Conjunctivitis: More Than Meets The Eye

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The conjunctiva is a mucous membrane extending from the eyelid margin to the corneoscleral limbus. It forms the posterior layer of the eyelids (tarsal or palpebral conjunctiva) and covers the anterior sclera and episclera (bulbar conjunctiva).

Modifications of ocular disease processes, brought about by topical and systemic medication, frustrate the diagnostician. Ophthalmologists rarely, if ever, get to see a pure (untreated) conjunctivitis of any type. For this reason it is critical the family physician has the knowledge and confidence to make an accurate diagnosis and manage each case appropriately.

Natural Defences

The eye exists in a hostile environment and to maintain the critical, clear optical pathway, it is armed with a plethora of exquisitely sophisticated defence mechanisms. These include anatomical, microbiological, mechanical and immunological systems. The constant blinking action of the eyelids, the flow of tears and the intact epithelium of both conjunctiva and cornea comprise the anatomical and mechanical systems. Lysozyme, lactoferrin, phospholipase A2 and immunoglobulins are among the agents that provide a second line of defence against gram-positive organisms. Pathogenic bacteria also may be inhibited by the normal bacterial flora of the conjunctiva.

The eye is linked to the common mucosal immune system and, therefore, benefits from a scheme of microbial defence triggered in the gastrointestinal tract.

The orchestration and interplay of these complex processes is far from being completely understood, but the frequency of conjunctivitis reveals just how difficult a defensive strategy this is.¹

Acute Conjunctivitis

Bacterial conjunctivitis. In acute bacterial conjunctivitis, there is a copious, purulent or mucopurulent discharge. Usually, both eyes are reddened and a critical sign is that the eyes are “stuck shut” on waking (Figure 1). Pain is not present, but there may be itching or a mild foreign-body sensation. Visual acuity is not impaired unless the cornea is
involved. Hyperacute forms may be gonococcal, while *staphylococci*, *streptococci*, and *hemophilus* form the bulk of the remainder. The latter three are usually self-limiting in seven to 10 days. *Neisseria* is the exception in that corneal perforation can occur. In “normal” bacterial conjunctivitis no preauricular lymphadenopathy is present, but in *N. gonorrhoeae*, there may be swelling of surrounding tissues, pyrexia and a preauricular node. This is a useful diagnostic sign since the discharge of viral disease, also associated with PAN, is quite different and lacks frank pus.

**Ophthalmia neonatorum.*** Ophthalmia neonatorum refers to purulent, mucopurulent or mucoid discharge from one or both eyes. It occurs in the first month of life and is accompanied by diffuse conjunctival injection. Eyelid edema and chemosis (swelling of the conjunctiva) also may be present. The most serious forms are gonococcal, but also can be due to silver nitrate, chlamydia, herpes simplex and both gram-positive and gram-negative bacteria. Differential diagnoses are dacryocystitis, nasolacrimal duct obstruction and orbital cellulitis.

Ophthalmia neonatorum can be extremely serious and specialist intervention is recommended at the earliest stage. Inadequately treated chlamydial conjunctivitis in neonates can lead to chlamydial pneumonia.2

When dealing with infants it is important to remember that **the photosensitive infant with tearing eyes has infantile glaucoma until proved otherwise.** This child also may have red eyes and blepharospasm. With early diagnosis, vision often can be saved by appropriate surgical intervention. Once the infant is buphthalmic, there is often severe and irreversible glaucomatous optic neuropathy.

Unless you are certain an infant has uncomplicated conjunctivitis, which is self-limiting, insist on an early consultation with an ophthalmologist or pediatric ophthalmologist.

**Viral conjunctivitis.*** Associated upper respiratory tract infection or contact with someone having “pink eye” is common, and the condition is often initially unilateral, later spreading to the other eye. The discharge is usually watery or mucoid, the lids red and swollen, there is a palpable preauricular node (PAN) and petechial subconjunctival hemorrhages are frequent. Tarsoconjunctival follicles are common. These are dense, localized subepithelial infiltrations of the conjunctiva by large, mononuclear, lymphocyte, plasma, mast and polymorphonuclear cells. They result from lymphatic tissue reaction to irritation and usually appear as small, round or oval translucent bodies.

**Adenoviral** infections are most common, and when corneal involvement is present, the disease...
becomes keratoconjunctivitis. At this point, the patient crosses over from having mild local symptoms of conjunctivitis to photophobia, foreign-body sensation and blurred vision. These are the cardinal signs of keratitis, whatever the cause.

Epidemic keratoconjunctivitis (EKC) is a notifiable disease and extremely contagious for up to 10 days. The virus can remain infective on fomites for several weeks. It is a particularly severe infection, often unilateral, with a marked constitutional upset, and PAN is almost invariably present. Membranes or pseudomembranes may form. Subepithelial infiltrates may be seen later on slit-lamp microscopy and may persist for months or years.

Pharyngoconjunctival fever and acute hemorrhagic conjunctivitis are usually adenoviral in origin. In the former, pharyngitis is particularly noticeable, and in the latter, subconjunctival hemorrhages are a prominent feature. There is no effective antimicrobial therapy (Figure 2).3

_Herpes simplex_ is not only common, but also protean in its manifestations. Isolated herpes simplex conjunctivitis can occur, and its presentation may mimic other viral (or chlamydial) infections. Unless the disease is modified by the use of topical steroids or steroid antibiotic drops, it is self-limiting in about 10 days. Corneal involvement leads initially to the classical dendritic ulcer.

Fluorescein or rosebengal will stain the ulcer(s), which can be seen with the naked eye, but are absolutely distinctive when observed with the slit-lamp microscope (Figure 3).

The use of steroids in any form at this stage can potentiate the spread of the virus and lead to permanent, severe corneal scarring.

_Herpes zoster ophthalmicus_ often will produce lid swelling and a mild conjunctival reaction. If the nasociliary branch of the trigeminal nerve is affected, however, there is almost certain intraocular involvement.

When nasociliary involvement is noted, the patient must be referred to an ophthalmologist immediately.

**Allergic conjunctivitis.** Simple (e.g., Hay fever) _allergic conjunctivitis_ is characterized by intense itching, redness, a watery discharge and variable chemosis (swelling of the conjunctiva). Small papillae and follicles often are seen when the upper lid is everted, and also may be found in the lower fornix (Figure 4).

Allergic conjunctivitis occurs when a specific antigen, such as pollen or dust mites, mediates a local immunoglobulin A (IgA) or circulating immunoglobulin E (IgE) response. This causes mast cell degranulation and the release of histamine, chemotactic factors and prostaglandin synthesis.

_Vernal or atopic conjunctivitis_ is mediated in a similar way, but is either seasonal or a history of atopy may be present. “Giant” papillae may be present under the upper lid, and limbal involvement may be noted. Giant papillary conjunctivitis is a variant of this process, usually associated with a chronic foreign body under the upper lid, such as surgical suture material, or the use of soft contact lenses (Figure 5).
In cases of allergic conjunctivitis, you must evert the upper eyelid to aid in diagnosis and look for abnormalities of the limbal area, either in the form of thinning close to the limbus (the so-called “shield ulcer”) or of small discrete elevations as seen in limbal vernal conjunctivitis.

Erythema multiforme major (Stevens-Johnson Syndrome). This is characterized by the acute onset of fever, rash, red eye, often with generalized malaise and arthralgias. The critical signs are red, centred vesicles on the skin, surrounded by a pale ring that has a red halo. These are the so-called “target” lesions, and are accompanied by hemorrhagic crusting of the lips and bilateral conjunctivitis, which may be severe and rapidly proceed to severe corneal involvement. It is very important to differentiate this disease from microbial causes of conjunctivitis and corneal ulceration. A history of drug therapy is important, especially sulphonamides, as well as barbiturates, chlorpropamide, thiazide diuretics, salicylates, tetracycline, codeine, phenytoin and penicillins. Erythema multiforme major also can be precipitated by bacteria viruses and fungi, especially herpes and mycoplasma.

Ocular cicatricial pemphigoid. Unlike Stevens-Johnson syndrome, the onset of redness, foreign-body sensation, tearing and photophobia are often insidious, but progressive. In rare cases, they may be acute. Involvement of other mucus membranes mimics Stevens-Johnson syndrome, but differentiates these two entities from other, simpler ocular conditions. The more insidious progressive onset of ocular pemphigoid and the classical target skin lesions of Stevens-Johnson syndrome, however, usually will help differentiate these otherwise similar diseases.

Phlyctenular conjunctivitis. A phlyctenule, or phlycten, is a small, yellowish or pinkish-white nodule surrounded by hyperemic conjunctiva. Phlycten may be single or multiple and can occur anywhere on the conjunctiva, and occasionally on the corneo scleral limbus where it can be mistaken for a corneal foreign body.

At one time, phlycten were thought to be pathognomonic signs of *tubercle bacillus* infection. Today, they are thought to be due to a delayed hypersensitivity reaction to an antigenic stimulus, such as *Staphylococcus aureus*. These patients always should be referred to an ophthalmologist, and investigations to rule out tuberculosis should be performed in high-risk individuals.

*Myiasis and ophthalmia nodosa.* Various flies, particularly the cattle bot fly, discharge living lar-
vae into the conjunctival sac of cattle, deer and other large animals. Occasionally, humans are the unfortunate recipients of these small maggots. Although the condition is most common in the southwestern United States, ocular myiasis does occur in Canada.4

Ophthalmia nodosa refers to conjunctivitis, keratoconjunctivitis or a granulomatous condition produced by the fine hairs from caterpillars and arthropods, particularly the tarantula.5

**Chronic Conjunctivitis**

Chronic conjunctivitis occurs when a patient has symptoms for more than three weeks.

*Chlamydial inclusion conjunctivitis.* This occurs in sexually active individuals and may be accompanied by urethritis or pelvic inflammatory disease. The signs are conjunctivitis of more than three weeks duration, which often has failed to respond to a host of medications. All too often, patients experience temporary relief with steroid/antibiotic combinations, further confounding the diagnosis (Figure 6).

Inferior tarsal follicles are prominent, and pannus, or micro pannus (superficial vascularization of the cornea associated with a membranous-like infiltration of granulation tissue) occurs, usually in the upper cornea. A PAN is palpable and there may be subepithelial infiltrates seen on slit-lamp examination. Inclusion bodies are seen in the epithelial cells on Giemsa staining — hence the name.6

There is a case to be made for treating all chronic follicular conjunctivitis as chlamydial, but if you do, you have a responsibility to treat sexual partners and evaluate them and the patient for other sexually transmitted diseases (STDs).

*Trachoma.* The worldwide ravages of this disease caused by *chlamydia trachomatis* continue unabated. Poverty, famine, overcrowding, lack of clean water, sanitation and personal hygiene all foster its continuation and complications. That such an eminently treatable and preventable disease should continue to cause blindness among millions is a tragedy and a source of shame to those in the so-called civilized world.

The early stages of trachoma mimic other forms of follicular inclusion conjunctivitis, but severe complications can and do occur. These include cicatricial entropion with lash/corneal contact, keratitis sicca, superior fibrovascular pannus, limbal follicles, which scar to form Herbert’s pits, secondary corneal ulceration with descemetocoele.
formation, and, ultimately, corneal perforation and blindness (Figure 7).

The World Health Organization estimates that 500 million people worldwide are infected with trachoma and that 5 million are blind as a result of this disease and its complications.

**Molluscum contagiosum.** This disease produces symptoms and signs similar to inclusion conjunctivitis, but is easily recognized by the presence of one or more dome-shaped umbilicated nodules, 1 mm to 2 mm in size, on the lids or lid margins.

**Toxic conjunctivitis.** *Molluscum contagiosum* is often described as a “toxic” conjunctivitis. Most other cases involve the use of topical eye medications and many different agents are implicated, including the preservative (*i.e.*, benzalkonium chloride) used in these drops. Neomycin, gentamycin, atropine, idoxyuridine, neosynephrine, trifluridine, dipevrin, phystostigmine, brimonidine, zinc sulfate, and pilocarpine are among the most frequent offenders.

Signs of toxic conjunctivitis include follicles, papillae and dermatitis of the lids. There is a history of recent use of ocular medication.

**Parinaud’s oculoglandular conjunctivitis.** The most common cause of the complex, known as “cat-scratch” disease, has recently been isolated and identified as *Bartonella henselae*.

Apart from a mucopurulent conjunctivitis, there is a foreign-body sensation, and both preauricular and submandibular lymphadenopathy may be present. A history of feline contact is critical in the awareness of this potentially devastating disease, once thought to be innocuous. There is now evidence to suggest it may be a cause of Leber’s neuroretinitis (formerly considered hereditary) and can produce inflammatory disease throughout the ocular tissues.

Tularaemia, tuberculosis, syphilis, leukemia, fungi, sarcoid, lymphoma, mononucleosis and mumps have all been implicated in Parinaud’s syndrome when there is no recent (within two weeks) history of being licked or scratched by a cat.

**Miscellaneous.** Associated chronic conjunctivitis occurs in ocular rosacea, blepharitis, keratitis sicca, and pediculosis. *P. pubis* has an affinity for the lashes and this can be a startling finding on slit-lamp examination.

## Practical Diagnosis and Management

As with all other aspects of medical practice, a good history is the key to an accurate diagnosis, the prevention of iatrogenic misadventures and the rapid resolution of the presenting problem.

In the very young, serious *ophthalmia neonatorum* can occur when there is pre-existing maternal chlamydial or gonococcal infection.

Topical measures are not reliable in infants whose mothers have gonorrhoea or chlamydia, and these two infections often coexist. Gonococcal conjunctivitis can lead to ocular perforation and chlamydia can cause infantile pneumonia, as well as a legion of ocular problems. Systemic antibiotic therapy is commenced in these infants on the second or third day of life.
Pearl 1. Ophthalmia neonatorum can be very serious and immediate specialist assessment is essential.

Pearl 2. Infantile glaucoma may mimic conjunctivitis. Photophobia and epiphora are the cardinal signs. One or both globes may be larger than normal. Urgent specialist referral can prevent blinding glaucomatous optic neuropathy.

The most common forms of acute conjunctivitis, be they bacterial, viral, allergic, or toxic, are self-limiting diseases leading to no permanent ocular damage. Appropriate therapy can, however, shorten the course of the disease, while inappropriate therapy, especially steroids in herpes simplex, can be exceptionally harmful.9

Gonococcal and trachomal infections are noteworthy exceptions to this rule, but they can often be diagnosed on the basis of history and clinical findings. Acute iritis, episcleritis, scleritis, corneal ulceration and acute glaucoma should never be mistaken for conjunctivitis, but frequently are, with potentially devastating consequences for the eye.

The key to the differential diagnosis is that in all of these conditions, ocular pain is a consistent finding. Blurred vision is found in iritis, scleritis and corneal ulceration, while in acute glaucoma, the vision may be totally lost and the patient may present with vomiting and prostration due to the oculo-gastric reflex.

Pearl 3. Any red eye with ocular pain does not have conjunctivitis, unless proved otherwise by slit-lamp examination.

Laboratory investigations are usually not necessary in allergic and viral conjunctivitis and most cases of inclusion conjunctivitis. The history, symptoms and clinical findings usually point the way to appropriate therapy.10

In ophthalmia neonatorum, suspected gonococcal conjunctivitis or resistant inclusion conjunctivitis, laboratory confirmation of diagnosis always should be sought. Traditional methods of culture and Giemsa staining of epithelial scrapings are making way for rapid and cost-effective deoxyribonucleic (DNA) tests, such as multiplex polymerase chain reaction (PCR). Multiplex PCR can identify viral and chlamydial conjunctivitis with up to 97% confidence, making errors in diagnosis and treatment much less likely.11,12

Microscopy of stained conjunctival smears reveals eosinophils in allergic disease, bacteria and polymorphonuclear leukocytes in bacterial disease, and monocytes and lymphocytes in viral disease. The most important single diagnostic tool, however, is probably the slit-lamp biomicroscope. These instruments are not inexpensive, but a simple one costing a few thousand dollars is adequate for most
emergency rooms and family practices. In the author’s opinion, no family physician should be without access to a serviceable slit-lamp microscope and no emergency room can be complete without one.

**Treatment**

The treatment of conjunctivitis depends on the underlying disease process, but unless you are sure of the diagnosis, follow the golden rule: “If you cannot do any good, at least do no harm.” When dealing with most adult, acute conjunctivitis (“pink eye”), the etiology will be viral for which only supportive measures are beneficial. With bacterial disease, antibiotic therapy can shorten the course from 10 days to three or four, but even with placebo, up to 64% of bacterial conjunctivitis will resolve within five days.9

The mainstay of treatment should be good hygienic practices to prevent the spread of infection, frequent ocular cleansing, cool compresses, analgesics and artificial tears to supplement the eyes’ greatest natural defence — tears. Artificial tears are safe, often give considerable symptomatic relief, especially when cooled, and may even shorten the disease process.

The tears and the nasolacrimal mucosa share in the scheme of disease defence, which includes immunoglobulins, defensins and other unidentified agents.13,14 The importance of these systems lies not only in our understanding of the ocular defences, but also in the future commercial use of these powerful, naturally occurring antimicrobial molecules.15,16

The choice of antibiotic therapy for treating acute bacterial conjunctivitis must be made with the full understanding that 64% of cases will resolve within five days with placebo only.9 The role of lysozyme, lactoferrin and phospholipase A2 is clearly evident here. Of the gram-negative pathogens encountered, *N. gonorrhoeae* is probably the most dangerous, requiring both topical and systemic therapy. *N. gonorrhoea*’s resistance to penicillins and tetracyclines has led to the widespread use of quinolones and combinations, such as cefozopran (penicillin, oral cephems and aztreonam). Unfortunately, worldwide resistance to these drugs is increasing and this is especially alarming with the knowledge that gonorrhoea can amplify transmission of human immunodeficiency virus (HIV).17,18

The third generation cephalosporin, ceftriaxone, appears to be the best choice for resistant strains of *N. gonorrhoeae*, but its use must be strictly controlled and strictly monitored if it is to retain its effectiveness.19

Topical fluoroquinolones, such as ciprofloxacin 0.3% and ofloxacin 0.3% have a broad spectrum of activity against both gram-negative and gram-positive organisms.20,21

Chloramphenicol is well tolerated, has a broad spectrum of mostly bacteriostatic activity against a wide range of gram-negative and gram-positive organisms. The Compendium of Pharmaceuticals and Specialties (CPS) 2002, however, recommends chloramphenicol not be used when less toxic agents can be expected to be effective. This precaution is necessary because of the extremely rare, but devastating, hematological effects of this drug, including aplastic anaemia first reported in the 1960s. It is, therefore, rarely used in North America.22

Fusidic acid, gramicidin and bacitracin are effective against many gram-positive pathogens and are often used in combination with polymyxin B, and/or neomycin.

Sodium sulphacetamide is bacteriostatic against a wide range of common ocular pathogens, including *P. aeruginosa* and some chlamydia.

Tetracycline ointment or an oil-based suspension is active against chlamydia. Erythromycin
ointment is commonly used for nocturnal treatment of blepharitis.

There is controversy as to which agent should be the first-line topical antibiotic used for bacterial conjunctivitis. In terms of safety, efficacy, cost and convenience the fluoroquinolones are the author’s preference. Despite the plethora of research to dissect their differences, in clinical use, there appears to be little or no difference between them.20

**Pearl 4.** Do not use steroid/antibiotic combinations of any type (i.e., betamethasone sodium phosphate gentamicin sulfate, tobramycin-dexamethasone, framycetin sulfate gramicidin dexamethasone, sulfacetamide-prednisolone) as your first line of treatment. Also, do not prescribe topical steroids, unless you have performed a slit-lamp examination.

Hyperacute conjunctivitis caused by *N. gonorrhoeae* should be treated only with a knowledge of the antibiotic sensitivity of the organism. Systemic and topical fluoroquinolones can be effective against non-resistant strains, and the macrolide antibiotic azithromycin has been shown to be very effective against both *N. gonorrhoeae* and chlamydia even used as a single one-gram dose.23 As was mentioned earlier for resistant strains of *N. gonorrhoeae* the third generation cephalosporin, ceftriaxone, appears to be our last line of defence.18

**Chlamydia** of any type responds well to oral tetracyclines or the macrolide antibiotics, erythromycin or azithromycin. It is essential to treat the patients’ sexual contacts at the same time.

Doxycycline 100 mg twice daily for three weeks is safe, effective and inexpensive. Tetracyclines cannot be given to pregnant women or to children under nine years of age because of the formation of tetracycline — calcium orthophosphate complexes at the site of tooth development or new bone formation.

Systemic medication should be combined with topical tetracycline, erythromycin, sulphaetamide or one of the fluoroquinolones for up to three weeks.
Adenoviral conjunctivitis currently has no effective antimicrobial agent. Supportive and symptomatic treatment, therefore, should be given as earlier described. The administration of topical antibiotics in these patients is of debatable value, but is still widely practised.

Herpes simplex and zoster often respond to the newer anti-virals (topical; trifluridine 1% systemic; valacyclovir and famcyclovir), but their use in ocular disease must always be managed by an ophthalmologist.

In allergic eye disease treatment, unless you suggest to your patients some simple measures aimed at reducing their antigen load, there is little point in prescribing any drugs!

Advise your patient to shower before going to bed. This effectively reduces the pollen/dust/mite contamination of the skin, hair, lashes and eyebrows. It alone can have dramatic benefits, but is the most forgotten of all the strategies for dealing with both ocular and other allergic disease.

Pearl 5. Have all your allergy prone patients take a shower before going to bed.

“Common sense” measures include vacuum cleaners that vent externally or have high efficiency particulate (HEPA) filtration, hypoallergenic bedding, which should be washed frequently, and the pillowcases changed daily, closing the windows at night, using an air filtration/air exchange/air conditioning system, keeping pets (especially cats) out of the bedroom and careful removal of eye makeup before bedtime. Contact lens wearers should deproteinise their lenses frequently or use disposable lenses.

All of these recommendations work equally well for seasonal and non-seasonal allergies, but usually require adjunctive therapy to give satisfactory relief, as few of your patients will follow your advice to the letter. They want a “fix” for their problem, not a total lifestyle change.

Start your therapy with artificial tears, given four or five times daily. There are many brands, and since no one preparation suits everyone, give your patient a selection of samples to use. They are particularly soothing if cooled before use. I do not recommend systemic antihistamines for localized ocular disease, since good therapeutic levels can be achieved in the eye using drops without risking the side effects of oral medication.

Over-the-counter antihistamine decongestants (antazoline 0.5% and naphazoline 0.05%, or pheniramine 0.3% with naphazoline 0.25%) can be beneficial for short-term use in cases of acute allergic conjunctivitis. Newer antihistamines are less irritating and more effective, but more costly. They include levocabastine 0.05% and emedastine 0.05%. These are potent H1 antagonists and often give relief within minutes.

Mast cell stabilizers include sodium cromoglycate 2% and lodoxamide 0.1%, which have no antihistaminic activity and, therefore, have no place in the treatment of acute allergic eye disease. They are best reserved for prolonged use in seasonal allergic disease and must be started several days before the anticipated onset of symptoms. Nedocromil 2% is similar to cromoglycate, but has additional anti-inflammatory properties.

Drugs having both mast cell stabilizing and antihistaminic activity include ketotifen 0.025% and olapatidine 0.1%. These drugs with their dual-or even triple- modes of action are the author's preferred medications for uncomplicated allergic eye disease.

Topical steroids, alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDS) can be used with great caution in severe allergic eye disease, especially vernal conjunctivitis. The best advice is to refer these patients for ophthalmological consultation before embarking on steroid therapy.
Summary
The role of the family physician in the management of red eye is pivotal because he/she is usually the first point of contact for the patient. The mucous membrane of the conjunctiva can literally be the “window” to a number of systemic diseases. It is hoped the information in this paper will guide and assist clinicians in their understanding and management of conjunctivitis and other conditions in which the red eye may be the early sign of disease.

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References