symptom complex, Azelastine qd vs. placebo (40% vs. 20% mean percent improvement, (p<0.01)), and Azelastine q12h vs. Placebo (45% vs. 20%, (p<0.01)). These groups also showed significant mean improvement in itchy eye symptoms, Azelastine qd vs. Placebo (.6 vs. .3, (p<0.05)) and Azelastine q12h vs. Placebo (.6 vs. .3, (p<0.05)).	"Azelastine nasal spray 0.1% solution in a once- or twice-daily regimen was effective in treating the symptoms of allergic rhinitis."	2 day placebo controlled trial conducted outdoors. Both Azelastine groups were superior to placebo as was Chlorpheniramine but Azelastine was better than Chlorpheniramine as 73% of Azelastine patients reported improved symptoms lasting 12-24hours.

Bousquet 2003 (Score = 5.0)		RCT	Sponsored by a grant from Aventis Pharma. COI, El-Akkad affiliated with Aventis Pharma.	N = 431 patients with a history of seasonal allergic rhinitis (SAR) for ≥ past 3 years and a positive skin prick test or serum grass pollen specific IgE positive for grass pollen allergy in the previous years.	Mean age was 33.1±10.0 years in guidelines group and 31.7±9.0 years in the free-choice group.	Guidelines group: physician followed simple strategy based on guidelines of International Consensus on Rhinitis consisting of oral ebastine 20 mg OD and/or intranasal triamcinolone acetonide 220 µg OD and nedocromil sodium 2% eye drops b.i.d. for those with moderate/severe conjunctivitis (N = 225) vs. free-choice treatment group: physicians treated as in normal practice, depot corticosteroids disallowed (N = 244). 3 week treatment period. Assessments at baseline, 7 days, and 21 days.	No follow-up time.	Mean overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score: decrease at day 7 guidelines group 1.63 vs. free choice group 1.22 (p=0.0001); decrease at day 21 guidelines group 2.19 vs. free choice group, 1.79 (p=0.0001). Mean RQLQ eye symptoms score: decrease at 7 days guidelines group 1.86 vs. free choice group 1.37 (p=0.0003); decrease at day 21 guidelines group 2.24 vs. free choice group 1.98 (p=0.0004).	"Using a simple method for the evaluation of the severity and a simple therapeutic scheme based on International Guidelines, patients with seasonal allergic rhinitis presented a significant improvement by comparison with those receiving a non-standardized treatment."	Open label trial for 3 weeks showing guideline treated group responded better than non-standardized group.
Mösges 1995 (Score = 5.0)		RCT	No mention of sponsorship or COI.	N = 242 with ≥1 year of seasonal allergic rhinitis (SAR);	age range of 12 to 70 years.	Levocabastine nasal spray (0.5 mg/ml), one puff per nostril twice daily for 1 week (N = 123) vs. Azelastine nasal	Follow-up after 1 week of treatment.	Relief reported by patients for levocabastine vs. azelastine: 53% vs. 54%. Incidence of adverse effects for levocabastine vs.	"[T]he two agents have similar therapeutic efficacy, but that levocabastine nasal spray is better tolerated. Coupled with the fact that this agent is also available as eye drops for the relief of concurrent ocular	Open label study design. Showing both drugs exhibit similar efficacy.

						spray (1 mg/ml), one puff per nostril twice daily for 1 week (N = 119).		azelastine: 11% vs. 19% (p=0.06).	symptoms, these findings suggest that levocabastine may be the preferred topical antihistamine for the treatment of allergic rhinoconjunctivitis."	
Abelson 2003 (Score = 5.0)		RCT Double-Blind Multi-Center	Sponsored by Alcon Laboratories, Inc. No mention of COI.	N = 131 with a history of seasonal allergic conjunctivitis (SAC) or rhinoconjunctivitis; mean age of 38.53±11.61 years for olopatadine and 38.16±11.31 years for placebo.		Olopatadine 0.1% ophthalmic solution (N = 64) vs. Placebo eye drops, over-the-counter artificial tear product (N = 67). All participants: one drop per eye, twice daily, for 10 weeks. Follow-up at baseline, and days 7, 14, 28, 35, 42, 56, and 70.		Mean scores for ocular itching: day 7: olopatadine vs. placebo: 1.06 vs. 1.58, (p<0.04); day 14: 1.19 vs. 1.60, (p<0.04); day 35: 0.88 vs. 1.43, (p<0.006); day 63: 0.69 vs. 1.15), (p<0.021); day 70: 0.55 vs. 1.00, (p<0.024). Mean scores for ocular hyperemia: day 14: 0.75 vs 1.22, p<0.011); day 28: 0.67 vs. 1.07, (p<0.030); day 42: 0.63 vs. 1.16, (p<0.004); day 63: 0.42 vs. 0.82, (p<0.03). Mean scores for tearing (rated): day 14: 0.61 vs. 1.01, (p<0.020).	"In the population studied, olopatadine 0.1% ophthalmic solution controlled ocular and nasal symptoms of allergic conjunctivitis and rhinoconjunctivitis and was well tolerated when administered twice daily for 10 weeks."	Lack of study details for allocation, blinding, control for co-interventions, and compliance. Data suggest efficacy of treatment.
Ciprandi 1996 (Score = 4.5)		RCT	Sponsored partially by P.F. CNR FATMA SP2 grant, "Ingegneria genetic" project, and by the ARMIA	N = 20 with sensitivity to parietaria judaica between the ages of 18-49 suffering from seasonal allergic	mean age of 33.2 years, range of 18 to 53 years.	Azelastine 0.05% drops in one eye (N = n/a) vs. Placebo drops in the right eye + single dose 30 minutes after allergen specific conjunctival challenge or ASCC + twice daily for 1		Early phase reaction induced by ASCC: azelastine group had a significant reduction in signs and symptoms vs. placebo within 10-20 minutes after drops were administered, (p<0.01). After 7 days, another ASCC was	"Azelastine eye drops exert anti-allergic activity, inducing a rapid improvement of clinical events when administered after ASCC, and reducing both symptoms and cellular infiltration when administered before ASCC. Finally, azelastine down-regulates ICAM-1 expression on epithelial conjunctival cells,	Data suggest efficacy.

			(Associazione Riderca Malattie Immunologiche e Allergiche) foundation. No mention of COI.	rhinoconjunctivitis;		week in the following eye (N = n/a). Clinical changes were assessed 5, 10, 15, 20 minutes after allergen challenge and 5, 10, 20 and 30 minutes after drug administration.		performed. Early phase reaction 30 minutes after challenge: total symptom score and total number of inflammatory cells was less in the treatment group vs. placebo, (p<0.01). Neutrophils, eosinophils, lymphocytes and monocytes were reduced in the treatment group vs. placebo, (p<0.01). 6 hours after challenge: signs and symptoms were less in the treatment group vs. placebo (p<0.01) which was the same for inflammatory cell infiltration (p<0.01).	confirming the results obtained at nasal level."	
Albu 2013 (Score = 4.5)		RCT	No sponsorship or COI.	N = 77 with a history of at least 2 years of moderate to severe grass pollen-induced seasonal allergic rhinitis (SAR);	mean age for Group A / B; 31.42±11.82 years / 33.56±12.45 years.	Group A received intranasal phototherapy 5% UVB, 25% UVA plus 70% visible light-VS three times a week for 2 weeks (N = 39) vs. Group B received azelastine hydrochloride nasal spray, two sprays per nostril, once daily with a total dose of 1.1 mg,	Follow-up for 2 weeks.	RQLQ scores of the two groups were not significantly different at baseline, (p>0.05). Better results in nasal Symptoms, (p=0.047) and sleep domains, (p=0.05) for Group A patients. The mean total nasal resistance in Group A patients decreased from 0.42±0.18 to 0.36±0.16 Pa/cm3/s, (p=0.12), and 0.45±0.15 to	"[B]oth azelastine and intranasal phototherapy are able to significantly improve individual nasal symptoms such as rhinorrhea, congestion, itching, and sneezing in patient affected by SAR."	Open label study. Both treatment groups show efficacy.

						continued until the last visit (N = 38).		0.37±0.12 Pa/cm3/s in Group B patients, (p=0.11) at the end of the therapy.		
Duarte 2001 (Score = 4.0)		RCT	No mention of sponsorship or COI.	N = 99 with severe rhinoconjunctivitis;	mean age of 33.8 years.	Azelastine eye drops, 0.03mL (1 drop in each eye 2 to 4 times daily) and nasal spray, 0.14 mL ,one spray in each nostril twice daily (N = 53) vs. Placebo eye drops (1 drop in each eye 2 to 4 times daily) and nasal spray, one spray in each nostril twice daily (N = 46). *The patients could take an oral antihistaminic agent, Cetirizine (1 tablet, 10mg/day) from third day of local treatment	Follow up on day 7 and 14.	The efficacy of Azelastine was significantly higher compared to placebo (49% vs. 28%, p=0.04) The decrease of ocular and nasal scores by 50% without the use of Cetirizine by day 7. The cetirizine rescue was higher in placebo patients, from day 0 to 7 (4.9 ±5.0 vs. 2.7 ±4.1, p=0.02) Global efficacy was rated higher for Azelastine by investigators (26% vs. 10%, p=0.05) and patients (20% vs. 7%, p=0.01)	"[T]he combination of Azelastine eye drops and azelastine nasal spray is an effective and well tolerated treatment for seasonal allergic rhino conjunctivitis. Topical treatment usually results in a more rapid onset of effects compared to systemic treatment and can avoid adverse events usually associated with anti-histamines."	Methodological details sparse. Data suggest combination treatment may be superior to placebo.
Alexander 2003 (Score = 4.0)		RCT	Sponsored by an unrestricted grant from Allergan, Inc. No mention of COI.	N = 89 with a history of ragweed allergic rhinoconjunctivitis for 2 or more years and a positive skin prick test to	mean age of 35.8 for fexofenadine bid nedocromil rescue, 36.3 for fexofenadine qd nedocromil	Fexofenadine (60 mg / capsule) BID / Nedocromil sodium 2% eye drops - one capsule twice daily and 1 drop per eye twice daily as needed (N = 30) vs. Fexofenadine QD/ Nedocromil sodium		Symptom scores improved for all groups for itching / burning / tearing / redness / grittiness / discharge / light sensitivity and swelling (p<0.003), but no significant between groups. A clinical sign (overall signs of	"Supplementation of oral fexofenadine therapy with nedocromil sodium 2% ophthalmic solution provided effective control of ocular and rhinal symptoms associated with seasonal allergic rhinoconjunctivitis using only one-half the recommended dose of fexofenadine."	28d FU. Quasi-randomized by consecutive enrollment.

				ragweed pollen extract;	bid, and 33.4 for fexofenadine rescue, nedocromil bid.	BID - one capsule per day and 1 drop in each eye twice daily (N = 29) vs. Fexofenadine rescue/ Nedocromil sodium BID, 1 drop per eye twice daily and fexofenadine up to twice daily as needed for 1 month (N = 30). All patients were allowed Levocabastine 0.05% nasal spray.		conjunctivitis) improved for all groups, (p<0.02), but no significance between groups.		
Conde Hernández 1995 (Score = 4.0)		RCT	No mention of sponsorship or COI.	N = 63 patients with a history of seasonal allergic rhinitis (SAR).	Age range 18 to 59 years.	Azelastine nasal spray 0.56 mg/day one spray into each nostril morning and evening (N = 31) vs. ebastine tablets 10 mg/day one tablet each evening (N = 32). 14 day study period. Assessments at the beginning and end of treatment.	No follow-up time.	There were no significant differences between groups (p=0.86).	"[A]zelastine nasal spray given at a dose of 0.56 mg/day and ebastine tablets 10 mg/day are comparable and effective treatments of the nasal and ocular symptoms of seasonal allergic rhinitis."	Similar efficacy and both treatments were well tolerated. Baseline comparability not described.
Crampton 2003 (Score = 3.5)		RCT	Sponsored by a grant from Novartis Ophthalmics, Inc., Duluth,	N = 80 with a history of Rhinoconjunctivitis.	Mean age of 42.8 years.	Ketotifen, 0.025% ophthalmic Solution, 1 drop in each eye, (N = 27) vs. Desloratadine, 1 drop in each eye, (N = 27) vs.	Follow-up on day 7± 2, and on day 35± 3	Both the ketotifen and ketotifen/desloratadine groups had significantly lower mean ocular itching scores compared with those in the desloratadine	"In this study using the CAC model, ketotifen ophthalmic solution used in conjunction with a desloratadine tablet was more effective in the management of the ocular and nasal signs and symptoms of	Methodological details sparse. Data suggest Ketotifen drops may be superior to placebo drops for itching score

			Georgia. No COI.			Ketotifen with Desloratadine, 0.025% ophthalmic solution, one drop in each eye (N = 26).		group (p≤0.05) Ketotifen alone was associated with significantly less total ocular redness compared with desloratadine alone at 10, 15, and 20 minutes (p≤0.05; 1.87-, 1.67-, and 1.77-unit differences, respectively); ketotifen alone was associated with significantly less total ocular redness compared with ketotifen/desloratadine at 15 and 20 minutes (p≤0.05; 1.67- and 1.56-unit differences, respectively)	allergic rhino conjunctivitis than the systemic agent alone."	and redness score.
Charpin 1995 (Score = 3.5)		RCT	No mention of sponsorship or COI.	N = 129 with at least 1-year of seasonal allergic rhinitis (SAR);	age range of 12 to 60 years, median of 30 years.	Azelastine via nasal spray (0.14mg/activation) every day, twice a day for 14 days (N = 54) vs. Cetirizine orally (10 mg capsule) once daily, for 14 days (N = 56).	Follow-up at day 7 and 14.	Percent decrease from baseline of total symptom score of the investigator (TSSI) for azelastine vs. cetirizine: 47% vs. 55% at day 7; and 61% vs. 67% at day 14. VAS for azelastine vs. cetirizine: -13.97±1.15 vs. -9.38±0.94 for nasal stuffiness (p=0.002); -14.71±0.79 vs. -11.74±1.25 for rhinorrhea (p=0.004).	"[T]hese findings give further support to our observations that azelastine nasal spray is better tolerated and is at least as effective as oral cetirizine in the treatment of seasonal allergic rhinitis."	Sparse methodology including baseline comparability. One treatment a spray and one a fill but claims double blinded similar efficacy.

Kalpaklioglu 2010 (Score = 3.5)		RCT	No mention of sponsorship or COI.	N = 132 with allergic rhinitis and nonallergic rhinitis;	mean age of 33.14±12.52 years; age range of 14 to 70 years.	Azelastine nasal spray (AZENS) twice daily, 1.1 mg/day for 14 days (N = 62) vs. Triamcicolone acetonide nasal spray (TANS) once daily, 220µg/day for 14 days (N = 70).	Follow-up at 2-weeks after treatment.	Mean changes from baseline of AZENS vs. TANS: 14.78±16.46 vs. 7.9±19.53 (p=0.05). Percentage of adverse effects of AZENS vs. TANS: 56.9% vs. 19% (p=0.001).	"In conclusion, our study has stablished the efficacy and tolerability of AZENS when compared with triamcinolone nasal spray in patients with rhinitis, irrespective atopy. Therefore, the choice of treatment for rhinitis should depend on patient's preference regarding additional ocular symptoms, adverse effects, and the cost of the drug."	Similar efficacy between groups although AZENS group had more adverse events (56.9% vs. 19.0%).

Atopic and Vernal Keratoconjunctivitis

OVERVIEW

Vernal keratoconjunctivitis is a relatively rare, chronic, severe allergic inflammation of the ocular surface mediated by Th2-lymphocytes. Yet, 50% of patients do not have IgE mediated mechanisms [689]. It is considered the ocular manifestation of atopic dermatitis. It primarily begins in childhood [592, 689], thus is largely considered non-occupational. It is more common in the tropics than the northern climates. [592] Occasional cases can occur throughout the United States and Canada. It may be worsened by non-specific hyperreactivity due to wind, dust and sunlight. [592]

The evaluation of patients with vernal keratoconjunctivitis is similar to other allergy investigations (see above). Limited RCTs on treatments result in a relatively weak evidence base. By inference, treatments recommended for other allergic eye diseases are also recommended for vernal keratoconjunctivitis.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Akpek 2004 (Score = 7.5)	Cyclosporine	RCT	Sponsorship, Supported, in part, by an unrestricted research grant from Allergan Inc. Dr Schein is supported in part by a National Institutes of Health grant (no. K24EY00395) and the Burton Grossman Fund for Preventive Ophthalmology..No mention of COI.	N = 22 with diagnosis of Atopical Keratonconjunctivitis (AKC).	Mean± SD age: 42.6±14.6 years.	Topical cyclosporine A 0.05% Cyclosporine, (N = 10) vs. Preservative-free artificial tears placebo, for 4 weeks (N = 12).	Follow ups were at day 7, day 14, day 21, and day 28.	Mean comparison scores / Mean scores for Bulbar conjunctival hyperemia, Upper tarsal conjunctival, and Punctate Keratitis before and after treatment / mean change in composite sign score: (4 vs. 0.5, p = 0.048) / (2.0 vs. 1.0, and after 1.5 vs. 1.0, p = 0.017, 3.0 vs. 1.5, and 2.0 vs. 2.0, p = 0.005, and keratitis 3.0 vs. 0.5, and 1.0 vs. 1.5, p = 0.007) / (5 vs. -1, p = 0.002 for mean change in composite sign).	"In this short-term, double-masked, randomized study, we used cyclosporine A 0.05% in an emulsion formulation in the treatment of patients with topical steroid-resistant AKC. Treated patients had great improvement of both signs and symptoms of AKC than did the placebo group."	Small sample size. Patients treated to different disease duration at baseline (96 v 150 m). Data suggest modest effect.
Daniell 2006 (Score = 6.5)	Cyclosporine	RCT	No COI. No mention of sponsorship.	N = 40 with Atopic Keratoconjunctivitis or Vernal Keratoconjunctivitis.	Mean± SD age Group 1: 26.2±18.0 years. Mean± SD age	Group 1: 0.05% topical ciclosporin A, Restasis, Allergen, Irvine, CA, USA (N = 20). vs. Group 2: Placebo,	Follow-up at baseline, week 1, month 1, month 2, and	At baseline, no significant differences between groups. At week 1, significant difference in steroid drop usage, treatment: 99.3 ± 45.1 vs. Placebo,	"The results of our trial failed to show a beneficial effect from the addition of topical ciclosporin 0.05% in steroid dependent allergic eye disease."	Data suggest lack of efficacy.

					Group 2: 26.2±16.3 years.	vehicle (N = 20).	month 3.	66.5 ± 45.9, but was not significant at any other time period.		
Avunduk 2003 (Score = 7.0)	NSAID vs. Corticosteroid drops	RCT	Sponorship, supported in part by US Public Health Service Grant EY02377 (H.E.K.) from the National Eye Institute, National Institutes of Health, Bethesda, Maryland, and an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York. No mention of COI.	N = 32 with keratonconjunctivitis with or without Sjögren syndrome.	Mean± SD age Groups 1: 51.2±12.4 years. Mean± SD age Group 2: 46.67±8.66 years. Mean± SD age Group 3: 57.6±12.4 years.	Group 1: artificial tears QID in both eyes (N = 8). vs. Group 2: NSAID opthalmic drops QID with artificial tears vs. and artificial tear (N = 9) vs. Group 3: corticosteroidal drops QID with artificial tears (N = 11).		Symptom severity scores / Staining scores on days 15 and 30: (p = 0.02 for group 3 vs. p = 0.03 for groups 1 and 2, and at day 30 p = 0.03 for groups 1, 2 and 3) / (3 vs. 1 and 2, p = 0.046 and at days 15 and 30, p = 0.01 for 3 vs. p = 0.02 for 1 and 2). At day 15 and 30, group 3 had significantly lower mean scores than group 2, p = 0.017, and higher PAS + cells vs. groups 1 and 2, p = 0.034 and 0.028, respectively.	"The results of the study implied that TSDs were more effective than topical NSAIDs or ATS in reducing the ocular surface inflammation in KCS patients. Topical steroids had a clear beneficial effect both on the subjective and objective clinical parameters of moderate-to-severe dry eye patients."	Data suggest efficacy of steroid drops compared with topical NSAID and artificial tears.

Oguz 1999 (Score = 6.0)	Lodoxamide tromethamine	RCT	No mention of sponsorship or COI.	N = 30 symptomatic patients with vernal conjunctivitis (VC) for at least 1 year.	Mean± SD age Group 1: 48.7±11.30 years. Mean± SD age Group 2: 51.9±10.9 years.	Lodoxamide tromethamine 0.1% ophthalmic solution (N =16) vs. Placebo in both eyes 4 times a day for 4 weeks (N =14).		The lodoxamide group had a significant reduction from baseline in the number of neutrophills, p = 0.051 and eosinophils, p = 0.020 vs. placebo.	"[L]odoxamide is effective in reducing inflammatory cells in the tear fluid in vernal conjunctivitis. These effects of lodoxamide on tear fluid cytology may be associated with relief of the signs and symptoms of this disease."	Limited patient description. Data suggest efficacy in cell counts. Symptoms not reported.
White 2008 (Score = 5.5)	Loteprednol etabonate	RCT		N = 280 with clinically diagnosed blepharoke-ratoconjunctivitis.		LE / T or loteprednol etabonate + tobramycin ophthalmic suspension, 0.5 % / 0.3% + self-administration of medication four times / day, 1 - 2 drops within four hour interval (N = 136) vs. DM / T or dexamethasone + tobramycin ophthalmic suspension, 0.3% / 0.1% + self-administration	Follow-up for 14 days.	At visit 2 / 3 / and 4 from baseline the mean sd change: (-7.1 vs. -7.6) / (-12.3 vs. -13.2) / and (-15.2 vs. -15.6 in DM / T). 78% reduction in signs and symptoms of ocular inflammation associated with blepharokeratoc-onjunctivitis from baseline for both treatments.	"The results of this study demonstrate that LE / T is as effective as DM / T in reducing the signs and symptoms of ocular inflammation associated with blehparokeratoconjunctivitis."	Study was described as a non inferiority study and no differences between groups were seen. However, authors present 90%CI not 95%CI. Possible differences may exist.

						of medication four times / day, 1 - 2 drops within four hour interval (N = 137).				
Ruggieri 1987 (Score = 5.0)	Sodium cromoglycate	RCT	No mention of sponsorship or COI.	N = 31 with active bilateral vernal Keratonconjunctivitis or seasonal allergen conjunctivitis.	Mean (Range) age treatment: 19.2 (6-37) years. Mean (Range) age placebo: 18.9 (6-40) years.	4% ointment of sodium cromoglycate (N = 15) vs. Placebo ointment 3 times daily for 4 weeks (N = 16).		The difference between two treatment groups was significant, p = 0.00002. Improvement continued during the third and fourth week, p < 0.01. Overall, the treatment with 4% sodium cromoglycate was more effective than placebo.	"[4]% sodium cromoglycate eye ointment is effective in the treatment of seasonal allergic conjunctivitis and vernal keratoconjunctivitis."	Data suggest efficacy.

Goes 1994 (Score = 5.0)	Levocabastine	RCT	Sponsorship, supported by a research grant from the Janssen Research Foundation. No mention of COI.	N = 49 with a history of vernal conjunctivitis or VC.	Mean (Range) age: Treatment group 15 (5-59) years. Mean (Range) age: Placebo group 14.5 (10-38) years.	Levocabastine 0.5 mg/ml (N = 31) vs. Placebo 1 drop / eye 4 times daily for up to 4 weeks (N =18).		Treatment duration was longer in the levocabastine group (22 days) vs. placebo (9 days), p < 0.02. More patients in the placebo group dropped out due to inefficacy, p = 0.013. Severest ocular symptom (start/endpoint - change from baseline): levocabastine (2.65/-1.54) vs. placebo (2.39 / -0.77), p = 0.04. Ocular irritation: 1.89/-1.24 vs. 1.77 / - 0.58, p = 0.05. Photophobia: 1.00/-1.24 vs. 0.85/-0.11, p = 0.008. Ocular itching: 2.50 / - 1.73 vs. 2.08 / -1.00, p = 0.05.	"Levocabastine eye-drops proved to be effective and well-tolerated for the treatment of vernal conjunctivitis. A dramatic improvement in symptoms was observed within one to two weeks of initiation of treatment and therapeutic efficacy was maintained throughout the study period."	One week trial. Data suggest efficacy, however few contained in open label.

Hillenkamp 2002 (Score = 4.0)	Cidofovir	RCT	No mention of sponsorship or COI.	N = 34 with acute adenoviral keratonconjunctivitis of recent onset.	Mean age: 48.6 years. No SD or Range given.	Cidofovir 1% drops 4 times daily to both eyes (N = 9) vs. Cidofovir 1% drops 10 times daily to both eyes (N = 5) vs. Cidofovir 1% eyedrops + cyclosporine A 1% eyedrops 4 times/day to both eyes (N =10) vs. Sodium chloride eyedrops 4 times/day to both eyes or controls (N = 10). All patients treated with preservative-free topical lubrication.	Follow-up for 21 days.	Side effects / pseudomembranes/ prevalence of severe corneal opacities: (44.4% vs. 100% vs. 30% vs. 0% sodium group) / (55.6% vs. 80% vs. 20% vs. 20%) / (higher prevalence in control group, p = 0.048).	"Cidofovir lowers the frequency of severe corneal opacities, but its clinical use 4 to 10 times daily at a 1% concentration is limited by local toxicity."	Pilot study. Data suggest high adverse effects.

Grönlund 2004 (Score = 2.5)	Acupuncture	RCT		N = 25 with keratoconjunctivitis.		Acupuncture treatment group or ATG (N = 12) vs. Control Group or CG underwent some examinations over corresponding period of time (N = 13)		There were no significant differences between groups in frequency of eye drops use and total number of subjective symptoms. At the first follow-up, there was a significant difference between groups in VAS recordings (ATG vs. CG, Better: 6 vs. 0, No Change: 4 vs. 8, Worse, 0 vs. 2, p = 0.036).	"In conclusion, although based on a small number of patients, our results indicate that sensory nerve stimulation has subjective beneficial effects in patients with KCS and therefore could be tried as a complement to ordinary treatment."	Study done in Sweden. Details sparse. Large dropout. Small sample size (N=25, 20 completed).

Chemical Burns

OVERVIEW

Workplace chemical eye burns result most commonly from exposures to either alkaline agents (e.g., lime or sodium hydroxide) or acids, although they can occur with petrochemicals and other substances. [690-696]. The specific chemical(s) involved, its concentration, quantity and duration of exposure are critical in determining extent of, and limiting the insults of, the injury. Rapid, initial management is likely the most critical aspect of the management and conveys subsequently improved prognosis when rapidly executed. [693, 694, 696-699].

Prevention

See sections above.

Education

See sections above.

TREATMENT RECOMMENDATIONS

Immediate treatment to irrigate the eye with copious water or other aqueous irrigating solutions is believed to be critical for improved, successful patient treatment [696, 698, 700]. Uncontrolled studies suggest better outcomes with longer duration of irrigation [699].

Copious Irrigation for Chemical Eye Exposures

Recommended.

Medications (including topical creams)

Copious Irrigation is recommended for chemical eye exposures.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	All chemical eye exposures and injuries. It is recommended to begin irrigation immediately after eye exposure, rather than waiting for symptoms to develop. It is also recommended to begin irrigation promptly while others attempt to identify the specific chemical(s)/agent(s), concentration(s) and duration of exposure. Irrigation should also be used until Morgan lens, if indicated, is available for more severe injuries.
Harms:	Negligible. Mild discomfort from solution and irrigation
Benefits:	Limiting extent of burn/injury, earlier relief of pain
Frequency/Dose/Duration:	Tap water is most commonly available and should be used if that is the most readily available solution, especially for first line, in-plant settings. Irrigation bottles with irrigating solutions

	are also useful in in-plant medical departments, clinical settings and distributed in some chemical laboratories and facilities. Normal saline, lactated Ringer's solution are additional options for initial irrigation and are preferable to tap water, but only if immediately available. Substitute normal saline or lactated ringer's or other balanced saline solution for tap water when available. Generally use topical anesthetic to anesthetize the eye when available, as it will assist in better tolerance of irrigation.
Indications for Discontinuation:	Only after extensive irrigation, usually at least 1-2 liters has been used to flush out the chemical. Neutralization of pH should be demonstrable for acid or alkaline exposures. The pH should be 7.0-7.2. The pH should be checked after discontinuing irrigation to assure that additional irrigation is not needed to maintain pH neutrality.
Rationale:	There are no quality studies identifying use compared with non-use of irrigation. There are experimental studies of irrigating solutions for treatment especially of animal models. These animal studies suggest superiority of balanced salt solutions (e.g., normal saline, lactate Ringer's solution) over hypotonic solutions (such as tap water). Still, experience suggests earlier irrigation with the most readily available solution, including tap water, is the preferred initial strategy and is recommended. Once irrigation is underway, tailoring of further irrigation, including possible use of an irrigating system (e.g., "Morgan lens") may be considered.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	[Can include harms, benefits, advantages, limitations, etc.]

Irrigating Systems (e.g., Morgan Lens) for Chemical Eye Exposures

Recommended.

Devices

Irrigating Systems (e.g., Morgan Lens) is recommended for chemical eye exposures.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	High volume exposures and/or highly alkaline/acidic and/or high-risk injuries. It is recommended to begin irrigation immediately after eye exposure (see Copious Irrigation above), rather than waiting for setting up an irrigation system. Irrigation should also continue while setting up the irrigation system.
Harms:	Mild to moderate discomfort from the irrigating system
Benefits:	Potential to further limit extent of burn/injury beyond that obtainable without the system for more severe exposures
Frequency/Dose/Duration:	Generally use a balanced salt solution (e.g., normal saline (0.9%), lactated Ringer's solution). For most chemicals, 500mL at fast rate (run in 'open') is recommended. Reassess and consider additional fluid depending on chemical, concentration, dose, duration of contamination, severity and clinical effects. For alkali burns, 2 liters wide open is recommended, then 50mL/hr until pH in eye cul-de-sac is neutral. If balanced salt solution unavailable, tap water may be substituted until balanced salt available or transit to definitive care from an in-plant setting.
Indications for Discontinuation:	Only after thorough irrigation of affected area. Neutralization of pH should be demonstrable for acid or alkaline exposures (pH 7.0-7.2).
Rationale:	There are no quality studies comparing use with non-use of irrigating systems. There are animal models suggesting successful use. Irrigating systems, including "Morgan Lenses" are minimally invasive, have minimal adverse effects, are low cost and are selectively recommended for chemical eye exposures.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and

	considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	

Artificial Tears or Lubrication for Chemical Ocular Burns

Recommended.

Medications (including topical creams)

Artificial tears or lubricants are selectively recommended for treatment of patients with chemical ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☒ Subacute ☒ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Chemical ocular burns of sufficient size and pain, and particularly among those with inadequate tearing.
Benefits:	May provide sufficient tears to reduce symptoms and potentially improve healing.
Harms:	Undefined but likely negligible.
Frequency/Dose/Duration:	Prn
Indications for Discontinuation:	Resolution of symptoms
Rationale:	There are no quality trials of artificial tears for chemical ocular burns. Patients with more extensive burns tend to have greater need for artificial tears. Artificial tears are inexpensive, noninvasive, and have low adverse effects and are recommended particularly for those patients with inadequate tears.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and

considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.

Comments:

Evidence for Artificial Tears or Lubrication

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Xiao 2012 [167] (score = 4.0)	Animal Trials: Mice: Phosphate buffered saline (PBS) vs Minocycline in alkali burns.	RCT	Supported by ''Fundamental Research Funds for the Central Universities'' in China (grant number: 3030901009015, Shi-you Zhou) and the NSFC-RGC HK joint project (grant number: 30731160617, Rong-biao Pi). No COI.	N = 105 mice treated with alkali burns.		Group 1- Phosphate buffered saline (PBS)-Control group (N = unknown) vs Group 2-Minocycline twice a day (60 mg/kg or 30 mg/kg) (N = unknown) vs Group 3- 14 consecutive days of minocycline (60 mg/kg or 30 mg/kg) (N = unknown)	Follow-up for 14 days.	The area of CNV increased over time in all three groups. The CNV percentage in the high-dosage group reduced significantly compared to the control group at all follow-up days; (all were $p < 0.01$). The only follow-up day were the low-dosage group vs. control group was the 4th day (20.62% vs. 32.39%), ($p < 0.01$).	"In summary, minocycline has more functions besides its antibiotic character, as shown in this study and in other reports. Minocycline may someday play a promising role in preventing CNV."	Group numbers not given. Data suggest intraperitoneal injection of Minocycline (60mg/kg) bid significantly inhibits neovascularization of alkali burned mice corneas also decreasing inflammation response.
Sharma 2011 [149] (score = 6.0)	Human Trials: Saline vs Lactated/Balanced Saline Solution	RCT	No mention of sponsorship. No COI.	N = 32 (33 eyes) with acute ocular chemical burns of grade III, IV, and V severity. Mean age for Umbilical Cord Serum /		Group I, 20% umbilical cord serum drops (N = 12) vs. Group II, 20% autologous serum drops (N = 11) vs. Group III, artificial tear drops, specifically 0.5% hydroxypropylmethylcellulose and 0.3% glycerin (N = 10).	Follow-up at day 1, 3, 7, 14, and 21 and at the end of months 1, 2, and 3.	16 / 33 eyes had a grade III injury, 9 grade IV, and 8 grade V injury. The mean time to complete epithelialization was 21.16 ± 26.81 / 56.6 ± 35.5 / and 40.13 ± 35.79 days in the cord serum / autologous serum / and artificial	"Umbilical cord serum therapy is more effective than autologous serum eye drops or artificial tears in ocular surface restoration after acute chemical injuries."	Data suggest umbilical cord serum more effective than autologous eye drops on artificial tears in restoration of ocular surfaces post chemical burn.

				Autologous Serum / and artificial Tears group: 30.1 ± 11.2 / 26.9 ± 7.8 / and 31.0 ± 8.2.				tear group, respectively, (p = 0.02). More patients had clear corneas with cord serum vs autologous serum and artificial tears, (p = 0.048).		
Panda 2012 [150] (score = 5.5)	Human Trials: Saline vs Lactated/Balanced Saline Solution	RCT	No sponsorship and or COI.	N = 20 (20 eyes) with grades III, IV, and V chemical injuries. Mean age for group I / and II; 31.5 ± 9.78 / and 39.6 ± 12.32.		Group I, treated with autologous PRP eye drops plus standard medical therapy (N = 10) vs. Group II, standard medical therapy plus artificial tears (N = 10).	Follow-up on days 3, 7, 14, 21, 30, 60, and 90.	At 3 months, significant corneal clarity improvement in group I, (63.64 ± 55.75 and 37.74 ± 9.66 group II, p = 0.048). The mean and median range time to complete epithelialization were 14 ± 7 days and 14 (7–21) days in group I vs 28.5 ± 3.67 days and 28.5 (21–30) days in group II, (p = 0.006).	"Topical autologous platelet-rich plasma therapy is safe and effective, and it promotes rapid reepithelialization of ocular surface and can be administered along with standard medical therapy."	Small sample. Some baseline differences between groups. Data suggest PRP speeds reepithelialization of the ocular surface post chemical injury compared to standard medical treatments.
Herr 1991 [151] (score = 5.0)	Human Trials: Saline vs Lactated/Balanced Saline Solution	RCT	No sponsorship and or COI.	N = 20 (20 eyes) with grades III, IV, and V chemical injuries. Mean age for group I / and II; 31.5 ± 9.78 / and		Group I, treated with autologous PRP eye drops plus standard medical therapy (N = 10) vs. Group II, standard medical therapy plus artificial tears (N = 10).	Follow-up on days 3, 7, 14, 21, 30, 60, and 90.	At 3 months, significant corneal clarity improvement in group I, (63.64 ± 55.75 and 37.74 ± 9.66 group II, p = 0.048). The mean and median range time to complete epithelialization	"Topical autologous platelet-rich plasma therapy is safe and effective, and it promotes rapid reepithelialization of ocular surface and can be administered	Small sample. Some baseline differences between groups. Data suggest PRP speeds reepithelialization of the ocular surface post chemical injury compared to

				39.6 ± 12.32.				were 14 ± 7 days and 14 (7–21) days in group I vs 28.5 ± 3.67 days and 28.5 (21–30) days in group II, (p = 0.006).	along with standard medical therapy."	standard medical treatments.
Márquez De Arancena Del Cid 2009 (score = 2.0)	Human Trials: Saline vs Lactated/Balanced Saline Solution	RCT	No COI. Supported by Señores de la Casa Real de los Godos.	N=35 eyes of 35 patients with ocular alkali burns. Mean age of all groups: 33.7 years.		5 groups according to severity of burns. Group 1 (control), N=10 with type II burns who received conventional topical treatment vs. Group 2: N=5 with type II burns who received topical treatment + subconjunctival RFRP (APT) and 3 groups with 3–6 hours of limbal involvement and 30%–50% conjunctival involvement (type III burns of Dua classification) vs. Group 3 (control): N=10 with type III burns who received conventional topical treatment vs. Group 4: N=5 with type III burns who received conventional topical treatment + subconjunctival injection of autologous blood (autohemotherapy) vs. Group 5: N=5 with type III burns who received topical treatment + subconjunctival RFRP (APT).	24h, 48h, 72h, and 5, 7, 10, 14, 20, 25, 30, and 40 days.	Average epithelization time of the cornea in the stage II burns (Groups 1 and 2): 5 days, SD 2.2 vs. stage III (Groups 3-5) 8.7 days, SD 6 days).	"Subconjunctival infiltration with autologous RFRP can be considered an effective, straightforward, and economical form of treatment for burns of the ocular surface"	Randomization dubious. Groups were stratified according to severity of burns. Data suggest in moderate ocular burns there was reduction in time to corneal and conjunctival epitheliazation and healing as well as sick time for group treated with RFRP compared to control group.
Haddox 2001[164] (score = 3.5)	Animal Trials: Rabbits: Phosphate-buffered saline	RCT	Sponsored by grants from the National Eye Institute and	N = 48 albino rabbits (2.0-2.5		Phosphate-buffered saline (PBS) control (N = 16) vs 800 µM RTR (dextrorotatory) tetramer in PBS alternating	One drop hourly startin	Inhibition of Ac-PGP–Induced Neutrophil Polarization (100	"The reduction in the frequency of corneal ulceration by the	Data suggest RTR tetramer may be beneficial in alkali

	(PBS) vs tetramer on eye burns.		the National Institutes of Health. No mention of COI.	kg) with right corneal burns		each hour with 1.5 mM RTR (levorotatory) tetramer in PBS (N = 16) vs 12 µM 5F in PBS. One drop hourly starting 2 hours after injury (14 times a day) for 33 days. Study ended on day 42.	g 2 hours after injury (14 times a day) for 33 days. Study ended on day 42.	nM/ 1 µM/ 10 µM/ ID50, 50% inhibitory dose: (L)-RTR tetramer 21% ±15.1% (n = 2)/ 75% ± 4.8% (n = 12)/ 94% ± 2.5% (n = 5)/ 580 nM (p<0.001); (D)-RTR tetramer 37% ± 13.2% (n = 7)/ 65% ± 10.6% (n = 6)/ 92% ± 2.4% (n = 6)/ 520 nM (p<0.001). Inhibition of Me-PGP–Induced Neutrophil Polarization (5 µM/ 70 µM/ 500 µM/ ID50): (L)-RTR tetramer —/ 60% ± 29.7% (n = 2)/ 100% (n = 2)/ 57 µM (p<0.01); (D)-RTR tetramer 14% ± 4.5% (n = 5)/ 45% ± 4.9% (n = 2)/ 100% (n = 5)/ 110 µM (p<0.001). Total ulcers from day 1 to day 33 (RTR Tetramer/PBS/5F) : 4/9/11 (p=0.0360). Total ulcers at day 42: 6/12/8 (p=0.0163). Total	RTR tetramer possibly resulted from its complementary binding to Ac-PGP and Me-PGP in the cornea shortly after alkali injury, leading to a reduction in the early and late infiltration of neutrophils.”	injured rabbit cornea.

								ulcers during study period: 7/14/11 (p = 0.0046).		
Shahriari 2008 [157] (score = 4.5)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 30 rabbits with alkaline corneal epithelial wound.		Group I, amniotic membrane suspension in the other eye (N = 10) vs Group II, autologous serum in one eye and amniotic membrane suspension in the other eye (N = 10) vs Group III, preservative-free artificial tears in 1 eye (N = 10).	Follow-up for 47 hours.	Average wound areas for Groups I / II / and III: 24.3 ± 6 2.1 mm2 / 25.7 ± 2.4 mm2 / and 24.5 ± 1.9 mm2. There was a difference in mean values among the treated groups comparing amniotic membrane suspension vs other groups, (p = 0.001).	"This study shows that alkali-injured corneal epithelial wounds heal faster when treated with amniotic membrane suspension than with autologous serum or preservative-free artificial tears."	Data suggest alkali burned rabbit corneas heal faster with treatment of amniotic membrane suspension compared to artificial tears or autologous serum.

NSAID Drops for Chemical Ocular Burns

Recommended.

Medications (including topical creams)

NSAID ophthalmic drops are recommended for treatment of chemical ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Chemical ocular burns
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	allergic reactions in susceptible patients, intolerance.
Frequency/Dose/Duration:	As per manufacturer's recommendation
Indications for Discontinuation:	With symptom improvement
Rationale:	There are no quality trials for treatment of chemical ocular burns with ophthalmic NSAID drops. NSAID drops are low cost, not invasive, associated with low risks and are recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	

Glucocorticosteroid drops have been used for treatment of chemical burns, sometimes in conjunction with vitamin C. ([701]) ([692]; [702, 703])

Evidence for NSAID Drops for Chemical Ocular Burns

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Simavli 2014 [170] (score = 5.0)	Animal Trials: Rats: Dexamethasone vs Propanolol in alkali corneal burns	RCT	No mention of sponsorship. No COI.	N = 24 Wistar rats with alkali-induced corneal neovascularization (CNV) using NaOH.		Group 1- received 0.9% NaCl (N = 6) vs Group II- received preservative-free dexamethasone sodium phosphate 1mg/mL (N = 6) vs Group III- propranolol hydrochloride 1 mg/mL (N = 6) vs Group IV- received 0.5 mg/mL propranolol hydrochloride drops twice a day for 7 days (N = 6).	7 days	There was no significant difference in percent areas of CNV between the groups (p = 0.004). Groups I, III and IV showed significantly higher anti-VEGF immunostaining intensity compared to group II (p<0.01). However, there were no differences between groups I, III and IV.	"Topical propranolol 1 or 0.5 mg/mL does not have a significant inhibitory effect on alkali-induced corneal NV in rats."	Data suggest that topical administration of propranolol for prevention of corneal neovascularization is not effective.
Yamada 2003 [173] (score = 4.0)	Animal Trials: Rats: Role of IL-1 on reducing corneal inflammation.	RCT	No mention of sponsorship or COI.	N = 28 Wistar rats with induced alkali injury through application of 1N NaOH. Rats aged ten to 12-week-old female rats.		Group 1- Topical interleukin-1 (IL-1) 20 mg/mL in 0.2% sodium hyaluronate (N = 14) vs Group 2- Vehicle alone (N = 14).		As early as day 3, the difference in CNV between the IL-1 and vehicle-treated eyes were as evident as early as day 3. On day 7, the IL-1 treated eyes demonstrated a significant decrease in the number of cells infiltrating the corneas; 12.4 cells x10-2 vs. 32.6 cells x 10-2 (p < 0.03).	"We conclude that local antagonism of IL-1 after alkali injury can significantly decrease corneal inflammation and lead to enhanced corneal transparency."	Small sample. Data suggest IL-1 significantly decreased corneal inflammation in rats with alkali corneal burns and thus lead to increased corneal transparency.

Glucocorticosteroid Drops for Chemical Ocular Burns

Recommended.

Medications (including topical creams)

Glucocorticoid ophthalmic drops are recommended for select treatment of chemical ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Moderate to severe chemical ocular burns
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	Increased risk of infection, increased risk of cataracts, intolerance.
Frequency/Dose/Duration:	As per manufacturer's recommendation
Indications for Discontinuation:	With symptom improvement. Generally discontinued at one week.
Rationale:	There are no quality trials for treatment of chemical ocular burns with ophthalmic glucocorticoid drops. These medications are used to attempt to reduce the inflammatory process associated with healing chemical burns. These drops are low cost, not invasive, associated with low to moderate risks and are recommended for more severely affected patients. Animal studies are also supportive of a week of treatment [704-706].
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, **6 human randomized trials** and **27 animal randomized trials** and 4 systematic studies met the inclusion criteria. No quality trials for treatment of chemical ocular burns with ophthalmic glucocorticoid drops were found.

Evidence for Glucocorticosteroid Drops for Chemical Ocular Burns

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Siganos 1998 [153] (score = 5.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 20 rabbits with a standardized alkali burn (1N NaOH) was performed in the center of the cornea.		Group 1- Topical zinc desferrioxamine, 220 µM (N = 10) vs. Topcial zinc desferrioxamine vehicle group (N = 10).	Follow-up for 28 days	Throughout the study period, the grade of mean corneal ulcerations ranged from 0.2 to 1.00 compared to 1.4 to 2.7 in group 2. The mean ulceration area was greater in group 2 compared to group 1; 5.4 vs. 1.5, ($p < 0.05$).	"Topical zinc desferrioxamine may be an adjunctive treatment in protecting the cornea against induced alkali injury. We suggest that Zn/DFO may have a role as an adjunctive treatment in alkali injury of the cornea."	Data suggest topical zinc desferrioxamine may be protective against corneal ulceration in alkali burned rabbit eyes.
Mello 2011 [154] (score = 5.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 20 rabbits underwent chemical trauma with sodium hydroxide.		Experimental group, a subconjunctival injection of bevacizumab 0.15 m; 3.75 mg (N = 10) vs. Control group received an injection of 0.15 ml saline solution (N = 10).	Follow-up for 14 days.	Neovascular vessel length was greater in Experimental vs control group, ($p < 0.010$). Vessel inflammation/diameter was 0.500 (0.269 – 0.731).	"Subconjunctival bevacizumab inhibited neovascularization in the rabbit cornea."	Data suggest subconjunctival bevacizumab did not reduce inflammation but does inhibit neovascularization in alkali burned rabbit eyes.
Marinho 2003 [155] (score = 4.5)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	Sponsored by Public Health Service Research Grant EY06819 to S.C.G.T. from the Department of Health and	N = 30 (30 eyes) rabbits underwent chemical burn.		Group 1, treated with conjunctival limbal autograft CLAU(N = 9) vs. Group 2, underwent conjunctival limbal autograft or CLAU and AMT	Follow-up at days 30, 60, and 90.	At 30 days after surgery, ($p = 0.057$), and at 60 and 90 days, ($p < 0.001$) significant difference between operated groups 1 and 2 and the control group. The corneas in the control group were significantly	"CLAU is effective in treating limbal deficiency."	Small sample size. Data suggest although groups 1 and 2 had better clinical outcomes compared with control group 3, AMT does not add a benefit to CLAU

			Human Services, National Eye Institute, National Institutes of Health, Bethesda, MD. S.C.G.T. has obtained U.S. patent on the method of preparation and clinical uses of human amniotic membrane.			(N = 8) vs Group 3, served as control without surgery (N = 7).		more opaque vs groups 1 and 2, ($p < 0.05$). Clear corneas was significantly more common in groups 1 and 2 vs controls, ($p < 0.001$).		and is not superior to CLAU alone.
Pfister 2006 [156] (score = 4.5)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	Sponsored by National Eye Institute Grant. No mention of COI.	N = 24 rabbits exposed to 1 N NaOH for 35 seconds.		Phosphate-buffered saline or PBS (N = 8) vs 1.5 mM L-RTR solution (N = 8) vs 800 mM D-RTR solution (N = 8).	Follow-up for 36 days.	The severity of cornea ulceration was statistically less in the L-RTR tetramer group vs PBS control on day 21, ($p < 0.001$). A statistically significant difference in the number of ulcers beginning on day 22 for L-RTR vs PBS (18.8% L-RTR vs 56.3% control, ($p < 0.05$). No appreciable increase in neutrophils from 12 to 48 hours in the RTR-treated group.	"Binding of the PGP molecules by RTR tetramer seems to deprive the cornea of this neutrophilic chemotactic stimulus, leading to a reduction in the severity and incidence of corneal ulceration."	Small sample. Data suggest at 22 days there was significant reduction in the number and severity of corneal ulcers in RTR group compared to controls.
Shahriari 2008 [157] (score = 4.5)	Animal Trials: Rabbits: Topical Steroids vs	RCT	No mention of sponsorship or COI.	N = 30 rabbits with alkaline corneal epithelial wound.		Group I, amniotic membrane suspension in the other eye (N = 10) vs Group II, autologous serum	Follow-up for 47 hours.	Average wound areas for Groups I / II / and III: 24.3 ± 6 2.1 mm2 / 25.7 ± 2.4 mm2 / and 24.5 ± 1.9 mm2. There was a difference in mean	"This study shows that alkali-injured corneal epithelial wounds heal faster when treated with amniotic	Data suggest alkali burned rabbit corneas heal faster with treatment of amniotic membrane

	Normal Saline					in one eye and amniotic membrane suspension in the other eye (N = 10) vs Group III, preservative-free artificial tears in 1 eye (N = 10).		values among the treated groups comparing amniotic membrane suspension vs other groups, (p = 0.001).	membrane suspension than with autologous serum or preservative-free artificial tears."	suspension compared to artificial tears or autologous serum.
Donshik 1978 [158] (score = 4.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	Sponsored in part by research, training grants and research fellowship award National Eye Institute, Biomedical research support grant, Eye research Core grant, and in part by Massachusetts Lions Eye Research Fund Inc. No mention of COI.	N = 18 rabbits with bilateral central alkali burns were produced in anesthetized albino rabbits by placing a filter paper disc (7 mm in diameter).		Group I, one eye treated with one drop (0.05 ml) of 0.1% dexamethasone sodium (Decadron) every hour, 12 times per day, plus mixture of neomycin sulfate and dexamethasone sodium phosphate (Neodecadron) after the last drop of steroid (N = 16) vs Group II, the other eye treated with normal saline solution 12 times per day, plus a mixture of neomycin sulfate, polymyxin B sulfate, bacitracin zinc (Neosporin Ointment) after the last saline drop (N = 10).	Follow-up for 36 days.	Steroids given the second and third weeks following the burn enhanced the severity and proportion of ulcers, ($p < 0.1$). When corticosteroids given daily for six first days, or fourth or fifth week following the burn, did not have an adverse effect on the cornea.	"Protein synthesis, as measured by tritium leucine incorporation into protein secreted into the media, was either unaffected or actually somewhat inhibited by the steroids at the concentrations tested."	Data suggest topical steroids may be administered in rabbits during the first week and after. The burn has stabilized without increasing frequency and severity of ulcerations.

Sharifipour 2007 [159] (score = 4.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 28 rabbits with severe corneal alkali injury.		Oxygen treatment, received 100% at a flow of 5 L/min for 1 hour daily, with one eye patched (N = 14) vs Control group, received chloramphenicol eye drops 4 times daily, plus eye patch for 1 hour daily and received (N = 14).	Follow-up for 1 month.	At 30 days, 1 anterior and 1 middle-stromal ulceration in control vs 3 anterior and 2 middle and 1 posterior ulceration in oxygen group, not statistically significant. Mean difference of ulceration was 13.45 days in control group vs 18.11 days in oxygen group, (p = 0.032).	"Oxygen therapy at a flow of 5 L/min for 1 hour daily reduces the possibility of corneal perforation in rabbits and may delay ulceration of the cornea compared with the control group."	Study states double blinding but methodology of double blinded not supported. Data suggest oxygen therapy may delay corneal ulceration in severe alkali burned rabbit corneas and may delay corneal perforation.
Brent 1991 [160] (score = 4.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 24 eyes of 12 adult albino rabbits weighing 2.1-2.9 kg with a standard conjunctival burn		Topical prednisolone phosphate 1% one drop every 6 hours in one eye (N = 12) vs Salt solution one drop every 6 hours in the other eye, control (N = 12).	Treatment for 6 days. No mention of follow-up time.	Mean ± SD goblet cells per unit area: treatment 97.38±34.8 vs. control 65.81±18.6, (p < 0.02).	"These results suggest that topical steroids are beneficial in suppressing goblet-cell loss after a conjunctival alkali burn."	Small sample. Data suggest topical steroids for alkali burned rabbit eyes had significantly greater numbers of goblet cells per units of conjunctiva suggesting benefit.
Sekundo 2002 [171] (score = 4.0)	Animal Trials: Rats: Allopurinlol vs Prednisolone vs Acetyl cysteine vs NS for corneal burns.	RCT	No mention of sponsorship or COI.	N = 20 rats with alkaline corneal burns.		Allopurinol 0.4% eye drops, 6 times a day (N = 5) vs Prednisolone acetate 1% eye drops, 6 times a day (N = 5) vs Acetyl cysteine 8% eye drops, 6 times a day (N = 5) vs Control, one drop of normal saline six times per day (N = 5).	Follow-up for about 50 hours.	Average inflammatory scores in control / Allopurinol / Acetyl cysteine / and Prednisolone: 3.65 (range 2.5-4.0) / 2.45 (1.5 – 3.0) / 2.23 (1.5 – 4.0) / and 2.28 (1.0 – 3.0). There was no difference between treatment groups or scores of each group given by individual investigators.	"In present study, topical allopurinol was as established drugs, namely steroids and acetyl cysteine, in the early treatment of experimental alkali corneal burns."	Small sample size. Data suggest similar efficacy between all treatment groups when compared to controls for early treatment of alkali burned rat corneas.

Eye Patching for Chemical Ocular Burns

Recommended.

Devices

Eye patching is selectively recommended for treatment of chemical ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Chemical ocular burn that is sufficiently large to have limited vision and inadequate tearing.
Benefits:	"May" provide comfort to affected eye.
Harms:	None
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There are no quality trials for patching eyes with extensive chemical burns. Extensive burns may involve significant discomfort and inadequate tearing. Patching with an ointment in place may facilitate healing and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.

Evidence for Eye Patching for Chemical Ocular Burns

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sharifipour 2007 [159] (score = 4.0)	Animal Trials: Rabbits: Topical Steroids vs Normal Saline	RCT	No mention of sponsorship or COI.	N = 28 rabbits with severe corneal alkali injury.		Oxygen treatment, received 100% at a flow of 5 L/min for 1 hour daily, with one eye patched (N = 14) vs Control group, received chloramphenicol eye drops 4 times daily, plus eye patch for 1 hour daily and received (N = 14).	Follow-up for 1 month.	At 30 days, 1 anterior and 1 middle-stromal ulceration in control vs 3 anterior and 2 middle and 1 posterior ulceration in oxygen group, not statistically significant. Mean difference of ulceration was 13.45 days in control group vs 18.11 days in oxygen group, (p = 0.032).	"Oxygen therapy at a flow of 5 L/min for 1 hour daily reduces the possibility of corneal perforation in rabbits and may delay ulceration of the cornea compared with the control group."	Study states double blinding but methodology of double blinded not supported. Data suggest oxygen therapy may delay corneal ulceration in severe alkali burned rabbit corneas and may delay corneal perforation.

Surgical Interventions

A minority of chemical exposures result in permanent defects, including scarring of the lens and blindness. These cases are generally amenable to surgical procedures, especially corneal transplantation for those with corneal defects and/or scarring involving the visual axis.

Amniotic membrane transplantation (AMT) has been used to treat chemical ocular burns. [702, 707-711]

Amniotic Membrane Transplantation for Chemical Ocular Burns

Recommended.

Surgical Considerations

Amniotic membrane transplantation in conjunction with medical therapy is selectively recommended for treatment of moderately severe chemical ocular burns.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

☒ Acute ☒ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Ocular burn Roper-Hall classification grades II-IV. [712, 713]
Benefits:	Patient comfort and decreased inflammation with potential for early re-epitheliazation.
Harms:	Potential allergic response to the membrane.
Frequency/Dose/Duration:	Medical therapy to be administered at the same time is: topical 1% prednisolone acetate Q 6 hrs, ofloxacin Q 6 hrs, sodium ascorbate (10%), sodium citrate (10%), plus preservative-free lubricants every 2 hours, plus homatropine (2%) 1-2 times QD, and vitamin C 500 mg PO Q 6 hrs for 2 to 4 weeks [712]
Indications for Discontinuation:	N/A
Rationale:	There are two moderate quality trials of amniotic membrane transplantation compared with medical therapy and both trials suggested earlier re-epithelialization [712] [713]. Amniotic membrane transplantation is invasive, has some adverse effects, is costly but has demonstrated efficacy and is selectively recommended for treatment of ocular burns.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: thermal Burn Cornea, thermal ocular burn, thermal eye burn, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 14 articles, and considered 4 for inclusion. In Scopus, we found and reviewed 44 articles, and considered 1 for inclusion. In

CINAHL, we found and reviewed zero articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 1 articles, and considered zero for inclusion. We also considered for inclusion 1 articles from other sources. Of the 6 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria.

Comments:

Evidence for Amniotic Membrane Transplantation: Human Trials

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Tandon 2011 [145] (score = 6.0)	Human Trials: Amniotic Membrane vs Conventional Medial Therapy	RCT	Sponsored by the Indian Council of Medical Research, Ansari Nagar, and New Delhi. No COI.	N = 100 with grade II to IV acute chemical or thermal ocular burns. The mean age of moderate group was 4 to 52 years, and to 61 years in the severe group.	Moderate group: Amniotic membrane transplantation or AMT and conventional medical therapy (N = 25) vs. Control group: conventional medical therapy (N = 25).	Severe group: AMT and conventional medical therapy (N = 25) vs. Control group: conventional medical therapy (N = 25).	Follow-up for day 1, day 7, 1 and 3 months.	Primary outcome variable of healing of epithelial defect in AMT group [2.45 (0.48 to 5.8)] faster vs. controls [0.8 (0.43 to 5.1)], (p = 0.0004). With increasing burn grade, number of quadrants of corneal vascularization also increased, (p = 0.001).	"Amniotic membrane transplantation in eyes with acute ocular burns promotes faster healing of epithelial defect in patients with moderate grade burns."	AMT significantly better than standard treatment for rapid epithelial healing in moderate ocular burns and only slightly better in acute ocular burns.
Liang 2012 [146] (score = 4.0)	Human Trials: Amniotic Membrane vs Conventional Medial Therapy	RCT	Sponsored by the National Key Technologies Research and Development Program of the Eleventh Five-Year Plan. No mention of COI.	N = 75 with acute ocular burns graded III to VI; Mean age of 35.4 ± 10.6.		Sutureless amniotic membrane or AMT with a modified symblepharon ring (N = 39) vs. Control group: the conventional sutured amniotic membrane patch (N = 36).	Follow-up for 6.0 ± 4.7 months.	Burns graded III/IV/V/VI in sutureless group were 7/8/13/11 and in suture group 6/9/13/8. Sutureless group had shorter epithelialization of 14.03 ± 7.36 days vs. 23.06 ± 10.87 days in suture group, (p < 0.01). Complete epithelialization breakdown of groups differed: 100% in III (7/7), 90.00% in IV (9/10), 61.54% in V (8/13), 44.44% in VI (4/9). In suture group, complete	"[This study] developed a MSR for the entire conjunctival sac to allow for sutureless AMP to treat the acute ocular surface burns. The efficacy of the sutureless AMP was better than the conventional sutured AMP for the ocular burns in grades III, IV, and V."	Sparse methods. Data suggest sutureless group had faster re-epithelialization time and slower re-vascularization time. Sutureless AMP better than conventional sutured AMP group for time and rate of epithelialization, although revascularization was faster in the sutured group.

								epithelialization in 47.22% of eyes (17/36), with 100% in III (6/6), 66.67% in IV (6/9), 30.77% in V (4/13), and 12.50% in VI (1/8).		
Tamhane 2005 [147] (score = 4.0)	Human Trials: Amniotic Membrane vs Conventional Medial Therapy	RCT	No mention of sponsorship. No COI.	N = 37 (7 with bilaterial involvement) with acute ocular burns (grades II-IV according to Roper-Hall classification) within 3 weeks of injury. Mean age for AMT / and Medical Management group: 8 ± 12 / and 16 ± 10.		Group A or amnotic membrane transplantation or AMT with conventional medical therapy (N = 20 eyes) vs. Group B received only conventional medial therapy or prednisolone acetate, twice daily, and oral vitamin C (500 mg) every 6 hours for 2 to 4 weeks (N = 24 eyes).	Follow-up at day 1, day 7, and months 1, 2, 3, 12, and 18 are presented.	Patients with moderate burns (grade II - III): had significant differences in discomfort scale at day 1 postoperatively (Group A: 1.44 ± 0.53 vs. Group B: 2.13 ± 0.92, p = 0.05), and percentage reduction of epithelial defect [Log Mean] at day 7 (Group A: 7.43 ± 0.89 vs. Group B: 6.23 ± 1.10, p = 0.01). Patients with moderate burns (grade IV): There was difference in discomfort scale at day 14; Group A: 1.22 ± 0.44 vs B: 2.00 ± 0.86, (p = 0.02).	"Amnotic membrane transplantation in eyes with acute ocular burns has advantages in terms of reduction of pain and promotion of early epithelialization in patients with moderate grade burns, burn not so in severe burns."	Details sparse.
Gupta 2011 [148]	Human Trials: Amniotic Membrane vs Conventional	RCT	No sponsorship and or COI.	N = 100 with acute ocular burns. The		Additional amniotic membrane transplantation or	Follow-up for 1 year.	Mean time for complete epithelial defect healing in group IV by Dua	“Dua classification by providing further subclassification of	Data suggest DUA classification is superior to Roper Hall by providing

(score = 4.0)	Medial Therapy			average age was 22 (4 - 52).		AMT (N = 50) vs. Conventional medical therapy alone or control group (N = 50).		system (31 days) was less than in group VI 60 days, (p = 0.082). Corneal clarity with grade IV burns was better vs grade V, (p = 0.045) or grade VI, (p = 0.024). At final visit, degree of conjunctival involvement more in those with symblepharon formation, (p = 0.016). AMT was efficacious in preventing symblepharon formation in group IV, not in group VI, (p = 0.0082).	grade IV ocular burns by Roper Hall into three separate grades has a superior prognostic predictive value in severe ocular burns."	further sub-classification of grade IV ocular burns and therefore treatment can enhance prognosis.

Evidence for Amniotic Membrane Patching: Animal Trials

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kim 2000 [152] (score = 4.0)	Animal Trials: Rabbits: Amniotic Membrane Patching vs. Controls	RCT	Sponsored by a grant of Good Health RND Project (HMP-97-M-0055), Ministry of Health and Welfare, Korea. No COI.	N = 115 rabbits with alkali wounds were inflicted on the central corneas.		Group I, immediately covered by AM with the amnion cell side down up to the perilimbal sclera (N = 26) vs. Group II, covered by AM with the stromal side down up to the perilimbal sclera (N = 19) vs. Group II, anchored to the fornix (N = 29) vs. Group IV, uncovered as a control (N = 41).	Follow-up for 8 weeks.	For epithelial defects, corneal thickness and its opacity of each eye healing was faster in all AM group vs control, ($p < 0.05$). Corneas became significantly thinner vs uncovered group after 4 weeks and to a normal level at 8 weeks, ($p < 0.05$). Groups except for the amnion cell side down group, showed no significant differences in corneal opacity, ($p > 0.05$).	"Immediate intervention for acute alkali burns with AM as a temporary patch promotes wound healing by inhibiting proteinase activity and PMNs infiltration."	Data suggest amniotic membrane patching promotes corneal wound healing.

Corneal Transplantation for Blindness or Other Corneal Scarring/Defects after Chemical Eye Exposures

Strongly Recommended.

Surgical Considerations

Corneal transplantation is strongly recommended for restoration of vision due to blindness or other effects such as corneal scarring post chemical eye exposures.

Strength of Evidence – **Strongly Recommended, Evidence (A)**
Level of Confidence – High

☒ Acute ☒ Subacute ☒ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Corneal scarring and/or blindness after chemical eye exposure with visual acuity less than 20/40. There should be reasonable expectation that the retina is normal (e.g., pre-injury status).
Harms:	Further degradation of vision if unsuccessful
Benefits:	Potential to resolve visual deficiency
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There is strong evidence that corneal transplants are highly successful. Transplants are invasive, do have some adverse effects, are high-cost, but are also potentially highly successful and are thus strongly recommended for those with uncorrectable and significant visual acuity deficits.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	

Corneal Transplantation for Blindness or Other Corneal Scarring/Defects after Chemical Eye Exposures

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Li 2014 [172] (score = 4.0)	Animal Trials: Rats: Autologous oral mucosal transplantation post corneal burns.	RCT	Sponsored by the Young Teachers Cultivation Project of Sun Yat-sen University, Doctoral Program of the Ministry of Education, Science of Technology Programs of Guangdong Province.	N = 14 rats (180-200 g) with alkali burn in right eye. Rats with ocular or systemic diseases were excluded.		Group A: autologous oral mucosa strip transplantation (N = 7) vs. Group B: no surgery after burn (N = 7). After surgery, treated eyes received tobramycin dexamethasone eye drops 4 times daily.	Follow-up unclear but possibly up to 20 days.	Infectious complications: non in treatment group vs. 1 in control group. Oral mucosal wound healing: completely healed by days 2-3 in the treatment group. Total corneal epithelial cell defects and corneal edema occurred in all treatment eyes on the day of surgery. Reepithelialization began in 6 of 7 eye in treatment group at days 2-5.	"Autologous oral mucosa strip grafting for limbal stem cell deficiency can be achieved by a rat model following chemical burn. "	Data suggest autologous oral mucosal epithelial transplantation post alkali burn in rats may be beneficial for corneal limbal stem cell failure.

Evidence for Hyperbaric Oxygen

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Hirst 2004 [163] (score = 4.0)	Animal Trials: Rabbits: Hyperbaric oxygen for the treatment of chemical burns	RCT	Sponsored by the Ophthalmic Research Institute of Australia. No mention of COI.	N = 24 rabbits (mean body weight of 2.94 kg) with alkali-induced corneal burns		Hyperbaric oxygen treatment at 2.4 ATA for 1 hour every day for 21 days starting 4 hours after burn (N = 12) vs Control (N = 12).	Eyes examined daily for 2 weeks and then weekly until the end of the trial.	There were no significant differences between groups for epithelial defects or vascularization of the corneas.	"Treatment with hyperbaric oxygen for 1 h daily for 21 days had no beneficial effect on alkali-induced corneal burns."	Data suggest lack of efficacy for alkali induced corneal burns in rabbits at 21 days.
Ling 2013 [165] (score = 4.5)	Animal Trials: Mice: Hyperbaric Oxygen Treatment	RCT	Sponsored by the China National Natural Science Fund, the Guangdong Natural Science Foundation, the Guangdong Provincial Science and Technology Projects; and the Young Teachers Training Program of Sun Yat-sen University. No COI.	N = 98 male BALB/c mice or C57Bl/c mice, 8-10 weeks old.		Group A, allogeneic corneal transplantation (N = unknown) vs Group B, topical use of doxycycline after allogeneic corneal transplantation (N = unknown) vs Group C, syngeneic corneal Transplantation (N = unknown).	Follow-up for 30 days.	The percentage of neovascularized area was 60.67 ± 2.46% in group A vs 34.10 ± 3.01% in group B vs 14.10 ± 2.62% in group C. Mean survival time in the group B mice (27.00 ± 2.00 days) was significantly longer vs group A mice; 11.67 ± 1.51 days, ($p < 0.05$).	"Doxycycline may have had a significant role in preventing corneal angiogenesis and inflammation in alkali-burned corneal beds, which resulted in higher allograft survival rates.	Data suggest doxycycline may prevent allograft rejection in alkali burned mouse corneas as doxycycline had a statistically significant effect in reducing inflammation and angiogenesis.

Evidence for Tumor Necrosis Factor Blocker

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Shi 2010 [168] (score = 4.0)	Animal Trials: Mice: Tumor Necrosis Factor Blocker	RCT	No mention of sponsorship or COI.	N = 150 mice with alkali burn to astablish models of corneal neuovascularization (CNV). 150 BALB/c mice of either sex, aged 6 to 8 weeks.		Alkali burn group (N = 25) vs Suturing group- mark made in the central cornea by a 2-mm-diameter trephine. (N = 25) vs Fungal infection model using 5 µl of Fusarium solani Liquor (N = 25) vs Bovine serum albumin (BSA) injection (N = 25) vs Tumor cell implantation model: 2 µl of mouse fibroma cell suspension (105/ml) was injected into the corneal stroma using a 32-gauge needle to form a corneal layer tunnel. (N = 25).	Follow-up for 21 days.	The rate of successfully induced CNV was 97% in the alkali burn model, 100% in the suturing model, 90% in the fungal infection model, 90% in the BSA injection group and 87% in the tumor cell implantation model.	"Corneal neovascularization and lymphangiogenesis induced by different etiological factors show different growth patterns. Inflammatory reaction plays a part in the induction of corneal neovascularization."	Data suggest different etiological agents express different growth patterns for neovascularization and lymphangiogenesis in mice. Also, the inflammation response plays a role in corneal neovascularization. Also, VEGFs in corneal tissue may sustain corneal neovascularization and lymphangiogenesis.

Ferrari 2013 [169] (score = 3.5)	Animal Trials: Mice: Tumor Necrosis Factor Blocker	RCT	Sponsored by a grant from the Bietti Eye Foundation, Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS). No mention of sponsorship.	N = 40 female mice (4-6 weeks old) with alkali burn on left eye of each mouse		Group 1: infliximab 10 µL of 10 mg/ml topically 6 times a day (N = 20, 10 for immunostaining and 10 for real-time PCR analysis) vs. Group 2: infliximab administered for 14 days to measure corneal neovascularization (N = 10) vs Control group: 10 µg topical saline 20 mice for 7 days and 10 for 14 days (N = 30). Treatment started immediately after caustication.	Follow-up after 7 days from burn.	Infliximab improved corneal transparency after burn, there was evidence of visual reduction of corneal neovascularization, and it increased the rate of epithelial healing compared to the control group ($p<0.05$) at day 7. Perforation rate: decreased by 50% (from 57.14% to 26.32%) with infliximab ($p=0.0489$). Mean±SEM corneal opacity index: untreated eyes 3.40±0.22 vs. treatment 2.41±0.34 ($p=0.0484$). Tear secretion: reduced in control group, 1.31±0.21 mm, but not in treatment, 1.71±0.29 mm vs. unburned eyes 2.39±0.12 mm ($p < 0.05$). Ocular phimosis index: reduced more rapidly by infliximab vs.	"Infliximab penetrates the cornea and is safe to the ocular surface in an animal model of ocular surface scarring. We suggest that topical application of infliximab may be a useful treatment in ocular caustications."	Data suggest infliximab penetrates the mouse cornea after alkali burns and reduced loss of conjunctiva, improved tears secreation and epithelial healing and reduced both hemangioneses and lymphangiogenesis.

								saline, from 2.39±0.18 to 0.68±0.23, from day 4 onwards ($p<0.05$). Goblet cells: treatment eyes 3x more cells vs. control, ($p < 0.05$).		

Haddox 1996 [161] (score = 4.5)	Animal Trials: Rabbits: Tumor Necrosis Factor Blocker	RCT	Sponsored by NEI grant. No mention of COI.	N = 60 right eyes if albino rabbits (2-2.5 kg) with alkali-injured eye.		Citrate drops: 10% citrate drops 153.13 g of trisodium citrate up to 1 L physiological saline (N = 20) vs calcium-magnesium citrate drops: 10% citrate 306.26 g trisodium citrate and 346 mM calcium and 346 mM magnesium up to 1 L with physiological saline (N = 20) vs 10% citrate in saline (N = 20) 2 drops in lower cul de sac of right eye on the hour, 14 times a day for 35 days. Medications were administered hourly starting 1.5 hours after alkali injury. Erthromycin ophthalmic ointment (0.5%) was applied twice a day to prevent infection.	Rabbits killed after final examination on day 35.	Fewer ulcerations in the citrate-treated eyes vs saline vs calcium group; 5/20 or 25% vs 13/20 or 65% vs 15/20 or 75%. Citrate-cation group had significantly more band keratopathies, ($p < 0.001$).	"The annulment of the favorable effect of citrate on ulceration in the alkali-injured eye by the addition of calcium and magnesium shows that the mechanism of action of citrate is the chelation of thee divalent citations."	Data suggest that the decrease in corneal ulcers in alkali burned rabbit eyes treated with sodium citrate is based on the mechanism of divalent cation chelation.

Evidence for Poly-D, L-lactic acid (PDDLA) membrane

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Du 2007 [162] (score = 4.0)	Animal Trials: Rabbits: Poly-D, L-lactic acid (PDDLA) membrane vs other types of membranes vs no membrane.	RCT	Sponsored by the Ministry of Education of the People's Republic of China. No mention of COI.	N = 12 rabbits weighing 2.0-2.5 kg with right cornea of each made into an alkali-burned model.		Poly-D, L-lactic acid (PDLLA) membrane using 0/0 silk thread sutured onto limbus and sclera (N = 3) vs. PDLLA/collagen membrane (N = 3) vs. PDLLA/chitosan membrane (N = 3) vs Control, no membrane (N = 3). After operation, 0.25% chloramphenicol eye drops 3 times per day.	Rabbits were killed after 12 days.	Conjunctival congestion: significant between the control and the 3 treatments, ($p < 0.05$) but not among 3 treatment groups. Conjunctival discharge: significant between the control and 3 treatments ($p < 0.05$) but not among 3 treatment groups. Corneal neovascularization 5 days postoperatively: significant between PDLLA/chitosan group vs PDLLA/collagen group and the PDLLA or control groups, ($p < 0.04$)	"This evidence suggests that PDLLA/chitosan may be an alternative treatment for corneal alkali burns."	Membranes visibly deteriorated by day 10 so no observations were made after 12 days. Small sample. Data suggest PDLLA/chitosan enhanced wound healing in alkali burned rabbit corneas.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Shen 2014 [166] (score = 4.0)	Animal Trials: Mice: The role of TC140112 vs CXCR7 in CNV in alkali burned eyes.	RCT	No mention of sponsorship or COI.	N = 54 mice treated with alkali burns. 6 to 8 week old male BALB/c mice.		Bilateral subconjunctival injections of TC14012 (a CXCR4 antagonist and CXCR7 agonist) for 3 consecutive days (N = 18) vs Bilateral subconjunctival injections of balanced saline (BS) for 3 consecutive days (N = 18) vs No treatment (blank control) (N = 18).	Follow-up for 14 days.	The area of corneal neovascularization (CNV) increased over time in the nontreatment and BS groups. At day 7, the TC14012 CNV area was significantly higher compared to the BS and Nontreatment groups; 35.59 vs. 28.38 vs. 28.09 ($p<0.05$). At day 14, the TC14012 was significantly lower compared to the other two groups; 27.56 vs. 40.77 vs. 39.01, respectively ($p<0.05$).	"TC14012 initially enhanced alkali burn-induced CNV but reduced CNV in later stages. In addition to CXCR4, CXCR7 is involved in the pathogenesis of CNV."	Data suggest TC 14012 initially increased alkali burn induced CNV in mice but reduced it after day 13.

Xiao 2012 [167] (score = 4.0)	Animal Trials: Mice: Phosphate buffered saline (PBS) vs Minocycline in alkali burns.	RCT	Supported by ''Fundamental Research Funds for the Central Universities'' in China (grant number: 3030901009015, Shi-you Zhou) and the NSFC-RGC HK joint project (grant number: 30731160617, Rong-biao Pi). No COI.	N = 105 mice treated with alkali burns.		Group 1- Phosphate buffered saline (PBS)-Control group (N = unknown) vs Group 2- Minocycline twice a day (60 mg/kg or 30 mg/kg) (N = unknown) vs Group 3- 14 consecutive days of minocycline (60 mg/kg or 30 mg/kg) (N = unknown)	Follow-up for 14 days.	The area of CNV increased over time in all three groups. The CNV percentage in the high-dosage group reduced significantly compared to the control group at all follow-up days; (all were $p < 0.01$). The only follow-up day were the low-dosage group vs. control group was the 4th day (20.62% vs. 32.39%), ($p < 0.01$).	"In summary, minocycline has more functions besides its antibiotic character, as shown in this study and in other reports. Minocycline may someday play a promising role in preventing CNV."	Group numbers not given. Data suggest intraperitoneal injection of Minocycline (60mg/kg) bid significantly inhibits neovascularization of alkali burned mice corneas also decreasing inflammation response.

Evidence for Tocilizumab

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sari 2015 [177] (score = 4.0)	Animal Trials: Rats: Tocilizumab for treatment of corneal burns	RCT	No sponsorship or COI.	N = 24 with alkali burn induced corneal neovascularization (CNV) in rats.		Group 1, received sub-conjunctival injection of 4 mg/0.2 ml tocilizumab (N = 12) vs Group 2, received sub-conjunctival injection of 0.2 ml normal saline at the 5th day of alkali burn (N = 12).	Follow-up for about 15 days.	The area of CNV was 26.9% in Group 1 vs 56.5% in Group 2, ($p < 0.001$). Significantly lower corneal inflammation score in Group 1 vs 2, ($p < 0.001$). The number of vessels stained with vWF were significantly higher in Group 2 vs 1 (15.23 and 5.46, respectively; $p < 0.001$). Vascular endothelial growth factor or VEGF levels were significantly lower in Group 1 vs Group 2, ($p = 0.013$).	"The present data demonstrated first time the beneficial effects of sub-conjunctival tocilizumab on decreasing CNV in alkali burn model of the rat cornea.	Data suggest sub-conjunctival tocilizumab significantly decreases CNV in alkali burned rat corneas as well as showing significantly less inflammation.

Güler 2009 [178] (score = 3.5)	Animal Trials: Rats: Role of Trastuzumab in neovascularization in burned corneas.	RCT	No sponsorship or COI.	N = 16 rats with chemical cauterization on the corneas.		Group 1, received intraperitoneally 1 ml, 4 mg/kg trastuzumab (N = 8) vs Group 2, received 1 ml Saline (N = 8).	Follow-up not given.	Average neovascularization area in treatment group was statistically smaller than control, (p = 0.008). The mean VEGF staining intensity of epithelial and endothelial layers of cornea in treatment group vs control, (p = 0.038 and p = 0.041, respectively).	"Systemic administration of trastuzumab is effective in prevention of the corneal neovascularization."	Small sample size. Data suggest trastuzumab prevents neovascularization in burned rat cornea.

Thermal Burns

OVERVIEW

Thermal Ocular Burns

Thermal ocular burns occur in occupational environments, although relatively infrequently compared with chemical injuries.

Immediate treatment to irrigate the eye with copious water or other aqueous irrigating solutions is believed to be important for the outcomes of thermal eye injuries. [696, 697, 700].

Ocular surface burns may be caused by intense ultraviolet exposures, most commonly welding while not wearing protective eye gear. They may also be incidental to being near a welder but without adequate eye protection. The presentation typically occurs one day after exposure with a red, painful irritated eye. A diffuse granular appearance of the cornea is usually seen. The history and initial physical examination are highly characteristic. Slit lamp examination findings are characteristic of diffuse granular uptake generally with sparing of the upper and lower corneal margins where the eyelids protect the cornea.

Eye burn accidents occur mostly at work and can result from exposure to alkaline agents (lime or sodium hydroxide), acids, liquid metals, or fireworks. Treatment can include immediate rinsing of the eye [714]. Another treatment is amniotic membrane transplantation (AMT) for acute ocular surface burns. A systematic review found lack of evidence to support the use of this treatment [132].

TREATMENT RECOMMENDATIONS

NSAID Drops for Welder's Flash

Recommended.

Medications (including topical creams)

NSAID ophthalmic drops are recommended for treatment of welder's flash.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Welder's flash
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	Allergic reactions in susceptible patients, intolerance.
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	Symptom resolution

Rationale:	There are no quality trials for treatment of welder's flash. NSAID drops are low cost, not invasive, associated with low risks and are recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: uv corneal burn, welder's eye, keratitis, corneal ulcers, keratouveitis, snow blindness, arc eye, welder's flash, bake eyes, corneal flash burns, flash burns, keratoconjunctivitis photoelectric, photokeratitis, ultraviolet keratitis, eye patch, antibiotics, antifungals, polyhexamethylene biguanide, NSAIDS, non-steroidal anti-inflammatory agents, steroids, eyeglasses, lubricating eye drops, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 362 articles, and considered 68 for inclusion. In Scopus, we found and reviewed 27 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 3 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 1 for inclusion. We also considered for inclusion 3 articles from other sources. Of the 75 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	[Can include harms, benefits, advantages, limitations, etc.]

Eye Patching for Welder's Flash

Not Recommended.

Devices

Eye patching for welder's flash is not recommended.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	N/A
Benefits:	N/A
Harms:	N/*A*
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There are no quality trials of patching for treatment of welder's flash. However, eye patching has been shown to have no

benefits for treatment of corneal abrasions and rust rings. Thus, patching is also not expected to be efficacious for welder's flash, and therefore patching is not recommended for welders flash.

Evidence: A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: uv corneal burn, welder's eye, keratitis, corneal ulcers, keratouveitis, snow blindness, arc eye, welder's flash, bake eyes, corneal flash burns, flash burns, keratoconjunctivitis photoelectric, photokeratitis, ultraviolet keratitis, eye patch, antibiotics, antifungals, polyhexamethylene biguanide, NSAIDS, non-steroidal anti-inflammatory agents, steroids, eyeglasses, lubricating eye drops, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 362 articles, and considered 68 for inclusion. In Scopus, we found and reviewed 27 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 3 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 1 for inclusion. We also considered for inclusion 3 articles from other sources. Of the 75 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.

Comments:

Copious Irrigation for Thermal Eye Exposures

Recommended.

Medications (including topical creams)

Copious Irrigation is recommended for thermal eye exposures.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications: All thermal eye exposures and injuries. It is recommended to begin irrigation immediately after eye exposure, rather than waiting for symptoms to develop.
Harms: Negligible. Mild discomfort from solution and irrigation
Benefits: Limiting extent of burn/injury, earlier relief of pain
Frequency/Dose/Duration: Tap water is most commonly available and should be used if that is the most readily available solution, especially for first

	line, in-plant settings. Irrigation bottles with irrigating solutions are also useful in in-plant medical departments, clinical settings and distributed in some facilities. Normal saline, lactated Ringer's solution are additional options for initial irrigation and are preferable to tap water, but only if immediately available. Substitute normal saline or lactated ringer's or other balanced saline solution for tap water when available. Generally use topical anesthetic to anesthetize the eye when available, as it will assist in better tolerance of irrigation.
Indications for Discontinuation:	Only after copious irrigation, usually at least 500mL has been used to flush out the eye.
Rationale:	There are no quality studies identifying use compared with non-use of irrigation. There are experimental studies of irrigating solutions for treatment especially of animal models. These animal studies suggest superiority of balanced salt solutions (e.g., normal saline, lactate Ringer's solution) over hypotonic solutions (such as tap water). Still, experience suggests earlier irrigation with the most readily available solution, including tap water, is the preferred initial strategy and is recommended. Once irrigation is underway, tailoring of further irrigation, including possible use of an irrigating system (e.g., "Morgan lens") may be considered although is less necessary in thermal than in chemical injuries.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: thermal Burn Cornea, thermal ocular burn, thermal eye burn *, cornea, , chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, 6 human randomized trials and 27 animal randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	[Can include harms, benefits, advantages, limitations, etc.]

Irrigating Systems (e.g., Morgan Lens) for Thermal Eye Exposures

Not Recommended.

Devices

Irrigating Systems (e.g., Morgan Lens) are not recommended for thermal eye exposures.

Strength of Evidence – **Not Recommended, Insuffcient Evidence (I)**
Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Rationale: There are no quality studies comparing use with non-use of irrigating systems for thermal injuries. They are generally not thought to be necessary for most thermal injuries. Exceptions may include combinations of chemicals and thermal. (see above)

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: *eye burn, cornea, cornea burn, chemical, lye, alkaline, burn or burns, alkali or lime or cement or ammonia or sulfurous acid or nitric acid;* controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 623 articles, and considered 72 for inclusion. In Scopus, we found and reviewed 1190 articles, and considered 4 for inclusion. In CINAHL, we found and reviewed 4 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 12 articles, and considered 1 for inclusion. We also considered for inclusion 14 articles from other sources. Of the 78 articles considered for inclusion, **6 human randomized trials** and **27 animal randomized trials** and 4 systematic studies met the inclusion criteria.

Artificial Tears or Lubrication for Thermal Ocular Burns

Recommended.

Medications (including topical creams)

Artificial tears or lubricants are selectively recommended for treatment of patients with thermal ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☒ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications: Thermal ocular burns of sufficient size and pain, and particularly among those with inadequate tearing.

Benefits:	May provide sufficient tears to reduce symptoms and potentially improve healing.
Harms:	Undefined but likely negligible.
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	Symptom resolution
Rationale:	There are no quality trials of artificial tears for thermal ocular burns. Artificial tears are inexpensive, noninvasive, and have low adverse effects and are recommended particularly for those patients with inadequate tears.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: uv corneal burn, welder's eye, keratitis, corneal ulcers, keratouveitis, snow blindness, arc eye, welder's flash, bake eyes, corneal flash burns, flash burns, keratoconjunctivitis photoelectric, photokeratitis, ultraviolet keratitis, eye patch, antibiotics, antifungals, polyhexamethylene biguanide, NSAIDS, non-steroidal anti-inflammatory agents, steroids, eyeglasses, lubricating eye drops, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 362 articles, and considered 68 for inclusion. In Scopus, we found and reviewed 27 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 3 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 1 for inclusion. We also considered for inclusion 3 articles from other sources. Of the 75 articles considered for inclusion, 48 randomized trials and 4 systematic studies met the inclusion criteria.
Comments:	[Can include harms, benefits, advantages, limitations, etc.]

NSAID Drops for Thermal Ocular Burns

Recommended.

Medications (including topical creams)

NSAID ophthalmic drops are recommended for treatment of thermal ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic

☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Thermal ocular burns
Benefits:	Reduced pain, decreased inflammatory response.

Harms:	Allergic reactions in susceptible patients, intolerance.
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation:	Symptom resolution
Rationale:	There are no quality trials for treatment of thermal ocular burns with ophthalmic NSAID drops. NSAID drops are low cost, not invasive, associated with low risks and are recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: uv corneal burn, welder's eye, keratitis, corneal ulcers, keratouveitis, snow blindness, arc eye, welder's flash, bake eyes, corneal flash burns, flash burns, keratoconjunctivitis photoelectric, photokeratitis, ultraviolet keratitis, eye patch, antibiotics, antifungals, polyhexamethylene biguanide, NSAIDS, non-steroidal anti-inflammatory agents, steroids, eyeglasses, lubricating eye drops, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 362 articles, and considered 68 for inclusion. In Scopus, we found and reviewed 27 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 3 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 1 for inclusion. We also considered for inclusion 3 articles from other sources. Of the 75 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	

Eye Patching for Thermal Ocular Burns

Recommended.

Devices

Eye patching is selectively recommended for treatment of moderate to severe thermal ocular burns.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Moderate to severe thermal ocular burn that is sufficiently large to have limited vision and inadequate tearing.

Benefits:	Comfort
Harms:	None
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	Symptom resolution
Rationale:	There are no quality trials of patching for treatment of thermal ocular burns. Thermal ocular burns may be selectively treated with eye patching to help provide better protection of the cornea when there is limited tearing and a considerable burn.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: thermal Burn Cornea, thermal ocular burn, thermal eye burn, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 14 articles, and considered 4 for inclusion. In Scopus, we found and reviewed 44 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed zero articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 1 articles, and considered zero for inclusion. We also considered for inclusion 1 articles from other sources. Of the 6 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria.
Comments:	

Amniotic Membrane Transplantation with Medical Therapy for Thermal Ocular Burns Recommended.

Surgical Considerations

Amniotic membrane transplantation in conjunction with medical therapy is selectively recommended for treatment of thermal ocular burns.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

☒ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Thermal ocular burn Roper-Hall classification grades II-IV. [712]; [713]
Benefits:	Faster re-epithelialization (healing) leading to improved vision.
Harms:	Few reported
Frequency/Dose/Duration:	Medical therapy recommended to be administered at the same time is: topical 1% prednisolone acetate Q 6 hrs, ofloxacin Q 6

	hrs, sodium ascorbate (10%), sodium citrate (10%), plus preservative-free lubricants every 2 hours, plus homatropine (2%) 1-2 times QD, and vitamin C 500 mg PO Q 6 hrs for 2 to 4 weeks (Tamhane 05)
Indications for Discontinuation:	
Rationale:	There are three moderate quality trials of amniotic membrane transplantation compared with medical therapy and both trials suggested earlier re-epithelialization (Tamhane 05, 10; Tandon 10). However, the benefits have not been shown to extend to improved visual function. Amniotic membrane transplantation is invasive, has some adverse effects, is costly but has demonstrated efficacy and is selectively recommended for treatment of ocular burns.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: thermal Burn Cornea, thermal ocular burn, thermal eye burn, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 14 articles, and considered 4 for inclusion. In Scopus, we found and reviewed 44 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed zero articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 1 articles, and considered zero for inclusion. We also considered for inclusion 1 articles from other sources. Of the 6 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria.
Comments:	

Standalone Amniotic Membrane Transplantation for Acute Ocular Burns

No Recommendation.

Surgical Considerations

AMT as standalone therapy for acute ocular burns is not recommended due to lack of high quality evidence to support the surgery (see AMP plus medications).

Strength of Evidence – **No Recommendation, Insuffcient Evidence (I)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☒ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Currently not indicated for acute ocular burns

Benefits:	Potential for improved vision
Harms:	None reported
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	N/A
Rationale:	There are no quality, sizeable studies of amniotic membrane transplantation, thus there is no recommendation.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: uv corneal burn, welder's eye, keratitis, corneal ulcers, keratouveitis, snow blindness, arc eye, welder's flash, bake eyes, corneal flash burns, flash burns, keratoconjunctivitis photoelectric, photokeratitis, ultraviolet keratitis, eye patch, antibiotics, antifungals, polyhexamethylene biguanide, NSAIDS, non-steroidal anti-inflammatory agents, steroids, eyeglasses, lubricating eye drops, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 362 articles, and considered 68 for inclusion. In Scopus, we found and reviewed 27 articles, and considered 2 for inclusion. In CINAHL, we found and reviewed 3 articles, and considered 1 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 1 for inclusion. We also considered for inclusion 3 articles from other sources. Of the 75 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.
Comments:	

Evidence for Amniotic Membrane Transplantation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Tamhane 2005 (score = 4.0)	Amniotic membrane transplantation vs conventional therapy for ocular burns.	RCT	Sponsored by The Indian Council of Medical Research. No COI.	N = 37 with acute ocular burns (grades II-IV according to Roper-Hall classification) within 3 weeks of injury. Mean±SD age: 18±12 years Amniotic Membrane. 16±10 years conventional.		Group A: eyes receive amniotic membrane transplantation with conventional medical therapy (N = 20) vs. Group B: received conventional medial therapy which included topical prednisolone acetate (1%; Allergan, Bangalore, India) every six hours, plus ofloxacin every 6 hours, plus sodium ascorbate (10%), sodium citrate (10%), plus preservative-free lubricants every 2 hours, plus homatropine (2%) once or twice daily, plus + oral vitamin C (500 mg) every 6 hours for 2 to 4 weeks (N = 24).	Follow-up up to 4 weeks.	Discomfort scale at day 1 / reduction of epithelial defect at day 7 / moderate burns: (significant difference, 1.44 ± 0.53 vs. Group B 2.13 ± 0.92, p = 0.05) / (7.43 ± 0.89 vs. Group B 6.23 ± 1.10, p = 0.01)/ (significant difference in discomfort scale at day 14, 1.22 ± 0.44 vs. B 2.00 ± 0.86, p = 0.02).	"Amniotic membrane transplantation in eyes with acute ocular burns promotes faster healing of epithelial defect in patients with moderate grade burns. There seems to be no definite long-term advantage of amniotic membrane transplantation over medical therapy and mechanical release of adhesions in terms of final visual outcome, appearance of symblepharon and corneal vascularization when compared in a controlled clinical setting."	Stratified randomization. Data suggest amniotic membrane transplantation in acute ocular eye burns promotes faster re-epithelialization.

Liang 2012 (score = 4.0)	Sutureless amniotic membrane vs conventional sutured approach.	RCT	Sponsored by the National Key Technologies Research and Development Program of the Eleventh Five-Year Plan. No mention of COI.	N = 75 with acute ocular burns graded III to VI; mean age of 35.4 ± 10.6. Causes of the ocular injury included alkali (54 eyes), acid (8 eyes), thermal (11 eyes), and unknown (2 eyes).		Sutureless amniotic membrane with a modified symblepharon ring (N = 39). vs. Control group: the conventional sutured amniotic membrane patch (N = 36).	Follow-up for 6.0 ± 4.7 months.	The burns graded III/IV/V/VI in the sutureless group were 7/8/13/11 and in the suture group were 6/9/13/8.	The sutureless group had significantly shorter epithelialization of 14.03 ± 7.36 days vs. 23.06 ± 10.87 days in the suture group ($p<0.01$). The complete epithelialization breakdown of the groups was statistically different as follows: 100% in III (7/7), 90.00% in IV (9/10), 61.54% in V (8/13), 44.44% in VI (4/9). In the suture group, complete epithelialization was observed in 47.22% of eyes (17/36), with 100% in III (6/6), 66.67% in IV (6/9), 30.77% in V (4/13), and 12.50% in VI (1/8). "[This study] developed a MSR for the entire conjunctival sac to allow for sutureless AMP to treat the acute ocular surface burns. The efficacy of the sutureless AMP was better than the conventional sutured AMP for the ocular burns in grades III, IV, and V. This modified method is simple, minimally invasive, free of trauma, symptomatic relief, and effective to promote the wound healing."	Sparse methods. Data suggest sutureless group had faster re-epithelialization time and slower re-vascularization time.

Tandon 2010 (score = 4.0)	AMT plus conventional therapy vc conventional therapy alone for acute chemical or ocular burns.	RCT	No COI. No mention of sponsorship.	N = 100 with grade II to IV acute chemical or thermal ocular burns. 50 patients had moderate ocular burns (grade II and III), and 50 patients had severe ocular burns (grade IV). Mean (Range) age: moderate group – control: 25(4-45) years, amniotic group 18(5-52). Severe group – control: 14 (3-61), amniotic 13(6-60) years.		Moderate group: Amniotic membrane transplantation (AMT) and conventional medical therapy (N = 25) vs Control group: conventional medical therapy (N = 25). Severe group: AMT and conventional medical therapy (N = 25) vs Control group: conventional medical therapy (N = 25).	Follow-up for day 1, day 7, 1 and 3 months.	Healing of the epithelial defect: AMT group [2.45 (0.48 to 5.8)] vs. the control group [0.8 (0.43 to 5.1)], (p=0.0004).	"Amniotic membrane transplantation in eyes with acute ocular burns promotes faster healing of epithelial defect in patients with moderate grade burns. There seems to be no definite long-term advantage of amniotic membrane transplantation over medical therapy and mechanical release of adhesions in terms of final visual outcome, appearance of symblepharon and corneal vascularisation when compared in a controlled clinical setting."	Stratified randomization. Data suggest amniotic membrane transplantation in acute ocular eye burns promotes faster re-epithelialization.

Thermal Burn Cornea Evidence

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: thermal Burn Cornea, thermal ocular burn, thermal eye burn, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 14 articles, and considered 4 for inclusion. In Scopus, we found and reviewed 44 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed zero articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 1 articles, and considered zero for inclusion. We also considered for inclusion 1 articles from other sources. Of the 6 articles considered for inclusion, 2 randomized trials and 2 systematic studies met the inclusion criteria.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Tandon 2010 (score = 6.0)	AMP plus conventional therapy for thermal corneal burns	RCT	Sponsored by the Indian Council of Medical Research, Ansari Nagar, New Delhi. No COI.	N = 100 with grade II to IV acute chemical or thermal ocular burns. 50 patients had moderate ocular burns (grade II and III), and 50 patients had severe ocular burns (grade IV). The man age of moderate group was 4 to 52 years, and to 61 years in the severe group. Alkali burn was the commonest type of chemical injury (72 of 100 eyes) followed by acid injury (20 of 100 eyes) and thermal injury (eight of 100 eyes).		Moderate group: Amniotic membrane transplantation (AMT) and conventional medical therapy (N = 25) vs Control group: conventional medical therapy (N = 25). Severe group: AMT and conventional medical therapy (N = 25) vs Control group: conventional medical therapy (N = 25).	Follow-up for day 1, day 7, 1 and 3 months.	In patients with moderate burns, the primary outcome variable of healing of the epithelial defect in the AMT group [2.45 (0.48 to 5.8)] was significantly faster vs. the control group [0.8 (0.43 to 5.1)], (p = 0.0004). It was found that with increasing grade of ocular burn, the number of quadrants of corneal vascularization also increased. The difference was statistically significant (p = 0.001).	"Amniotic membrane transplantation in eyes with acute ocular burns promotes faster healing of epithelial defect in patients with moderate grade burns. There seems to be no definite long-term advantage of amniotic membrane transplantation over medical therapy and mechanical release of adhesions in terms of final visual outcome, appearance of	AMT significantly better than standard treatment for rapid epithelial healing in moderate ocular burns and only slightly better in acute ocular burns.

									symblepharon and corneal vascularisation when compared in a controlled clinical setting."	
Liang 2012 (score = 4.0)	AMP comparison using sutures or no sutures	RCT	Sponsored by the National Key Technologies Research and Development Program of the Eleventh Five-Year Plan. No mention of COI.	N = 75 with acute ocular burns graded III to VI; mean age of 35.4 ± 10.6. Causes of the ocular injury included alkali (54 eyes), acid (8 eyes), thermal (11 eyes), and unknown (2 eyes).		Sutureless amniotic membrane with a modified symblepharon ring (N = 39). vs. Control group: the conventional sutured amniotic membrane patch (N = 36).	Follow-up for 6.0 ± 4.7 months.	The burns graded III/IV/V/VI in the sutureless group were 7/8/13/11 and in the suture group were 6/9/13/8. The sutureless group had significantly shorter epithelialization of 14.03 ± 7.36 days vs. 23.06 ± 10.87 days in the suture group (p<0.01). The complete epithelialization breakdown of the groups was statistically different as follows: 100% in III (7/7), 90.00% in IV (9/10), 61.54% in V (8/13), 44.44% in VI (4/9). In the suture group, complete epithelialization was observed in 47.22% of eyes (17/36), with 100% in III (6/6), 66.67% in IV (6/9), 30.77% in V (4/13), and 12.50% in VI (1/8).	"[This study] developed a MSR for the entire conjunctival sac to allow for sutureless AMP to treat the acute ocular surface burns. The efficacy of the sutureless AMP was better than the conventional sutured AMP for the ocular burns in grades III, IV, and V. This modified method is simple, minimally invasive, free of trauma, symptomatic relief, and effective to promote the wound healing."	Sparse methodology. Data suggest sutureless group had faster re-epithelialization time and slower re-vascularization time. Sutureless AMP better than conventional sutured AMP group for time and rate of epithelialization, although revascularization was faster in the sutured group.
Acar 2011 (score = 4.0)	Keratoplasty versus Different Surgical Technique	RCT	No mention of industry sponsorship. No COI.	N = 26 with hard cataract that had previous PKP; mean age of 53.53±9.57 years,		Phacoemulsification (N = 14) Vs Extracapsular Cataract Extraction	Follow ups at preop, and months 1, 3, and 6.	Mean±SD for ECD: phaco vs ECCE: 3 months: 1944.17±184.27 vs 2094.00±139.10, (p=0.016); 6 months: 1869.50±158.50 vs	"Extracapsular cataract extraction seemed to cause less endothelial cell damage than	Small sample. Data suggest at 6mo, ECD was associated with less endothelial cell loss than phacoemulsification

				range of 35 to 67 years.		(ECCE) (N = 12). All patients: ofloxacin 0.3% and prednisolone acetate 1% were used 4 times per day for 4 weeks.		1996.00±127.96, (p=0.024); endothelial cell area: 3 months: 512.40±108.5 vs 450.80, (p=0.002); 538.60±120.4 vs 479.20±100.2, (p=0.004).	phacoemulsification in post-PKP patients with hard nuclear cataract."	in post-PKP patients with hard nuclear cataracts.
Alpar 1981 (score = 3.0)	Keratoplasty versus Different Surgical Technique	RCT	No mention of industry sponsorship or COI.	N = 40 undergoing keratoplasty; mean age not reported.		Group 1, underwent intracapsular cataract extraction, intraocular lens implantation, and penetrating keratoplasty (N = 20) Vs Group 2, underwent intracapsular cataract extraction and intraocular lens implantation (N = 10) Vs Group 3, with corneal dystrophy underwent penetrating keratoplasty (N = 4) Vs Group 4 with decompensated corneas who had intraocular lenses in situ and who underwent	Follow up at preop, week 4, and 6 months.	Group 1, controls: endothelial cell loss: 4 weeks vs 6 months: 24.3% vs 20.6%, (p=0.025); Group 1, Healon: 14.3% vs 12.2%, (p<0.005); Corneal thickness: Healon, Group 1: 18.3% vs 8.7%, (p=0.005).	"Healon was found to be beneficial to the patient and a safe adjunct in penetrating keratoplasty surgery."	Small sample. Sparse methods. Baseline comparability unknown. Data suggest Healon group lost fewer endothelial cells and had thinner corneas than controls although IOP slightly elevated.

						corneal graft surgery (N = 6). Half of the patients in each group were operated with the use of Healon; the remaining patients served as the control group and were operated in the conventional manner using air/BSS to maintain the chamber during surgery.				
Barney 1994 (score = 3.5)	Medications for Keratoplasty	RCT	Sponsored by the Heed Ophthalimc Foundation. No mention of COI.	N = 23 undergoing penetrating keratoplasty for herpes simplex keratitis; mean age not reported.		Group A, received prophylactic perioperative oral acyclovir beginning before surgery or on the first postoperative day, 800 or 1000 mg (N = 14) Vs Group B, control group, did not receive perioperative acyclovir (N = 9). All patients: Polysporin ointment two times daily for	Follow up on the first postoperative day, at 1, 2, and 4 weeks, and then monthly for the first year.	Mean±SD for recurrence-free interval (mos): Group A vs Group B: 16.5±11.1 vs 7.1±6.2, (p≤0.02; in favor of group A).	"[B]ased on these findings we believe that postoperative oral acyclovir significantly reduces the risk of herpes simplex keratitis recurrence after penetrating keratoplasty."	Sparse methods. Small sample. Data suggest long term oral acyclovir decreased occurrence of herpes simplex keratitis and reduced graft failure.

						10 days and prednisolone sodium phosphate 1% four times daily tapered during 3 months; Diflunisal 200 mg, twice daily for one month.				
Baumeister 2009 (score = 3.5)	Medications for Keratoplasty	RCT	Sponsored by a grant from Bayer Vital GmbH. No mention of COI.	N = 20 patients scheduled for phototherapeutic keratoplasty (PTK) due to recurring corneal erosion (RCE); mean age of 37.5 for treatment group and 40.1 for placebo group.		Bepanthen (dexpanthenol) eye and nose ointment (N = 10) Vs Placebo, ointment vehicle without the active substance (N = 8).	No follow up time reported.	Average time to close the corneal epithelium: treatment vs placebo: 57.5 h vs 64.8 h (p=0.177).	"Planimetric measurement of the slit-lamp photographs of standardized epithelial defects is an adequate method for monitoring the progress of corneal epithelial wound healing. Although wounds treated with dexpanthenol showed a slightly shorter average healing time, the difference the placebo was not significant."	Small sample. Data suggest lack of efficacy of dexpanthenol.
Bhatti 2013 PJMS (score = 4.5)	Medications for Keratoplasty	RCT	No mention of industry sponsorship or COI.	N = 81 with high risk corneal transplantation with corneal neovascularization; mean age of 52.07±5.54.		Group A, topical bevacizumab, 2.5%, 25mg/ml, four times daily for 24 weeks (N = 40) Vs Group B, sham eye	Follow up from 2 to 8 months, patients were asked to follow up every 4 weeks from	The mean corneal neovascular invasion area was the minimum in Group A, (p<0.03).	"When topical Bevacizumab is used, it reduces the recurrence of neovascularisation and thus helps increasing the frequency of	Data suggest topical bevacizumab superior to placebo for graft rejection prevention in high-risk corneal transplant patients.

						drops, control group (N = 41).	the first postoperative day.		graft survival in cases of high risk corneal transplants."	
Bhatti 2013 JOTPMA (score = 3.0)	Medications for Keratoplasty	RCT	No mention of industry sponsorship or COI.	N = 122 with high-risk corneal transplantation with corneal neovascularization; mean age of 52.07±5.54, range of 39 to 67.		Group A, subconjunctival bevacizumab, 2.5 mg /0.1ml, on or two injections (N = 41) Vs Group B, sham injection,, one or two injections (N = 41) Vs Group C, topical bevacizumab, 2.5%, 25mg/ml, 4 times daily for 24 weeks (N = 40).	Follow up from 2 to 8 months, patients were asked to come for follow up every 4 weeks from the first postoperative day.	The mean corneal neovascular invasion area was the minimum in Group A, (p<0.03).	"Subjunctival bevacizumab reduces the recurrence of neovascularisation and, thus, helps increasing the frequency of graft survival in cases of high-risk corneal transplants. When used topically, it is less effective."	Sparse methods. Data suggest subconjunctival bevacizumab is superior to topical bevacizumab and placebo by reducing recurrence of neovascularization and increasing frequency of graft survival in high risk corneal transplant patients.
Blavin 2012 (score = 4.0)	Medications for Keratoplasty	RCT	No mention of sponsorship. No COI.	N=46 who underwent penetrating keratoplasty in one eye. Mean±SD age: 67±15 years.		One drop of tobramycin 0.3% after taken bandage from transplanted eye, 4 times daily until cornea re-epithelialized (N=23) vs. Azithromycin 1.5%, one drop twice daily for a fixed period of further 3 days (N=23). Both groups were	Outcomes assessed daily until re-epithelialization.	Mean±SD to complete re-epithelialization for tobramycin vs. azithromycin: 4.14±1.17 vs. 4.13±1.82 (p=0.89). Superficial punctuate keratitis (SPK) scores on day 10 for tobramycin vs. azithromycin: 1.39 vs. 1.34 (p=0.80, Mann-Whitney test).	"Postkeratoplasty epithelial healing and ocular tolerance were not significantly different between the azithromycin- and tobramycin-treatment groups. Our results support the use of azithromycin as an alternative to tobramycin after corneal surgery	Small sample. Sparse methods. Data suggest similar efficacy.

						treated with dexamethasone and carmellose sodium 1 drop 4 times a day.			such as keratoplasty."	
Dellaert 1997 (score = 5.5)	Medications for Keratoplasty	RCT	Sponsored by Chiron Vision. No mention of COI.	N=36 undergoing penetrating keratoplasty. Mean age: 48.01 years.		100µg/ml topical human epidermal growth factor (hEGF) concentration in phosphate buffered with saline stabilization (N=9) vs. Placebo consisting in same vehicle solution excluding hEGF (N=9) vs. 30µg/ml topical human epidermal growth factor (hEGF) concentration in phosphate buffered with saline stabilization (N=9) vs. Matching placebo (N=9)	Follow up at 1 week, 1 month, 6 months, 1 year, and if possible, 2 years postoperatively.	Mean±SD of healing time of 100µg/ml hEGF group compared with the placebo: 5.1±4.3 days vs. 3.4±1.0 days (p=0.232) and for 30µg/ml hEGF group compared with the placebo: 3.9±3.1 days vs. 3.5±1.7 days (p=0.718). Mean percentage decrease of the defect area per 12 hours in the 100 µg/ml hEGF group vs. placebo group: 29% vs. 44% (p<0.0005); and for the 300 µg/ml hEGF group vs. placebo: 52% vs. 35% (p=0.147).	"No significant acceleration of corneal re-epithelialisation was demonstrated with the use of recombinant hEGF after penetrating keratoplasty in humans."	Small sample size. Data suggest lack of efficacy of topical hEGF for PK re-epithelialization.
Fukuda 2012 (score = 4.5)	Medications for Keratoplasty	RCT/ Cross over	Sponsored by the Waksman Foundation of Japan. No COI.	N = 63 patients scheduled to undergo penetrating		0.5% moxifloxacin ophthalmic solution vs.	No follow up. Patients went into surgery 60	Mean±SD (µg/g) corneal concentrations of fluoroquinolones: moxifloxacin 12.66±8.93	'These results show that 0.5% moxifloxacin achieved superior	Study of drug penetration and not of relevant health outcomes. Data

				keratoplasty (PKP). Age range 27-82 years.		0.3% gatifloxacin ophthalmic solution vs. 0.5% levofloxacin ophthalmic solution sequentially in crossover setting: group 1 – moxifloxacin, gatifloxacin, and levofloxacin (M/G/L) (N=20) vs. group 2 – gatifloxacin, levofloxacin, and moxifloxacin (G/L/M) (N=21) vs. group 3 – levofloxacin, moxifloxacin, and gatifloxacin (L/M/G) (N=22). Each drug administered 3 times every 15 minutes within the 30 minute period running from 90 to 60 minutes before surgery. For each administration cycle, patients	minutes after last dose.	vs. levofloxacin 5.95±4.02 vs. gatifloxacin 4.71±3.39, M vs. L (p<0.0001), L vs. G (NS), G vs. M (p<0.0001). Mean±SD (µg/g) aqueous humor: moxifloxacin 1.40±1.17 vs. levofloxacin 0.89±0.86 vs. gatifloxacin 0.65±0.80, M vs. L (p=0.0138), L vs. G (NS), G vs. M (p=0.0001).	ocular concentration than both 0.3% gatifloxacin and 0.5% levofloxacin."	suggest 0.5% moxifloxacin superior to Gatifloxacin and levofloxacin in penetrating into the aqueous humor.

						received 2 drops of each drug at 2 minute intervals. Drug concentrations determined from standard curves generated from known concentrations of the drug per weight of tissue or volume of aqueous humor used.				
Garzozi 2006 (score = 5.0)	Medications for Keratoplasty	RCT	No mention of sponsorship or COI.	N = 27 patients undergoing perforating keratoplasty (PKP). Mean age 57.6±23 years.		0.05 mg/kg i.v. droperidol (3-5 mg) in addition to general anesthesia fentanyl 2 mg/kg, diprivan 2-3 mg/kg and endotracheal intubation by rocuronium 0.5 mg/kg (N=15) vs. control group: general anesthesia only (N=12).	Follow-up at 1 day, 3 and 7 days, 1 and 6 months.	Mean±SD intraocular pressure (IOP) preoperative/postoperative: droperidol 13.1±2.63/10.27±1.98 (p<0.0001) vs. control 14±2.56/13.33±3.37 (p=0.2027). Mean+SD intraoperative anterior chamber (AC) depth: droperidol 2.8±0.1 mm vs. control 1.83±0.72 mm (p=0.0002).	"Droperidol effectively reduces intraoperative and postoperative complications in keratoplasty surgery."	Small sample. Data suggest droperidol effective in reducing intra- and postoperative complications in PKP.
Healy 2004 (score = 3.5)	Medications for Keratoplasty	Experimental Study	Sponsored by Santen Inc. No mention of COI.	N = 67 adult volunteers from patients scheduled to undergo penetrating keratoplasty with		Topical administration 15 minutes before surgery of ciprofloxacin 0.3% (N=18) vs.	No follow-up time reported.	Mean±SD cornea concentration (µg/g): ciprofloxacin 9.92±10.99 vs. ofloxacin 10.77±5.90 vs. levofloxacin 18.23±20.51 (p=0.014)	"The topical administration of all 3 agents was well tolerated in patients undergoing	Experimental study. Sparse methods. Study claims double blind, but method unclear. Data suggest levofloxacin

				intact corneal epithelium for corneal diseases stromal scarring, keratoconus, pellucial marginal degeneration, stromal dystrophy, or endothelial disease. Age not reported.		ofloxacin 0.3% (N=24) vs. levofloxacin 0.5% (N=25). All patients received 1 drop of proparacaine hydrochloride 0.5% to operative eye followed 3 minutes later by 1 drop of the treatment medication, second drop of medication was given 5 minutes after first drop.		levofloxacin favored vs. ciprofloxacin. Mean±SD aqueous humor concentration (µg/mL): ciprofloxacin 0.13±0.23 vs. 0.13±0.11 vs. 0.37±0.54 (p<0.001) levofloxacin favored.	penetrating keratoplasty. Two drops of levofloxacin 0.5% solution results in a 1.7- to 2.7-fold greater penetration into human corneal stromal and aqueous humor tissues than ofloxacin 0.3% or ciprofloxacin 0.3%. The mean intracorneal concentrations of all three agents following 2 drops exceeds the MIC90 for the majority of pathogens causing bacterial keratitis. Topical levofloxacin appears to offer pharmacokinetic and pharmacodynamic advantages over ofloxacin and ciprofloxacin in terms of enhanced transcorneal penetration; however, clinical comparative	superior for greater trans-corneal penetration.

									trials are needed to confirm these relative advantages."	
Jansen 2009 (score = 5.5)	Medications for Keratoplasty	RCT	No mention of sponsorship or COI.	N=68 scheduled for PK.		400 mg acyclovir (N=35) Vs. Identical placebo (n=33) tablets twice per day following PK.	6 weeks	Monthly event rates for epithelial herpetic eye disease (HED), stromal HED, and kerato-uveitis (KU) combined: events/month acyclovir 0.0089 vs. placebo 0.0172, rate ratio 0.52, 95% CI 0.27-0.96 (p=0.037), NS when evaluated individually or in conjunction with graft rejection episodes. NS between groups for visual acuity differences (no p-value reported).	"The results of our study suggest that oral acyclovir prescribed during the first 6 months after PK for HED protects against clinically evident HED recurrences during the first 5 years following PK."	Data suggest at 5yrs, oral cyclovir effective for prevention of recurrence of herpetic eye disease.
Kanellopoulos 1997 (score = 5.5)	Medications for Keratoplasty	RCT	Sponsored by the Lions Club International Foundation. No mention of COI.	N= 40 patients undergoing penetrating keratoplasty (PK) either combined with cataract extraction and intraocular lens implantation or without. Mean age not reported.		One dose of timolol gel forming solution immediately after surgery and before eye patching (N=21) vs. two doses of oral 500 mg sustained release acetazolamide, one after completion of surgery in recovery room and one that evening (N=19).	Follow-up first postop day.	Mean intraocular pressure (IOP) 1 day postop: timolol 12.9 mm Hg vs. acetazolamide 17.9 mm Hg (p=0.003).	"Prophylactic use of timolol gel for viscoelastic-induced ocular hypertension after PK appears to offer better IOP control than oral acetazolamide, with potentially fewer adverse systemic effects."	Small sample. Data suggest timolol gel superior to oral acetazolamide for IOP control and fewer adverse events.

Nguyen 2007 (score = 4.5)	Medications for Keratoplasty	RCT	Sponsored by Deutscher Akademischer Austausch Dienst, the International Council of Ophthalmology and BMBF. No mention of COI.	N = 305 who experienced penetrating keratoplasty in their past with mean follow up of 3.1 (± 0.9) years; the mean (± SD) age 50 (± 18) for short-term group and 52 (± 20) for long-term group		Short-term group without topical steroid treatment after the 6 months of postoperative treatment until 12 months (N = 161) Vs. Long-term group who continued prednisolone acetate 1% eye drops 1x a day until 12 months after surgery after the 6 months of prior treatment (N = 144) Both groups received 250mg acetazolamide 3x daily for 1 day, ofloxacin 3% ointment and atropine sulphate 1% ointment 3x daily for 2 weeks postoperatively. Prednisolone acetate 1% 5 x daily started on the fifth day postoperatively, and tapered off by reducing	Assessments at baseline, 6 weeks, 6, 12, 18 and 24 months.	No statistically significant results reported between short-term and long-term group comparisons.	"Long-term, low-dose, topical steroid treatment does not seem to prohibit chronic endothelial cell loss after normal-risk penetrating keratoplasty, in contrast to its favorable effect on immunological graft reactions. Our results may indicate that the etiology of chronic endothelial cell loss is not of inflammatory origin. Further studies are needed to investigate this phenomenon."	Large sample size. Data suggest at 2yrs, low dose steroid does not prevent chronic endothelial cell loss after PK.

						one drop every 6 weeks for the first 6 months.				
Olson 1979 AOO (score = 3.0)	Medications for Keratoplasty	RCT	Sponsored by Merck, Sharp and Dohme, the National Institutes of Health and Bausch and Lomb. COI, Dr. Olson was on a fellowship from Bausch and Lomb.	N = 23 requiring penetrating keratoplasty in combination with cataract extraction or aphakic penetrating keratoplasty, whose IOP was ≥ 30mm Hg 1 day postoperatively; the mean (± SD) age 71.2 (± 10.6) for Timolol group, 72.0 (± 8.3) for Daranide group, 57.8 (± 21.2) for Timolol & Daranide group and 66.7 (± 12.5) for Placebo group		Timolol medication group (N = 5) Vs. Daranide medication group (N = 4) Vs. Timolol and Daranide medication group (N = 8) Vs. Placebo control group (N = 6) Both groups received an ophthalmic solution for 1 drop 2x a day and took their perspective oral medication every 8 hours.	Assessment at baseline, 1 day, 2 days and 3+ days.	No statistically significant differences in intraocular pressure measured between medication groups and control group.	"Although Timolol, a beta-adrenergic blocking agent, has been shown to effectively lower intraocular pressure in both normal eyes and those with open-angle glaucoma, and Daranide, a carbonic anhydrase inhibitor, has been shown to be effective in treating secondary glaucoma, we found that those drugs, either alone or in combination , caused no significant difference in intraocular pressure after penetrating keratoplasty."	Small sample size. High dropouts due to uncontrollable IOP. Data suggest lack of efficacy for any of the study drugs vs. placebo.
Franzco 2008 (score = 6.5)	Medications for Keratoplasty	RCT	Sponsored by Allergan Australia. No mention of COI.	N = 108 with acute endothelial rejection of a penetrating corneal graft; the	0.05% topical CsA treatment group	Assessment at baseline, 1 day postoperatively , weekly for 1 month,	No statistically significant differences reported	"[C]sA 0.05% (Restasis) does not appear to have any beneficial effects in the treatment of graft rejection when intensive	High dropouts. Data suggest lack of efficacy of CsA in combination with topical	

				mean (± SD) age 57.9 (± 17.7) for CsA group and 62.31 (± 18.5) for control group	instilling 1 drop 4x daily to the rejecting eye (N= 54) Vs. Placebo control group (N = 54). Both groups received standard steroid protocol dosage of 1% prednisolone acetate to be instilled hourly day and night for 72 hours, followed by hourly in the day and every two hours in the	biweekly for 2 months and then monthly for 3 months.	between the CsA treatment group and placebo control group.	steroids are already being used. Other preparations of CsA could be tried."	steroids for prevention of graft rejection.	

					night for 4 days, followed by hourly in the day and every four hours in the night for 1 week.					
Price 2014 (score = 5.5)	Medications for Keratoplasty	RCT	Sponsored by the Cornea Research Foundation of America. COI, F. Price has received grants and consulting or lecture fees from Alcon, Allergan, and Bausch & Lomb.	N = 264 (325 eyes) requiring DMEK corneal transplantation; the median (range) age 67 (42-94) for prednisolone group and 68.5 (35-91) for fluorometholone group		1% Prednisolone acetate group (N = 130, 164 eyes) Vs. 0.1% Fluorometholone group (N = 134, 161 eyes). Both groups instilled 1% prednisolone acetate 4x daily for the 1st month. After randomization, each group took their respective assigned medication 4x daily for the second and third months, followed by 3x daily for the fourth month,	Assessments at baseline, 1, 3, 6, and 12 months postoperatively.	Postoperatively, the prednisolone group experienced significantly higher intraocular pressure elevation by ≥ 10mm Hg (or a base measurement of ≥24mm Hg) in the participants' eyes versus the Fluorometholone group: eyes (percent) – 32 (21.9) vs. 9 (6.1), (p=0.0005). Significantly more participants in the prednisolone group experienced intraocular pressure values ≥ 30 mm Hg and ≥40 mm Hg versus the fluorometholone group: eyes (percent) ≥30 mm Hg- 15 (11.6) vs. 2 (1.4), (p=0.0023), eyes (percent) ≥40 mm Hg- 3 (1.9) vs. 0 (0), (p=0.095). Eyes requiring or	"DMEK has a remarkably low rejection episode rate (,1% through 1 year), as confirmed in this prospective randomized study. This provides a unique opportunity to reduce postoperative topical corticosteroid strength and thereby reduce the risk of steroid associated complications."	Large sample size. Open label trial. Data suggest at 1yr post DMEK, rejection low (<1%) although prednisolone arm had higher IOP threshold elevations.

						2x daily for the fifth month and 1x daily until 1 year assessment.		increasing glaucoma medications had a significantly higher demand in the prednisolone group versus the fluorometholone: eyes (percent) – 28 (17.4) vs. 7 (4.6), (p=0.0003).		
Shimazaki 2011 (score = 4.5)	Medications for Keratoplasty	RCT	No sponsorship or COI.	N = 40 requiring high-risk (defined by deep neovascularization in >1 quadrant or a history of corneal transplantation regrafting) corneal transplantation who were >20 years old; the mean (± SD) age 63.7 (± 13.0) for CsA group and 71.1 (± 9.0) for control group		Postoperative Cyclosporine A (CsA) group receiving 3mg/kg intravenously from the operation to day 6, 5mg/kg orally daily after. C2 levels were to be maintained between 800 and 1000 ng/mL for the first 3 months followed by 600 to 800 ng/mL after for up to 12 months (N = 20) Vs. Control group (N = 20)	Assessments at baseline, daily for 2 weeks postoperatively, and then every 2 to 4 weeks for 24 months.	No statistically significant differences in graft clarity and rejection between CsA and control group.	"No positive effect of systemic CsA administration for suppressing rejection in high-risk corneal transplantation was observed. With a relatively high incidence of systemic side effects, the results suggest that this protocol should not be recommended for corneal transplant recipients, especially those of advanced age."	Open label trial but control group older than study group. Data suggest lack of efficacy of CyA in prevention of high risk corneal transplantation. Rejection with increased risk of adverse events.
Shimazaki 2012 (score = 4.0)	Medications for Keratoplasty	RCT	No sponsorship or COI.	N = 42 with a history of penetrating keratoplasty who sustained graft clarity >1 year with steroid eye drops;		0.1% fluorometholone steroid group (N = 22) Vs. No steroid control group (N = 20)	Assessments at baseline, 1 month, 3, 6, and 12 months.	Incidences of rejection significantly greater in the control group compared to the steroid group: 1 participant (4.54%) vs. 6 participants (30%), (p=0.027).	"Prolonged use of 0.1% fluorometholone was beneficial for the prevention of rejection after PKP. Because no	Data suggest at 1yr post keratoplasty use of 0.1% fluorometholone beneficial for rejection prevention.

				the mean (± SD) age 68.1 (± 12.7) for steroid group and 62.1 (± 18.7) for control group					adverse consequences were noted, we recommend continuing use of the low-dose corticosteroids, even in non–high-risk cases."	
Ünal 2008 (score = 3.5)	Medications for Keratoplasty	Randomized Trial	Sponsored by Akdeniz University Scientific Research Projects Unit. No COI.	N=47 undergoing high risk penetrating keratoplasty. Age: ≥21 years.		One drop of topical ciclosporin 0.05%, 4 times a day, and topical dexamethasone 0.1% 6 times a day simultaneously postoperatively (group 1; N=25) vs. Dexamethasone 0.1%, 6 drops tapered off appropriately (group 2; N=22)	Follow up at 1 day, 1 week, 1 month, and every month thereafter for 30 months.	There was non-statistically significant differences comparing group 1 vs. group 2 for the mean duration of immunosuppression with dexamethasone (p=0.095), the graft survival rate (p=0.518) or any other variables assessed (p>0.05).	"[W]e found that dosing four times a day with commercially available topical ciclosporin 0.05% with topical dexamethasone was not as effective as topical dexamethasone alone in high-risk corneal grafts. Prepared formulations with higher ciclosporin concentrations may be needed."	Sparse methods. Data suggest lack of efficacy of combination dexamethasone with topical CyA vs. dexamethasone alone for prevention of rejection
Arora 2013 (score = 4.5)	Keratoplasty with different time frames	RCT	No mention of industry sponsorship. No COI.	N = 24 with corneal edema resulting from pseudophakic bullous keratopathy (PBK) of more than 4 months duration and awaiting keratoplasty;		Group A, underwent penetrating keratoplasty 1 month after corneal collagen cross-linking (CXL) (N = 12) vs Group B, underwent penetrating	Follow-up at one week, one month and 3 months.	Mean±SD for VAS score: before surgery vs 1 week after: group A: 4.25±1.14 vs 1.67±0.65, (p=0.002); before surgery vs 1 month after surgery: 4.25±1.14 vs 1.83±0.84, (p=0.002). Group B: before surgery vs 1 week after: 5.25±1.357 vs 2.08±1.084, (p=0.002);	"Collagen cross-linking causes symptomatic relief and a decrease in central corneal thickness	Small sample. Data suggest corneal collagen cross linking leads to symptom relief and reduced corneal thickening and anterior stromal compaction but these effects decrease over time

				between the ages of 30 and 70 years.		keratoplasty 3 months after CXL (N = 12).		before surgery vs 1 month after: 5.25±1.357 vs 2.17±1.03, (p=0.002); before surgery vs 3 months after: 5.25±1.357 vs 2.67±1.231, (p=0.003). Mean CCT using anterior segment OCT: Group A: before surgery vs 1 week after surgery: 837.83±83.96 vs 780.92±78.45, (p=0.007); before surgery vs 1 month after CXL: 837.83±83.96 vs 787.58±84.69, (p=0.011); Group B: before surgery vs 1 month after surgery: 855.08±96.202 vs 774.42±114.62, (p=0.013); Mean OCT using ultrasound: Group A: before surgery vs 1 week after: 817.09±65.08 vs 757.45±63.05, (p=0.00) before surgery vs after 1 month: 817.09±65.08 vs 788.73±77.82, (p=0.029); Group B: before surgery vs 1 week after surgery: 809.08±88.703 vs 734.20±83.50, (p=0.025); before surgery vs 1 month after surgery: 809.08±88.703 vs 704.40±74.123, (p=0.001); before		and are disease severity dependent.

								surgery vs 3 months after surgery: : 809.08±88.703 vs 732.30±79.762, (p=0.010).		
Baradaran-Rafi 2013 (score = 6.5)	Different types of Keratoplasty techniques	RCT	Sponsored by the Ophthalmic Research Center, University of Medical Sciences, Iran. No COI.	N = 57 with a clinical diagnosis of keratoconus; mean age of 27.4±7.2 (range of 15-42).		Anwar Deep Anterior lamellar Keratoplasty technique (N = 24) Vs Melles Deep Anterior lamellar Keratoplasty Technique (N = 25).	Follow up postoperatively on days 1, 3, 7, 14, and 28; then biweekly until 3 months; then monthly until one year; and quarterly thereafter.	Mean±SD CDVA: Anwar group vs Melles group: 0.17±0.09 logMAR vs 0.18±0.11 logMAR (95% CI -0.07 to 0.05; p=0.803). The difference in photopic and mesopic contrast sensitivity function between the two groups was statistically significant (p=0.023, p=0.030, respectively).	"The Anwar and Melles techniques of DALK have comparable visual acuity and refractive outcomes, aberrometric profiles, biomechanical properties, corneal thicknesses, and endothelial cell densities. However, patients who underwent the Anwar technique showed better contrast sensitivity."	Data suggest comparable efficacy between both techniques for all outcome measures but Anwar technique resulted in sig. superior contrast sensitivity.
Behrens 2000 (score = 5.0)	Different types of Keratoplasty techniques	RCT	Sponsored by DAAD, a German Academic Exchange Service. No COI.	N = 96 with keratoconus who required PKP; mean age for NMT group was 38.2±10.8, and 34.4±9.0 for MT group.		Nonmechanical Trephination (NMT) (N = 46) Vs Mechanical Trephination (MT) (N = 50). All patients: 250 mg of acetazolamide 3 times on the first day,	Follow up at 3 months.	No statistically significant differences were seen in any of the outcomes measured.	"In addition to its optical advantages, nonmechanical corneal trephination appears to have no adverse impact on cataract formation after	Data suggest at 5yrs, both non-mechanical and mechanical corneal trephination for keratoplasty in keratoconus have similar efficacy.

						gentamicin ointment 3% 3 times a day for 5 days, and topical eye drops of scopolamine 0.25% 2 times a day and prednisone acetate 1% 5 times a day for 6 weeks starting on the fifth postoperative day.			PKP for keratoconus."	
Birnbaum 2010 (score = 4.0)	Different types of Keratoplasty techniques	RCT	No mention of industry sponsorship or COI.	N = 20 with Fuchs endothelial dystrophy or keratoconus; mean age not reported.		Received the intrastromal corneal ring (N = 10) Vs Control group, no surgery (N = 10)	Follow up at 6 weeks, and at 4, 12, 18, and 24 months postoperatively, and thereafter annually.	No statistically significant difference between groups for astigmatism (p=0.695). Endothelial cell loss: ring vs control group: 15.1% vs 8.7%, (p=0.146).	"The use of the intrastromal corneal ring after penetrating keratoplasty caused no reduction in postoperative astigmatism. However, its use was statistically significantly associated with adverse events."	Small sample. Sparse methods. Data suggest lack of efficacy of insertion of intrastromal corneal ring post PK.
Busin 1998 (score = 3.5)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship or COI.	N = 30 eyes of 29 patients with keratoconus. Age range: 14-48 years (mean: 27.4 years).		Penetrating keratoplasty (PK) surgery with intraoperative cauterization (group A; N=) vs. PK surgery	Outcomes assessed before surgery, 6 months and 13 months after surgery.	Mean±SD equivalent spherical equivalent recorded after surgery between group A vs. group B at 6 months: +1.72diopters (D) ±1.13D vs. -3.16D±2.84D; and at 13 months:	"[O]ur results suggest that cauterization of the central cornea to flatten the cone of patients with keratoconus	Small sample. Sparse methods. At 13mo, data suggest intraoperative corneal cauterization in postPK patients

						without intraoperative cauterization (group B; N=).		+0.09D±1.52D vs. -3.98D±1.52D (P<0.001). Mean±SD keratometric readings postoperatively between group A vs. group B at 6 months: 41.82D ±1.33D vs. 45.88D±2.60D; and at 13 months: 42.21D±1.61D vs. 46.24D±3.44D (P<0.001). Mean±SD keratometric astigmatism postoperatively between group A vs. group B at 6 months: 2.5 ±1.6D vs. 4.1D±2.3D; and at 13 months: 2.7D±1.5D vs. 4.4D±2.4D (P<0.05).	before transplantation can improve postkeratoplasty refraction as well as visual acuity by reducing both myopia and astigmatism."	with keratoconus improves refraction.
Cheng 2011 American Journal of Ophthalmology (score = 4.5)	Different types of Keratoplasty techniques	RCT	Sponsored by the Netherlands Organization for Health Research and Development (ZonMw). No mention of COI.	N=80 with corneal endothelial dysfunction. Mean age: 70.2 years old.		FLEK or femtosecond laser-assisted Descemet stripping endothelial keratoplasty (FS DESK) prepared with 30-kHz femtosecond laser + 15 degree blade (N = 40) vs. penetrating keratoplasty (PK) cornea was trephined using 7.75 or 8.0 mm Hessburg-Barron vacuum	Follow up at 3, 6 and 12 months.	Mean±SD of straylight values for FS DESK vs. PK at 3 months: 1.43±0.2 log vs. 1.40±0.2 log (p=.582); 6 months, 1.42±0.3 log vs. 1.41± 0.2 log (p=.960); 12 months, 1.37±0.2 log vs. 1.46±0.2 log (p=0.151). Both groups improved over time (p<0.001). Improvement at 12 months for refractive and topographic astigmatism comparing FS DESK vs. PK: -2.98 diopters (D) vs. -1.22 D (p<0.001); and 3.67 D vs .1.58 D (p<0.001), respectively.	"In conclusion, this randomized study showed that FS DSEK resulted in an equally good improvement of straylight and contrast sensitivity when compared with PK. In addition, corneal astigmatism did not increase after FS DSEK. However, although the UCVA in both groups was	See Cheng 2009. Data suggest comparable efficacy in both groups. Slight trend favoring PK.

						trephine + 11 - 0 nylon suture (N = 40). Postoperatively all received, topical dexamethasone 0.1% drops 6 times/day + chloramphenicol 0.5% 3 times/day.			comparable and the visual symptom score decreased in both groups, BSCVA was slightly better in the PK group. Our results indicate that the quality of vision measured by contrast sensitivity, straylight, and changes in visual acuity after FS DSEK is comparable with that achieved after PK."	
Cheng 2011 Ophthalmology (score = 5.0)	Different types of Keratoplasty techniques	RCT	Sponsored by the Netherlands Organization for Health Research and Development (ZonMw). No COI.	N=56 eyes of 56 patients with keratoconus intolerant for contact lens wear and stromal. Mean age: 43.15 years.		Deep anterior lamellar keratoplasty (DALK); recipient cornea was trephined using a 7.75-8.0mm Hessburg-Barron, and removal of Descemet's membrane and endothelium. (N=28) vs. Penetrating keratoplasty (PK), cornea	Follow up at 3, 6, and 12 months.	Mean±SD of endothelial cell loss based on analysis without perforation of the Descemet's membrane comparing DALK vs. PK at 3 months: 6.6±17.1 vs. 22.4±9.8 (p=0.003); at 6 months: 9.9±16.8 vs. 22.5±10.9 (p=0.024); at 12 months: 12.9±17.6 vs. 27.7±11.1 (p=0.007). Endothelial cell loss based on analysis with perforation of Descemet's membrane was not significant at any time point. Visual	"DALK procedures performed without perforation of Descemet's membrane resulted in a significantly lower EC loss, while at the same time achieving equally good visual outcomes as a PK procedure."	Data suggest at 1yr post-procedure, endothelial cell loss lower in DALK vs. PK. DALK group had no endothelial rejection.

						was trephined using 7.75 or 8.0 mm Hessburg-Barron vacuum trephine + 11 - 0 nylon suture (N=28)		outcomes were just significant at for uncorrected visual acuity at 3 months: 0.89±0.4 vs. 0.78±0.4 (p=0.021); for best spectacle-corrected visual acuity at 3 months: 0.59±0.4 vs. 0.30±0.2 (p=0.006), and at 6 months: 0.52±0.4 vs. 0.30±0.2 (p=0.019).		
Elbaz 2014 (score = 5.0)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship. No COI.	N=20 eyes of 20 patients with Fuchs endothelial dystrophy and pseudophakic bullous keratopathy undergoing Descemet stripping automated endothelial keratoplasty. Mean± SD age: 68±9.1years (range: 54.6-88.4 years)		Tan EndoGlide device opposed to limbal incision and Tan forceps inserted through nasal paracentesis to assist in grasping and the tissue into anterior chamber (N=10) vs. For EndoSerter, the device inserted into temporal incision after removing of blocking guard, while the deployment rings were held firmly in order to prevent pre-ejection of the graft (N=10). Combination of	Follow up at 6 and 12 months.	No significant difference between EndoGlide group vs. EndoSerter group for CDVA (p=0.19) or endothelial cell loss (p=0.45) at 12 months.	"[T]he EndoSerter provides comparable results to the Tan EndoGlide. Mean ECD, ECL, CDVA, and rebubbling rate were similar in both groups after 12 months of follow-up, with slight trending toward better results with the EndoSerter."	Small sample. Data suggest similar efficacy at 1yr postop.

						tobramycin 0.3% and dexamethasone 0.1% 4 times daily for 1 month, and then switched to dexamethasone 0.1% once daily over 4 months postoperatively.				
Javadi 2006 (score = 4.5)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship or COI.	N = 103 eyes of 103 patients with keratoconus, contact lens intolerant and/or had best contact lens-corrected visual acuity (VA) less than 20/80 undergoing penetrating keratoplasty (PKP). Mean age IR 27.2±8.4 year, SR 28.9±8.7, CIR 30.3±8.7 years.		Interrupted suture (IR) technique (N=26) vs. single running (no torque) suture (SR) technique (N=26) vs. combined interrupted and single running suture (CIR) technique (N=35).	Follow-up at 1 and 2 days, 1, 3, and 6 weeks, 2, 6, 9, and 12 months postop; and 2 months after complete suture removal and every 6 months thereafter.	Amount of astigmatism (Mean±SD): 1.5 mo postop – IR 3.77±1.68 vs. SR 5.48±2.1 vs. CIR 4.1±1.79 (p=0.015); NS between groups at all other follow-up times (p=0.637-0.851). NS between groups uncorrected visual acuity (UCVA) after PKP at any follow-up time (p=0.211-0.635). NS between groups best corrected visual acuity (BCVA) after PKP at any follow-up time (p=0.211-0.635).	"Post-keratoplasty astigmatism and BCVA are comparable with the 3 common suturing techniques (IR, SR, and CIR) in patients with keratoconus, provided that regular postoperative examinations and topography-guided suture adjustment and/or removal are performed."	Data suggest comparable efficacy between all 3 suturing techniques.
Karabatsas 1998 (score = 4.0)	Different types of Keratoplasty techniques	RCT	Sponsored by the Greek State Foundation. No COI.	N = 31 with post-keratoplasty (performed >1 year before study) astigmatism >4 diopters, all		Group A following a surgical plan based on CVK information only (N = 16	Assessments at baseline, 1 day, 1 month, 3, 6	At 12 months assessment, Group B keratometric and refractive astigmatism values statistically significant over Group A:	"[T]his study indicates that in terms of astigmatic correction, CVK offers a limited	Small sample. At 12mo., data suggest CVK better than keratometric and refraction alone for surgical treatment

				sutures removed for at least 3 months, intolerance to spectacle or contact lens correct, no signs of active corneal disease; participants' ages not reported		eyes) Vs. Group B following a surgical plan based on manifest refraction and keratometric readings only (N = 15 eyes) Both groups received relaxing incisions and compression sutures.	and 12 months.	Keratometric- 5.77 ± 0.52 D vs. 3.60 ± 0.81 D, (p=0.035). Refractive- 4.88 ± 0.52 D vs. 2.34 ± 0.37 D, (p=0.000).	advantage in designing astigmatic surgery after PKP, but this is likely because most of these highly astigmatic corneas follow spherocylindrical optics with regular astigmatic patterns. However, in cases in which irregular patterns are seen, CVK may be of value. A prospective, multicenter, cohort study with larger numbers of irregular astigmatic subjects should be conducted to answer this question. The suggestion, however, from the current study is that a significantly greater surgical effect should be expected with regular (preoperatively) astigmatic	of high post-graft astigmatism.

									patterns, irrespective of the treatment group. It seems that the biomechanics of corneas probably respond better in symmetric than in asymmetric surgery. Finally, although 1-year data as reported here are important, some sutures still are in place, and when they come out the cylinder is likely to change."	
Küchle 1998 (score = 5.0)	Different types of Keratoplasty techniques	RCT	Sponsored by the German Minister of Education, Science, Research and Technology. No mention of COI.	N = 52 receiving PKP for Fuchs endothelial corneal dystrophy or keratoconus; ages 20-67 years in mechanical trephination group and 17-66 in nonmechanical group		Nonmechanical excimer laser trephination group (N = 25 (20 with keratoconus and 5 with Fuchs dystrophy)) Vs. Conventional mechanical trephination group (N = 27 (22 with keratoconus and 5 with Fuchs dystrophy)) Both groups	Assessments at baseline, 3, 5, 7, 9 days and 6 weeks postoperatively.	Aqueous flare (photo counts per msec) mean (± SD) values significantly greater in mechanical trephination group over Nonmechanical trephination group for both keratoconus and Fuchs dystrophy diagnosed eyes at days 3, 5, 7 and 9, but not at 6 weeks: day 3- 27.1 (± 5.7) vs. 22.7 (± 4.5), (p=0.002); day 5- 23.1 (± 4.3) vs. 16.5 (± 3.7), (p=0.001); day 7- 17.5 (± 3.6) vs. 13.0 (± 3.2), (p=0.001); day 9- 12.7 (± 2.5) vs. 9.6 (± 2.4),	"[R]educed impairment of the blood aqueous barrier is an additional feature and possible advantage of nonmechanical trephination for penetrating keratoplasty that may favorably influence surgical outcome."	

						received acetazolamide 250 mg 3x a day on day 1, 3% gentamicin ointment 3x a day for 5 days after, 0.25% scopolamine eye drops 2x a day for 6 weeks after and 1% prednisolone acetate eye drops 5x a day after the 5th postoperative day.		(p=0.002). No significant differences reported between keratoconus and Fuchs dystrophy comparisons.		
McLaren 2009 (score = 4.0)	Different types of Keratoplasty techniques	RCT	Sponsored by Mayo Clinic Department of Ophthalmology and Research to Prevent Blindness Inc. No COI.	N = 28 eyes (25 patients) with corneal edema caused by Fuchs dystrophy; participants' ages not reported		DLEK group with a 9mm to 10mm incision (N = 13) Vs. PK with double-running sutures group (N = 15)	Assessments at baseline, 1 month, 3, 6, 12, and 24 months.	During all assessments postoperatively, total high-order wavefront aberrations statistically significant for PK corneas over DLEK corneas, ($p \leq 0.006$). At 24 month follow up, keratometric astigmatism and mean keratometric power values were statistically significant and greater after PK (4.0 ± 1.9 D and 46.1 ± 1.6 D) than after DLEK (1.3 ± 0.9 D and 43.9 ± 1.3 D), ($p<0.001$). Mesopic LCVA significantly better for DLEK versus PK after 24 months: 0.90 ± 0.16	"HOAs from the anterior corneal surface were higher after PK compared with after DLEK but did not correlate with visual function after PK."	Small sample. Data suggest at 2yrs, High Order Aberrations from anterior corneal surface highest in PK group vs. DLEK group but did not correlate with visual function after PK.

								logMAR vs. 1.0 ± 0.13 logMAR, p=0.02.		
Musch 1989 (score = 6.5)	Different types of Keratoplasty techniques	RCT	Sponsored by NEI and Research to Prevent Blindness. No mention of COI.	N = 120 requiring penetrating keratoplasty; the mean age 68.5 for DR group and 69.3 for IR group		Double running 10-0 and 11-0 sutures (DR) group (N= 60) Vs. Combination of 12 interrupted 10-0 sutures with a single running 11-0 suture (IR) group (N= 60)	Assessments at baseline, 1, 3, 6 weeks, 2, 3, 6, and 12 months.	At 12 months assessment, the difference of median astigmatism approached statistical significance for DR group versus IR group: Median (range)-4.00 (0, 16.00) vs. 2.50 (0, 9.50), (p=0.06). As 12 months, visual acuity of 20/40 or better significantly greater for DR group versus IR group: 38/54 (70.4%) participants vs. 24/54 (46.3%) participants, (p=0.02).	"[A]ssessment of the rate of visual rehabilitation was limited by a greater proportion of IR patients showing cystoid macular edema (CME) after surgery. These results, while favorable toward the IR/selective suture removal technique must be substantiated by a final assessment after all sutures have been removed."	Data suggest IR group had less astigmatism one year post-op.
Panda 2000 (score = 4.5)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship or COI.	N = 40 requiring lamella keratoplasty to correct partial-thickness corneal opacities comprising the visual axis; the mean (± SD) age 30.1 (± 9.7) for air group, 30.8 (± 10.6) for 2% hydroxypropyl methylcellulose group, 30.2 (± 9.1) for balanced saline		Intralamellar air injection group (N = 10) Vs. 2% Hydroxypropyl methylcellulose injection group (N = 10) Vs. Balanced Saline Solution injection group (N = 10) Vs. Control group (N = 10) All treatment groups (except for control)	Assessments at baseline, weekly postoperatively for 1 month, fortnightly for 3 months and monthly after for a year.	Significantly less dissection time reported for groups using adjuncts versus control group, (p<0.05). No statistically significant differences between groups in regards to endothelial cell counts, postoperative visual acuity, spherical equivalent and astigmatism.	"[H]ydrodelamination makes recipient lamellar dissection easier and safer to perform and should be undertaken routinely to facilitate intralamellar dissection. No significant difference in visual outcome, refractive status,	Data suggest hydrodelamination with balanced saline solution decreased prep time, dissection time and total time vs. other lamellar keratoplasty dissection techniques.

				solution group, and 33.7 (± 8.6) for control group.		received their appropriate adjunct both anteriorly and intralamellarly.			or endothelial cell counts with or without an adjunctive substance used to facilitate recipient bed dissection reflects the facts that the procedures are comparable."	
Sari 2013 (score = 4.5)	Different types of Keratoplasty techniques	RCT	No sponsorship or COI.	N = 82 eyes (54 participants) requiring penetrating keratoplasty for macular corneal dystrophy without endothelial involvement; the mean (± SD) age 29.7 (± 11.3) for DALK group and 33.0 (± 13.0) for PK group		Deep anterior lamellar keratoplasty (DALK) group (N =41 eyes) Vs. Penetrating keratoplasty (PK) group (N = 41 eyes)	Assessments at baseline, 6, 12, 24 and 30.5 (± 8.75) months for DALK group/ 31.2 (± 9.78) months for PK group	During the last follow up assessment, the DALK group exhibited a significantly greater mean UCVA (logMAR) versus the PK group: 0.62 (0.27) vs. 0.47 (0.21), (p=0.02). At 24 month and final follow up, the DALK group had significantly lower endothelial cell density loss versus the PK group, (p=0.03 and p < 0.01 respectively).	"Deep anterior lamellar keratoplasty with the big-bubble technique provided comparable visual and optical results as PK and resulted in less endothelial damage, as well as eliminating endothelial rejection in macular corneal dystrophy. Deep anterior lamellar keratoplasty surgery is a viable option for macular corneal dystrophy without endothelial involvement."	Data suggest comparable efficacy for visual and optical results for PK associated with less endothelial damage and eliminated rejection in macular corneal dystrophy.

Schein 1993 (score = 4.5)	Different types of Keratoplasty techniques	RCT	Sponsored by Alcon Surgical Inc, Ethicon and NIH. No COI.	N = 176 requiring penetrating keratoplasty for pseudophakic corneal edema with a planned intraocular lens exchange; the mean age 77.5 for AC IOL group, 78.3 for iris fixation PC IOL group, and 76.1 for Transscleral PC IOL group.		Anterior chamber intraocular lens (AC IOL) group (N = 60) Vs. Iris fixation posterior chamber intraocular lens (PC IOL) group (N = 56) Vs. Transscleral fixation posterior chamber intraocular lens (PC IOL) group (N = 60)		Iris fixation group demonstrated significantly less cystoid macular edema than the AC IOL group and transscleral fixation group, (p=0.02) and (p=0.02) respectively. Iris fixation group also exhibited significantly less complications than the transscleral fixation group, (p=0.02). No significant differences reported between groups for visual acuity.	"[T]ransscleral fixation of the PC IOL at the time of penetrating keratoplasty for pseudophakic corneal edema is associated with a greater risk of adverse outcome than iris fixation of a PC IOL."	Sparse methods. Data suggest trans-scleral fixation of PC IOL at time of keratoplasty associated with greater risk of adverse outcomes than iris fixation.
Seitz 1999 (score = 6.0)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship. No COI.	N = 179 requiring penetrating keratoplasty; the mean (± SD) age 51 (± 17) for excimer group and 50 (± 19) for motor trephination control group		Meditec excimer laser group (N = 88) Vs. Motor trephination control group (N = 91).	Assessments at baseline, prior to removing the first suture (15.2 ± 4.2 (mean ± SD) months), and 6 weeks after removal of the second suture (21.4 ± 5.6 months).	After suture removal assessment, mean (± SD) refractive/keratometric/topographic astigmatism exhibited significantly lower values in the Excimer group versus control group: 2.8 ± 2.0 D/3.0 ± 2.1 D/ 3.8 ± 2.6D versus 4.2 ± 2.4 D/ 6.1 ± 2.7 D/ 6.7 ± 3.1 D, (p<0.0009). Prior to and after suture removal, mean visual acuity increased significantly in Excimer versus control group: prior- 20/100 to 20/31 versus 20/111 to 20/38, (p=0.001); after- 20/31 to 20/28 versus 20/38 to 20/39,	"Postkeratoplasty results seem to be superior using nonmechanical excimer laser trephination. Thus, this methodology is recommended as the procedure of first choice in avascular corneal pathologies requiring PK."	Data suggest non-mechanical trephination provides superior outcome.

								(p<0.00001). After suture removal, the Excimer group showed significantly lower mean SRI versus the control group: 0.91 ± 0.45 versus 1.05 ± 0.46, (p=0.04).		
Seitz 2002 (score = 3.5)	Different types of Keratoplasty techniques	RCT, Longitudinal	Sponsored by Interdisziplinares Zentrum fur klinische Forschung. No mention of COI.	N = 170 requiring primary central penetrating keratoplasty for Fuchs' dystrophy or keratoconus receiving a 16-bite double running diagonal sutures; the mean (± SD) age 51 (± 18) for both groups		Excimer laser group (N=82) Vs. Motor trephination control group (N= 88)	Assessments at baseline, 6 weeks, 3, 6, 9, 12, 15, 18 and 24 months.	No statistically significant differences reported between groups for intraocular pressure.	"There was no detectable impact from the trephination method, the diagnosis, or simultaneous cataract surgery. With meticulous microsurgical technique, careful suturing, and peripheral iridotomy, the development of secondary glaucoma with disc cupping seems to be the exception."	Longitudinal follow-up. Similar results for trephination methods.
Serdarevic 1994 (score = 4.0)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship. No COI.	N = 25 requiring penetrating keratoplasty for avascular corneal pathology; the mean (± SD) age 43 (± 19) for intraoperative suture adjustment group and 37 (± 16) for control group		Intraoperative Suture Adjustment Group (N = 12) Vs. Control group without Intraoperative Suture Adjustment (N= 13) Both groups received 1% hydroxymethylc	Assessments at baseline, 1 month, 3, 6, and 9 months postoperatively	During the 1 month postoperative follow up, mean surface asymmetry index and mean refractive cylinder presented significantly lower and mean topographic astigmatism presented significantly higher in the intraoperative suture group versus the control	"Visual rehabilitation with decreased post-keratoplasty astigmatism and more regular corneal topography was attained more rapidly and safely with intraoperative	Small sample. At 6mo., data suggest visual rehab and reduced post-keratoplasty astigmatism and more regular corneal topography achieved faster with intraoperative suture adjustment.

						ellulose and gentamicin drops tapered over one week, neomycin and dexamethasone drops 4x daily for one month tapered gradually for 1 year postoperatively .		group: mean surface asymmetry index- 0.70 ± 0.25 D vs. 1.23 ± 0.68 D, (p<0.02); mean refractive cylinder- 1.33 ± 0.86 D vs. 4.65 ± 1.63 D, (p<0.0001); mean topographic astigmatism- 1.50 ± 0.74 D vs. 4.89 ± 1.99 D, (p<0.0001). At 6 month assessment, the intraoperative group exhibited significantly better mean visual acuity scores over the control: 0.8 (20/25) vs. 0.6 (20/30), (p=0.0434).	suture adjustment."	
Serdarevic 1995 (score = 4.0)	Different types of Keratoplasty techniques	RCT	No mention of sponsorship. No COI.	N = 25 requiring penetrating keratoplasty for avascular corneal pathology; the mean (± SD) age 43 (± 19) for intraoperative suture adjustment group and 37 (± 16) for control group		Intraoperative Suture Adjustment Group (N = 12) Vs. Control group without Intraoperative Suture Adjustment (N= 13) Both groups received 1% hydroxymethylc ellulose and gentamicin drops tapered over one week, neomycin and dexamethasone drops 4x daily for one month tapered	Assessment s at baseline, 1 month, 3, 6, 9 and 12 months postoperati vely	At 12 months assessment before suture removal, significantly less topographic astigmatism and mean refractive astigmatism in intraoperative suture group versus control group (mean ± SD diopters): topographic- 1.53 ± 0.72 vs. 2.82 ± 1.19, (p=0.004); mean refractive- 1.33 ± 0.74 vs. 2.75 ± 1.53, (p=0.008).	"The authors demonstrated low astigmatism and good visual results at 15 months postoperatively after either intraoperative or postoperative running suture adjustment, but intraoperative suture adjustment permitted more rapid visual rehabilitation, increased safety, and increased	See 1994 report. Small sample. At 15mo, results suggest comparable efficacy. Interoperative suture group trended towards more rapid visual rehab and increased safety and refractive stability.

						gradually for 1 year postoperatively .			refractive stability."	
Terry 2009 (score = 5.0)	Different types of Keratoplasty techniques	RCT	Sponsored by Angiotech Pharmaceuticals, Inc. No COI	N=20 corneal-scleral donor tissues. No mention of age of donors.		Trephination by a 8.0mm diameter Barron trephine (N=10) vs. Trephination by a 8.0mm diameter UltraFit Cornet trephine (N=10)	No mention of follow up.	Mean±SD percentage of trephination damage for Barron group vs. UltraFit group: 6.50%±0.95% vs. 5.64%±0.85% (p=0.084).	"Donor mechanical trephination of full-thickness corneal tissue creates relatively consistent amounts of peripheral edge damage and likely no central endothelial damage. There may exist differences in edge damage between different mechanical trephination systems, and a direct comparison to laser-created trephination is needed."	Small sample. Data suggest comparable damage between trephination systems. Mechanical trephination associated with consistent peripheral damage.
Terry 2013 (score = 7.5)	Different types of Keratoplasty techniques	RCT	Sponsored by Lions VisionGift Research Laboratory, Portland, Oregon. COI, Dr. Terry receives royalties from Bausch&Lomb	N=100 eyes of 79 patients undergoing Descemet stripping automated endothelial keratoplasty (DSAEK) surgery for Fuchs corneal		Forceps insertion, 60% portion of the donor taco was oriented anteriorly into the chamber. The tissue was unfolded with	Follow up at 6 months.	Mean±SD of endothelial cell density at 6 months comparing Neusidl group vs. forceps group: 1713.2±454.9 vs. 1930.7±468.4 (p=0.026). Mean±SD of percentage loss at 6 months comparing Neusidl group	"The Neusidl Corneal Inserter yielded a low immediate complication rate for DSAEK surgery for novice and experienced	Data suggest comparable efficacy between methods with no primary graft failures either group. Some evidence of higher cell loss in Neusidl group.

			Surgical for the specialized instruments he designed for endothelial keratoplasty surgery. Dr. Shamie has served as a consultant, a member of the speaker's bureau, or both for Bausch & Lomb, Merck, and Allergan. Dr. Straiko has served on the speaker's bureau for Merck and is an investigator on 2 studies funded by the National Eye Institute. Dr. Terry and Mr. Davis-Boozer participated in a laboratory study of the Neusidl Corneal Inserter that was funded by Fischer Surgical, Inc. Drs Goshe, Shah, and Alqudah.	dystrophy. Mean age: 69.95 years.		deepening of the anterior chamber with balanced salt solution and injection of air to complete unfolding of the tissue into position (N=50) vs. Neusidl Corneal Inserter, the tip of the device was placed into the wound, and the integrated irrigation of balanced salt solution through the tube was used on low flow to maintain the anterior chamber, tissue was released from the platform, the platform then was retracted, and the tube tip was removed from the incision (N=50).		vs. forceps group: 33.1±16.0 vs. 25.2±14.9 (p=0.017).	surgeons. Although still at an acceptable level, short-term endothelial survival was significantly worse after Neusidl tissue insertion than that after forceps tissue insertion."	
Bock 2014 (score = 4.5)	Medications and Different	RCT	Sponsored by LuxBioscience, German	N = 97 with graft loss due to rejection, and graft		Cyclosporine A (CsA) 0.5-inch LX201 implant,	Outcomes assessed at baseline,	Mean±SD for grade of vascularization at baseline for low dose vs.	"High-dose subconjunctival CsA implants do	Data suggest comparable (in) efficacy across

	Keratoplasty Approaches		Research Foundation, European Commission and Ruth und Helmut Lingen Stiftung. COI, Felix Block, Claus Cursiefen and Daniel Bohringer received financial support from LuxBioscience.	position closer than 1mm from the limbus, more than 1 quadrant stromal neovascularization. Mean age: 59 years.		with a dose of 5.13mg CsA (low dose; N=36) vs. CsA 0.75-inch LX201 implant with a dose of 7.7 mg of CsA (high dose; N=40) vs. 0.71 placebo implant with only carrier (N=21). Topical antibiotic 4times/daily for 1 week, and prednisolone acetate 1% 4 times/daily for 10 weeks postoperative.	week 1, week 24, and week 52 after surgery.	high dose vs. placebo: 3.07±2.44% vs. 2.98±2.56% vs. 3.87±4.33% (p=0.89). Mean±SD neovascularization at visit 12 (week 52) for low dose vs. placebo: 2.32±1.79% vs. 2.79±2.11% (p=0.45); and high dose vs. placebo: 2.74±2.22% vs. 2.79±2.11% (p=0.94).	not significantly affect corneal neovascularizatio n after high-risk penetrating keratoplasty. This suggests that local CsA has negligible antiangiogenic effects in the human cornea, at least in the transplant setting."	groups including placebo, suggesting CsA has no demonstrable efficacy.
Chan 2014 (score = 5.5)	Corneas stored in different mediums before Keratoplasty	RCT	Sponsored by the Victorian Government of Australia. No COI.	N = 33 eyes with symptomatic RCES not responding to conservative treatment including topical lubrication and bandage contact lens.		50µL (4-5 drops) of 25% ethyl alcohol, placed on the well for 40 seconds, and then removed with cellulose sponge, and cornea rinsed with balanced salt solution or BSS; (ALD; N=17) 50µL (4-5 drops) of BSS placed for 40 seconds, and removed with	Follow-up at 3, 6, 12, and 24 months.	Participants with presence of pain at waking for ADL vs. PTK at baseline: 14 vs.14 (p=1.00); at 3 moths: 3 vs. 5 (p=0.659); at 24 months: 3 vs. 7 (p=0.342). Mean±SD pain score for ADL vs. PTK at baseline: 6.7±2.9 vs. 6.8±1.8 (p=0.739); at 3 months: 1.7±3.3 vs. 2.4±3.2 (p=0.557); 24 months: 1.7±2.7 vs. 1.0±1.7 (p=0.878).	"The findings of this study suggest that both ALD and PTK reduce the symptoms of RCES. Compared with PTK, ALD may have a greater effect in reducing the postoperative pain score. As PTK requires expensive equipment, ALD should be considered an alternative	Small sample. Data suggest comparable efficacy.

						cellulose sponge, and cornea was rinsed with BSS (PTK; N=16)			treatment option."	
Farias 2008 (score = 4.5)	Corneas stored in different mediums before Keratoplasty	RCT	Sponsored by CNPq. No COI.	N=20 with keratoconus. Mean age: 30.35 years.		Lyophilized corneas, and rehydrated for 30 minutes in three washouts of 11mL of balance saline solution one day before surgery. (N=10) vs. Cornea preserved in Optisol GS (control; N=10).	Follow up at 1-, 3- and 6 months.	Mean±SD improvement for best spectacle visual acuity (BSCVA) for lyophilized group vs. Optisol group: 0.16±0.10 vs. 0.26±0.14 (p=0.074). Mean±SD for UCVA at 6 months for lyophilized group vs. Optisol group: 0.46±0.20 vs. 0.70±0.25 (p=0.038). There was difference in the development on punctuate keratitis by seventh postoperative day benefiting lyophilized cornea (p=0.021).	"DALK using lyophilized corneas seems to yield clinical results that are as good as and perhaps better than DALK using tissues preserved in Optisol. Keratocyte repopulation occurs in lyophilized tissue and likely contributes to the long-term health of the tissue."	Small sample. Data suggest comparable efficacy at 6 mo.
Li 2011 (score = 4.5)	Corneas stored in different mediums before Keratoplasty	RCT	Sponsored by the Medicine & Health Foundation of Zhejiang Province. No COI.	N = 68 with herpes simplex virus keratitis, bacterial keratitis, fungal keratitis and ocular burns requiring deep anterior lamellar keratoplasty (DALK); the mean (± SD) age 50.7 (± 13.5) for GCCT group and 45.9 (± 11.5) for FCT group		Glycerol-preserved corneal tissue (GCCT) group (N =34) Vs. Fresh corneal tissue (FCT) group (N = 34)	Assessments at baseline, 1 week, 1 month, 3, 6, 12 and 24 months after surgery.	At 2 year assessment, Rejection-free rate of survival significantly higher for the GCCT group (100%) over the FCT group (78.8%), (p=0.006). No statistically significant differences between groups for BCVAs postoperatively.	"[O]ur study reports successful clinical outcomes of high-risk corneal transplantation using GCCT, as compared with FCT. The therapeutic success rate and postoperative visual acuity are comparable, but GCCT offers the	Data suggest increased graft survival in GCCT group at 2yrs.

									advantages of long-term graft survival without graft rejection. Although further long-term studies are required, we suggest that DALK with GCCT should be considered as a better surgical option for high-risk corneas with healthy endothelium. At present, thousands of nonlyophilized, glycerol preserved corneas are available through Global Sight Network, lots of which are suitable for DALK. This type of corneal transplantation has a great significance in the developing world, where cornea collection programs and infrastructure for eye banking are deficient; this	

									potential advantage must not be overlooked."	
Naor 2002 (score = 7.5)	Corneas stored in different mediums before Keratoplasty	RCT	Sponsored by the Toronto Eye Foundation and the Ontario Division of the Eye Bank of Canada. No mention of COI.	N = 90 requiring corneal transplantation alone or with cataract extraction, intraocular lens insertion or intraocular lens exchange; mean (± SD) age 63.1 (± 18.7) for optisol-GS group and 63.0 (± 21.3) for CM group		Optisol-GS Group (N = 45) Vs. Chan Medium (CM) Group (N = 45)	Assessments at baseline, 1 day, 7, 30, and 90 days.	No statistically significant differences reported between groups.	"The clinical outcomes of corneal transplantation with tissue that was preserved in CM were similar to those of grafts preserved in Optisol-GS.	
Gal (Cornea Donor Study Investigator Group) 2008 (score = 7.0)	Varying cornea donor age in Keratoplasty	RCT	Sponsored by the National Eye Institute, Eye Bank Association of America, Bausch & Lomb, Tissue Banks International, Vision Share, San Diego Eye Bank, Cornea Society, Katena Products Inc., Midwest Eye- Banks, Konan Medical Group, Eye Bank for Sight Restoration and SightLife. No mention of COI.	N = 1090 patients between the ages of 40-80 years with corneal disease that placed them at moderate risk for graft failure. Mean age 70±9 years.		Donor eye age 66-75 years (N=383) vs. donor eye age 12-65 years (N=707) used for corneal transplant.	Follow-up at 6 months (up to investigator's discretion), 1 visit between 6 and 12 months, and 1 visit every 12 months through to 5 years.	Graft survival rate: donor age 12-40 years 93% vs. donor age 41-75 years 85% (p=0.001). Graft failures: 135 eyes, 90 in donor eye age <66 and 45 in donor eye age ≥66 (no p-value reported).	"Five-year graft survivals for cornea transplants at moderate risk for failure are similar using corneas from donors ≥ 66.0 years and donors < 66.0. Surgeons and patients now have evidence that corneas comparable in quality to those used in this study from donors through age 75	At 5-years, data suggest corneal age does not influence outcomes.

									are suitable for transplantation."	
Heidemann 1985 (score = 4.5)	Varying donor eye size in Keratoplasty	RCT	Sponsored by the Michigan Eye bank and Research to Prevent Blindness. No mention of COI.	N= 173 aphakic or phakic penetrating keratoplasty procedures. Mean age same size donor 49.8 year, larger size donor 56.1 years.		Same size donor eye (N=80) vs. 0.5 mm larger size donor eye (N=93).	Follow-up everyday postoperative while patient was in hospital, 4 weeks after last interrupted suture was removed, and 2 months postop.	NS between group for final visual acuity or mean intraocular pressure (IOP) (no p-value reported). Mean±SD postoperative keratometry: interrupted and running sutures combined – same sized 42.98±2.07 vs. oversized 45.69±1.95 (p<0.0001); interrupted sutures – same sized 43.39 vs. oversized 45.53 (p<0.0001); running sutures – same sized 41.90 vs. oversized 45.92 (p<0.0001).	"Our data suggest the possibility that oversize grafting may decrease the incidence of postoperative wound leaks, although the numbers were too small to be of statistical significance."	Data suggest oversized graphs (may) decrease wound leaks, wound dehiscence, and IOP. No differences in astigmatism between groups.
Olson 1979 (score = 3.5)	Varying trephine size in Keratoplasty	RCT	Sponsored by the US Public Health Service, the National Institutes of Health, Fight-for-Sight Inc, and Research to Prevent Blindness Inc. No mention of COI.	N = 46 requiring aphakic and combined keratoplasties; participants' ages not reported		Group A receiving donor tissue with use of same size trephine as was used on the recipient (N = 25) Vs. Group B receiving donor tissue obtained with use of a trephine 0.55 mm larger than used on the recipient (N = 21)	Assessments at baseline and postoperatively.	No statistically significant results reported between groups for refractive error.	"[T]he results showed no statistically significant difference in refractive error, either in spherical equivalents or in astigmatism. The larger donor tissue may have some value in reducing high plus-refractive error and in reducing intraocular pressure after surgery."	Sparse methods. Data suggest no difference in refractive error, either in spherical equivalents or astigmatism when donor tissue larger but (may) have some value for reducing high plus-refractive error and decreasing IOP post surgery.

Saethre 2014 (score = 4.5)	Patient positioning after keratoplasty	RCT	No mention of sponsorship or COI.	N = 40 requiring descemet stripping automated endothelial keratoplasty (DSAEK); the mean (± SD) age 74 (± 8.6) for group 1 and 72 (± 8.3) for group 2		Group 1 who sat in a chair comfortably postoperatively (N = 20) Vs. Group 2 who laid face up in a bed postoperatively (N = 20)	Assessments at baseline, 1 day, 7 days, 1 month, 3 months and 6 months.	No statistically significant changes between group 1 and group 2 were reported.	"Supine positioning does not seem to be of crucial importance in avoiding graft dislocation in DSAEK when the anterior chamber is fully filled with air for 2 hr postoperatively."	Small sample. Data suggest similar efficacy between 2 groups' positioning.

Evidence for Keratoplasty

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Musch 1990 (score = 5.0)	Addition of various solutions immediately following Keratoplasty	RCT	Sponsored by Pharmacia, Inc. No mention of COI.	N = 78 requiring penetrating keratoplasty who would not have an intraocular lens post-surgery; the mean age 49.2 for Healon group and 47.9 for BSS group		Healon solution group (N = 41) vs. Balanced Salt Solution (BSS) group (N = 37)	Assessments at baseline, 1 week, 3, 6, 12, 18, and 24 months.	At 2 year follow up, the Healon group showed significantly less ECD loss than BSS group: 17.3% vs. 30.2%, (p=0.05). Healon group exhibited significantly higher mean (SD) Intraocular pressure (mm Hg) at 1 day and 2 years postoperatively over BSS group: 1 day- 18.2 (9.3) vs. 13.7 (4.6), (p<0.05), 2 years- 16.5 (3.4) vs. 13.7 (3.9), (p<0.05).	"[O]ur results do not provide support for a marked protective effect of Healon use against endothelial rejection following PK. Given the small sample size, however, we cannot conclude definitively that there was indeed no effect."	Data suggest comparable outcomes between groups, although corneal thickness slightly greater in Healon group.

Pterygium

OVERVIEW

Pterygium is an abnormal growth consisting of a triangular fold of tissue that advances progressively over the cornea, usually from the nasal side [715, 716] [717]. Localized conjunctival inflammation may be associated with pterygiae [116, 715]. Most cases occur in tropical climates, dry climates, and amongst those who work outside with ultraviolet exposure. Most cases are cosmetic, although a minority may be symptomatic. However, surgical excision is indicated if the pterygium encroaches on the visual axis.

Topical NSAIDs function as local anesthetics and analgesics. Topical NSAIDS are administered to provide relief from inflammatory pain associated with inflamed pterygia, pingueculae [718], corneal abrasions [429], postoperative pain from various surgical procedures [433] and pain associated with many other disorders.

TREATMENT RECOMMENDATIONS

NSAID Drops for Inflamed Pterygia or Pingueculae

Recommended.

Medications (including topical creams)

NSAID ophthalmic drops are recommended for inflamed pterygia or pingueculae.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Moderate

☒ Acute ☒ Subacute ☒ Chronic

☐ Preoperative ☒ Perioperative ☒ Postoperative

Indications:	Inflamed pterygia or pinguecuae [719]
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	allergic reactions in susceptible patients, intolerance.
Frequency/Dose/Duration:	Per manufacturer's recommendations. The one quality trial utilized indomethacin 0.1% drops 6 times daily for 3 days, then 4 times daily to complete 2 weeks [719].
Indications for Discontinuation:	Symptom resolution, intolerance or adverse effects.
Rationale:	There is one moderate-quality trial suggesting equal efficacy of NSAID drops compared with glucocorticoid drops for treatment of in flamed pterygia or pinguecuae [719]. There also are multiple moderate quality trials comparing NSAIDs with placebo or drug vehicle for analgesia of simple corneal abrasion. [428-433] (see above). NSAID drops are low cost, not invasive, associated with low risks and are recommended.
Evidence:	
Comments:	

Topical glucocorticosteroids have been used to provide relief from inflammatory pain associated with inflamed pterygia, pingueculae [719].

Glucocorticosteroid Drops for Inflamed Pterygia or Pingueculae

Recommended.

Medications (including topical creams)

Glucocorticosteroid ophthalmic drops are recommended for inflamed pterygia or pingueculae.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Moderate

☒ Acute ☐ Subacute ☐ Chronic

☐ Preoperative ☐ Perioperative ☐ Postoperative

Indications:	Inflamed pterygia or pinguecuae [719]. Generally preferable to use NSAID drops first as the adverse effects are generally lower.
Benefits:	Reduced pain, decreased inflammatory response.
Harms:	allergic reactions, intolerance.
Frequency/Dose/Duration:	Per manufacturer's recommendations. One moderate quality trial utilized 0.1% dexamethasone drops 6 times daily for 3 days, then 4 times daily to complete 2 weeks. [719]
Indications for Discontinuation:	Symptom resolution, intolerance, adverse effects or completion of a course.
Rationale:	There is one moderate-quality trial suggesting equal efficacy of NSAID drops compared with glucocorticoid drops for treatment of in flamed pterygia or pinguecuae [719]. Glucocorticosteroid drops are low cost, not invasive, associated with low risks for short course and are recommended.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: eye, pterygium, pterygia, recurrent pterygia, mitomycin C, surgery, mitomycin, indomethacin, beta irradiation, beta particles, radiation, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 216 articles, and considered 109 for inclusion. In Scopus, we found and reviewed 7 articles, and considered 0 for inclusion. In CINAHL, we found and reviewed 176 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 0 for inclusion. We also considered for inclusion 1 articles from other sources. Of the

110 articles considered for inclusion, 1 randomized trial and 0 systematic studies met the inclusion criteria.

Pterygia have been surgically removed using many different techniques and approaches (Ozsutcu 14)

Pterygium Excision for Pterygia

Recommended.

Surgical Considerations

Pterygium excision is recommended for pterygia that near the visual axis.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☒ Preoperative ☒ Perioperative ☐ Postoperative

Indications:	Pterygia that near the visual axis.
Benefits:	Reduced risk of peripheral vision impairment. Reduced risk of visual axis impairment if more extensive.
Harms:	Recurrence, surgical complications.
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	
Rationale:	There are many trials of various approaches for removal of pterygia. There are no trials comparing removal with non-removal. Surgical excision is invasive, has adverse effects, is costly, but may prevent serious complications and is selectively recommended for those with impending visual impairments.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: eye, pterygium, pterygia, recurrent pterygia, mitomycin C, surgery, mitomycin, indomethacin, beta irradiation, beta particles, radiation, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 216 articles, and considered 109 for inclusion. In Scopus, we found and reviewed 7 articles, and considered 0 for inclusion. In CINAHL, we found and reviewed 176 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 0 for inclusion. We also considered for inclusion 1 articles from other sources. Of the 110 articles considered for inclusion, 100 randomized trials and 10 systematic studies met the inclusion criteria.

Pterygia have been intra- and postoperatively treated to attempt to prevention recurrence and/or complications.

Bevacizumab for Prevention of Pterygia Recurrence

Recommended.

Surgical Considerations

Bevacizumab is recommended for pterygia that near the visual axis.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Moderate

☐ Acute ☐ Subacute ☐ Chronic
☐ Preoperative ☐ Perioperative ☒ Postoperative

Indications:	Surgical cases of excision of pterygia, especially in younger patients at higher risk of recurrences.
Benefits:	Reduced risk of recurrence.
Harms:	Intolerance, adverse effects.
Frequency/Dose/Duration:	Topical bevacizumab (5 mg/mL) 4 times daily for 2 months. [720][181]
Indications for Discontinuation:	Intolerance, adverse effects, completion of a course.
Rationale:	There are many trials of various approaches for removal of pterygia. There are no trials comparing removal with non-removal. Surgical excision is invasive, has adverse effects, is costly, but may prevent serious complications and is selectively recommended for those with impending visual impairments.
Evidence:	A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: eye, pterygium, pterygia, recurrent pterygia, mitomycin C, surgery, mitomycin, indomethacin, beta irradiation, beta particles, radiation, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 216 articles, and considered 109 for inclusion. In Scopus, we found and reviewed 7 articles, and considered 0 for inclusion. In CINAHL, we found and reviewed 176 articles, and considered 0 for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered 0 for inclusion. We also considered for inclusion 1 articles from other sources. Of the 110 articles considered for inclusion, 101 randomized trials and 10 systematic studies met the inclusion criteria.
Comments:	

Evidence for NSAID Drops for Inflamed Pterygia or Pingueculae

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Frucht-Pery 1997 [245] (score = 5.0)	Mitomycin: different applications	RCT	Sponsored by the Laboratoire Chauvin, Montpellier, France. No mention of COI.	N = 51 inflamed pterygium and pinguecula. Mean age: 42.6 years.		Group 1: treated with indomethacin 0.1% drops (N = 25) vs. Group 2: treated with placebo Group 2: antation (tion (LCAT, n(N = 26).	Follow up was at days 3, 7, and 14.	Total score decreased for group 1 by 74% (10.08 ± 2.91 to 2.67 ± 3.21) and for group 2 by 47% (8.65 ± 1.92 to 4.58 ± 3.34); the score of total signs decreased by 73% in group 1 (5.12 ± 1.72 to 1.38 ± 1.1) and for group 2 by 52% (4.38 ± 1.6 to 2.13 ± 1.26).	"This study indicates that topical indomethacin solution 0.1% is a useful treatment for inflamed pterygium and pinguecula."	Details sparse. Data suggest short term efficacy.
Goldberg 1985 [246] (score = 8.0)	Mitomycin: different applications	Randomized Crossover Trial	Sponsored by the Medical Research Council of Canada and by Merek Frosst Canada, Ltd. No mention of COI.	N = 10 healthy patients with no history of ocular disease. No mention of age of subjects.		Indomethacin 1% eye drops in each eye concurrently four times a day with timolol maleate 0.5% during days 4 through 7 inclusive vs. identical treatment but in reverse order (N = 10) After a washout period of 7 days, timolol maleate 0.5%	Outcome assessed at days 1, 4, 7, 10, 18, 21, 24, 27, and 34.	Significant decrease in intraocular pressure for all ten subjects using timolol maleate 0.5% alone (p< 0.05). No adverse events from either medication during the study.	"[W]e found that significant ocular hypotension was achieved with timolol alone.	Experimental study. Data suggest NSAID does not affect timolol and ocular pressure.

						eye drops were administered during days 21 through 24 vs. identical medication with reverse application (N = 10). Each subject served as his/her own control.				
Miyake 1983 (score = 5.0)	Indomethacin (NSAID) vs Placebo	RCT [273]	No mention of sponsorship or COI.	N = 140 with rhegmatogenous retinal detachments. Mean: 47.9 years.		Indomethacin 0.5% (N = 63) vs. Placebo (N = 61).	Twelve week follow-up.	Angiographic evidence in 11/63 (13%) of indomethacin group compared to 20/61 (33%) ($p < 0.01$). More clinically severe cases of cystoid macular edema in placebo group (11 eyes) vs. indomethacin group (3 eyes) ($p < 0.05$).	"[T]opical pretreatment with indomethacin prevented the development of cystoid macular edema after retinal detachment surgery."	Data suggest indomethacin reduced cystoids macular edema.
Sand 1991 (score = 4.0)	Steroids	RCT [274]	No mention of industry sponsorship or COI.	N = 49 eyes of 49 patients between the ages of 18-80 with mild to moderate acute anterior uveitis (AAU). Age range: 20-73 years.		1% indomethacin in ricinus oil (N = 25) vs. 0.1% dexametason in water with addition of hydroxypropylmelthylcellulose and benzalkonium	Follow up at day 1, 3, 7, and 14.	Inflammatory score: day 1 NS; day 7 indometacin 2 vs. dexametason, ($p<0.05$); day 14 NS. Percentage cured patients:	"[A]cute anterior uveitis will show the fastest recovery when treated with local application of a strong corticosteroid	Data suggest NSAID drops inferior to steroid drops at 7 days.

						chloride 6 times daily (N = 24).		day 7 indometacin 8% vs. dexametason 46%, (p<0.05); daily 14 NS.	as compared to indometacin."	
Aragona 2000 (score = 5.0)	Steroids	RCT [276]	No mention of sponsorship or COI.	N = 90 normal healthy subjects. Mean age: 27.1±5 (21-46) years.		Group 1: Placebo or control group (N = 15) vs. Group 2: 0.1% diclofenac (N = 15) vs. Group 3: 0.1% indomethacin solution (N = 15) vs. Group 4: 0.03% flurbiprofen (N = 15) vs. Group 5: 0.5% ketorolac tromethamine (N = 15) vs. Group 6: topical anaesthetic solution of 0.4% oxybuprocaine chloridrate drops in 1 eye 4 times at 5 minute intervals and ocular surface studied by fluorescein stain before drug instillation and 5, 15, 30, and 60 min after last drop was instilled (N = 15).	Other eye was placebo.	Diclofenac treated group showed a statistically significant decrease in corneal sensitivity (p<0.001), at 15 minutes after instillation and up to the end of the study.	"Despite a similar mechanism of action and analgesic activity to the other NSAIDs tested, diclofenac was able to induce a reduction in corneal sensitivity."	Experimental study. All medication cause discomfort c/w placebo. Oxybuprocaine associated with mill erosionas w/i 5 min.

Tutton 1996 (score = 7.5)	Steroids	RCT[277]	Sponsored by CIBA Vision Ophthalmics, Bïdach, Switzerland. No mention of COI.	N = 63 undergoing invasive correction of myopia. No mention of age.		Diclofenac sodium 1% (N = 31) vs. Placebo (N = 32).	Follow up at 1, 2, 4, 6, and 24 hours postoperatively.	Mean Pain Score (SE) at 1 /2 /4 /6 / and 24 hours for diclofenac vs. placebo: 8.9(2.3)/16.0 (4.0)/16.4 (3.9)/ 16.9 (5.3), and 26.0 (6.6) vs. 24.8 (2.8)/ 43.8 (6.2)/57.9 (7.0)/ 36.3 (8.0), and 29.3 (6.7), ($p < 0.05$/ < 0.0001/ < 0.0001/ < 0.05/NS.)	"Topical diclofenac significantly reduced the ocular pain and discomfort immediately after excimer PRK without any clinically significant complications or adverse effects."	Data suggest diclofenac effective.
Öksüz 2005 (score = 5.0)		RCT[280]	No mention of sponsorship or COI.	N = 54 who were undergoing excision and autograft for pterygium. Mean age: 43.3 years.		Group 1; 1 ml lidocaine 2% hydrochloride solution with 0.125 epinephrine injected under direct vision via a 27-gauge needle subconjunctivally beneath the pterygium (N = 28). vs. Group 2: lidocaine 2% gel applied topically +1 ml of unpreserved lidocaine 2% gel in the inferior conjunctival	No mention of follow up time.	There were significant differences in the pain felt during anaesthetic administration (4.26 ± 1.18 vs. 0.92 ± 0.56 in group 2, $p = 0.01$, mean volume of local anesthetic used (1.5 ± 0 ml vs. 2.53 ± 0.51 ml ($p < 0.001$).	"We conclude that 2% lidocaine gel is effective and safe anesthesia in pterygium surgery."	Details sparse.

						fornix 5 minutes before surgery every 10 minutes during the operation (N = 26).				
Frucht-Pery 1990[179] (score = 6.0)	Indomethacin vs. Dexamethasone	RCT	Sponsored by Laboratoire Chauvin, Montpellier, France. No COI.	N=50 with inflamed pterygia or pingueculae. Mean±SD age: 43.96±15.63years.		Indomethacin 0.1% drops 6 times daily for 3 days, then 4 times to complete 2 weeks (N=25). vs. 0.1% dexamethasone drops 6 times daily for 3 days, then 4 times to complete 2 weeks (N=25).	Outcomes assessed at 3, 7, 14, 30, and 45 days.	Total signs scores increased on group 2 compared to group 1 after discontinuation of treatment (p=0.02 and p=0.023, respectively), but there was not difference for total symptoms (p=1.00 and p=0.83, respectively) and total scores (p=0.22 and p=0.36, respectively).	"[T]opical indomethacin 0.1% solution is as effective as topical dexamethasone phosphate 0.1% solution for the treatment of inflamed pterygium and pinguecula and, therefore, is suggested as an effective treatment for these conditions. The need for longer duration of treatment or retreatments for recurrent inflammatory phenomena should be further investigated."	Crossover Study, Data suggest topical indomethacin may reduce ocular pain and discomfort associated with corneal scars and edema.
Frucht-Pery 1999 [218]	Mitomycin C vs. Conjunctival Autograft	RCT	Sponsored by the Laboratoire Chauvin,	N = 50 with symptomatic inflamed pterygia. Mean±SD age:		Group 1 treated with indomethacin 0.1% drops (N =	Follow up on days 3, 7, 14, 30 and 45.	Total score decreased significantly for group 1 and	"[T]opical indomethacin 0.1% solution is as effective as	Data suggest similar efficacy.

(score = 6.5)			Montpellier, France. COI, Drs. Richard and Trinquand are employees of the Laboratoire of Chauvin.	43.96±15.63 (23-81) years.		25) vs. Group 2: treated with 0.1% dexamethasone solution (N = 26).		group 2 at day 3, 7, and 14 (p = 0.001), no significant difference between groups.	topical dexamethasone phosphate 0.1% solution for the treatment of inflamed pterygium and pinguecula and, therefore, is suggested as an effective treatment for these conditions."	
Neumayer 2006 (score = 7.0)	Steroids	RCT two - way crossover [275]	No mention of sponsorship or COI.	N = 32 with pronounced regeneratory posterior capsule opacification (PCO). No mention of age.		Groups one treated with Verum prednisolone 5% + diclofenac 1% tropically four times for 1 week (N = 32) vs. After a wash-out period of two weeks, placebo treated tropically for 1 week four times lubricating eye drops (N = 32).	1 year follow up.	Analysis variance, appeared pearls between verum series (p > 0.05).	"In conclusion, this study showed that the instillation of topical prednisolone and diclofenac for one week does not influence the change in rophology of Elschnig pearls."	Crossover trial. Data suggest comparable (in) efficacy.

Evidence for Glucocorticosteroid Drops for Inflamed Pterygia or Pingueculae

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Frucht-Pery 1990[179] (score = 6.0)	Indomethacin vs. Dexamethasone	RCT	Sponsored by Laboratoire Chauvin, Montpellier, France. No COI.	N=50 with inflamed pterygia or pingueculae. Mean±SD age: 43.96±15.63 years.		Indomethacin 0.1% drops 6 times daily for 3 days, then 4 times to complete 2 weeks (N=25). vs. 0.1% dexamethasone drops 6 times daily for 3 days, then 4 times to complete 2 weeks (N=25).	Outcomes assessed at 3, 7, 14, 30, and 45 days.	Total signs scores increased on group 2 compared to group 1 after discontinuation of treatment (p=0.02 and p=0.023, respectively), but there was not difference for total symptoms (p=1.00 and p=0.83, respectively) and total scores (p=0.22 and p=0.36, respectively).	"[T]opical indomethacin 0.1% solution is as effective as topical dexamethasone phosphate 0.1% solution for the treatment of inflamed pterygium and pinguecula and, therefore, is suggested as an effective treatment for these conditions. The need for longer duration of treatment or retreatments for recurrent inflammatory phenomena should be further investigated."	Crossover Study, Data suggest topical indomethacin may reduce ocular pain and discomfort associated with corneal scars and edema.
Sand 1991 (score = 4.0)	Steroids	RCT [274]	No mention of industry sponsorship or COI.	N = 49 eyes of 49 patients between the ages of 18-80 with mild to moderate acute anterior uveitis		1% indomethacin in ricinus oil (N = 25) vs. 0.1% dexametason in water with addition of hydroxypropylmethylcellulose and benzalkonium	Follow up at day 1, 3, 7, and 14.	Inflammatory score: day 1 NS; day 7 indometacin 2 vs. dexametason, ($p<0.05$); day 14 NS. Percentage cured patients: day 7 indometacin 8% vs. dexametason	"[A]cute anterior uveitis will show the fastest recovery when treated with local application of a strong corticosteroid as compared to indometacin."	Data suggest NSAID drops inferior to steroid drops at 7 days.

				(AAU). Age range: 20-73 years.		chloride 6 times daily (N = 24).		46%, (p<0.05); daily 14 NS.		
Aragona 2000 (score = 5.0)	Steroids	RCT [276]	No mention of sponsorship or COI.	N = 90 normal healthy subjects. Mean age: 27.1±5 (21-46) years.		Group 1: Placebo or control group (N = 15) vs. Group 2: 0.1% diclofenac (N = 15) vs. Group 3: 0.1% indomethacin solution (N = 15) vs. Group 4: 0.03% flurbiprofen (N = 15) vs. Group 5: 0.5% ketorolac tromethamine (N = 15) vs. Group 6: topical anaesthetic solution of 0.4% oxybuprocaine chloridrate drops in 1 eye 4 times at 5 minute intervals and ocular surface studied by fluorescein stain before drug instillation and 5, 15, 30, and 60 min after last drop was instilled (N = 15).	Other eye was placebo.	Diclofenac treated group showed a statistically significant decrease in corneal sensitivity (p<0.001), at 15 minutes after instillation and up to the end of the study.	"Despite a similar mechanism of action and analgesic activity to the other NSAIDs tested, diclofenac was able to induce a reduction in corneal sensitivity."	Experimental study. All medication cause discomfort c/w placebo. Oxybuprocaine associated with mill erosionas w/i 5 min.
Karalezli 2014[184] (score = 5.0)	Bevacizumab: different	RCT	No mention of sponsor	N = 88 with primary pterygium undergoing excision with		Group 1, received dexamethasone 0.1% and tobramycin 0.3, medications	Follow up on the first postoperative day, weekly until one	Recurrence rate: group 1 vs group 2: 2 eyes (4.3%) vs one eye (2.4%), (p=0.092).	"Topical bevacizumab seems to have no additional effect on pterygium	Data suggest the addition of topical bevacizimal-postop pterygium surgery does

	applications		ship. No COI.	limbal – conjunctival autograft transplantation (LCAT). Mean±SD age: Group 1: 53.04±11.81 years. Group 2: 58.82±12.02 years.		tapered over the course of four weeks (N = 46) Vs. Group 2, same as group 1 with the addition of 5mg/ml topical bevacizumab, four times daily for one month postoperatively.	month, and monthly thereafter.		recurrence after LCAT."	not have any effect on recurrence rates.
Frucht-Pery 1999 [218] (score = 6.5)	Mitomycin C vs. Conjunctival Autograft	RCT	Sponsored by the Laboratoire Chauvin, Montpellier, France. COI, Drs. Richard and Trinquand are employees of the Laboratoire of Chauvin.	N = 50 with symptomatic inflamed pterygia. Mean±SD age: 43.96±15.63 (23-81) years.		Group 1 treated with indomethacin 0.1% drops (N = 25) vs. Group 2: treated with 0.1% dexamethasone solution (N = 26).	Follow up on days 3, 7, 14, 30 and 45.	Total score decreased significantly for group 1 and group 2 at day 3, 7, and 14 (p = 0.001), no significant difference between groups.	"[T]opical indomethacin 0.1% solution is as effective as topical dexamethasone phosphate 0.1% solution for the treatment of inflamed pterygium and pinguecula and, therefore, is suggested as an effective treatment for these conditions."	Data suggest similar efficacy.
Prabhasawat 2006 (score = 5.0)	Steroids	RCT [268]	No mention of	N = 120 who previously underwent		Subconjunctival 5-fluorouracil 5 mg, 0.1 cc, 5-UF, with	Follow up was done at 1 and 2 weeks,	Success rates were higher in both treatment groups	"[T]he current study showed that intralesional	Data suggest 5-FU and triamcinolone efficacious to reduce

			sponsorship. No COI.	pterygium excision within the previous 6 months. Results given for 109 patients. Mean age: 50.5±13.4 years.		1% prednisolone acetate (N = 39) vs. 1% prednisolone acetate only (N = 35) vs. 1% prednisolone acetate with 1 dose of 20 mg (0.5 cc) of triamcinolone (N = 35).	and 1, 3, 6, 9, and 12 months.	compared to control, 5-UF 34/39 eyes (87.2%), triamcinolone 25/35 eyes or 71.4% vs. control 17/35 (48.6%), p = 0.001. Recurrence rate was 11/35 eyes (31.4%) for the control group, 3/39 eyes (7.7%) in the 5-FU group, 5/35 eyes (14.3%), 5-FU vs. control (p = 0.009).	injection of either 5-FU or triamcinolone effectively stops the progression of impending recurrent pterygia, results in an impressive appearance at the surgical site, and helps to avoid repetitive surgery."	recurrence but higher complication rate.
Ozgurhan 2013 (score = 5.5)	Steroids	RCT [269]	No mention of sponsorship. No COI.	N = 45 with primary pterygium who underwent pterygium excision with conjunctival autograft transplantation. The mean age was 46 ± 14 years in the fluorometholone group, 50 ± 15 years in the dexamethasone group, and 54 ± 15 in the		Fluorometholone group: topical fluorometholone 0.1% vs. Dexamethasone group: topical dexamethasone 0.1% vs. Fluorometholone /tetrahydrozoline group: topical fluorometholone 0.1% tetrahydrozoline HCl 0.025% fixed combination. Treatments were administered with topical Moxifloxacin drops 4 times	Follow-up for 1 week, 2 weeks, 1 month, and 3 months.	At 2 weeks and 1 month, there was a significant difference in the conjunctival graft thickness after surgery in the fluorometholone group (274 ± 61 and 178 ± 59) vs. dexamethasone group (290 ± 60 and 168 ± 46) vs. fluorometholone/tetrahydrozoline group (203 ± 43 and 118 ± 10), (p<0.01 and p<0.01). The mean graft thickness was significantly lower in the	"The findings of the present study revealed that treatment with the fluorometholone/tetrahydrozoline fixed combination may be helpful to decrease graft edema and to achieve better cosmetic appearance at 2 weeks and 1 month after pterygium excision."	Data suggest patients treated with flourometholone/tetrahydrozoline fixed combination experienced increased graft healing and better cosmetic results.

				fluorometholone/tetrahydrozoline group		daily for a month after surgery.		fluorometholone/tetrahydrozoline group vs. the fluorometholone and dexamethasone groups at 2 weeks (p = 0.002 and p = 0.012) and 1 month (p = 0.003 and p = 0.013). The mean graft hyperemia score was significantly lower in the fluorometholone/tetrahydrozoline group vs. the fluorometholone and dexamethasone groups at 2 weeks (p = 0.000 and p = 0.000) and 1 month (p = 0.039 and p = 0.040).		
Wishaw 2000 (score = 7.5)	Steroids	RCT [270]	No mention of sponsorship or COI.	N = 20 undergoing pterygium surgery. Age range: 18-73 years.		Lignocaine 1% 2 ml (N = 10) vs. Lignocaine 1% 1.6 ml plus morphine 4 mg in 0.4 ml (N = 10).	Follow up at 24 hours after surgery	At 24 hour postsurgery, mean pain scores for lignocaine plus morphine group was 1.63 and for the lignocaine group was 3.86, (p = 0.035); the difference was no longer significant at 48 hours.	"Our study suggests that peribulbar morphine is an effective analgesic modality for 24 hours postoperatively in pterygium surgery and is not accompanied by serious side-effects."	Data suggest morphine and lignocaine superior for pain relief. 2 day follow-up.

Rietveld 2005 (score = 7.0)	Steroids	RCT [271]	Sponsored by the Dutch College of General Practitioners (ZonMw). No COI.	N = 181 with red eye and either (muco)-purulent discharge or sticking of the eyelids. Mean age: 43.4 years.		Fusidic acid gel one drop four times daily + daily diary (N = 81) vs. Placebo ne drop four times daily + daily diary (N = 100).	Follow-up at 7 days.	Primary outcome, difference in recovery rate: 62% vs. 59% in the placebo group. Secondary outcome, difference in bacterial eradication rates: after 7 days, 76% vs. 41%.	"In conclusion, at 7 days, cure rates in both the fusidic acid gel and placebo group were similar, although the trial lacked power to demonstrate equivalence conclusively."	Data suggest that when compared to placebo, fusidic acid is non-superior in treating acute infectious conjunctivitis.
White 2008 (score = 6.0)	Steroids	RCT [272]	Sponsored by Bausch & Lomb, Inc. COI, Drs. Bateman and Comstock were employed by Bausch & Lomb, Inc.	N = 280 with clinically diagnosed blepharoke-ratocon junctivitis. Mean age: 55.5 years.		LE / T or loteprednol etabonate + tobramycin ophthalmic suspension, 0.5 % / 0.3% + self-administration of medication four times / day, 1 - 2 drops within four hour interval (N = 136) vs. DM / T or dexamethasone + tobramycin ophthalmic suspension, 0.3% / 0.1% + self-administration of medication four times / day, 1 - 2 drops within four hour interval (N = 137).	Follow-up for 14 days.	At visit 2 / 3 / and 4 from baseline the mean sd change: (-7.1 vs. -7.6) / (-12.3 vs. -13.2) / and (- 15.2 vs. -15.6 in DM / T). 78% reduction in signs and symptoms of ocular inflammation associated with blepharokeratocon junctivitis from baseline for both treatments.	"The results of this study demonstrate that LE / T is as effective as DM / T in reducing the signs and symptoms of ocular inflammation associated with blehparokeratoconj unctivitis."	Data suggest LE/T decreases signs and symptoms of inflammation associated with blepharokeratoconjunc tivits.
Neumayer 2006 (score = 7.0)	Steroids	RCT two -	No mention of	N = 32 with pronounced regenerator		Groups one treated with Verum	1 year follow up.	Analysis variance, appeared pearls	"In conclusion, this study showed that the instillation of	Crossover trial. Data suggest comparable (in) efficacy.

		way cross over [275]	sponsorship or COI.	y posterior capsule opacification (PCO). No mention of age.		prednisolone 5% + diclofenac 1% tropically four times for 1 week (N = 32) vs. After a wash-out period of two weeks, placebo treated tropically for 1 week four times lubricating eye drops (N = 32).		between verum series (p > 0.05).	topical prednisolone and diclofenac for one week does not influence the change in rophology of Elschnig pearls."	
Öksüz 2005 (score = 5.0)		RCT [280]	No mention of sponsorship or COI.	N = 54 who were undergoing excision and autograft for pterygium. Mean age: 43.3 years.		Group 1; 1 ml lidocaine 2% hydrochloride solution with 0.125 epinephrine injected under direct vision via a 27-gauge needle subconjunctivally beneath the pterygium (N = 28). vs. Group 2: lidocaine 2% gel applied topically +1 ml of unpreserved lidocaine 2% gel in the inferior conjunctival fornix 5 minutes before surgery every 10 minutes during the operation (N = 26).	No mention of follow up time.	There were significant differences in the pain felt during anaesthetic administration (4.26 ± 1.18 vs. 0.92 ± 0.56 in group 2, p = 0.01, mean volume of local anesthetic used (1.5 ± 0 ml vs. 2.53 ± 0.51 ml (p < 0.001).	"We conclude that 2% lidocaine gel is effective and safe anesthesia in pterygium surgery."	Details sparse.

Turan-Vural 2011 (score = 4.0)	Cyclosporine A	RCT [266]	No sponsorship. No COI.	N= 36 eyes of 34 patients with primary pterygium. Mean age: group1: 57.05 ± 11.65 group 2: 53.27 ± 10.88 years.		Bare sclera technique was performed in both groups. In Group I, 0.05% cyclosporine A (CsA) was administered postoperatively at 6-hour intervals for 6 months. (N= 18) vs. Group II did not receive CsA treatment (N= 18)	Follow up: at postoperative 1 and 7 days as well as each month during the following year.	In Group I, while four cases exhibited recurrence Figure 1, 14 (77.8%) did not show recurrence, and the mean recurrence-free follow-up time was 9.92 ± 0.92 months. In Group II, while eight cases exhibited recurrence, 10 (55.6%) cases did not show recurrence, and the mean recurrence-free follow-up time was 7.50 ± 1.19 month.	"Postoperative application of low-dose CsA can be effective for preventing recurrences after primary pterygium surgery"	Small sample. Data suggest low dose CSA may prevent pterygium recurrence.
Ibáñez 2009 (score = 4.0)	Cyclosporine A	RCT [267]	No mention of sponsorship. No COI.	N = 80 eyes is 76 consecutive patients with primary pterygium; mean age of 48.5 years.		Conjunctival autograft (CA) plus 0.1ml injection of 0.125mg/ml Mitomycin C (MMC) topical cyclosprin A 1% twice a day for 3 months (N = 37) vs Control (CA+MMC) group (N = 38). All patients: chloramphenicol 0.5% and prednisolone	Follow-up at day 1, 1, 3, and 6 weeks, and 3 and 6 months.	Response rate: women: treatment vs placebo: 0% vs 24%, (p=0.03).	"This study indicates that pterygium excision with a free conjunctival autograft combined with intraoperative low-dose MMC is a safe and effective technique in pterygium surgery."	Data suggest comparable efficacy with cyclosporine A being slightly better for prevention of pterygium recurrence.

						acetate 1% twice a day for 2 weeks and then prednisolone acetate 1% twice a day for 1 week. All patients used hypromellose 0.5% drops four times daily during the 3 months.				

Evidence for Bevacizumab for Prevention of Pterygia Recurrence

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Ozsutcu 2014[180] (score = 3.0)	Mitomycin vs. Bevacizumab vs. placebo	RCT	No mention of sponsorship or conflict of interest.	N = 90 with primary pterygia. Mean±SD age: Group A: 42.55±8.23 years. Group B: 40.8±10.23 years. Group C: 43.25±9.60 years.		All patients underwent pterygium excision and rotational conjunctival flap plus: Group A: subconjunctival salt solution injected as placebo. (N = 30) vs. Group B: adjunctive mitomycin C (0.02%) administered on bare sclera (N =30). vs. Group C: adjunctive bevacizumab (2.5mg/0.1ml) injection (N=30).	Follow up visits at day 1, week 1, and 1, 3, 6 and 9 months.	Percentage of reoccurrence rate of pterygium at 9 months for group A vs. group B vs. group C: 26.6% vs. 13.3% vs. 10%. Reoccurrence was lower for group B and C compared to group A (p=0.1806), and similar comparing group A and B (p>0.05).	"Subconjunctival bevacizumab injection may decrease the recurrence rate of primary pterygium surgery with rotational conjunctival flap."	Quasi-randomization by MRN. Data suggest subconjunctival be vacizumed injections may decrease the recurrence rate of pterygium surgery.

Ozgurhan 2013[181] (score = 4.5)	Bevacizumab vs. Placebo	RCT	No mention of sponsorship. No COI.	N = 44 who underwent recurrent pterygium excision with conjunctival autograft transplantation. Mean±SD age was 48.4±11.3 years in the study group and 50.5±17.8 years in the control group.		Study group: topical bevacizumab (5 mg/mL) (N = 22) vs. Control group: artificial tear (N = 22). Treatments were administered 4 times daily for 2 months.	Follow-up for 1 day, 1 week, 1 month, 2 months, 3 months, and 6 months.	There was no pterygium recurrence in the study group vs. 2 eyes (9.1%) in the control group (p = 0.244). At 3 and 6 months, the study group did not develop corneal neovascularization vs. 5 eyes (22.7%) in the control group (p = 0.024).	"Topical bevacizumab therapy 1 month after surgical excision of recurrent pterygium is well tolerated and effective to prevent neovascularization. Although the recurrence rate is lower in the study group without significant difference, further studies are required to support this result."	Data suggest adding topical bevacuzumab 1 month after recurrent pterygium surgery prevents neovascularization.
Razeghinejad 2010[182] (score = 4.0)	Different flaps for excision	RCT	No mention of sponsorship or COI.	N = 38 with primary pterygium. Mean±SD age: Cases: 45.8±16.07 years. Controls: 41.6±13.9 years.		Case group received pterygium excision and rotational conjunctival flap with adjunctive subconjunctival bevacizumab (N = 17) vs. Control group received pterygium excision and rotational conjunctival flap with subconjunctival balanced salt solution (N = 21).	Follow-up for 1 month.	No statistically significant differences between the two groups regarding prevalence of pterygium recurrence risk factors (p=0.84).	"[A] single intraoperative subconjunctival bevacizumab injection has no effect on the recurrence rate of pterygia or on early postoperative conjunctival erythema, lacrimation, photophobia or healing of corneal epithelial defects after primary pterygium excision."	Quasi-randomized on MRN. Variable length of last FU. Data suggest not effective.

Razeghinejad 2014 [183] (score = 6.0)	Different flaps for excision	RCT	Sponsored by Shiraz University of Medical Sciences. No COI.	N=44 eyes of 44 patients decreased visual acuity, due to visual axis or induced astigmatism, discomfort and irritation unresponsive to lubricants, restricted ocular motility, cosmetic concerns, or >3mm extension of the pterygium over the cornea. Mean age: 43.04 years.		Pterygium excision with rotational conjunctival flap, and 7.5mg of subconjunctival bevacizumab, 5mg/0.2ml on day of the surgery, and 2.5mg/0.2ml on 4th day after surgery (N=22) vs. pterygium excision and a rotational conjunctival flap, and 0.2ml of balanced salt solution (BSS) at the end of surgery (N=22)	Outcomes assessed at day 1, week 1, and months 1, 3, and 6.	No significant difference between bevacizumab group vs. BSS group on recurrence of any fibrovascular overgrowth on the cornea (p=0.17); Recurrence of > 1.5 mm fibrovascular overgrowth on the cornea (p=0.62), keratometry (p=0.29), spherical equivalent (p=0.54) and corneal astigmatism (p=0.61).	"[S]ubconjunctival bevacizumab injections had no statistically but a probably clinically significant effect on the recurrence rate of pterygia."	Data suggest each of efficacy of subconjunctival bevacizumab on recurrence rate of pterygium when compared to placebo.
Karalezli 2014[184] (score = 5.0)	Bevacizumab: different applications	RCT	No mention of sponsorship. No COI.	N = 88 with primary pterygium undergoing excision with limbal – conjunctival autograft transplantation (LCAT). Mean±SD age: Group 1: 53.04±11.81 years. Group 2: 58.82±12.02 years.		Group 1, received dexamethasone 0.1% and tobramycin 0.3, medications tapered over the course of four weeks (N = 46) Vs. Group 2, same as group 1 with the addition of 5mg/ml topical bevacizumab, four times daily for one month postoperatively.	Follow up on the first postoperative day, weekly until one month, and monthly thereafter.	Recurrence rate: group 1 vs group 2: 2 eyes (4.3%) vs one eye (2.4%), (p=0.092).	"Topical bevacizumab seems to have no additional effect on pterygium recurrence after LCAT."	Data suggest the addition of topical bevacizimal-postop pterygium surgery does not have any effect on recurrence rates.

Shenasi 2011 [185] (score = 3.5)	Bevacizumab: different applications	RCT	No mention of sponsorship. No COI.	N=80 eyes of 80 patients with primary pterygium. Mean±SD age: 58.94±14.60 years.		Group A: pterygium excision and 1.25mg/0.1ml subconjunctival bevacizumab injected by a 27 gauge needle adjacent to the location of excised pterygium (N=40) vs. Group B: pterygium excision and distilled water applied same way as group A (N=40).	Follow up for 9 months.	Recurrence of pterygium comparing group A vs. group B: 45.5% vs. 57.6% (p=0.33).	"Subconjunctival injection of bevacizumab immediately after surgical excision of primary pterygium is well-tolerated, but it cannot significantly prevent the recurrence of this condition."	Data suggest lack of efficacy for addition of subconjunctival bevacizumal immediately post pterygium excision.
Fallah 2010 [186] (score = 4.5)	Bevacizumab: different applications	RCT	No mention of sponsorship. No COI.	N = 54 undergoing pterygium excision. Mean age: 49.96 years.		Group A: received an eye drop of bevacizumab (5mg/ml) twice a day in combination with betamethasone, four time daily for one week (N = 26) vs. Group B: administered betamethasone only 4 times daily for 1 week (N = 26).	Follow up at 1 week, 1 month, and 3 months.	Mean progression at one week was 1.916 ± 0.375 vs. 2.740 ± 0.517 for group B, (p<0.01); at one month 15.998 ± 1.22 vs. 27.230 ± 4.700 (p<0.01); at three months 37.671 ± 13.1 vs. 59.247 ± 9.472 (p<0.01).	"[S]hort-term use of topical bevacizumab seems to be a safe and effective treatment for delaying recurrence in patients with impending recurrent pterygium."	Variable length of final follow-up. Both groups favored although data formed
Nava-Castañeda 2014 [187] (score = 4.0)	Bevacizumab: different applications	RCT	Sponsored by Consejo Nacional de Ciencia y Tecnología. No COI.	N = 49 with primary pterygium. Mean±SD age: 48.8±15.5 years.		Group 1: bevacizumab (2.5 mg/0.1 mL) was applied once after surgery (N=16) vs. Group 2: the	Follow-up for 1 year.	There was a significant difference in the final appearance grading: Group 1 vs.	"A single 2.5 mg/mL subconjunctival bevacizumab injection in conjunction with primary pterygium	At 1 year, data suggest single dose of 2.5 mg/mL subconjunctival bevacizumal in addition to

						bevacizumab (2.5 mg/0.1 mL) was applied after surgery, with another same dose 15 days after surgery (N=17) vs. Group 3: the control group, surgery was performed without bevacizumab application (N=16).		2. vs. 3: 0 vs. 0 vs. 12.5%, p<0.04.	surgery accomplishing a conjunctival autograft procedure is safe and well tolerated, and is capable of preventing pterygium recurrences when compared with a control group."	pterygium surgery significantly prevents pterygium recurrences.

Evidence for Pterygium Excision for Pterygia

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sati 2014 [188] (score = 4.0)	Conjunctival Fixation: Suture vs. Fibrin glue vs. In situ blood coagulum		No mention of sponsorship. No COI.	N=90 with primary pterygium grades 1-3, and at least 2mm extension from the limbus. Bare sclera technique for excision. Mean±SD age: Suture group: 40.9±2.73 years. Fibrin glue: 40.1±2.32 years. Blood coagulum group: 40.63±2.54 years.		Group I: 8/0 vicryl sutures used to suture the graft with surrounding conjunctiva (N=30) vs. Group II: one drop of fibrin glue was placed under the graft and another drop of thrombin was put on the scleral bed to secure the graft (N=30) vs. Group III: conjunctival autograft (CAG) was applied over the bare area with bleeding vessels and allowed to adhere spontaneously over it after tucking surrounding conjunctiva (N=30).	Outcomes assessed at 1, 3, 6, 9, and 12 months.	Percentage recurrence comparing group I vs. group II vs. group III: 10% vs. 6.67% vs. 3.33% (p=0.585). Percentage of graft retraction comparing group I vs. group II vs. group III: 0% vs. 3.33% vs. 10% (p=0.160). Mean±SD operative time comparing group I vs. group II vs. group III: 27.63 ± 1.63 vs. 15.5 ± 1.2 vs. 16.97 ± 1.35 (p<0.001)	"[A]ll the three techniques of conjunctival fixation are safe and effective and are associated with similar rates of recurrence. Moreover, the use of fibrin glue or autologous in situ blood coagulum in pterygium surgery significantly reduces operative time and postoperative discomfort. Further studies with a larger population and longer follow-up period are needed to supplement this study.	Data suggest similar efficacy between all 3 groups.
Singh 2013 [189] (score = 4.5)	Conjunctival autografting: fibrin glue vs.	RCT	No mention of sponsorship. No COI.	N=20 eyes of 20 patients with pterygium.		Group I: conjunctival autograft with fibrin glue (N=10) vs. Group	Follow up for 12 months.	Mean±SD time of surgery comparing group I vs.	"[C]onjunctival grafting using the patient's own blood as bioadhesive can	Small sample case control. Data suggest autologous fibrin "may" be useful

	Blood coagulum			Mean age: 32.2 years.		II: onjunctival autograft left to adhere spontaneously trusting bioadhesive properties of fibrin in patient's blood (N=10).		group II: 14.74±2.35 vs. 17.45±2.89. Recurrence rate comparing group I vs, group II: 10% vs. 10%. For overall complication rate p=0.2783 (p>0.05).	be used for pterygium surgeries safely without any increased chances of graft failure, graft loss, graft dislodgement, and recurrences and found the results to be comparable with autografting using fibrin glue for small- to average-sized grafts."	for graft fixation in pterygium surgery.
Kurian 2014 [190] (score = 7.0)	Conjunctival Fixation: Suture vs. Fibrin glue vs. In situ blood coagulum	RCT	No mention sponsorship. No COI.	N = 194 with primary pterygia undergoing surgery. Mean±SD age: Group 1: 42.5±10.4 years. Group 2: 37.4±12.6 years.		Group I: securing conjunctival autograft (CAG) with autologous blood (N = 96) vs. Group II: CAG with fibrin glue (N = 98).	Follow-up for day 1, week 1, month 1, month 3, month 6 and 1 year after surgery.	Primary outcomes: the difference in success rate between group I vs. group II was −1.09% (CI: −4.84% to 2.66%), (p<0.05). The difference in success rate between group I vs. group II, in terms of recurrence was +1.91% (CI: −4.192%	"Feasibilty of adherence of the graft without glue in pterygium surgery is promising and has results comparable with the fibrin glue technique in terms of long-term outcome and recurrence, suggesting the potential for autologous blood to replace fibrin glue in graft fixation."	Data suggest compariable results between the 2 methods.

								to 8.012%), (p<0.05).		
Choudhury 2014 [191] (score = 4.0)	Conjunctival autografting: Sutures vs. Blood coagulum	RCT	No mention of sponsorship or COI.	N=32 undergoing primary pterygium excision. Mean±SD age: 45±20 (23-67) years.		Group I: conjunctival autografting with nylon 10-0 sutures (N=16) vs. Group II: conjunctival autografting with autologous fibrin in in situ blood coagulum (N=16).	Follow up 2nd day after surgery, and weeks 1, 2, 4, and at 12 months.	Mean surgical duration comparing group I vs. group II: 67±2 vs. 15±2, p<0.001. Intensity of pain, foreign body sensation, tearing and discomfort was lower, and symptoms were fewer and disappeared more quickly in group II compared to group I (p<0.001).	"[A]utologous in situ blood coagulum is an effective and safe method for attaching conjunctival autografts during pterygium surgery. The use of autologous in situ blood coagulum can significantly shorten operating times and produce fewer postoperative symptoms and discomfort."	Data suggest similar efficacy for recurrence but autologous in situ clood coagulum group had shorter surgical times and reported less postoperative discomfort.
Wong 2007 [192] (score = 7.0)	Conjunctival autografting: Sutures vs. Blood coagulum	RCT	No mention of sponsorship or COI.	N = 32 eyes of 32 participants with primary pterygium. Mean±SD age: Nylon group: 60.9±13.5 years. Polyglactin group: 54.9±6.6 years.		Group 1 nylon sutures (N = 17) vs. Group 2 polyglactin sutures for conjunctive autograft (N = 15).	Follow up was at 1 day, 1 week, 4 weeks, and 3 months postoperatively.	Polyglactin sutures notes more tarsal conjunctival papillary reaction at day 1 (p = 0.01) and more graft hyperemia at 1 week (p = 0.019). At 4 weeks, more	"[B]oth polyglactin and nylon sutures are effective for conjunctival autograft suturing in pterygium surgery and cause comparable levels of	Data suggest more discomfort with polyglactin at 1 week.

								nylon sutures remained on the autograft (p = 0.021).	postoperative discomfort."	
Hall 2009 [193] (score = 4.0)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N=50 with primary nasal pterygia undergoing surgery with conjunctival autograft. Mean age: Fibrin glue: 47.8 years. Vicryl suture: 49.8 years.		Conjunctival autograft sutured with interrupted 8.0 Vicryl (N=25) vs. fibrin glue applied the scleral bed and graft was slid into position and manipulated for 3 seconds, and then left for the cure time for 3 minutes (N=25)	Follow up at days 1, 7, 14, 30, 90, 180 and 365.	Mean surgical time comparing fibrin glue vs. sutures: 12.04 minutes vs. 26.04 minutes (p<0.001) Recurrence comparing fibrin glue vs. sutures: 0 vs. 2 at 3 months. Postoperative pain was lower on fibrin glue group at day 1 (p<0.001) and day 2 (p<0.05).	"Both glued and sutured conjunctival autografting procedures are safe and effective methods for pterygium surgery. Given the savings in operating time, the authors believe the technique may be cost-effective overall. In addition, the decreased postoperative discomfort with fibrin glue is a significant advantage in the first 48 h. A disadvantage is the possibility of complications, but with good surgical technique and patient selection these will be minimized."	At 12 months post surgery, data suggest comparable recurrence rates in both groups but glued autografts took less time and surgical patients reported less pain but there were higher numbers of complications.

Jiang 2008 [194] (score = 5.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N = 40 with primary nasal pterygium undergoing surgery. Mean age: FS group: 57.5±11 years. Suture group: 57±9 years.		Fibrin sealant or FS (N = 20) vs. Sutures (N = 20).	Follow up on postoperative days 1, 3, 7, 14, and months 1, 2, 6, and 12.	Pain scores were lower for FS compared to sutures at days 1, 3, 7 (p<0.00) but was no longer significantly different by day 14 (p=1.00).	"[W]ith the use of FS for graft fixation in pterygium surgery, considerable time can be saved while reducing complaints of postoperative discomfort."	Fibrin group had shorter operation time and less population pain. Suture recurrence 10% vs. fibrin 5%.
Karalezli 2008 [195] (score = 6.0)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of industry sponsorship. No COI.	N = 50 eyes of 50 participants with primary nasal pterygium. Mean±SD age: Fibrin glue: 53.4±11.8 years. Vicryl sutures: 58.8±12.3 years.		Fibrin glue (N = 25) vs. 8-0 Vicryl sutures (N = 25).	Follow up was conducted for 12 months.	Intensity of pain, foreign-body sensation, irritation and epiphora was significantly lower in patients treated with fibrin glue than sutures on day 1 and 10, p<0.001. Postoperative itching sensation was lower in fibrin glue than sutures at the first two postoperative visits (20% vs. 48%, p<0.05). Recurrance occured in 4% (N = 1)	"In conclusion, the use of fibrin glue for the attatchment of conjunctival autografts in pterygium surgery is safe and effective in reducing early postoperative complications and patient discomfort."	Data suggest fibrin glue faster (16 vs. 32 min), less discomfort and lower recurrence rates (4 vs. 12%).

								patients in the fibrin glue group and 12% (N = 3) patients in the suture group, p < 0.05.		
Hall 2009 [193] (score = 5.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N = 50 with primary nasal pterygia >4 mm in size and with a history of change undergoing excision surgery. Mean age: 47.8 (21-77) years.		Vicryl 8.0 buried knots conjunctival autograft (N = 25) vs. Tissue glue conjunctival autograft group or Tisseel fibrin glue (N = 25).	Follow up was on days 7, 14, 30, 90,180 and 365.	Mean surgical time for glue group was 12.04 min vs. 26.04 min for suture group (p<0.001). At 3 months, no recurrence in the glue group and two recurrence in the suture group. Subjective assessment of postoperative pain was significantly less for the fibrin glue group at day 1 (p < 0.001) and day 2 (p < 0.05).	"Both glued and sutured conjunctival autografting procedures are safe and effective methods for pterygium surgery."	Less discomfort with fibrin glue. Recurrence in 8.7% in suture group vs. 0% in fibrin glue.
Yüksel 2010 [196] (score = 3.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N=58 eyes of 58 patients with primary nasal pterygium. Mean age:		Group 1: autologous conjunctival graft attached to the sclera with a Beriplast P fibrin	Follow up was on the 3rd and 10th postoperative days and	Mean surgery time (min) Group 1 vs. Group 2: 23.42±13.34 vs.	"Using fibrin glue for graft fixation in pterygium surgery causes significantly less	Data suggest the use of fibrin glue for pterygium surgery graft fixation is associated with

				48.4 ±13.3 years in group 1 and 52.6 ±12.1 years in group 2.		tissue adhesive (N=29) vs. Group 2: autologous conjunctival graft attached with 8-0 virgin silk sutures (N=29)	at the 1st, 3rd and 6th months.	41.45±3.20; p<0.05. Recurrence rates at 6 months after surgery: 2 (6.8%) vs. 4 (13.7%), p<0.05.	postoperative pain and shortens surgery time significantly"	less surgical time and less post-op pain.
Ozdamar 2008 [197] (score = 4.0)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship. No COI.	N = 24 eyes of 24 participants who underwent pterygium surgery. Mean±SD age: 42.6±3.8 year (range, 38–52 years).		Fibrin glue used to attach limbal conjunctival autograft (N = 12) vs. Limbal-conjunctival autograft with vicryl sutures (N = 12).	Follow-up on 1, 3, 5, 7, 15, 22, 30, and 45 days after surgery and every month thereafter for 6 months.	Patient satisfaction was significantly higher in the fibrin tissue glue vs. sutures on postoperative day 1, and 1, 2, 3, and 4, weeks after surgery (p<0.05).	"[L]imbal conjunctival autografting is an effective surgical technique for the treatment of pterygium, and tissue glue was efficacious in securing the limbal conjunctival autograft in pterygium surgery."	Tissue glue had less irritation post-op.
Küçükerdönmez 2014 [198] (score = 5.0)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No sponsorship or COI.	N = 26 with primary pterygium. Mean (range) age: Suture group 52.1 (38-59) years. Fibrin group 57.1 (41-62) years.		Suture group, (N = 13) Vs Fibrin Glue group (N = 13)	After surgery: topical antibiotic (ofloxacin 0.3% 4 times daily) and corticosteroid (dexamethasone 0.1% 4 times daily)	Mean±SD for vascularized graft area: suture group vs fibrin glue: first postoperative day: 18.1±7.8 vs 34.8±10.2, (p<0.01). 7th postoperative day: 25.3±8.6 vs 66.1±17.8, (p<0.01).	"Fibrin glue fixation of conjunctival autografts led to more vascularization in the early postoperative period than suture fixated grafts, which in turn may have significance in terms of graft	Data suggest fibrin glue groups had increased vascularization in immediate postoperative phase.

									health and pterygium recurrence."	
Koranyi 2004 [199] (score = 4.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of industry sponsorship or COI.	N = 43 eyes of 43 participants with primary nasal pterygium. Mean±SD age: 44±14 years glue group. 48±16 years suture group.		Fibrin glue (N = 20) vs. 7-0 Vicryl Rapid sutures (N = 23).	6 months.	Pain scores were lower at day 0 and each point in time for the first postoperative week for the fibrin glue group ($p < 0.05$). Surgery time was 10 vs. 17 minutes in the sutures group ($p < 0.001$).	"Using glue instead of sutures when attaching the conjunctival transplant in pterygium surgery causes significantly less postoperative pain and shortens surgery time significantly."	Less population pain. Recurrence in 8% glue vs. 20% suture.
Mahdy 2012 [200] (score = 2.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship. No COI.	N = 40 with recurrent pterygium who had been operated on only once. Mean age: 51 years.		Group 1: Vicryl-sutured grafts (N=20) vs. Group 2: Fibrin-glued grafts that were prepared from autologous blood (N = 20).	Follow-up for 1, 6, and 12 months.	Group 2 (mean time approx. 15 min) had a decreased of surgery time vs. group 1 (mean time approx. 21 min), ($p<0.05$). Postoperative pain and discomfort were marked in 4 patients in group 1 vs. 2 patients in group 2 (10%). Also,	"[T]he use of fibrin glue in pterygium surgery with amniotic membrane grafting was safer, less toxic and less time-consuming, and resulted in fewer complications than graft surgery with sutures."	Some baseline comparibility omissions. Data suggest future glue use in pterygium surgery with ammotic membrane grafting was quicker and had fewer complications compared with sutures.

								group 2 had a decreased in inflammation and redness (p<0.05).		
Bahar 2007 [201] (score = 4.0)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N = 81 eyes of 81 participants with primary nasal pterygium undergoing surgery. Mean age: 49.5±15 (27-75) years.		Study group: conjunctival closure with fibrin adhesive or glue Quixil (N = 42) vs. Control group: conjunctival closure with Vicryl sutures (N = 39).	Clinical assessment was performed on days 1, 3, 10 and 21 and at 3, 6, and 12 months.	Mean operative time for fibrin-glue group was 16 min vs. 28 min in the suture group (p<0.05). Fibrin-glue group had significantly lower score for average pain, photophobia, foreign body sensation, irritation, epiphora, and dry eye sensation in fibrin-glue group vs. suture group (p<0.05). At the end, 11.9%patients in the study group developed recurrent pterygium vs. 7.7% in the	"The use of fibrin glue in pterygium surgery significantly reduces operative time and patient pain compared with suturing."	Quasi-randomized. Some details sparse. Data favor fibrin glue for immediate postop.

								control group (p<0.05).		
Ratnalingam 2010[202] (score = 6.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	Sponsored by the Institute of Medical Research, Malaysia. No mention of COI.	N = 175 with primary pterygium undergoing excision surgery. Mean age: 60.07±10.35 years (range: 40-84).		Conjunctival autograft with sutures (N = 69) vs. With fibrin adhesive (N = 68).	Follow up of at least 36 months.	Recurrence rate for fibrin adhesive group 3/68 (4.41%) compared to the suture group 11/69 (15.9%), p = 0.03. 1 and 6 month postoperative showed no statistically differences between groups. Mean duration of surgery time for fibring group was 16.93 ± 2.85 min compared to 29.84 ± 5.65 min for suture group, p<0.0001.	"The use of fibrin adhesive in primary pterygium surgery with conjunctival autografts reduces the recurrence rate, surgical time, and postoperative pain with compared with sutures."	Patients not well described. High dropouts. Lower recurrence in fibrin adhesive.
Uy 2005 [203] (score = 4.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship. No COI.	N = 22 with primary pterygia undergoing excision surgery. Mean age: 45±20 years.		Fibrin glue + fibrinogen solution + tobramycin and dexamethasone eye drops applied 6 times daily for 1 month after surgery (N	Follow up was performed on weeks 1, 2, 4, and 8.	Operative time was significantly longer for the suture group, 67.0±2.6 minutes vs. fibrin group 27.8 ± 1.0	"Fibrin glue is a safe and effective method for attaching conjunctival autografts. The use of fibrin glue results in shorter	Patients not well described. Less population discomfort with fibrin glue.

						= 11) vs. Sutures + tobramycin and dexamethasone eye drops 6 times daily (N = 11)		min, (p<0.001). Subjective symptoms of pain, foreign body sensation, tearing, and discomfort were significantly lower for the fibrin group (p<0.001).	operating times and less postoperative discomfort. "	
Küçükerdönmez 2010 [204] (score = 7.5)	Conjunctival autografting: Fibrin glue vs. suture.	RCT	No mention of sponsorship or COI.	N = 70 eyes of 70 participants with primary nasal pterygium undergoing pterygium excision. Mean±SD age: fibrin glue: 52.7±9.8 years, Suture group: 54.2±11.3 years.		Amniotic membrane transplantation or AMT with fibrin glue (N = 32 eyes) vs. 8-0 vicryl sutures (N = 38 eyes).	Follow-up was monthly for the first 6 months and at 3-month intervals thereafter for 12 months.	Operative time was significantly longer for the suture group (18.7 ± 2.2 vs. 11.2 ± 2.4 min, (p = 0.018) compared to the fibrin glue. Recurrence rates were not significantly different between groups.	"Amniotic membrane grafts can be successfully attached without any major complication in patients undergoing pterygium surgery."	Data suggest fibrin superior in 1st week, but subsequently no differences, including recurrences.
Xu 2013 [205] (score = 5.5)	Conjunctival autograft: Sutures vs.	RCT	Sponsored by the Health Department of Guangxi Zhuang	N=80 eyes of 80 patients with primary pterygium. Mean age: ECP group:		Sutureless and glueless conjunctival autografting using electrocautery	All the patients were followed up postoperatively on	The mean surgical time for the glue group was significantly shorter at	“[U]sing ECP for the attachment of conjunctival autografts in pterygium surgery is safe,	Data suggest comparable recurrence between ECP and mylon but ECP had shorter

	electrocautery pen.		Autonomous Region, China. No COI.	57.1 years, Suture group: 53.6 years.		pen or ECP group (N=40) vs. autografting using nylon 10-0 sutures or suture group (N=40)	days 1, 2, 3, 5, 7, and 14 and then at months 1, 3, 6, and 12.	20.4 minutes compared with the suture group at 27.1 minutes ($p < 0.001$). Postoperative pain, irritation, and epiphora were significantly less at postoperative days 5 and 7 ($p< 0.05$). Postoperative foreign body sensation was significantly less at postoperative days 2, 3, 5, and 7 ($p < 0.05$). During the follow-up period, conjunctival recurrence (grade 3) developed in 1 (2.5%) eye in the ECP group, and in 2 (5%) eyes in the suture group. Both groups had 1	fast, simple, and economical with less postoperative discomfort. The recurrence rate seems not to be higher than that with sutures on long-term follow-up."	surgical times and patients reported less postop complaints.

								(2.5%) corneal recurrence (grade 4).		
Shahin 2012 [206] (score = 4.0)	Pterygium excision: with vs. without bevacizumab	RCT	No mention of sponsorship. No COI.	N=41 eyes of 41 patients with grade 3 or grade 2 pterygium undergoing excision surgery. Mean age: 58.12±4.91 years.		Group 1: pterygium excision with conjuctivo-limbal graft only (N=21) vs. Group 2: pterygium excision with conjuctivo-limbal graft plus 1.25mg/0.05ml of bevacizumab subconjuctivally at the end of procedure (N=20).	Follow up for 6 to 10 months.	Number of patients that showed recurrence of pterygium comparing group 1 vs. group 2: 2 vs. 4 (p=0.4) Number of patients that showed improvement in best corrected visual acuity (BCVA) comparing group 1 vs. group 2: 18 vs. 16 (p=0.7)	"[A]n intraoperative subconjunctival bevacizumab injection is not helpful and is possibly a harmful procedure with trend toward a greater recurrence rate."	Small samle size. Data suggest subconjunctival bevacizimal as adjuncture treatment post pterygium surgery is not beneficial.
Manning 1997 [207] (score = 4.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of industry sponsorship or COI.	N=56 primary pterygia in 50 patients. Mean age: 48.1 (21-77) years.		Group 1: conjunctival autograft (N=18) vs. Group 2: postoperative mitomycin 0.2mg/ml 4 times a day for 7 days (N=19). vs. Group 3: intraoperative mitomycin 0.4mg/ml for 3 minutes (N=19).	Follow up for 16 months.	Recurrence of pterygia comparing group 1 vs. group 2 vs. group 3: 22.2% vs. 21.1% vs. 10.5% (group 3 vs. group 1: p=0.41; group 3 vs. group 2: p=0.66). Patients older than 55 years	"Intraoperative mitomycin is a simple and effective alternative to postoperative mitomycin therapy, showing the lowest recurrence rate in their series with no toxicity during the study period."	Data suggest pterygium recurrence rates were similar for autograft and postoperative mitomycin 0.2 mg/mL four times a day but less frequent in less frequent in intraoperative mitomycin 0.4 mg/mL X 3 minutes.

								of age had fewer recurrences (p=0.05)		
Mandour 2011 [208] (score = 3.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship. No COI.	N = 91 with primary nasal pterygium undergoing excision. Age range 25–65 years in group A and 22–60 years in group B.		Group A: scleral excision of the primary nasal pterygium 1 month after subconjunctival injection of 0.1mL of 0.15mg/mL MMC into the body of the pterygium (N = 48) vs. Group B: limbal conjunctival autograft transplantation (LCAT) after pterygium excision (N = 43).	Follow-up for 1, 3, 6, 9, and 12 months.	The visual acuity in group A improved 1-2 lines in 18 eyes (37.5%) vs. 11 eyes (25.58%) for 1-3 lines in the group B.	"Both techniques used in the current study proved to be effective in reducing the recurrence rate after excision of primary nasal pterygium with minimal postoperative complications. Preoperative MMC injection was technically easier, with shorter operative and preservation of healthy conjunctiva. However, LCAT is a onestage procedure and independent from adjunctive pharmacological or radiation therapies with their hazards."	Data suggest similar efficacy with MMC preoperative injection being a quicker procedure but LCAT as a single stage procedure.
Sharma 2000 [209] (score = 3.5)	Mitomycin C vs. Conjuncti	RCT	No mention of sponsorship or COI.	N=41 eyes of 37 patients with primary pterygium		Group I: blunt excision and dissection of pterygium and	Follow up at week 1, 3, 6, and months 3,	Recurrence of pterygium comparing Group I vs.	"[C]onjunctival autograft and intraoperative mitomycin-C are	At 3 years, Data suggest comparable efficacy. Data

	val Autograft			undergoing excision surgery. Age range: 20-60 years.		intraoperative application of 0.2 mg/mL (0.02%) Mitomycin-C for 2.5 minutes on sclera under the cover of conjunctiva (N=21) vs. Group II: blunt excision and dissection of pterygium and conjunctival autograft secured to sclera and by passing 2 interrupted sutures at the limbus (N=20).	and there after 6 months intervals. Minimum of 12 month follow up.	Group II: 14.3% vs. 5%. (0.3174). Age less than 40 years was associated with recurrences (p=0.0384).	both equally effective adjuncts to primary pterygium surgery on long term follow up."	suggest pterygium recurrence associated with younger age.
Singh 1990 [210] (score = 4.5)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship or COI.	Study 1: N=80 pterygia (recurrent or primary) of 60 eyes of 48 patients. Mean age: Autograft 38.2 years. Mitomycin 39 years. Study 2: N=30 pterygia of 27 eyes of 26 patients. Mean age 8.6 years.		Study 1: Pterygia excision and: Group A: 1.0mg/ml mitomycin 4 times daily for 2 weeks (N=20) vs. Group B: 0.4mg/ml mitomycin 4 times daily for 2 weeks (N=38) vs. Group C: placebo (distilled water) drops 4 times daily for 2 weeks (N=22) Mean follow up for mitomycin	Mean follow up time: 4 months for mitomycin group and 6 months for conjunctival autograft group.	Study 1: Recurrence of pterygia after treatment comparing group A vs. group B vs. group C: 5% vs. 0% vs. 73% (p<0.05). Study 2: No recurrence were present on mitomycin group compared to 1 recurrence on conjunctival	"Long term effectiveness, simplicity, economy, and relative lack of complications favor the adjunctive use of mitomycin eye drops in the treatment of primary and recurrent pterygia."	

						1.0mg was 20 months, for mitomycin 0.4mg was 14 months, and for placebo was 3 months. Study 2: 0.4mg/ml of mitomycin 4 times following excision of pterygia (N=15) vs. Conjunctival autograft transplantation (N=15).		autograft group. Photophobia, tearing, and foreign body sensation were common symptoms presented in both groups to varying degrees.		
Panda 1998 [211] (score = 6.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of industry sponsorship or COI.	N = 50 eyes of 50 with primary pterygia. Mean±SD age Group 1: 41.44 (22-59) years. Group II: 41.64 (23-61) years.		Group 1: received a 3-min scleral application of a 5 x 5 mm sterile sponge soaked in a solution of 0.02 mg/ml mitomycin C (N = 25) vs. Group 2: received same procedure with gentamicin solution 0.3% (N = 25).	Follow up was on days 1, 7, 15, and 20, then at monthly intervals for a minimum of 1.5 years.	Recurrence in mitomycin C-treated group was 12% compared to gentamicin-treated group 32% ($p < 0.001$).	"[A] diluted solution of mitomycin C, 0.02 mg/ml, applied intraoperatively with an accurately sized sterile sponge for 3 minutes to the bare sclera after excision of the pterygium, reduces the rate of recurrence of pterygium and minimizes corneoscleral toxicity.	Minimum 1.5 year FU. Higher recurrence in gentamicin vs. MIT-C.
Biswas 2007 [212] (score = 3.5)	Mitomycin C vs. Conjuncti	RCT	No mention of sponsorship or COI	N = 60 eyes of 52 patients with progressive		Group A: pterygium excision with ipsilateral	Follow up for an average of 6 months	Mitomycin C that was applied in a strength of	"Conclusively, it was found that both conjunctival-	Short report. Sparse details. Data suggest conjunctival

	val Autograft			pterygium Age range 25-60 years with average 35.56 years.		conjunctival-limbal autografting. (N = 30) vs Group B: pterygium excision with adjunctive mitomycin C 0.02% for two minutes. (N = 30).	(3-12 months).	0.02% for two minutes, reduced the recurrence rate to 3.3%-12% while adjunctive conjunctival autograft reduced the recurrence rate between 3.8 and 39%. No p-value report in regards to the difference.	limbal autografting and preoperative mitomycin C (0.02%) were safe and simple procedure with significant reduced rate of recurrence, after primary progressive pterygium surgery. However conjunctival autografting is preferable technique over mitomycin C considering rate of recurrence, postoperative complication and ocular morbidity in the later group".	limbal autografting better due to fewer pterygium recurrences and fewer ocular complications.
Fallah 2008 [213] (score = 2.0)	Mitomycin C vs. Conjunctival Autograft	RCT	Sponsored by a grant from Tehran University of Medical Sciences. No COI.	N=40 eyes of 40 patients with recurrent pterygium. Mean age 49.25 years.		Conjunctival limbal autograft plus amniotic membrane transplantation or CLAU/AMT (N=20) vs. 0.02% mitomycin C applied with sponge for 3 minutes plus amniotic	Patients were followed daily until corneal epithelial defect healed, and then at 1 weeks, 2 weeks, 1, 2, 3, 6	Recurrence of pterygium during follow-up comparing CLAU/AMT vs. MMC/AMT: 0 vs. 4 eyes (p=0.035). Recurrence happened 3-4 months post-surgery.	"CLAU with AMT seems to be more effective than intraoperative MMC with AMT for treatment of recurrent pterygium."	Failed randomization. High dropout rate. Methodological details sparse.

						membrane transplantation or MMC/AMT (N=20).	months, and then every three months (follow up raged 6-19 months).			
Ari 2009 [214] (score = 4.5)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship. No COI.	N= 113 patients with a primary fleshy or growing pterygium that invaded >2 mm into the cornea. Mean age: MMC group: 48.0 years, LCAU group: 49.0 years.		0.02% mitomycin C (MMC) intraoperatively for 2 minutes after pterygium excision: (N= 57) vs. Limbal-conjunctival autograft (LCAU) after pterygium excision: (N= 56)	Mean follow up period for group 1: 16 months, group 2: 17 months	The rate of recurrence for pterygium was significantly higher in the MMC group than the LCAD group (10 [20%} vs 2 [4%} patients; p=0.035).	"Recurrence and postoperative complications were less frequently observed in primary excision with LCAD than with MMC in these Turkish patients who completed the study. This study found that pterygium excision with LCAD was well tolerated and effective in these patients."	Data suggest pterygium recurrence and adverse events less frequent in LCAU group compared to MMC group.
Young 2013 [215] (score = 4.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship. No COI.	N=115 patients with primary pterygium undergoing surgery. Mean±SD age: MMC group: 64±13 years. LCAU group 65±14 years.		Intraoperative 0.02% mitomycin C (MMC) for 5 minutes (N=63) vs. Limbal conjunctival autograft (LCAU) transplants (N=52)	The mean follow-up time was 138 ±2 months (range, 132-140 months) for the MMC group and 137 ± 2 months	At 10 years, there were 12 recurrences in the MMC group (25.5%) and 2 recurrences in the LCAU group (6.9%). The difference in recurrence rate between	"Limbal conjunctival autograft was more effective than intraoperative MMC in minimizing pterygium recurrence at the 10-year follow-up.	At 10 years, data suggest limbal conjunctival autograft more effective than intraoperative MMC for prevention of pterygium recurrence. High dropout rate at 10 years.

							(range, 130-140 months) for the LCAU group.	the 2 groups was statistically significant (t= 2.366; p= 0.021, Student t test) The LCAU group had a significantly lower recurrence rate compared with the MMC group. At 10 years, 47% (22/47) of the eyes had grade A appearance in the MMC group, and 72% (21/29) of the eyes had grade A appearance in the LCAU group. None of the eyes in either group had grade D appearance [20 patients had died and 18 patients were lost to follow-up	Treatment with intraoperative MMC was not associated with long term corneal endothelial cell loss."	

								(dropout rate of 33.3%)]		
Sodhi 2005 [216] (score = 5.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship or COI.	N = 56 with primary pterygium undergoing excision. Mean±SD age: 38.1±10.7 years.		Intraoperative 0.2 mg/ml mitomycin C (MMC) (N = 28) vs. Intraoperative 0.2 mg.ml doxorubicin (N = 28).	Follow up was at 2 weeks, 1, 6 and 12 months postoperatively.	Recurrence rates were not statistically different between groups (p=0.68).	"The two antimitotic agents, MMC and doxorubicin, when used intraoperatively along with primary pterygium excision, had a comparable role both in terms of adverse events and prevention of recurrence of pterygium."	Data suggest baseline changes in gender, question the impact. Data suggest equivalency.
Mutlu 1999 [217] (score = 4.5)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship. No COI.	N = 81 with recurrent pterygia. Mean age: 34.55 years.		Limbal conjunctival autograft transplantation or LCAT (N = 41) vs. MMC 0.2 mg/ml mitomycin C solution with conjunctival flap or MMC (N = 40).	Follow-up was minimum 1 year postoperatively.	Rate of recurrence 14.6% vs. 12.5% in the MMC group (p>0.05). LCAT procedure took 1.5 hours vs. 20 minutes for MMC group.	"Both techniques showed similar recurrence rates in the treatment of recurrent pterygia."	No changes in recurrence rates.
Frucht-Pery 2006 [219] (score = 4.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship or COI.	N = 126 with primary pterygia underwent pterygium excision. Mean±SD age: 42.3±11.7 years.		Group 1, single intraoperative dose of MMC 0.02% (0.2 mg/ml) for three minutes (N = 30) vs. Group 2, free conjunctival autografting (N =	Follow-ups at days 1, 7, 15, 30, and 90, then at 3 months intervals during the first year and at six-	Recurrence Rate number (%): group 3 vs group 1: 14 (46.6%) vs 2 (6.6%), (p=0.0005); group 2 vs group 3: 4	"[P]terygium excision with a free conjunctival autograft combined with intraoperative low-dose MMC is a safe and effective	Data suggest combining low dose mitomycin C intraoperatively along with autografting is effective in preventing

						30) vs. Group 3, Sodium Chloride 0.9% (N = 30) vs. Group 4, MMC 0.02% for one minute, plus conjunctival autograft (N = 30).	month intervals after one year.	(13.3%) vs 14 (46.6%), (p=0.0048); group 4 vs group 2: 0 (0%) vs 4 (13.3%), (p=0.038); group 3 vs group 4: 14 (46.6%) vs 0 (0%), (p=0.0001).	technique in pterygium surgery."	pterygium recurrence.
Koranyi 2012 [220] (score = 4.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship or COI.	N = 115 with consecutive patients with primary nasal pterygium undergoing excision surgery. Mean±SD age: MMC group was 48.3±15 and 48.6±16 years in the CA group.		Adjunctive MMC 0.04% (N = 56) vs. Free conjunctival autograft (CA) (N = 59). After surgery: dexamthason eye drops, six times daily together with chloramphenicol ointment three times daily.	Follow-ups at 1 week, and 1, 3, 6, 12, 24, 36 and 48 months after surgery.	Recurrence rate: MMC vs CA: after 1 year: 32.6% vs 12.3%; 4 years: 37.5% vs 15.2%, (p<0.05). Surgery time: MMC vs CA: 13±4 vs 26±5, (p<0.01).	"Pterygium surgery including free autologous conjunctival grafting is associated with fewer recurrences, re-operations and complications than using the bare sclera technique together with single-dose intraoperative MMC."	At 4 years, data suggest free autologous conjunctival grafting in pterygium surgery is significantly better than the bare sclera technique with single dose MMC for fewer recurrences. reoperations and complications.
Katricioglu 2007 [221] (score = 2.0)	Mitomycin C vs. Conjunctival Autograft	RCT	No mention of sponsorship or COI.	N = 49 eyes of 49 subjects with pterygium tissue extending more than 2 mm beyond the limb and		Group 1: Conjunctival autografts (N = 25 eyes) vs. Group 2: Amniotic membrane transplantation (N = 16 eyes) vs.		There was no overall significant difference found between groups or recurrence rates after	"[A]mniotic membrane and conjunctival autograft transplantation seems to be equally effective for the prevention of	Methodological details sparse.

				who underwent pterygium excision.		Group 3: MMC or mitomycin C + conjunctival autografts (N = 8 eyes).		conjunctival autografts p > 0.05.	recurrence in primary pterygium."	
Chen 2014[222] (score = 5.5)	Conjunctival Autograft: different approaches	RCT	Supported by Health Department of Guangxi Zhuang Autonomous region and Science Fund Project People's Hospital of Guangxi Zhuang Autonomous region. No COI.	N=80 eyes of 80 patients undergoing primary pterygium surgery. Mean age 55.8 years.		Inferior conjunctival autografting or ICA (N=40) vs. Superior conjunctival autografting or (SCA; N=40).	Follow up on days 1, 2, 3, 5, 7, and 14, and then at months 1, 3, 6, and 12 postoperatively.	Mean±SD for complete corneal epithelial healing time revealed by fluorescein staining comparing ICA vs. SCA: 3.1±0.5 d vs. 3.3±0.6 d (p=0.11). Conjunctival and corneal recurrence comparing ICA vs. SCA: 5% vs. 7.5% (p=0.64) Pain scores comparing were lower on ICA group compared to SCA at day 3 and 5 (p<0.01, p=0.04, respectively).	"[P]terygium excision with ICA led to less postoperative discomfort for patients with primary pterygium. This technique should be viewed as a useful method for all patients with primary pterygium, especially when there is a potential filtering glaucoma surgery."	Data suggest similar efficacy between ICA and SCA with some patient preference for ICA for less postoperative discomfort.
Al-Fayez 2013 [223] (score = 7.0)	Conjunctival Autograft: different	RCT	No mention of industry sponsorship. No COI.	N= 224 with advanced recurrent pterygia. Mean age for		Group 1: free conjunctival autograft transplant (N= 112) vs. Group 2:	Follow up on postoperative days 1, 7. 14 and	For conjunctival recurrence, 6 patients in the conjunctival	"Limbal-conjunctival transplant is safe and more effective than	Data suggest significant benefit of limbal conjunctival transplant versus

	approaches			group 1: 36.9, group 2: 36.1 years.		Limbal-conjunctival autograft transplant (N=112)	30 and then every 3 months for the first year and then every 6 months.	autograft group had grade 1 and 1 patient in group 2 had recurrences. In the limbal-conjunctival autograft group, 4 patients had grade 1 and no patient had grade 2 recurrences. These differences were not statistically significant (p=.53 and p=.49, respectively)	free conjunctival transplant in preventing recurrence after excision of recurrent pterygia (p=0.004)"	free conjunctival transplant for preventing recurrent pterygium.
Akinci 2007 [224] (score = 5.0)	Conjunctival Autograft: different approaches	RCT	No mention of sponsorship or COI.	N = 112 with primary pterygium. Mean age: 43.55 years.		Group 1; received intraoperative 0.02% MMC for 5 min after simple excision (N = 52) vs. Group 2; or LCAG received limbal-conjunctival autograft (N = 60).	Follow-up was assessed at 3, 6, 9, and 12 months.	Recurrence occurred in 5.76% (N = 3) of the MMC group compared to 3.33% (N = 2) of the LCAG group, p>0.05. Complications were not significantly different between groups.	"[S]imple excision then intraoperative use of 0.02% (MMC) for 5 min and LCAG has similar success rates in the treatment of primary pterygia."	1 year follow-up. No changes in recurrences.

Küçükerdönmez 2007 [225] (score = 4.5)	Conjunctival Autograft: different approaches	RCT	No mention of sponsorship. No COI.	N = 27 with primary pterygium. Mean age: 43.9 years.		Limbal-conjunctival autograft transplantation or LCAT (N = 14) vs. Amniotic membrane transplantation or AMT (N = 13).	Follow up on postoperative days 1, 7, and 30.	No differences between groups, (p = 0.443). During follow up, no pterygium recurrence was observed.	"[G]graft vascularization and perfusion after pterygium excision with LCAT or AMT could be demonstrated by anterior segment ICGA."	Variable followup length. Small sample size. Possible randomization failure. Data suggest comparable results for recurrence but conjunctival autograft led to better cosmetic result.
Küçükerdönmez 2007 [226] (score = 5.5)	Conjunctival Autograft: different approaches	RCT	No mention of sponsorship. No COI.	N = 78 eyes of 78 participants with primary or recurrent pterygium. Mean±SD age: 52.4±12.40 for CAT group and 57.1±9.91 for AMT group. years		Amniotic membrane transplantation or AMT (N = 38) vs. Conjunctival autograft transplantation or CAT (N = 40).	Follow up for 6 months.	Recurrence rate: CAT vs AMT: 7.5% vs 7.9%, no p-value to report. Final appearance: 10.0% vs 21.1%, (p=0.048).	"[A]cceptable recurrence-free rates could be achieved with the AMT technique in patients with primary or recurrent pterygium."	Data suggest anterior segment ICGA is helpful for watching graft vascularization post pterygium surgery. AMT patients experiences delayed graft vascularization for one month post operatively.
Castello de Almeida [227] 2008 (score = 4.5)	Conjunctival Autograft: different approaches	RCT	Sponsored by the Fundação de Amparo e Pesquisa (FAEPE-FAMERP), São José do Rio Preto (SP), Brasil. No COI.	N = 29 with recurrent nasal pterygium. Mean age: 47.8 years.		Group 1 conjunctival autograft transplantation with placebo eye drops for 12 days prior to surgery (N = 9) vs. Group 2 conjunctival autograft transplantation +	Follow up was conducted for 6 months post-surgery.	No significant differences between groups of epithelial cells stained brown by the Ki-67 antigen (p=0.923) or temporal side (p=0.447).	"MMC used by the subconjunctival or topical routes did not alter the percentage of conjunctival positive epithelial cells for the Ki-67 antigen in	Small sample size. Histological study. Does not clearly support a mechanism. 6 month follow-up.

						subconjunctival injection on 0.1 ml of 0.015% MMC and placebo eye drops in the pterygium head 30 and 14 days prior to surgery (N = 11) vs. Group 3 conjunctival autograft transplantation using 0.02% MMC eye drops for 12 days prior to surgery (N = 9).			recurrent pterygia."	
Al-Fayez 2002 [228] (score = 4.5)	Conjunctival Autograft: different approaches	RCT	No mention of industry sponsorship. No COI.	N = 79 with advanced primary or recurrent pterygia. Age range: 27-39 years.		Group A: free conjunctival autograft transplantation (N=36) vs. Group B: limbal conjunctival autograft transplantation (N=43)	Follow up was evaluated on postoperative days 1, 7, 14, and 30, then every 3 months for the first year, and then every 6 months.	Recurrence of pterygia comparing group A vs. group B: 16% vs. 0% (p=0.007). Recurrences in patients with past recurrent pterygia was significant (p=01.028), while recurrence in patients with primary pterygia was not (p=0.208).	"We found limbal–conjunctival autograft transplantation safe and effective in preventing recurrence of advanced and recurrent pterygia in a uniform group of a high-risk population (mainly young males)."	Data suggest limbal transplantation more effective than free conjunctival transplantation for treatment of recurrent pterygia.

Yeung 2013[229] (score = 5.0)	Conjunctival Autograft: different approaches	RCT	No mention of sponsorship. No COI.	N=60 eyes of 60 patients with primary pterygium. Mean age: Superior conjunctival autograft (CAU): 49.5; Inferior CAU: 57.0 years.		Superior CAU (N=30) vs. Inferior CAU (N=30)	The patients were seen on day 1 and day 7, 1 month, 3 months, and 6 months after their surgery	One eye in the superior CAU group (4.2%) and 1 eye in the inferior CAU group (4.0%) developed pterygium recurrence. There was no statistically significant difference in the recurrence rates between the 2 groups. In the inferior CAU group, mild localized donor site scarring was noted in 2 patients (8.3%).	"Pterygium excision with superior or inferior CAU secured with fibrin glue is safe and effective. There was no significant difference in surgical time, pain, and recurrence rates of pterygium after excision with superior or inferior CAU."	Data suggest comparable efficacy between superior and inferior.
Kheirkhah 2012 [230] (score = 5.0)	Conjunctival Autograft: different approaches	RCT	No mention of sponsorship. No COI.	N = 87 eyes of 86 patients with primary or recurrent nasal pterygia who underwent surgery. Mean±SD age: 43.5±11.8 years.		Free conjunctival autograft (CAU) (N = 44 eyes) vs. Conjunctival-Limbal Autograft (CLAU) (N = 43 eyes). All eyes underwent pterygium surgery and application of 0.02% mitomycin C for 3 minutes.	Follow-ups at 1 day, 1 week, 1 month, and 3, 6, 12, months after surgery.	Recurrent pterygia CAU vs. CLAU: 12.5% vs. 0%, p=0.37. No differences between groups were found.	"There was no significant difference in recurrence rates of pterygium after surgery with mitomycin C application between the CAU and CLAU groups, more remarkably in primary cases.	Data suggest comparable efficacy between groups.

						After surgery: topical antibiotic for 1 week and tapering topical steroids for 3 months; 0.1% betamethasone 4 times daily for 1 months followed by 0.1% fluorometholone 4 times daily for 2 weeks, 3 times daily for 2 weeks, twice daily for 2 weeks, and once daily for 2 weeks.			Limbal damage was seen in some eyes with CLAU."	
Young 2009 (score = 5.5)	Pterygium excision: Different anesthetics	RCT	No mention of sponsorship. No COI.	N=40 patients with primary pterygium Mean age: 60.80±11.97 years.		Group 1 received tetracaine 1% drops every 5 minutes for 3 times before surgery and solcoseryl eye gel 5 minutes before surgery (N= 21) vs. Group 2 received one normal saline drop every 5 minutes 3 times before surgery and 1ml of lidocaine 2% gel 5 minutes before surgery (N=19) Both	Immediately postoperative after patching.	From the patients' perspective, the mean pain score for stage 2 was 3.98±2.18 in the tetracaine group and 3.03±2.35 for the lidocaine gel group. There was no significant difference in mean pain scores experienced at stage 2. The mean	"Topical administration of lidocaine 2% gel or tetracaine 1 % drops are both effective anesthetic agents for primary Pterygium surgery and mitomycin C. However, lidocaine gel is superior to tetracaine eye drops and its application is more convenient with a less	Data suggest similar efficacy but lidocaine gel requires less frequent application and has a sustained effect.

						treatments were repeated intraoperatively, and Tetracaine 1% eye drop(s) were used as required intraoperatively.		pain scores at stage 3 were less. The mean pain score was 1.43±1.66 and 0.47±0.84 (p=0.03, Student's t-test) for the tetracaine group and gel group, respectively. In stage 3, there was a statistically significant difference in the mean pain scores (p<0.05). - From the surgeon's point of view, the subjective pain score at stage 2 was 2.84±1.07 for eyes receiving lidocaine gel and 4.52±1.03 for eyes receiving tetracaine drops (Table 3). There was a statistical significant	frequent application and a sustained duration of action."	

								difference in the mean pain scores for all the stages.		
Bazzazi 2010 [231] (score = 3.5)	Conjunctival autograft vs. Minimal invasive surgery	RCT	No mention of industry sponsorship or COI.	N = 122 with primary pterygium Mean±SD age for Group A: 45.8± 8.5, Group B: 48.0± 11.5		Group A: conjunctival autograft transplant (N =36) vs. Group B: underwent minimal invasive Pterygium Surgery (N = 86).	Follow-up at 1 weeks, 1, 2, 3, and 6 months and 1 year, postoperatively.	Recurrences were detected in 4 patients (11.1%) in group A and 5 patients (5.8%) in group B with no significant difference in this regard (p=0.447)	"[R]ecurrence-free rates could be achieved using MIPS technique in patients with primary pterygium and can be considered as good alternative in the surgical management of pterygia because of its simplicity and low surgical time."	Possible unequal random scheme not well described. Number of recurrences CAG vs. MIPS: 36 vs. 86. Details sparse. More recurrence in autograft 11.1 vs. 5.8%.
Oguz 1999 [232] (score = 4.0)	Mitomycin: different applications	RCT	No mention of industry sponsorship or COI.	N = 44 eyes of 36 with primary and recurrent pterygia. Mean±SD age: 48.7±11.30 years.		Intraoperative single dose of 0.02% mitomycin for 5 min (N = 20) vs. Postoperative topical mitomycin in 0.02% (0.2 mg/ml) four times a day for 1 week (N = 20).	Follow up at days 1, 7, 15, and 30, at 6-week intervals for the next 3 months, at 6 week intervals for the next 3 months.	The intraoperative group had recurrence rate of 3/20 (15%) vs. postoperative group of 4/20 (20%) (p=0.41).	"This study indicated possible advantages of administration of a single dosage of 0.02% mitomycin C over postoperative mitomycin therapy."	Limited patient description. Sparse details. Comparable efficacy. Reported complications in drop group but non-sig. (not powered for complications.
Yanyali 2000 [233] (score = 4.0)	Mitomycin: different applications	RCT	No mention of industry sponsorship or COI.	N = 38 eyes of 35 participants undergoing pterygium excision for		Intraoperative mitomycin C 0.02% solution (N = 19) vs. Bare sclera excision alone (N =19).	Follow up was on days 1, 7, 15, and 30 and every 3	Recurrence occurred in 21% (4 eyes) of the mitomycin C treated group	"In conclusion, the results of our study show that intraoperative application of	Data suggest efficacy.

				primary pterygium. Mean age: 25.14 years.			months thereafter.	compared to 57.8% (11 eyes) in the control group, (p = 0.045).	0.02% mitomycin C is effective in preventing the recurrence of primary pterygium."	
Mastropasqua 1996 [234] (score = 5.0)	Mitomycin: different applications	RCT	No mention of sponsorship or COI.	N = 90 eyes of 90 participants undergoing surgical treatment for recurrent pterygium. Mean age: 40.75 years.		Intraoperative 0.02% Mitomycin C treated group (N = 45) vs. Pterygium excision performed by bare sclera technique (N = 45).	Follow up period ranged from 6 to 54 weeks.	Recurrence rate was 12.5% vs. 35.6% in the control group (p=0.027).	"This study confirms the efficacy of intraoperative mitomycin C in improving the success rate after recurrent pterygium surgical excision."	Variable follow-up.
Tseng 2001 [235] (score = 4.0)	Mitomycin: different applications	RCT	Sponsored by the National Council of Science, Taiwan, R.O.C.	N = 45 eyes of 38 participants with primary pterygium. Mean age: 58.5 years.		Group 1: simple excision of pterygium (N = 15) vs. Group 2: bare-sclera procedure with low-dose intraoperative 0.02% MMC for 30 seconds (N = 15) vs. Group 3: pterygium excision followed by conjunctival autografting (N = 15).	Follow up was performed at 1 and 2 weeks, 1, 3, 6, and 12 months.	At 1 year, only group 2 had a goblet cell density significantly below normal controls, (p=0.02).	" After pterygial excision by a bare-sclera procedure with or without an intraoperative dose of MMC or conjunctival autografting, the wound heals by a four-stage process with appearance and proliferation of nongoblet epithelial cells in the first three stages and marked proliferation of	More recurrences in base sclera procedures.

									goblet cells in stage 4."	
Kaya 2003[236] (score = 4.0)	Mitomycin: different applications	RCT	No mention of sponsorship or COI.	N = 500 with either primary or recurrent pterygium. Mean age 44 (18-65) years		Group 1 were operated on using a vertical conjunctival bridge flap technique (N = 250) vs. Group 2 operated on with bare sclera technique (N = 250).	Follow up 1 day, 1 week, 3 weeks, 3 months, and 6 months.	Pterygium recurrence; 2% vs.40% in group 2 (p<0.01). No other complications were significantly different between the two groups.	"[V]ertical conjunctival bridge flap technique is a safe and effective method offering good control rates without any significant complications for primary and recurrent pterygium."	If bilateral one eye two each group. Variable follow-up length. Dropouts somewhat unclear. Data favor vertical conj. bridge flap for lower recurrence.
Tan 1997 [237] (score = 6.0)	Mitomycin: different applications	RCT	Sponsored by the Singapore National Medical Research Council and the Singapore Eye Foundation. No mention of COI.	N = 157 with primary pterygium and with recurrent pterygium). Age range: 20-79 years.		Bare sclera only group 62 with primary pterygium, 17 with recurrent pterygium) (N = 79) vs. Conjunctival autograft only group 61 with primary pterygium, 17 with recurrent pterygium). (N = 78).	Follow up occurred at 1 day, 1 week, 1, 3, 6 and 12 months.	Recurrence rate was 38/62 eyes (63%) who underwent bare sclera excision vs. 1/61 (2%) who underwent conjunctival autografting, (p < 0.001). Cumulative survival rates at 3, 6, and 12 months after surgery was 0.71, 0.53, 0.31 in the bare sclera group compared to	"[C]onjunctival autografting is significantly superior to bare sclera excision for primary and recurrent pterygium, even when performed in a tropical environment."	1 year study. Variable length FU.

								cumulative survival still above 0.98 at 12 months for conjunctival autografting group.		
Mourits 2008 [238] (score = 6.5)	Mitomycin: different applications	RCT	No mention of sponsorship. No COI.	N = 96 eyes of 91 participants 91 with nasally located pterygia. Mean age: 50 years (range: 24–77).		200 and 250 cGy/min β-RT with 90Sr (N = 44) vs. Sham irradiation without 90Sr (N = 42).	Follow up at 6 weeks, 6, 12, 24, and 36 months after treatment.	Recurrence in β-RT was 5/44 (11%) compared to 32/42 (76%) in the sham group (p<0.001). In β-RT group significant change of keratometry was found in 5 eyes (12%) compared to 16 eyes (38%) in the sham group (p=0.002).	"Bare sclera extirpation of a pterygium without adjunctive treatment has an unacceptably high recurrence rate and therefore should be considered obsolete."	2nd report apparently same trial data.
Gupta 2003 [239] (score = 4.0)	Mitomycin: different applications	RCT	No mention of industry sponsorship or COI.	N = 80 eyes of 72 participants with primary and recurrent pterygia. Age range: 16-50 years.		Group 1: excision of pterygium by the bare sclera technique or BSE (N = 20) vs. Group 2: BSE plus single drop of 0.02% MMC at end of surgery (N = 20). vs. Group 3: BSE + postoperative	Follow up was day 1, 7, 15, and 30 followed by biweekly for 3 months.	Ocular pain / Recurrence: greater for group 2 (p=0.04), group 3 (p=0.004), and group 4 (p=0.0004), vs. group 1 / evident in 70% Vs. 20% vs. 20% vs.	"To conclude, the single drop instillation of 0.02% MMC at the end of bar scleral excision of pterygium appears safe and efficacious compared to other MMC regimes in the	Recurrence higher for BSE alone. Lowest complications with one drop 0.02% MIT-C.

						instillation of 0.02% MMC eye drops, 2x/d for five days (N = 20) vs. Group 4: BSE plus a single intraoperative sponge application of 0.02% MMC to the exposed sclera, cornea and the resected pterygium site (N = 20).		15% of group 4, significantly lower for groups 2, 3, and 4 vs. 1 (p=0.001, 0.001, 0.004) while no differences between group.	treatment of pterygium."	
Cano-Parra 1995 [240] (score = 6.0)	Mitomycin: different applications	RCT	No mention of sponsorship. No COI.	N = 66 eyes of 54 participants with primary pterygia. Mean age: 51.8 (range 25-71) years.		Single intraoperative application mitomycin C 0.1 mg/ml for 5 min, (N = 30) vs. Without mitomycin C (N = 36).	Follow up was evaluated on postoperative days 1, 7, 15 and monthly thereafter.	Recurrence rate was 38.8% in the control group (N =14) vs. 3.33% (N =1) in the treatment group, p = 0.0006. In the mitomycin group, conjunctival wound healing was delayed by 7-15 days for all eyes, vs.no delays for control. Conjunctival granuloma occurred in 14 eyes in the	"We have shown that the single intraoperative exposure to mitomycin C (0.1 mg/ml) reduces the recurrence rate of primary pterygium without serious complication over a mean follow up of 14.1 months. We suggest That the single intraoperative exposure of mitomycin C appears to be a safe, simple, effective and useful form of adjunctive	Data show efficiency. Dropouts unclear. Blinding not well described.

								control group and only 5 eyes in the treatment group.	therapy to the surgical treatment of the primary pterygium."	
Cardillo 1995 [241] (score = 4.5)	Mitomycin: different applications	RCT	No mention of sponsorship. No COI.	N=227 patients undergoing surgery for primary pterygia. Ages 40 to 60 years (mean, 48.2 years)		Group 1: single intraoperative application of 0.2 mg/ml mitomycin C for 3 minutes. (N=45) vs. Group 2: single intraoperative application of 0.4 mg/ml mitomycin C for 3 minutes. (N=49) vs. Group 2: mitomycin C eye drops 0.2 mg/ml 3 times daily for 7 days. (N=47) Vs. Group 3: mitomycin C eye drops 0.4 mg/ml 3 times daily for 14 days. Group 4 (N=45) Vs. Surgery alone or Control (N=41).	Outcomes assessed at days 7. 14, and 30, and monthly for 6 months, and every 3-4 months thereafter. Mean follow up: 28 months.	Recurrence of pterygium after treatment comparing group 1 vs. group 2 vs. group 3 vs group 4 vs. control: 6.66% vs. 4.08% vs. 4.26% vs. 4.44% vs. 12.27% ($p<0.0001$ among all groups, and $p\leq0.0001$ comparing each group to control; and $p\geq0.0681$ between groups receiving mitomycin).	"These results support the efficacy and relative safety of a single, low concentration, intraoperative application of mitomycin C in pterygium surgery together with the use of conjunctival flap, avoiding excessive cauterization of the sclera and leaving bare sclera."	Data suggest single dose of intraoperative mitomycin C in pterygium surgery in beneficial for preventing recurrence compared to controls (surgery only).
Ghoneim 2011 [242] (score = 4.0)	Mitomycin: different applications	Randomized Trial	No mention of industry sponsorship or COI.	N=70 eyes of 70 patients with primary pterygia. Mean age: 33.5 years (27-51 years).		Group A: 0.15mg/ml subconjunctival mitomycin C (MMC) injected in the limbus 24 hours before	Follow up at 1 day, 1 week, 1 month, 3 months, 6 months, and 1 years	Recurrence rate at 1 year comparing group A vs. group B: 5.7% vs. 8.57% (p=0.99). No	"In conclusion, preoperative local injection of MMC 0.15 mg/ml is as effective as intraoperative	Data suggest similar efficacy in recurrence rates of pterygium between subconjunctival injection of

						pterygium excision with bare sclera technique (N=35) vs. Group B: 0.15mg/ml MMC applied to bare sclera for 3 minutes after pterygium excision (N=35).	postoperatively.	statistical difference between groups (p>0.05).	topical application of MMC 0.15 mg/ml for prevention of the recurrence of pterygium after surgical removal with the bare sclera technique."	mitomycin C versus intraoperative topical application of mitomycin C at one year follow-up.
Zaky 2012 [243] (score = 4.0)	Mitomycin: different applications	Randomized Trial	No mention of sponsorship or COI.	N=50 eyes with recurrent pterygium Mean age: MI group: 35.15 years. MA group: 36.11 years.		The mitomycin injection (MI) group: received 0.1 ml of 0.15 mg/ml mitomycin C injected subconjunctivally into the head of the pterygium one day before surgical excision using the bare sclera technique. (N=25) vs. The mitomycin application (MA) group: underwent surgical removal with the bare sclera technique and intraoperative topical application of 0.15 mg/ml of	One year.	The recurrence rate was 4% in the MI group and 8% in the MA group. The mean preoperative best corrected visual acuity (BCVA) was 0.53th + 0.15 in the MI and 0.58th + 0.20 in the MA groups upon inclusion into the study. The mean postoperative BCVA was 0.8 + 0.11 in the MI and 0.83+ 0.16 in the MA groups. There was a highly	"Preoperative subconjunctival injection of mitomycin C in low dose (0.1 ml of 0.15 mg/ml) a day before pterygium surgery is a simple and effective modality for management of recurrent pterygium. It has the advantage of low recurrence and complications' rate."	Data suggest preoperative low dose subconjunctival mitomycin C, 24 hours pre pterygium surgery is associated with low recurrence and complication rates.

						mitomycin C. (N=25)		statistically significant difference between the preoperative and postoperative results (p <0.05), while the difference between the two groups was statistically insignificant (P >0.05).		
Frucht-Pery 1994 [244] (score = 4.5)	Mitomycin: different applications	RCT	No mention of sponsorship or COI.	N = 40 eyes of 40 participants with primary and recurrent pterygia. Mean age: 45.7 years.		Group 1, received a single dosage of 0.02% mitomycin for 5 minutes (N = 20) vs. Group 2, received single dosage of saline for 5 min (N = 20).	Follow up was at day 1, 7, 15, 30, and then monthly for 3 months, at 6-week intervals for the next 3 months, and finally at 3-month intervals.	Recurrence occurred in 5% (for group 1 vs. 46.7% for group 2, (p = 0.0001).	"We therefore believe that topical intraoperative use of mitomycin C may be beneficial in a population of healthy patients with pterygia."	
Kheirkhah 2011 Am J Ophthalmol Vol. 151 [247] (score = 4.5)	Mitomycin: different applications	RCT	No sponsorship or COI.	N = 56 eyes of 56 patients with primary pterygium who underwent surgery;		Received 0.20% MMC on the perilimbal sclera (N = 28) vs Under the conjunctiva, away from the limbus (N = 28).	Follow-up at 1 week, 1, 3, and 6 months after surgery.	There were no statistically significant differences between the groups in any of the outcomes measured.	“Regardless of application location, MMC use during pterygium surgery can cause a significant decrease in central	At 6 months, data suggest location not a factor when applying MMC during pterygium surgery.

									endothelial cell count."	
Benyamini 2008 [253] (score = 3.5)	Flaps: different approaches.	RCT	No mention of sponsorship or COI.	N= 34 eyes of 33 patients with primary pterygium seeking surgical removal Mean age: 45.5 ± 12.9 years in group A, 43.3 ± 15.4 years in group B.		Group A received pterygium surgery with either 1 rotational flap (N=19 eyes) vs. Group B received double sliding flaps by using a biologic adhesive to secure the flaps (N=15 eyes)	Follow up was on 1st postoperative day, 1 week, 4th week and was followed till 24 weeks	At last follow up week 24, no more changes in position of flaps in both groups. No pterygium recurrence in either group. Complication rate between these 2 techniques was not significant (p>0.05)	"The use of tissue adhesive is a promising technique in pterygium surgery. In this study, gluing 1 rotational flap resulted in excellent postoperative results, but it seemed less suitable for use with double sliding flaps."	Data suggest equivalency
Benyamini 2008 [253] (score = 3.5)	Flaps: different approaches.	RCT	No mention of sponsorship or COI.	N = 34 eyes of 33 participants with primary pterygium.		Group A: rotational flap (N =18) vs. Group B: sliding flaps (N = 15).	Follow up was assessed weeks 1, 2, 4, 12 and 24 post surgery.	First day postoperative 100% of flaps in group A were still in place, and group B saw 24% of flaps which did not retain their potion from the end of surgery. At one week, 94.7% of group A flaps were in place and there was not change in group B.	"In summary, the use of Tisseel tissue adhesive is a promising technique in pterygium surgery."	Data suggest equivalency.

Akhter W 2014 [254] (score = 4.5)	Flap vs. Autograft	RCT	No mention of sponsorship or COI.	N=57 eyes of 57 patients with pterygium corneal encroachment of ≥2mm responsible for visual disability Mean age: 58.5 years		Pterygium excision followed by free conjunctival autograft or CAG group (N=26) vs. Pterygium excision followed by conjunctival rotation flap or CRG group (N=31)	Follow up period not reported.	Surgical duration in conjunctival auto-graft and conjunctival rotation flap group was 28.50 and 16 minutes respectively. This was statistically significant, (p<0.001) Recurrence was seen in 2 (7.96%) cases in CAG and in 3 (9.67%) cases in CRG. This difference was not statistically significant.	"The surgical time for conjunctival rotation flap procedure is less as compared to free auto-graft, while their recurrence and complications are comparable."	Quasi-experimental. Data suggest comparable efficacy but conjunctival rotation flap procedure requires less surgical time.
Tok 2008 [255] (score = 4.0)	Bare sclera method with vs. without implantation of collagen matrix.	RCT	No mention of sponsorship or COI.	N = 31 with bilateral pterygium who underwent excision using the bare sclera techniques. Mean age: 62.97±9.36 years.		Right eye treatment group with topical 0.05% cyclosporine ophthalmic emulsion applied twice daily for 6 months (N = 31) vs. Left eye used as a control with no treatment (N = 31).	Mean follow up was 9.39±4.14 months (range 1-12 months).	Recurrence rate in treatment group was 4/31 (12.9%) compared to controlled group 14/31 eyes (45.2%) (p = 0.005).	"This study suggests that primary excision of pterygium with postoperative instillation of 0.05% cyclosporine is both safe and efficient."	Randomized crossover. All right received intervention and left eye controls. Data suggest efficacy.

Arish 2013 (score = 3.5)	Bare sclera method with vs. without implantation of collagen matrix.	RCT[256]	No mention of sponsorship. No COI.	N= 20 with unilateral or bilateral pterygium. Mean age= 23-67 years		Intervention group: sub conjunctival implantation of a collagen matrix (iGen™) following pterygium removal by the bare sclera method (N=N/A) vs. Control group: pterygium removal using bare sclera method only (N=N/A)	Follow up visits on 1st day, 1st week, 1st month, 3rd month and 6th month post operatively.	A higher rate of recurrence was found in control group. The statistical difference was not significant (p>0.05)	"In conclusion, the implantation of collagen matrix is a quick and easy technique, may be associated with lower rate of pterygium recurrence and subsequently may improve outcomes from the bare sclera method of surgery. Further studies with a larger sample size and longer duration of follow up are recommended to further explore this technique."	Small sample size. Data suggest biodegradable collagen matrix implants post pterygium surgery appear to be associated with lower recurrence rates but not statistically significant.
de Farias 2014 [257] (score = 5.0)	Amniotic membrane transplantation.	RCT	Sponsored by the CAPES Foundation, Ministry of Education, Brasília, Brazil. No COI.	N=26 eyes of 26 different patients with scleral thinning due to beta therapy after pterygium surgery. Age: ≥18 years.		Amniotic membrane transplantation or AMT (N=9) vs. Lamellar corneal transplantation or LST (N=9) vs. Lamellar scleral transplantation or LCT (N=8)	Outcomes measured preoperatively, and a 1, 3, and 6 months after surgery.	Median corneal thickness before surgery comparing AMT vs. LST vs. LCT: 0.45 vs. 0.48 vs. 0.52 (p=0.257). 6 months after surgery median	"LCT was the best option for the structural treatment of scleral thinning, followed by LST with a conjunctival flap. A high rate of reabsorption was found with AMT, which was the least effective of the 3	Sparse methods. Data suggest LCT> LST for the treatment of AMT was the least effective of all 3 therapies due to a high reabsorption rate.

								thickness of 0.19 was less compared to 0.57 for LCT (p=0.27) or 0.76 for LST (p=0.19). No statistical difference between groups (p>0.05).	therapeutic options and should not be used for this condition."	
Lam 1998 [258] (score = 4.5)	Amniotic membrane transplantation	RCT	No mention of sponsorship or COI.	N =180 with primary or recurrent pterygia. Mean age: 54.2 years		Group A control (N = 29/7) vs. Group B with 0.02% intraoperative MMC for 5 minutes (N = 29/7) vs. Group C with 0.04% intraoperative MMC for 5 minutes (N = 28/7) vs. G group D with 0.02% intraoperative MMC for 3 minutes (N = 29/6) vs. Group E with 0.04% intraoperative MMC for 3 minutes (N = 28/7).	Follow up was on postoperative days 1, 7, 15 and 30 then monthly for 2 months, bi-monthly for 10 months, and finally tri-monthly.	Mean follow up of 20 and 30 months for A to E: 75% vs. 8.3% vs. 8.6% vs. 42.9% vs. 22.9%. No major postoperative complications.	"In conclusion, our mid-term results show that a single application of intraoperative MMC at the concentration of 0.02% for 5 minutes appears to be a safe and effective adjunct."	2 year follow-up. Blinding poorly described.
Katircioglu 2014 [259] (score = 4.0)	Amniotic membrane	RCT	No mention of sponsorship. No COI.	N = 55 with recurrent pterygium; mean age		Group 1: 0.02% MMC (0.2mg/ml) and Amniotic Membrane	Follow-ups at 1 day, 1 week, 1, 3, and 6	Recurrence rate: Group 1 vs Group 2: 8% vs 13.3%,	"Amniotic membrane combined with MMC has similar	Data suggest similar efficacy.

	transplantation			59.1±12.1 for group 1, and 55.4±12.9 for group 2.		Transplantation (N = 25) vs. Group 2: Free Conjunctival Autograft (CA) and 0.02% MMC (N = 30). After surgery: Tobramycin 0.3% ointment was applied with an eye patch, at least once a day; ciprofloxacin 0.3% and tear substitute four times a day for one week, and prednisolone-acetate 1% for one month; after one month, steroid drops were changed to fluorometholone 0.1% four times to twice daily and then tapered.	months, and every 12 months thereafter.	(p=0.531, CI= -0.12-0.22).	recurrence rate to CA combined with MMC, in patients with recurrent pterygium. Similar outcomes and complication rates make AMT-MMC a promising method for the treatment of recurrent pterygium cases.	
Kheirkhah 2011 [260] Am J Ophthalmol Vol. 152 (score = 4.5)	Amniotic membrane transplantation	RCT	No mention of sponsorship. No COI.	N = 42 with primary nasal pterygium; mean age of 45.6±13.9.		Amniotic Membrane Transplantation (AMT), MMC 0.02% was applied on the sclera (N = 21) vs Free Conjunctival Autgraft, MMC	Follow up at 1 day, 1 and 2 weeks, 1 month, and 3, 6, 9 and 12 months after surgery.	Conjunctival inflammation: AMT vs conjunctival autograft group: 16 eyes (84.2%) vs 3 eyes (15%), (p=0.02)	"After pterygium surgery, conjunctival inflammation was significantly more common with AMT than with conjunctival autograft. However, with	Data suggest postoperative conjunctival inflammation post pterygium surgery was more frequent in AMT group than with conjunctival autograft group.

						was applied on the sclera (N = 21). After surgery: topical antibiotics for 2 weeks and tapering topical steroids for 3 months; 0.1% betamethasone 4 times daily for 1 months followed by 0.1% fluorometholone 4 times daily for two weeks, thrice daily for 2 weeks, twice daily for 2 weeks and once daily for 2 weeks.			control of such inflammation and intraoperative application of mitomycin C, similar final outcomes were achieved with both techniques."	
Liang 2012 (score = 3.5)	Amniotic membrane transplantation	RCT[261]	No mention of sponsorship or COI.	N = 118 (133 eyes) with pterygium; age range 30 – 85 years.		Pterygium surgery combined with conjunctival autograft (N = 81) vs. Pterygium resection combined with amniotic membrane transplantation (N = 52).	Follow-up for 1 year.	There statistically significant difference between groups in the foreign body sensation or discomforts ($\chi2 = 6.9600$, $p = 0.0083$), eyelid edema and conjunctival hyperemia edema $\chi2 = 4.3192$ $p = 0.0377$) and	"Patients receiving pterygium surgery combined with conjunctival autograft had lower recurrence rates and experience faster recovery compared with those undergoing pterygium resection combined with amniotic	At 12 months data suggest pterygium surgery plus conjunctival autograft groups had quicker recovery and less pterygium recurrence.

								recurrence rate χ2 = 4.1833 p = 0.0408).	membrane transplantation."	
Ma 2005 (score = 4.5)	Amniotic membrane graft	RCT[296]	No mention of sponsorship. No COI.	N = 95 eye of 94 with recurrent pterygia. Mean age: 53.4 ±11.3 years.		Amniotic membrane graft or AMG (N = 46) vs. With mitomycin C 0.025% (AMG-MMC (N = 48).	12 months.	Conjunctival recurrence AMG group12.5% vs. AMG-MMC group 8.5%, p = 0.62. Corneal recurrence; 12.5%vs. AMG-MMC 12.8%, p = 0.97.	"AMG alone can be considered an effective alternative adjunctive treatment of recurrent pterygia. The addition of intraoperative mitomycin C did not further reduce the recurrence rate."	Data suggest no significant difference. Comparable efficacy.
Luanratana-korn 2006 (score = 5.0)	Amniotic membrane graft	RCT	Sponsored by the Faculty of Medicine, Khon Kaen University. No COI.	N = 187 with primary; N = 254) or recurrent; (N = 33) pterygium. Mean age: 45.96 years.		Conjunctival autograft (N = 120) vs. Amniotic membrane graft (N = 167).	Follow up was at 6 weeks and 6 months.	Recurrence rate at 6 months for the conjunctival group was 13.3% and 28.1% in the amniotic membrane group (p=0.003).	"Amniotic membrane graft had a higher recurrence rate than conjunctival autograft."	Data suggest higher recurrence with Amniotic membrane.

Other

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Viani 2012 Int. J. Radiation Oncology Biol. Phys., Vol. 82 No. 2. (score = 6.5)	β-radiation	RCT[262]	No mention of sponsorship. No COI.	N=200 patients with fresh pterygium. Mean age: Group A: 56, Group B: 54 years.		Group A: β radiation of 5 Gy within 7 fractions postoperatively (N=112) vs. Group B: β radiation of 2 Gy within 10 fractions postoperatively (N=104)	The follow-up period was 12–47 months.	The 3-year local control rate for Groups 1 and 2 was 93.8% and 92.3%, respectively (p = .616). A statistically significant difference for cosmetic effect (p = .034), photophobia (p = .02), irritation (p = .001), and scleromalacia (p = .017) was noted in favor of Group 2.	"The results of our clinical trial have shown that bare sclera surgery combined with postoperative low-dose fractionation β-RT (2 Gy in 10 fractions) results in a similar low relapse rate, fewer complaints (irritation and photophobia), and better cosmetic effects than high-dose fractionation (5 Gy in 7 fractions). Moreover, these data have shown that pterygium can be safely treated in terms of local recurrence using RT schedules with a BED of 24–52.5 Gy10."	Data suggest for recurrence there was comparable efficacy between low and high dose of radiation but better cosmetic results with low dose.
Viani 2012 (score = 6.0)	β-radiation	RCT[263]	No mention of sponsorship or COI.	N=108 eyes patients with pterygia Mean age: group 1: 52.7		Group A received Conjunctival autografts (CAG)+ β radiation (β-RT)	The follow up was 6 weeks and then 6, 12, 24, and at least 36 months	At a mean follow-up of 18 months, in CAG+ β-RT group, 5 relapses occurred	"[L]ow single-dose of b-RT of 10 Gy for pterygium show that CAG surgery combined with b-RT resulted	At 18 months data suggest fewer recurrences better cosmetic results and

				group 2: 51.9 years.		10Gy per 1 fraction (N= 54) vs. Conjunctival autograft surgery (CAG) alone (N= 60)	after treatment.	compared with 12 recurrences in CAG, for a crude control rate of 90.8 % vs. 78%; p =0.032, respectively. *The treatment complications as hyperemia, total dehiscence of the autograft and dellen were significantly more frequent in the CAG (p < 0.05). The arm of b-RT resulted in better cosmetic results and improves of symptoms than CAG.	in a simple, effective, and safe treatment. β-RT reduced the risk of primary pterygium recurrence and improved symptoms after surgery, resulting in a better cosmetic effect than CAG surgery."	fewer post-op symptoms in CAG +, B-RT group.
Jürgenliemk-Schulz 2004 [264] (score = 6.5)	β-radiation	RCT	No mention of sponsorship or COI.	N = 86 eyes with pterygium; age range of 24 to 77 years, average of 50 years.		Study group, β-RT (N = 44) vs. Control group, pterygium excision alone (N = 42).	Follow-up at 6 weeks, and 6, 12, 24, and 36 months after treatment.	Recurrence number: No RT vs RT: 9 vs 34, (p<0.001). Cosmetic effects: 28 vs 37, (p=0.06).	"Single-dose β-RT after bare sclera surgery is a simple, effective, and safe treatment that reduces the risk of primary pterygium recurrence."	Patients not well described. Data favor treatment over sham.
Turan-Vural 2011 (score = 4.0)	Cyclosporine A	RCT[266]	No sponsorship. No COI.	N= 36 eyes of 34 patients with primary pterygium. Mean age: group1: 57.05		Bare sclera technique was performed in both groups. In Group I, 0.05% cyclosporine A	Follow up: at postoperative 1 and 7 days as well as each month during	In Group I, while four cases exhibited recurrence Figure 1, 14 (77.8%) did not	"Postoperative application of low-dose CsA can be effective for preventing recurrences after	Small sample. Data suggest low dose CSA may prevent pterygium recurrence.

				± 11.65 group 2: 53.27 ± 10.88 years.		(CsA) was administered postoperatively at 6-hour intervals for 6 months. (N= 18) vs. Group II did not receive CsA treatment (N= 18)	the following year.	show recurrence, and the mean recurrence-free follow-up time was 9.92 ± 0.92 months. In Group II, while eight cases exhibited recurrence, 10 (55.6%) cases did not show recurrence, and the mean recurrence-free follow-up time was 7.50 ± 1.19 month.	primary pterygium surgery"	
Ibáñez 2009 (score = 4.0)	Cyclos porine A	RCT[267]	No mention of sponsorship. No COI.	N = 80 eyes is 76 consecutive patients with primary pterygium; mean age of 48.5 years.		Conjunctival autograft (CA) plus 0.1ml injection of 0.125mg/ml Mitomycin C (MMC) topical cyclosprin A 1% twice a day for 3 months (N = 37) vs Control (CA+MMC) group (N = 38). All patients: chloramphenicol 0.5% and prednisolone acetate 1% twice a day for 2 weeks and	Follow-up at day 1, 1, 3, and 6 weeks, and 3 and 6 months.	Response rate: women: treatment vs placebo: 0% vs 24%, (p=0.03).	"This study indicates that pterygium excision with a free conjunctival autograft combined with intraoperative low-dose MMC is a safe and effective technique in pterygium surgery."	Data suggest comparable efficacy with cyclosporine A being slightly better for prevention of pterygium recurrence.

						then prednisolone acetate 1% twice a day for 1 week. All patients used hypromellose 0.5% drops four times daily during the 3 months.				
Olusanya 2014[248] (score = 5.0)	Fluorouracil vs. Mitomycin	RCT	Sponsored by the University of Ibadan. No mention of COI.	N = 80 with primary pterygium; age range 17 – 81 years (mean age 50.7 ± 13.1 years).		Primary pterygium excision combined with conjunctival autograft (CAG) 5-Fluorouracil (5-FU) (50 mg/ml) plus CAG (N = 46) vs. Mitomycin C (MMC) (0.01%) plus CAG (N = 34)	Follow-up for days 1, 7, 21, 30, 60, and 90 and every 3 months subsequently.	The overall recurrence was 10%, with a rate of 8.7% in the 5-FU group and 11.8% MMC group (p = 0.7). The mean age of patients who had a recurrence was 38.1 ± 12.4 years vs. 52.1 ± 12.4 years in those without a recurrence (p = 0.003).	"Younger age remains a risk factor for recurrence when both CAG and antimetabolites are combined in the treatment of pterygium, while the effect of gender, size and morphology of the pterygium may be diminished by such combination."	Data suggest younger age is associated with pterygium recurrence.
Bekibele 2012 [249] (score = 5.0)	Fluorouracil vs. Mitomycin	RCT	Sponsored by the University of Ibadan Senate. No COI.	N= 80 eyes of 80 patients with fleshy pterygium encroaching on the cornea of at least 2 mm. Mean age for group 1: 49.8, group 2: 51.9		Group 1: 50mg/ml of 5-fluorouracil plus Autograft (5-FU) for 5 minutes after excision, and conjunctival autograft (N=46) vs. Group 2: 0.01%	Postoperative follow-up visits were at days 1, 7, 21, 30, 60, and 90 and every 3 months subsequently.	Recurrence rate in the 5-FU group was 8.7% compared to 11.8% in the MMC group (recurrence risk ratio = 0.71, 95% CI 0.17-3.1, p = 0.7).	"[A]lthough both MMC and 5-FU were found to be effective in preventing pterygium recurrence when combined with conjunctival autograft, MMC is not readily	Data suggest similar efficacy.

						mitomycin C (MMC) plus conjunctival autograft (N=34)			available, and it is more expensive when compared to 5-FU in developing countries. Thus, when effectiveness in preventing pterygium recurrence is added to cost and safety issues, 5-FU (combined with conjunctival autograft) would appear to compare favorably with low-dose MMC (combined with conjunctival autograft) for the treatment of pterygium in developing countries. We would, however, suggest further randomized controlled studies be performed, preferably using larger sample sizes with longer follow-up periods."	

Rahman 2008 [250] (score = 4.5)	Fluoro uracil vs. Mitom ycin	RCT	No mention of sponsorship or COI.	N = 84 eyes of 65 participants with primary pterygium invading more than 2 mm on the cornea from the limbus. Mean age: 45.57 year.		Group 1 underwent surgical excersion of pterygium using bare scleral technique under an operating microscope followed by application of mitomycin-C 0.02% intraoperatively for 3 minutes (N = 42) vs. Group 2 received mitomycin-C 0.02% eye drops after pterygium excision postoperatively twice a day for two weeks (N = 42).	Follow up was on day 1, 7, 15 and the monthly for 6-12 months.	Keratitis occurred in 4 eyes for group 1 vs. 13 eyes in group two. Avascularised sclera occured in 8 eyes vs. 0 eyes in group 2. Scleral thinning occurred in one person from each group. Tenon cyst only occurred in 1 eye from group 2. Complication rate was statistically different between groups, p = 0.00.	"In this study, following pterygium excision, application of mitomycin-C in concentration 0.02% intraoperatively for 3 minutes or postoperatively topically mitomycin-C 0.02% eye drops twice a day for two weeks, did not show a statistically significant difference in the recurrence rate of pterygium among the two groups. "	Data suggest similar efficacy between intraoperative and postoperative Mitomycin C application but intraoperative application led to fewer complications.
Khakshoor 2010[251] (score = 5.0)	Fluoro uracil vs. Mitom ycin	RCT	Sponsored by the Mashhad University of Medical Sciences, Mashhad, Iran. No COI.	N = 82 eyes of 82 participants with primary pterygium. Mean age: 48.48±13.67 years.		Group A received subconjunctival injection of 0.02% MMC 1 month before bare scleral excision (N = 66) vs. Group B underwent conjunctival excision with a	Follow up were postoperatively at 1, 3, 6, 9 and 12 months.	Drop out for group A was 45% or 30 participants. No statistical difference between groups of recurrence, in the third and sixth months of follow-up (p = 0.312).	"We can conclude that subconjunctival injection of MMC 1 month before the bare scleral excision of pterygium is a simple and quick surgical procedure and is at least as effective as a	No significant differences. High dropout rate.

						rotational flap from the superior conjunctiva and intraoperative 0.02% MMC (N = 51).			conjunctival rotational flap with intraoperative MMC application in terms of recurrence and complication rate for primary pterygium treatment."	
Kareem 2012 [252] (score = 4.5)	Fluoro uracil vs. Mitom ycin	RCT	No mention of sponsorship. No COI	N = 50 with bilateral primary pterygium; mean age of 36.4.		Group 1, bare sclera technique for one eye and MMC (0.5mg/ml) was applied intraoperatively for the other eye (N = 25) Vs Group 2, same technique as used in group 1 but 5-FU (50mg/ml) was used in place of MMC (N = 25). All patients: ciprofloxacin (antibiotic) and dexamethasone (steroid) eye drops, four weeks, postoperatively.	Follow-up at 12 to 24 months.	Recurrence rate: MMC vs bare sclera: 8% vs 32%, (p=0.03); 5-FU vs bare sclera: 18% vs 34%, (p=0.07).	“Both MMC and 5-FU were safe during the follow up period but a statistically significant high success rate and more cosmetically acceptable appearance after MMC use justifies recommending its use to be superior to 5-FU as a medical adjuvant in the surgical management of primary pterygium.”	Data suggest MMC better than 5-FU in preventing pterygium recurrence post-surgery.
Dadeya 2001 (score = 5.0)	Other treatm ents	RCT[300]	No mention of sponsorship. No COI.	N = 60 with primary pterygium		Treatment group with 0.02%	Follow-up was evaluated postoperatively	Recurrence rate was 6.67% in the treatment group	"The results of this study (recurrence rate of 6.67% vs.	Data suggest short term efficacy.

				having 2 mm or more encroachment onto the cornea. Mean age: 32.6 years.		Daunorubicin for 3 min (N = unknown) vs. Normal saline for 3 min (N = unknown).	on days 1,7, and 15 then monthly for 5 months and then bimonthly until the last follow-up.	and 33% in the control group (p < 0.005).	33% in the treatment and control group, respectively) clearly indicate that single intraoperative application of daunorubicin appears to be a safe, simple, effective and useful form of adjunctive therapy to the surgical treatment of pterygium."	Variable follow-up lengths. Patients not well described.
Wishaw 2000 (score = 7.5)	Steroids	RCT[270]	No mention of sponsorship or COI.	N = 20 undergoing pterygium surgery. Age range: 18-73 years.		Lignocaine 1% 2 ml (N = 10) vs. Lignocaine 1% 1.6 ml plus morphine 4 mg in 0.4 ml (N = 10).	Follow up at 24 hours after surgery	At 24 hour postsurgery, mean pain scores for lignocaine plus morphine group was 1.63 and for the lignocaine group was 3.86, (p = 0.035); the difference was no longer significant at 48 hours.	"Our study suggests that peribulbar morphine is an effective analgesic modality for 24 hours postoperatively in pterygium surgery and is not accompanied by serious side-effects."	Data suggest morphine and lignocaine superior for pain relief. 2 day follow-up.

Appendix 1: Evidence Tables for Low-Quality Randomized Controlled Trials and Non-Randomized Studies

The following low-quality randomized controlled studies (RCTs) and other studies were reviewed by the Evidence-based Practice Eye Disorders to be all inclusive, but were not relied upon for purposes of the development of this document's guidance on treatments because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.

Corneal Abrasions: Simple and Lateral

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Patterson 1996 (score = 3.5)		RCT		N = 33 treated for eye pain and corneal abrasion on fluorescein staining.		Control group: eye patched with tobramycin ointment (N = 16) vs. Study group: non-patched eye with tobramycin drops to be used every 4 hours while awake (N = 17).	Patients had follow-up at 24 hrs.	At 24 hours, the mean changes in the pain scores (patched 3.09 vs. non patched 2.77) and in analgesic use (1.56 vs. 1.75) were not significantly different (p > 0.50). Healing was also not significantly different (14/17 patched vs. 11/16 non-patched) (p > 0.05)	"[R]outine eye patching does not appear to favorably affect the pain produced by simple corneal abrasion."	No slit lamp exam to confirm diagnosis. Lack of details for baseline comparability, compliance, cointerventions. No blinding. 34% loss to follow up. Small sample size. Data suggest no differences in treatment outcomes.
Solomon 2000 (score = 3.5)		RCT	No mention of COI or Sponsorship.	N = 28 with minor ocular trauma associated with corneal abrasion of different causes < 3 mm diameter.		Patch (1% topical cyclopentolate, 2 drops 0.3% chloramphenicol) vs. No patch (1% topical cyclopentolate, 1 drop 0.3% chloramphenicol, 1 drop 1% indomethacin)	Follow ups were 6-9 hours after treatment began and 24 hours after first visit.	6-9 hours post treatment pain relief was significantly greater in group 1 (p=-0.032) Itching was significantly greater in group 2 at hour 9 (p=0.025) and 24 (p=0.017). Abrasion healing – not reported.	"[E]ye patching or alternative use of indomethacin following minor ocular trauma and symptomatic corneal abrasion was effective and led to similar anatomical results."	Lack of details for randomization, allocation, baseline comparability, compliance, cointerventions. Small sample size. Lack of reported data precludes conclusions.

Faraldi 2012 (score = 3.5)		RCT	No mention of study sponsorship. PCOI: Vincenzo Papa, Daria Rasà, Debora Santoro, Annamaria L Mazza, and Simona Russo were employees of SIFI SpA.	N=40 patients with traumatic corneal abrasions occurring within 24 hours of the beginning of the study. Mean age 37 years.		Eye patch for 12 hours (dressed with 0.15% sodium hyaluronate, 1% xanthan gum and 0.3% netilmicin. (Control Group) (N=20) Vs. Same eye patch for 3 days. (N=20)	Patients were evaluated at 1, 3 and 7 days.	Both treatments showed significant increases from baseline, but did not show a difference compared to one another for decreasing the total surface area of the epithelial defect, Control vs. Intervention; 0.04 vs. 0.07 (p=0.367). No significant differences for erosion score (p=0.752) and for conjunctival hyperermia (p=0.888).	"[A]lthough a reduction of the duration of patching followed by the topical administration of Xanternet eye gel does not affect the healing of the corneal defect, it does improve patient compliance.	Lack of study details limits conclusion. No control groups limits conclusions on efficacy of the interventions. 3-day patching not standard of care in the U.S.
Kirkpatrick 1993 (score = 3.5)		RCT	No mention of sponsorship or COI.	N = 44 with corneal abrasions there was no previous history of eye trauma or disease in the affected eye. Mean age 36.3±11.0 years for group A and 35.0±11.5 years for group B.		Group A: oc. Chloramphenicol, gutt. Homatropine 2% and a double eye pad with bandage (N = 22) vs. Group B: oc. Chloramphenicol 4 times daily, and gutt. Homatropine 2% daily with no eye pad (N = 22).	Patients were reviewed at 24-hour intervals to monitor healing and the subjective level of discomfort.	Mean±SD time to heal (days) comparing Group A vs. Group B: 2.00±0.71 vs. 1.55±0.61; p=0.044. No group differences were found for abrasion size, time since injury or pain score at 24hrs.	"[T] results suggest that it does seem reasonable to treat primary corneal abrasions in the first instance with antibiotic ointment and mydriatic and no eye pad, and that this will lead to rapid corneal healing	Lack of details for randomization method, allocation, control of co-interventions, compliance. No blinding.

									within 1-4 days."	
Donnenfeld 1995 (score = 3.0)		RCT	Sponsored by the Lion Club International Foundation, Oakbrook, Illinois, and an unrestricted grant from the Allergan Pharmeceutical Company, Irvine, California. No mention of COI.	N = 47 with traumatic corneal abrasions <24 hours duration. Mean age in group A: 30 years; group B: 38 years; group C: 35 years.		Group A: 1 drop of polymyxin B sulfate/trimethoprim hemisulfate (polytrim), 1 drop of 1% cyclopentolate hydrochloride (Cyclogyl), and a standard pressure patch composed of three eye pads and tape (N = 15) Vs. Groups B and C were given etafilcon A 58% water-0.50 diopter therapeutic disposable contact lenses (N = 13, N = 19). Patients in Groups B and C were given a drop of polymyxin B sulfate/trimethoprim hemisulfate, followed by 1 drop of 1% cyclopentolate hydrochloride 5 minutes later; group b then received a bottle of polymycin B sulfate/trimethoprim sulfate in conjunction with a bottle of the placebo; group C received a bottle of	*N/A*	Number of days to heal did not differ significantly between groups (p=0.068 for pressure patching group vs. lens/placebo group, p=0.17 for pressure patching group vs lens/ NSAID group, and p=0.24 for lens/placebo group vs lens/NSAID). Returning to daily activities: contact lenses/NSAID vs pressure patching: 1.37 days vs 1.93 days, (p=0.031); lenses/placebo vs pressure patching: 1.23 vs 1.93, (p=0.007)	"Use of a bandage contact lens significantly shortens the time required for a patient to return to normal activities. Moreover, addition of a nonsteroidal anti-inflammatory drug to a treatment regimen significantly decreases the pain associated with traumatic corneal abrasions. Use of a bandage contact lens with a topical nonsteroidal anti-inflammatory may prove to be an effective adjunct in treating traumatic corneal abrasions."	Lack of details for randomization method, allocation, control of co-interventions, compliance. Data suggest no difference in healing rates.

						polymycin B sulfate/ trimethoprim hemisulfate in conjunction with a bottle of NSAID 0.5% ketorolac tromethamine. Both groups were instructed to administer 1 drop of both the polymycin B sulfate/trimethoprim sulfate and the contents of the masked bottle four times daily, 5 minutes apart.				
Acheson 1987 (score = 2.0)		RCT	No mention of sponsorship or COI.	N = 28 with traumatic abrasions (surface area >4mm2). Mean±SD age 33.28±7.43 years for pad group, and 38.28±15.77 years for bandage contact lens.		Occlusive Pad (N = 14) vs. Bandage Contact Lens (N = 14). All patients received guttae chloramphenicol 0.5% and homatropine 2%.	Patients were reviewed daily and the abrasions considered healed when local punctuate keratitis only could be observed on slit-lamp biomicroscopy of the injured site.	Those treated with the bandage lens had less mean±SD pain (33.46±21.34) after 24 hours than those treated with a pad and bandage (71.43±55.11); 0.05>p>0.02, and this group also reached the healing point more quickly (0.05>p>0.03).	"The study suggests that the primary treatment of traumatic corneal abrasions with soft contact lenses has an apparent advantage over the traditional occlusion in terms of reduced pain during healing and speedier healing."	Lack of study details limits conclusion. Small sample size.
Hulbert 1991 (score = 2.5)		RCT	No mention of COI or Sponsorship.	N = 30 with corneal epithelial		Eye pad with chloramphenicol (N =16) vs. Control	*No mention of FU.*	Discomfort at 24 h: 75% vs. 29% control, risk ratio	"The findings reported here suggest that	Lack of details.

				defect after removal of corneal foreign bodies.		group: chloramphenicol without eye pad (N = 14).		7.5, 95% CI: 1.17-55.6, chi² = 4.73, p = 0.03.	antibiotic treatment alone may be the best way to treat corneal epithelial loss after foreign body removal."	
Brahma 1996 (score = 1.0)		RCT	No mention of sponsorship. No COI.	N = 323 with corneal abrasions and foreign bodies; mean age of 35.1 for group 1, 33.3 for group 2, 32.7 for group 3, and 33.8 for group 4.		Group 1: Polyvinyl alcohol 1.4% (liquifilm tears), four times daily for 48 hours (control group) (N = 81) vs. Group 2: Stat instillation of homatropine 2% drops at presentation only (normal practice group) (N = 84) vs. Group 3: Flurbiprofen 0.03% drops, four times daily for 48 hours (first treatment group) (N = 74) vs. Group 4: Stat Instillation of homatropine 2% drops at presentation only, and flurbiprofen 0.03% drops four times daily for 48 hours (the second treatment group) (N = 84).	Follow-up for 24 hours.	Oral analgesia comparing group 1 vs. 2 vs. 3 vs. 4: 29 vs. 37 vs. 13 vs. 16; p<0.01. Sleep disturbance: 22 vs. 24 vs. 10 vs. 12; P<0.01. Groups 3 and 4 had reduced pain scores (p<0.05) compared to groups 1 and 2 during the first 24 h.	"In conclusion, flurbiprofen eye drops provide effective and significant pain relief compared to the traditional treatments for superficial corneal injuries. All patients attending a general A&E department or a dedicated eye casualty department with superficial corneal injuries should be assessed and treated appropriately."	Lack of study details limits conclusions. Outcome measured by self-reported questionnaire. High dropout rate.

Eke 1999 (score = 0.5)		RCT	Sponsored by Allergan Ltd. No COI.	N = 42 with traumatic corneal abrasion (TCA) caused by fingernails; mean age not reported.		Standard regimen: g. cyclopentolate 1% sta. and oc. Chloramphenicol q.d. for 5 days. (N = 20) vs. Standard regimen followed by Allergan Lacrilube ointment for 2 months. (N = 22)	Follow-up questionnaire at 3 months. Case-notes reviewed at 2 years.	Additional use of Lacrilube ointment was associated with higher prevalence of symptoms at 3 months compared to standard regimen (p = 0.016).	"When TCA is managed as above, there is a high prevalence of recurrent symptoms in the following 3 months. Additional nightly ointment appears to worsen prognosis."	Details sparse. Lack of study details limit conclusion. RCT nestled in prospective study.
Boberg-Ans 1998 [123] (score = 3.0)		RCT	Study supported by Allergan Ltd. No COI.	N=153 patients with clinical symptoms of traumatic corneal epithelial defects for longer than 5 years. Mean age was 35 years.		Fucithalmic® group (carbomer-containing ocular gel with fusidic acid 1%) (N=76) vs. Chloramphenicol (broad spectrum antibiotic available as 1% chloramphenicol) treatment group (N=77)	Follow-up occurred 24 hours after treatment.	The primary response was decrease in lesional area of the cornea. There was not a significant difference between the mean decrease in lesion area in the Fucithalmic® group vs. the Chloramphenicol group; 3.99 vs. 3.75 (p=0.84). There was no significant difference for frequency of cured patients (area of abrasion= 0 mm) for Fucithalmic®	"The unexpected results challenge the preconceptions that patients are generally symptom-free within days of TCA, and that nightly ointment is of symptomatic benefit. Our results also demonstrate that any future evaluation of treatment for TCA should include a follow-up of patient symptoms."	Lack of study details.

								vs. Chloramphenicol; 31 vs. 34 (p=0.78).		
Studer 1984[124] (score = 3.5)	Eye ointment, lubricants heading	RCT	No mention of sponsorship or COI.	N = 99 non perforating foreign bodies. Age range: 20-39 years.		Solcoseryl® Eye-Gel (N=49) vs. Cysteine Eye-Gel 2.4% (N=50).	Follow up: N/A.	Healing rates for Solcoseryl group vs. Cysteine group: 63% vs. 53% healed (0.10>p>0.05). 4% of Solcoseryl group reported itching sensation vs. 15% of Cysteine group reported burning sensation followed by blepharospasm, and fine deposits in the epithelium.	"At the end of treatment clear infiltrates and maculae corneae were very much less frequently observed in the test group, with 28%, than in the reference group, with 51%. The results provide clear evidence of the beneficial effect of Solcoseryl Eye-Gel on the course of healing of corneal injuries.	No baseline comparability. Sparse study methodology. Solcoseryl showed more complete epithelium closure (63%) versus cysteine eye gel (53%).
Valk 1970 [125] (score = 3.5)	Eye ointment, lubricants heading	RCT	No mention of sponsorship or COI.	N=95 with corpora aliena corneae s. conjunctivae of metallic or non-metallic nature.		Tanderil eye ointment, 10% for 4 days, 3 times a day (Verum group; N=47) vs. Placebo (N=48)	Follow up	Redeness on verum group was more significant than in the placebo group ($\alpha<0.05$, Yates test). Tendril was favored for the number of days in which produced symptoms disappeared	"The symptoms swelling as well as redness and pain disappeared faster in the verum group (statistically significant) than in the placebo group."	Sparse methodological details.

								(α<0.05, Yates test).		
Sigurdson 1987[126] (score = 3.0)	Rust Ring	RCT	No mention of sponsorship or COI.	N = 60 with corneal rust rings. Age mean: 32.5 years.		rust ring removed with 25 gauge needle attached to 1ml syringe (N=30) vs. rust ring removed with electric drill with burr sizes of 0.3-0.5mm (N=30)	Outcomes assessed 2 days after rust ring removal.	Time of rust ring removal for needle group vs. drill group: 129.1 seconds vs. 47 seconds (p<0.0001).	"Our conclusion is, therefore, that both methods are very acceptable for removing rust rings, but the electric drill is a quicker method compared to a hypodermic needle."	Sparse baseline comparability. High dropout rate. Electric drill takes less time for rust ring removal
Kruger 1990 [127] (score = 3.5)	Other	RCT	No mention of sponsorship or COI.	N=94 patients with foreign body injuries. Age: N/A		Topical framycetin sulphate (Soframycin), 2 drops every 6 hours (N=54) vs. Placebo (sterile saline), 2 drops every 6 hours N=40)	Outocmes assessed at days 1, 2, 3, and 4.	"No difference between using antibiotic or placebo."	"[T]he results of this small study indicate that the most common injuries are foreign body injuries (57%) and burns (17%)."	Sparse methodological details, timing is variable. No difference between groups.
Rao 1994 (score = 3.0)		RCT		*N*= 40		Eye patch vs. no patch. Both groups received guttae cyclopentolate 1% and oculentum chlamphenicol 1%.		Patch vs. no patch Abrasion size: No differences between groups on day 1 or 2. Pain: no differences. Paracetamol use: No differences in use.	"Although there is no indication for padding the eye for the treatment of simple corneal abrasions, conversely, there is no contraindication to its use unless an infection is suspected."	Study results reported in letter to editor, thus lacking study details. Data suggest no differences in outcomes.

Schulze 2006 (score = 2.5)		RCT		N = 23 with cataract extraction and intraocular lens (IOL) implantation who received corneal abrasion for better intraoperative visualization.		Autologous Serum: received autologous serum drops every hour + standard postoperative local therapy - (N = 13) vs. Hyaluronic Acid (Vislube): received 0.18% hyaluronic acid drops every hour (N = 10).		Time of Epithelial closure was 4.3 ± 2.0 Serum group vs. 7.1 ± 4.8 Vislube group. A Mann-Whitney U test showed significant advantages for the serum group ($p<0.05$)	"From our results concerning the wound healing in standardized erosions, we suggest the use of autologous serum eye drops for the treatment of corneal defects, especially postoperative epithelial lesions."	Details sparse.
Jackson 1960 (score = 2.5)		RCT		N = 195 with simple corneal abrasions.		Eye padded (N = 77) vs. Not padded eye (N = 80). Of the 195 only 157 completed the trial		No significant difference in the rate of healing between the two groups (p value not given).	"This survey has failed to show any increase in the rate of healing of simple corneal abrasions in the padded as compared with the unpadded group; moreover, though the series is small and the complications are correspondingly few, such complications as occurred were all in the padded series."	Lack of details. Study suggests no benefit associated with pads for corneal abrasion. Loss of total 10%.

Hulbert 1991 (score = 2.5)		RCT		N = 30 with corneal epithelial defect after removal of corneal foreign bodies.		Eye pad with chloramphenicol (N = 16) vs. Control group: chloramphenicol without eye pad (N = 14).		More patients in the eye pad group had discomfort vs. the control group at 24 hrs. (75% vs. 29%; risk ratio 7.5, 95% CI: 1.17-55.6; chi^2 = 4.73, p = 0.03).	"The findings reported here suggest that antibiotic treatment alone may be the best way to treat corneal epithelial loss after foreign body removal."	Lack of details. Pads suggested to be ineffective.
Hulbert 1991 (score = 2.5)		RCT		*N* = 33		Patch vs. no patch, both groups received chloramphenicol 0.5% drop.		Patch vs. no patch Discomfort @ 24 hrs: 75% vs. 29%, RR 7.5 (95% CI 1.17-55.6) Healed at Day 1: 14/16 vs. 14/14 p=ns	"An eyepad seems to confer no benefit in healing and is uncomfortable."	Lack of study details for randomization, allocation, baseline comparability, compliance. No blinding. Data suggest no difference in techniques.
Wedge 1992 (score = 2.0)		RCT		N = 30 with corneal abrasions suffered within the preceding 24 hours.		Collagen Shield or CSG groups received a Bio-Cor collagen shield supplied by Bausch & Lomb Pharmaceuticals Inc., Richmond hill, Ont., with a dissolution time of 12, 24, or 72 hours depending on the severity of the abrasion (N = 18). vs. The standard care or SCG group received antibiotic ointment (polymyxin B-neomycin,		By first follow up 50% showed complete healing, by day 4 72% demonstrated full healing and 22% showed small epithelial defects. Significant difference found showing the collagen healed was more comfortable than the patch, (p <	"In summary, although collagen shields are relatively expensive (about $40 each), they may provide an alternative form of management of traumatic corneal abrasion in carefully selected cases."	Details sparse.

						sulfacetamide or gentamicin), and a tight double patch was applied with adhesive paper tape (N = 12).		0.05). No significance difference in number of days required for total healing (p value not given). 33% reported no discomfort.		
Jackson 1960 (score = 1.5)		RCT		*N* = 222		Patch (mydratic + sulphacetam 10% t.i.d.) vs. no patch (mydriatics + sullphacetam 10% t.i.d.)		Patch vs. no patch. Healing rate: no differences found Day 1: 42/77 vs. 48/80 Day 2: 61/77 vs. 65/80	"This [study] failed to show any increase in the rate of healing in the padded as compared with the unpadded group."	Quasi-randomization (odd/even days of presentation). Lack of study details. 30% drop-out/loss to follow-up. Data suggest no differences between groups.

Pterygia

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/ Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Dadeya 2002 (score = 3.5)		RCT[278]	No mention of mention of sponsorship or COI.	N = 39 eyes of 31 patients who underwent pterygium surgery. Mean age 46.55 years.		Group A conjunctival rotation autograft (N = 17 eyes of 13 patients) vs. Group B conjunctival autograft (N = 18 eyes of 15 patients).	Follow up on 1, 7, 15 postoperative days, thereafter every month for 6 months, then every 2.	Recurrence Rate was not significant between Group A (5.88%) and group B, (5.55%) p value not given.	"[C]onjunctival rotation autograft and conjunctival autograft are both equally effective methods to reduce the recurrence rate after pterygium surgery."	Data suggest comparable results. Group size does not add up to population size.

Öksüz 2006 (score = 3.5)		RCT[279]	No mention of sponsorship or COI.	N = 45 eyes of 45 patients who underwent pterygium surgery. Mean age: 46.69 years.		Topical lidocaine gel 2% (N = 23) vs. Artificial tear gel for pain relief (N = 22).	Pain was evaluated at 4, 7, and 10 hours postoperatively.	Mean pain scores at 4/7/10 hour for lidocaine gel was 4.13 ± 1.86/4.00 ± 1.16/2.39 ± 0.89 and for the artificial tear gel 6.50 ± 1.47/6.63 ± 1.49/3.63 ± 1.00 (p = 0.001, p=0.000, and p=0.001 respectively).	"In conclusion, the current study demonstrates beneficial effect of lidocaine gel for the control of pain after pterygium surgery with negligible side effects.	Data suggest efficacy for pain.
Verma 1998 (score = 3.5)		RCT[281]	No mention of sponsorship or COI.	N = 130 undergoing pterygium surgery. No mention of age.		Group 1: without mitomycin C (N = 65) vs. Group 2: intraoperative application of mitomycin C 0.02% (N = 65).	Follow up was weekly for the first month, biweekly the second month, and bimonthly for a total period of 12 months.	Postoperative recurrence for group 2 was 48% (N = 31) and 3% (N = 2) for group 1. At the 99% confidence level, a significantly lower recurrence rate was observed with the use of Mitomycin C. Postoperative complications were higher for group 2 compared to group 1 for	"The present study shows clearly that the intraoperative use of Mitomycin C in conjunction with the bare sclera technique seems to be a safe and effective way to reduce the rate of recurrence of pterygia."	Patients not well described. Data show efficiency.

								granuloma (14 vs. 2), hyperaemia (31 vs. 7), and subconjunctival haematoma (5 vs. 3).		
Young 2004 (score = 3.5)		RCT[282]	Sponsored by Action for Vision (AFV) Eye Foundation, Hong Kong. No COI.	N = 115 eyes in 114 patients with primary pterygium. Mean age: 59.5 years.		Group 1: intraoperative MMC (Mitomycin C) 0.02% applied to the bare sclera for 5 minutes (N = 63) vs. Group 2: LCAU (Limbal conjunctival autograft (N =52).	Follow up for a minimum of one year with recurrence rates assessed at 3, 6, 9 and 12 months.	Recurrence total was 15.9% (N = 10) vs. 1.9% (N = 1), (p=0.04).	"In conclusion, LCAU resulted in better one year success rates in primary pterygium. Further study is underway to compare the outcome of MMC and LCAU in recurrent pterygia."	Unclear if dropouts numbers as appears to report completers. Data suggest lowest recurrence with limbo con. Autograft.
Birt 2003 (score = 3.0)		RCT[283]	No mention of sponsorship or COI.	N = 36 requiring a cyclodestructive laser procedure. Mean age: 64. 8 years.		Prednisolone acetate 1% plus atropine 1% drops each 4 times a day (N = 16) vs. Prednisolone acetate 1% plus atropine 1% plus ketorolac 0.5% drops each 4 times a day for 1 week (N = 20).		Daily and overall pain ratings (postoperative day 1/day 2/day 3/day 4/day 5/day 6/day 7/ average): ketorolac 18.2/7.4/6.8/ 6.4/6.4/5.4/5. 2/7.9 vs. standard therapy 47.7/26.9/25. 9/25.4/34.8/2 7.5/16.9/29.3 , p = 0.01/ 0.01/ .02/0.007/0.0	"Patients given topical nonsteroidal anti-inflammatory drops following a cycloablative ND: YAG laser procedure experienced statistically significantly less pain for the first 7 days following the treatment, and this group of drugs should be considered for routine use in this patient population."	Data suggest ketorolac reduces postoperative pain.

								02/0.015/0.05/0.004.		
Frucht-Pery 1996 (score = 3.0)		RCT[284]	No mention of sponsorship. No COI.	N = 81 with primary and recurrent pterygia who underwent excision. Mean age: 45.2 (19-81) years		Group 1, 0.02% mitomycin C (N = 49) vs. group 2 saline (N = 32).	Follow up at days 1, 7, 15, and 30, then monthly for 3 months, at 6-week intervals for the next 3 months, and finally at 3-month intervals.	Recurrence occurred in 2/49 (5%) in group 1 compared to 15/32 (46.7%), p = 0.0001.	"[I]ntraoperative administration of a single dosage of 0.02% mitomycin C is an effective treatment for prevention of recurrence of pterygium."	Data suggest lowest result autograft plus Mitomycin C.
Goldberg 1995 (score = 3.0)		RCT [246]	Supported by grants from Pacific Vision Foundation and Research to Prevent Blindness. No mention of COI.	N = 30 (healthy patients) with no history of ocular disease and not currently taking systemic medications.		Group 1: 0.1% diclofenac sodium ophthalmic solution (Voltaren) in one eye while the other eye served as the control (N = not reported) vs. Group 2: Artificial Tears solution with the same preservatives as Voltaren in one eye while the other eye served as the control (N = not reported) vs. Group 3: Received a non-preserved artificial tears solution in one eye while the other eye served as the control (N= not reported).	Table indicates a follow-up of 5.5 hours.	There were no significant differences between groups in corneal swelling p>0.05, or rate of deswelling (p>0.05).	"[A]t the dosage we used, Voltaren does not appear to have an effect on contact lens induced edema."	Experimental study. Data suggest NSAI does not affect hypoxia-induced corneal edema.

Yactayo-Miranda 2009 (score = 3.5)		RCT[285]	No mention of sponsorship. No COI.	N = 60 with chronic blepharoconjunctivitis or CBC. Mean age: 62.2 years.		No treatment group received no antibiotics (N = 20) vs. Levofloxacin only group treated with 0.5% topical levofloxacin in both eyes four times a day for seven days (N = 20) vs. Combined group received levofloxacin + scrub eyelid margins with a moistened cotton tip in (N = 20).		94% of patients with CBC had positive thioglycolate broth cultures vs. 58% in patients without CBC, $p < 0.0001$. Treated eyes resulted in significant reduction $p < 0.05$, in number of thioglycolate compared to non-treated eyes, ≥ 88%.	"CBC eyes have a significantly higher number of positive cultures than eyes without CBC."	Sparse methods. Data suggest 0.5% topical levofloxacin is effective for reducing bacterial flora in chronic blepharoconjunctivits patients.
Fallah 2008 (score = 3.5)		RCT[213]	Sponsored by the Tehran University of Medical Sciences. No COI.	N = 40 eyes of 40 patients with recurrent pterygium.		Conjunctival Limbal Autograft (CLAU) and Amniotic Membrane Transplantation (AMT) N= 20 eyes). vs. Intraoperative Mitomycin C (MMC) and AMT (N=20 eyes).	Followed up daily until corneal epithelial defect healed, 1 week, 2 weeks, 1, 2, 3, 6 months, then every 3 months.	During the follow-up period there was a significant difference in the recurrence of pterygium [CLAU/AMT = 0 (0%) vs. MMC/AMT = 4 (20%), ($p = 0.035$)]	"Thus, even considering the limited number of cases in this study, we concluded that CLAU/AMT is more effective in treatment of recurrent pterygium than MMC/AMT."	Data suggest better efficacy with CLAU with AMT versus intraoperative MMC with AMT for treating recurrent pterygium.
Helal 1996 (score = 2.5)		RCT[286]	No mention of sponsorship or COI.	N = 156 with primary or recurrent pterygia. Age		Postoperative MMC drops 0.05 mg/ml for 2 weeks (N = not given) vs. Single, 0.1 mg/ml intraoperative	Patient number randomized into each group not	Recurrence rate for intraoperative group 5.75%	“A single, intraoperative application of MMC is a simple, effective alternative adjunctive	Uneven follow ups. Patients not well described. Data suggest comparable efficacy.

				range: 24-65 years.		application of MMC for 3 minutes (N = not given).	given. Follow up at 1 day, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months postoperative.	compared to topical MMC, 6.9%.	treatment for pterygium."	
Keklikci 2007 (score = 2.5)		RCT[287]	No mention of sponsorship. No COI.	N = 94 eyes of 94 patients with primary pterygium. Mean age: 42.13 years.		Conjunctival-limbal autograft transplantation (N = 32 eyes of 32 patients) vs. Amniotic membrane transplantation (N = 30 eyes of 30 patients) vs. Topical mitomycin C (N = 32 eyes of 32 patients).	Outcomes assessed at 1 day, 3 days, 1 week, and 1 month, and thereafter 3 months interval for 36 months.	At 3 months, recurrence rate the no recurrence rate was 93.3% in amniotic membrane graft group vs. 93.8% in conjunctival-limbal autograft vs. 84.4% in mitomycin C group, long rank= 2.091 (p=0.351).	"[C]onjunctival-limbal auto grafting and amniotic membrane transplantation are safer than intraoperative Mitomycin C application in primary pterygium surgery."	Methodological details sparse.
Tananuvat 2004 (score = 2.5)		RCT[288]	Sponsored by the Faculty of Medicine Endowment Fund, Faculty of Medicine, Chiang Mai University. No COI.	N = 86 eyes of 78 participants with primary pterygium. Mean age: 43.38 years.		Amniotic membrane graft transplantation (N = 39) vs. Conjunctival autograft transplantation (N = 41).	Follow up postoperatively on day 1, week 1, 3, 6, and 12 months.	Recurrence rates for amniotic membrane group was 40.9% vs. conjunctival autograft was, 4.76% (p<0.001).	"In summary, the surgical results of primary pterygium excision followed by amniotic membrane and conjunctival autograft transplantation were compared."	Methodological details sparse.

Lewallen 1989 (score = 2.5)		RCT[290]	Sponsored by NIH training grant and by the International Eye Foundation. No mention of COI.	N = 39 with pterygia causing significant irritation to the patient after a trial of topical astringent drops or artificial tears. Age range: 23-68 years.		Conjunctival autograft (N = 19) vs. Bare sclera technique (N = 16).	Mean follow up was 15 months.	Recurrence was not significantly different between groups, 21% of grafted pterygia and 37% of those with bare sclera technique, (p>0.1). Younger patients were statistically associated with recurrence, p < 0.005.	"It is likely that a number of factors, including host response, determine whether a pterygium will recur after removal."	Variable FU length (6-33 months). Patients not well described and many details sparse. Only able to obtain follow up on 34 patients (4 moved, 1 refused to be examined)
Özer 2009 (score = 2.5)		RCT[291]	No mention of sponsorship or COI.	N = 163 with primary pterygium excisions between the ages of 22 and 74. Mean age: 52.98 years.		Group 1 (G1, underwent pterygium surgery using Bare Sclera Technique or BST (N = 48). vs. Group 2underwent pterygium surgery using Limbal-Conjunctival Autograft Technique or LCAT (N = 63). vs. Group 3 underwent pterygium surgery using Amniotic Membrane Graft Technique or AMGT (N = 52).	Follow up after 2, 5, 7, 15, and 30 days, and then every months.	There was a significant difference between groups with respect to Corneal Epithelializati on (G1: 5.62 ± 1.74 days vs. G2: 4.33 ± 0.91 days, p < 0.01; G2: 4.33 ± 0.91 days vs. G3: 4.79 ± 1.39 days, p < 0.05), Recurrence Rates [G1:	"LCAT was found to be more effective procedure than BST and AMGT, with decreased recurrence rates after pterygium excision."	Details sparse.

								19/48 eyes vs. G2: 11/63 eyes, (p<0.001); G1: 19/48 eyes vs. G3: 12/52 eyes, (p<0.001); G2: 11/63 eyes vs. G3: 12/52, (p < 0.001)], and Mean time from surgery to recurrence [G1: 7.28 ± 2.89 months vs. G2: 9.61 ± 2.94 months, (p<0.05); G1: 7.28 ± 2.89 months vs. G3: 9.04 ± 3.14 months, (p<0.05)].		
Tananuvat 2004 (score = 2.5)		RCT	Supported by the Faculty of Medicine Endowment Fund, Faculty of Medicine, Chiang Mai University. No mention of COI.	N =86 eyes of 78 patients with primary pterygium.		Amniotic membrane (N = 44 eyes of 39 patients) vs. Conjunctival autograft (N = 42 eyes of 41 patients).	Follow-up period at 1 week, 1, 3, 6, and 12 months.	No statistical difference regarding age / sex / laterality / extension onto the cornea or limbal involvement: (p = 0.2) / (p = 0.9) / (p = 0.7)/ (p = 0.7). Significant	"It was found that amniotic membrane transplantation for pterygium surgery has an unacceptably high recurrence rate."	Details sparse.

								difference found regarding average-follow up time / recurrence developed / recurrence-free at 12 months: (p = 0.03) / (40.9% vs. 4.76% in CG group) / (p = 0.0003).		
Bahar 2006 (score = 2.0)		RCT[292]	No mention of sponsorship. No COI.	N = 65 eyes of 65 patients with primary nasal pterygium. Mean age: 49±12 years.		Fibrin glue (N = 39) vs. Vicryl sutures (N = 26).	Follow up assessed postoperatively on days 1, 3, 10, and 21.	Fibrin glue reported significantly lower average pain, photophobia, foreign body sensation, irritation, epiphora, itching, local hyperemia, conjunctival chemosis, dry eye sensation and overall satisfaction at all follow-up examinations, p < 0.05 for all. Overall patient satisfaction was higher	"We conclude that using fibrin glue in pterygium surgery significantly reduces operative time, as well as patient pain and discomfort."	Quasi-randomized on ID#. Short trial. Patients not well described. Sparse details. Fibrin glue had shorter operation time and less pain.

								for the fibrin glue group, p < 0.001.		
Bekibele 2008 (score = 2.0)		RCT[293]	No mention of sponsorship or COI.	N = 68 eyes of 62 subjects with fleshy pterygium encroaching 2 mm or more into cornea. Mean age: 49 years.		Bare sclera conjunctival excision + 5 fluorouracil (5-FU) (N = 35 eyes) vs. Excision and conjunctival autograft group (N = 33 eyes).	Follow-up visits were at post-op days 1, 7, 21, monthly for 2 months and every 3months for between 1 and 2 years.	Pterygium recurrence / postoperative complications : (11.4% vs. 12.1% in conjunctiva autograft, p > 0.05) / (11.4% vs. 3.0% with granuloma formation and 5.7% with surface infection in 5-FU group).	"5-FU is marginally superior to conjunctiva autograft in the prevention of pterygium recurrence but neither gives 100% success rate, randomized studies combining both conjunctival autograft and 5-FU in pterygium treatment are desirable."	Methodological details sparse
Biswas 2007 (score = 3.5)		RCT[294]	No mention of COI or Sponsorship.	N = 60 eyes with primary progressive pterygium.		Group A Pterygium excision with Ipsilateral conjunctival-limbal auto grafting (N = 30 eyes) vs. Group B Mitomycin C 0.02% for two minutes after excision (N = 30 eyes).		Recurrence rate was 3.3% (N = 1) for group A and 10.0% (N = 3) for group B (p value=not given).	"Conclusively, it was found that both conjunctival-limbal auto grafting and preoperative mitomycin C (0.02%) were safe and simple procedure with significant reduced rate of recurrence, after primary progressive pterygium surgery."	Short report. Sparse details. Data suggest conjunctival limbal autografting better due to fewer pterygium recurrences and fewer ocular complications.
De Keizer 1998 (score = 2.0)		RCT[295]	No mention of sponsorship or COI.	All 3 studies together N = 57 eyes of 54 patients undergoing pterygium excision with		Study A free conjunctival autograft (N = 16) vs. Treatment with postoperative 90Sr beta-irradiation (N = 9). Study B:	Minimum follow up of 6 months.	Postoperative complications and follow-up were not different between randomized	"Based upon our overall data we prefer the superficial conjunctival autograft avoiding the potential risk of other methods."	Report of 2 RCT's and one open study resulting in one long range in FU. Well described study. No significant changes in recurrent rates.

				superficial free conjunctival autograft FCG. First Randomizatio n study (Study A) N=25 eyes of 22 patients Second Randomizatio n study (Study B) N= 16 eyes Open Study N=16 eyes treated without randomization		pterygium; FCG (N = 8) vs. 90 Sr-irradiation (N = 8).		groups. (p>0.05)		
Katricioglu 2007 (score = 2.0)		RCT[221]	No mention of sponsorship or COI.	N = 49 eyes of 49 subjects with pterygium tissue extending more than 2 mm beyond the limb and who underwent pterygium excision. Mean age: 53.8 years.		Group 1: Conjunctival autografts (N = 25 eyes) vs. Group 2: Amniotic membrane transplantation (N = 16 eyes) vs. Group 3: MMC or mitomycin C + conjunctival autografts (N = 8 eyes).	Follow up period from 6-30 months.	There was no overall significant difference found between groups or recurrence rates after conjunctival autografts (p>0.05)	"In summary, amniotic membrane and conjunctival autograft transplantation seems to be equally effective for the prevention of recurrence in primary pterygium."	Methodological details sparse.
Salman 2010 (score =1.5)		RCT[297]	Sponsored by the Ophthalmology Department, Ain Shams University. No COI.	N = 60 eyes of 48 participants with recurrent pterygia. Mean age: 44.5 years.		Group 1: Excision of the pterygium plus application of limbal stem cell transplantation + conjunctival autograft (N = 20	Follow up: > 6 months.	Progression of healing process between the three groups shows significance	"Limbal stem cell transplantation together with conjunctival auto grafting proved to be more effective in prevention of	Sparse methodological details. Possible failed randomization.

						eyes) vs. Group 2: Excision of the pterygium followed by amniotic membrane transplant (AMT) (N = 20 eyes) vs. Group 3: surgical excision of pterygium followed by intra-operative application of low dose MMC (0.05%) for 3 minutes followed by the use of AMT (N = 20 eyes).		difference, p < 0.001. Rate of recurrence significantly different (p < 0.001) between groups Group1 had recurrence rate of 2 eyes or 10%, Group2 had 6 eyes or 30% recurrence and Group 3 had 4 eyes or 20% recurrence	pterygium recurrence and in rapid restoration of normal epithelial morphology."	
Schellini 2006 (score = 1.0)		RCT[298]	Sponsored by the FAPESP-Fundação de Amparo à Pesquisa do Estado De São Paulo (SP), Brazil. No mention of COI.	N = 61 with pterygium. Age range: 33-72 years.		Primary pterygium (N = 42) vs. Recurrent pterygium (N =19). Each group was treated with matrix metalloproteinase-9 (MMP-9) vs. MMP-9/tissue area (TA).	No mention of follow up period.	MMP-9 showed no difference in normal Tenon's capsule (p > 0.05) and in primary or regular pterygia (p > 0.05).	"The similar expression of the matrix metalloproteinase in normal Tenon's capsule and in primary or recurrent pterygia allowed us to conclude that matrix metalloproteinase is not implicated in the genesis or the recurrence of pterygium lesion."	Study not well described, though labeled RCT. Data suggest metalloproteinase unrelated to pterygia.
Mahar 1993 (score = 0.5)		RCT[299]	No mention of Sponsorship or COI.	N = 32 eyes of 30 patients with pterygium. Mean age: 34 years.		Group 1: operated by bare sclera technique (N = 15 eyes of 15 patients) vs. Group 2: operated by bare sclera technique +	Follow up postoperatively at 1 and 2 weeks, 1 month then	Recurrence in group 1 was 9/15 (60%) from 3 to 10 months postop. Recurrence in group 2 was	"We think this form of adjunctive therapy is superior in comparison with the other modes of treatment such as	Sparse methods. Data suggest efficacy. Study design unclear.

						postoperative mitomycin C drops (N = 17 eyes of 15 patients).	2 to 3 month intervals.	0/15 (0%). (p value= not given)	topical thiotepa drops, radiation, and laser treatment."	

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