Pharmacotherapeutic Options for Ophthalmic Conjunctivitis

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Abstract

Conjunctivitis is a common eye condition involving inflammation and in some instances infection of the conjunctiva. In the majority of cases it is caused by adenoviruses and, to a lesser extent, bacteria. Conjunctivitis can also occur secondary to Chlamydial and Gonococcal infections and new-born infants can acquire it during the birthing process from infected mothers. *Herpes simplex* and *Herpes zoster* are the infective organisms also responsible for conjunctivitis while seasonal pollens are usually the cause for allergic conjunctivitis. Common symptoms and signs are redness, tearing, oedema of the eyelids, sensation of a foreign body and it may be accompanied by itching. Most often a purulent discharge and adherence of eyelids at awakening are indicators of a bacterial infection. Most of the uncomplicated acute cases are self-limiting. There is however a challenge in distinguishing between the various types of conjunctivitis due to the similarity in the symptoms and due to a lack of tests and prediction algorithms, thus antibiotic therapy is often incorrectly initiated. Treatment of acute uncomplicated conjunctivitis caused by adenoviruses and bacteria is mostly symptomatic. Topical eye drops and ointments are preferred to oral agents in the treatment of more severe bacterial and allergic conjunctivitis while oral agents are used in the treatment of conjunctivitis caused by *Herpes simplex, Herpes zoster, Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Keywords: Infective conjunctivitis; Allergic conjunctivitis, Viral conjunctivitis; Bacterial conjunctivitis, Pink eye

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Conjunctivitis

Conjunctivitis is an inflammatory eye condition that involves the conjunctiva, a highly vascularised, thin and translucent membrane that covers the anterior portion of the sclera and the inside of the eyelids.[1-7] It presents as a red or pink eye due to the dilation of the blood vessels that leads to hyperaemia and oedema of the conjunctiva. This process typically is associated with some form of discharge.[1-6] The most common causes of conjunctivitis are viruses, bacteria, allergens and irritants.[1-10] Infectious conjunctivitis is most often caused by viruses as opposed to bacteria. Furthermore, conjunctivitis can be classified into acute, hyperacute and chronic as well as primary and secondary to a systemic disease, e.g. chlamydia or gonorrhoea.[1,2,4,11] Patients are usually initially seen by their primary health care providers and not ophthalmologists or optometrists, with a typical diagnosis of acute conjunctivitis. In the majority of cases, conjunctivitis will be self-limiting. Because of the difficulty in distinguishing between bacterial and viral conjunctivitis, in the majority of the cases, topical antibiotic therapy is initiated as there is a lack of tests or prediction algorithms available to confirm the diagnosis.[1,5,12,13]

Infectious conjunctivitis

Viral conjunctivitis (adenoviruses)

Adenoviruses are most often the cause of acute infectious conjunctivitis.[1,2,4,6,8,9,11] Unfortunately, due to the similarity of presenting clinical symptoms, it is usually misdiagnosed as caused by bacteria.[4,10,12] Presenting symptoms include a high fever, pharyngitis, bilateral conjunctivitis and swelling of the periauricular lymph nodes (pharyngoconjunctival fever) or in more severe cases as hyperaemia, swelling of the conjunctiva, watery discharge and swollen lymph glands (epidemic keratoconjunctivitis). Swollen lymph glands are more prevalent in viral conjunctivitis and this infection is also highly contagious. Strict sanitation measures and isolation of patients should be advocated, as the incubation period is estimated at 5–12 days and the period of communicability is 10–14 days. Symptoms usually resolve over 1–3 weeks. This condition is usually self-limiting.[1-4,6-9,11] Topical antibiotics are sometimes mistakenly prescribed for this viral infection due to incorrect diagnosis of the causative agent. This not only leads to an increased risk of toxicity and allergies, but also delays the diagnosis of other ocular diseases and increases the risk of resistance developing.[1,4,5,12,13] Unfortunately,

antiviral medication is not useful and because there is no effective treatment for this condition, the use of topical antihistamines, cold compresses and artificial tears might help in the alleviating of symptoms (Table I).[1-4,6-9,11,14,15] If the condition does not resolve within 7–10 days, the patient should be referred to an ophthalmologist.[1,15]

Viral conjunctivitis (Herpes)

Conjunctivitis caused by the *Herpes simplex* virus is not as common and presents usually only in one eye with accompanying thin and watery discharge as well as vesicular eyelid lesions. Patient should be referred to a specialist ophthalmologist. Treatment is preferentially topical and oral aciclovir or alternatively oral valaciclovir (Table I). Topical aciclovir is occasionally associated with transient stinging after administration while the oral anti-viral agents are usually well-tolerated.[1,2,4,7,11,15-17]

Conjunctivitis caused by the *Herpes zoster* virus that is responsible for shingles, usually involves the eyelids or conjunctiva and may result in uveitis and corneal complications. Patients should be referred to an ophthalmologist with any eye involvement. Treatment usually consists of oral aciclovir, famciclovir or valaciclovir (Table I).[1,2,4,7,11,15-17]

Bacterial conjunctivitis

The second most common acute infectious conjunctivitis is bacterial conjunctivitis.[1,10,11] It is also the most common cause of conjunctivitis in children.[11,18] Transfer can occur easily from an infected individual by means of direct contact or infection can occur via conjunctival flora over-proliferation. Certain conditions that may also predispose an individual to bacterial conjunctivitis include trauma, compromised immune system, dry eyes, epithelial barrier disruption and adnexal ocular structure abnormalities.[1,11,19] Presenting symptoms include redness, lack of itching, photophobia and a sensation of a foreign body in the eye. Discharge is usually purulent, yellowish in colour causing bilateral eyelid crusting that results in eyelids sticking together upon waking. The incubation period is estimated at 1–7 days and the period of communicability is 2–7 days.[1-5,11,13,14,18-20] The causative agents are either *Staphylococcus aureus*, *Staphylococcus epidermis, Streptococcus pneumoniae, Pseudomonas aeruginosa* or *Haemophilus influenzae* in adults and *Haemophilus influenza, Streptococcus pneumoniae* or *Moraxella catarrhalis* in children.[1,2,4,6,8,9,11,18,20,21] This eye infection is usually self-limiting within 1–2 weeks, however topical antibiotics are usually prescribed if symptoms do not improve on their own with supportive care within 2 days. Topical antibiotics render the patient less infectious to others and decrease the duration of the disease.[1,2,4,6-11,1315,18-23] The first line treatment for acute bacterial conjunctivitis in South Africa is chloramphenicol eye drops or ointment (Table I).[3,15,17] Treatment should not exceed 5 days, to limit adverse effects and resistance developing. With frequent application, serious over-use and long-term use, optic neuropathies, blood dyscrasias and aplastic anaemia have been reported.[15-17] In the event of inadequate response to chloramphenicol or confirmed resistant organisms, topical fusidic acid eye drops, aminoglycoside eye drops or ointment (tobramycin, neomycin) or fluoroquinolone eye drops (ciprofloxacin and gatifloxacin) can be prescribed (Table I).[1,2,4,5,8,9,11,16-23] Fusidic acid is effective against staphylococci, however due to an increased risk of resistance it is not a first line agent. Adverse effects are usually transient stinging and hypersensitivity.[15,16] Aminoglycoside treatment should be reserved only for severe sight-threatening infections caused by Gram negative bacteria, as they have incomplete Gram positive bacterial coverage. Transient burning and stinging and an increased risk of hypersensitivity and *Pseudomonas* resistance have been reported.[5,15-17,20] Fluoroquinolones have a broad spectrum of activity, however they are not first line agents due to the possibility of resistance developing.[5,15-17,20]Adverse effects are common and include burning, eye discomfort, conjunctival hyperaemia, crusting, and a bad taste. In rare cases allergic reactions, lid oedema, keratitis, light sensitivity, tearing and visual disturbances were noted.[15]

The use of topical steroids for the treatment of bacterial conjunctivitis should be avoided as there is an increased risk of potentiating the infection and prolonging the length of the disease.[1,5,16,17,12,15,22] Where the conjunctivitis lasts for more than 4 weeks it can be considered a chronic infection and patients should be referred to an ophthalmologist. The causative agents in this instance are usually *Staphylococcus aureus*, *Moraxella lacunata* and enteric bacteria. In the event of conjunctivitis caused in patients wearing contact lenses, the contact lenses should be removed. Patients should be treated with topical antibiotics effective against Gram negative organisms e.g. fluoroquinolones as mentioned above.[1,19]

Chlamydial conjunctivitis

Adult inclusion conjunctivitis

Conjunctivitis that occurs in adults that are sexually active is caused by *Chlamydia trachomatis* and usually presents unilaterally accompanied in many instances by a concurrent genital infection. It is associated with a purulent or mucopurulent discharge, foreign body sensation, hyperaemia, pre-auricular lymphadenopathy and lymphoid follicle formation. Corneal involvement may occur after a 2-week period of infection and otitis media is a complication. The incubation period is approximately 5–19 days.[1,2,4,7,10,11,23-25] Treatment options include either oral azithromycin or oral doxycycline (Table I).[2,4,15] It is important to treat the genital tract disease as well. Sexual partners also need to be treated and a gonorrhoea co-infection needs to be investigated.[1,11,13,15,23-26]

Table I. Pharmacotherapy for various types of conjunctivitis.[1-5,11,13,16-17,19,22,23,24,25,27]

Category	Causative organism	First line treatment	Alternative treatment
Acute viral conjunctivitis	Adenoviruses	Usually self-limiting • *Cold compress* • *Artificial tears* • *Topical antihistamines*	
Herpes conjunctivitis	*Herpes simplex*	• *Topical acyclovir eye drops in the lower conjunctival sac (1 drop 5x daily at 4 hour intervals for 14 days or till 3 days after healing, whichever is shorter)* • *Oral aciclovir (400 mg, 5x daily for 7–10 days) (dose adjustment in children)*	• *Oral valaciclovir (500 mg, 3x daily for 7–10 days)* • *Oral famciclovir (250 mg, 3x daily for 7–10 days)* • *(dose adjustment in children)*
Herpes conjunctivitis	*Herpes zoster*	• *Oral aciclovir (800 mg, 5x daily (4 hourly while awake)) for 7–10 days (dose adjustment in children)*	• *Oral famciclovir (500 mg, 3x daily for 7–10 days)* **OR** • *Oral valaciclovir (1000 mg, 3x daily for 7–10 days) (dose adjustment in children)*
Acute bacterial conjunctivitis	*S. aureus*, *S. epidermis*, *S. pneumoniae* *H. influenza* *M. catarrhalis* *P. aeruginosa*	Usually self-limiting • *Chloramphenicol eye drops (0.5%, 1 drop in the lower conjunctival sac, very 2 hours for the first 2 days, then every 4 hours for the next 3 days) Maximum 5 day treatment* **OR** • *Chloramphenicol ointment (1%, 1 cm strip in the lower conjunctival sac, every 4 hours or alternatively before bedtime if drops are also used during the day) Maximum 5 day treatment* **OR** • *Aminoglycosides: Tobramycin (1-2 drops every 4 hours or 1 cm ointment strip in the lower conjunctival sac, 2-3x daily for 7 days)*	No response or resistance suspected • *Fusidic acid eye drops (1 drop 2x daily continue until 2 days after resolution)* **OR** Aminoglycosides: • *Neomycin: (1 – 2 drops every 4 hours or 1 cm ointment strip in the lower conjunctival sac, 2 – 3x daily for 7 days)* **OR** Fluoroquinolones: • *Ciprofloxacin or gatifloxacin eye drops (1 drop every 2 hours for 2 days followed by 1 drop every 4 hours for 5 days while awake) or moxifloxacin (1 drop 3x daily for 4 days) or ofloxacin (1 drop every 2–4 hours for 2 days followed by 1 drop 4x daily for a maximum of 10 days)*
Chlamydial inclusion conjunctivitis	*C. trachomatis*	Adults: • *Oral azithromycin (single 1 g oral dose)* Neonatal: • *Clean both eyes immediately after birth* Prophylaxis: • *Chloramphenicol eye ointment (1%) or povidone-iodine aqueous solution (2.5%)* **AND** • *Oral erythromycin (50 mg/kg/ day in 4 divided doses for a period of 14 days)* **OR** • *Oral azithromycin (20 mg/kg single dose or 10 mg/kg/day for 3 days)*	Adults: • *Oral doxycycline (100 mg 2x daily for 7–14 days)*
Trachoma	*C. trachomatis* (subtypes A–C)	Adults: • *Oral azithromycin (single 1 g oral dose)* Children: • *Oral azithromycin (20 mg/kg maximum 1 g) single dose* Pregnant women, children < 6 months or patients allergic to macrolides: • *Topical tetracycline (1% eye ointment 2x daily for 6 weeks)*	Adults: • *Oral doxycycline (100 mg 2x daily for 21–28 days)* **OR** • *Oral erythromycin (500 mg 4 x daily for 21–28 days)*
Gonococcal conjunctivitis	*N. gonorrhoeae*	• *Irrigate eyes multiple times with sodium chloride eye drops (0.9%) to remove the discharge* Neonatal: • *Clean both eyes immediately after birth* Prophylaxis: • *Chloramphenicol eye ointment (1%) or povidone-iodine aqueous solution (2.5%)* **AND** • *IV or IM ceftriaxone (25–50 mg/kg, maximum 125 mg as a single dose)* Adults and adolescents: • *IM ceftriaxone (1 g single dose)* **AND** • *Oral azithromycin (1 g single dose)* Chlamydial dual therapy is indicated Cephalosporin allergic patients: • *Oral azithromycin (2 g single dose)*	Adults and adolescents: • *IM ceftriaxone (1 g single dose)* **AND** • *Oral doxycycline (100 mg 2x daily for 7–14 days)* Chlamydial dual therapy is indicated

Allergic conjunctivitis			
Acute	Pollens, animal dander, mould, environmental pollutants etc.	Usually self-limiting Topical Vasoconstrictor/ antihistamine combination (1–2 drop up to 4x daily for up to 48 hours) • *Naphazoline/antazoline* **OR** • *Tetryzoline/antazoline*	Topical antihistamines with mast cell stabilizing effects • *Olopatadine, epinastine, ketotofen, (1 drop 2x daily up to 2 weeks)*
Seasonal		Topical antihistamines with mast cell stabilizing effects • *Olopatadine, epinastine, ketotofen, (1 drop 2x daily 2-4 weeks before expected onset of symptoms)*	Topical mast cell stabilisers • *Lodoxamide (1-2 drops 4x daily up to 4 weeks) or cromoglicic acid (1 drop 4x daily)*
Perennial		Topical antihistamines with mast cell stabilizing effects • *Olopatadine, epinastine, ketotofen, (1 drop 2x daily)*	Topical mast cell stabilisers • *Lodoxamide (1-2 drops 4x daily) or cromoglicic acid (1 drop 4x daily)*

Neonatal inclusion conjunctivitis

Transmission occurs during birth when the mother is infected with *Chlamydia trachomatis* and the condition is left untreated. Presenting symptoms in the infant include swollen eyelids, hyperaemia and a purulent discharge. The period of incubation is 1–3 weeks and can persist for 3–12 months if left untreated. There is also an increased risk of pneumonitis and otitis media in these infants. It is strongly recommended that cultures be taken and treatment be based on clinical findings. The infant should be treated systemically with oral erythromycin after cleaning of the eyes immediately after birth (Table I).[1,2,4,7,15,22,23,25]

Trachoma

Trachoma predominantly effects children and occurs mostly in developing countries with low socioeconomic status and poor hygiene.[1,7,25] It is caused by *Chlamydia trachomatis* (subtypes A–C) and can result in blindness if left untreated.[1,24,25] Presenting symptoms include mucopurulent discharge, discomfort, redness and swollen eyelids. At least two of the following signs are indicators of trachoma: follicles in the upper tarsal conjunctiva, limbal follicles/ sequelae and scarring of the conjunctiva, cornea and eyelids accompanied by intense inflammation.[1,,3,7,24,25] The WHO (World Health Organization) recommends community-wide treatment if the active incidence of 1–9 year-old children within the community is > 10%. Treatment is either oral azithromycin or topical tetracycline alternatively, oral doxycycline or oral erythromycin (Table I).[1,3,7,15,24,25]

Gonococcal conjunctivitis

This severe form of conjunctivitis is caused by *Neisseria gonorrhoeae* in new-born infants that acquire it during birth, and sexually active adults and adolescents. It presents as severe swollen eyelids, profuse thick purulent discharge with an accompanying increased risk of perforation or ulceration of the corneas.[1-4,7,11,20] Eyes should be irrigated to remove the discharge and treated topically. Infants should also be treated systemically with either IV or IM ceftriaxone. Treatment of adults and adolescents consists of IM ceftriaxone and oral azithromycin (Table I). The possibility of a co-infection with *Chlamydia trachomatis* should be considered and treatment should be accordingly.[1-4,7,11,13,15,17,18,20,22,26]

Non-infectious conjunctivitis

Allergic conjunctivitis

The presence of allergens, e.g. pollen and animal dander, may result in an inflammatory response of the conjunctiva. Three types exist, i.e. acute, seasonal and perennial.[2,4,27] Presenting symptoms are itching, redness, eyelid oedema and watery discharge.[1-5,7-9,11,21] Patients should be instructed to avoid the offending allergen and encouraged to irrigate the eyes with saline or artificial tears. Treatment options include topical antihistamines, decongestants and mast cell stabilisers (Table I).[1,3,4,5,7,11,16,27] Topical decongestants should not be used long-term due to the risk of reactive hyperaemia.[11,15,16,27] Adverse effects of topical agents are usually transient stinging and in some instances CNS effects.[15,16] The use of non-sedating oral antihistamines may be indicated although topical agents were found to be superior. Topical corticosteroids should be discouraged for mild inflammatory conditions due to complications.[1,8,9,11,15,27]

Chemical-induced conjunctivitis

Various topical agents instilled into the eyes can induce allergic reactions with symptoms similar to those observed for viral conjunctivitis, e.g. the presence of the preservative benzalkonium chloride in eye drops. Usually symptoms will cease after stopping these offending agents.[1,2,3,7]

Conclusion

Conjunctivitis is one of the most common eye disorders seen by health care providers at the primary level, and the two most common forms of infectious conjunctivitis are non-herpetic viral (adenovirus) and bacterial in nature. Seasonal allergic conjunctivitis is also very common and due mostly to pollens. Most are self-limiting, however in more severe cases, antibiotic therapy is inappropriately initiated due

to the similarity of symptoms which leads to an inaccurate diagnosis. Treatment is usually topical eye drops or ointments except in the cases of herpes, chlamydial and gonococcal infections where topical, oral and in some instances IV or IM medications are indicated.

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