Acute infectious conjunctivitis in childhood

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OBJECTIVE: To review the etiology, clinical features and management of acute infectious conjunctivitis in children after the newborn period.

DATA SOURCES: Articles obtained from MEDLINE published before March 2000.

DATA SELECTION AND EXTRACTION: Representative articles on the etiology and clinical features were selected. Twenty-four clinical trials were also selected. From these articles, the main findings from three placebo controlled trials and two comparative clinical trials involving children are summarized in detail. The main findings from 19 comparative clinical trials in adults are briefly summarized.

DATA SYNTHESIS AND CONCLUSIONS: Acute infectious conjunctivitis caused by bacteria or viruses is a very common problem in children after the neonatal period. The most common bacterial pathogens are nontypable *Haemophilus influenzae* and *Streptococcus pneumoniae*. Diagnostic microbiology tests are not indicated for uncomplicated cases but may be useful for very young or very ill children if there is no response to initial therapy; for nosocomial cases; for cases suspected to be caused by sexually transmitted pathogens; and for outbreaks. Conjunctivitis is usually a mild, self-limited disease, but topical antibiotics are superior to placebo in reducing the duration and severity of symptoms. Most topical agents have equivalent efficacy; therefore, the selection of first-line agents should include inexpensive drugs with few adverse effects. Good choices include polymyxin/gramicidin, polymyxin/trimethoprim or sulfacetamide. Referral to an ophthalmologist should be considered in situations in which the diagnosis of uncomplicated conjunctivitis is in doubt or if there is no prompt response to therapy.

Key Words: *Conjunctivitis; Drug therapy; Etiology*

La conjonctivite infectieuse aiguë pendant l'enfance

OBJECTIF : Examiner l'étiologie, les caractéristiques cliniques et la prise en charge de la conjonctivite infectieuse aiguë chez les enfants après la période néonatale.

SOURCES DES DONNÉES : Articles obtenus dans MEDLINE publiés avant mars 2000.

SÉLECTION ET EXTRACTION DES DONNÉES : Des articles représentatifs de l'étiologie et des caractéristiques cliniques ont été sélectionnés. Vingt-quatre essais cliniques ont également été retenus. Tirés de ces articles, un résumé détaillé des principales observations de trois essais contrôlés contre placebo et de deux essais cliniques comparatifs portant sur des enfants ainsi qu'un bref résumé des principales observations de 19 essais cliniques comparatifs portant sur des adultes sont présentés.

SYNTHÈSE DES DONNÉES ET CONCLUSION : La conjonctivite infectieuse aiguë causée par des bactéries ou des virus représente une pathologie très courante chez les enfants après la période néonatale. Les pathogènes bactériens les plus courants sont l'*Haemophilus influenzae* et le *Streptococcus pneumoniae* ne pouvant être typés. Les examens de microbiologie diagnostique ne sont pas indiqués lorsque les cas sont simples, mais peuvent être utiles dans les situations suivantes : chez les enfants très jeunes ou très malades qui ne réagissent pas au traitement initial, qui souffrent d'une maladie nosocomiale, dont le cas est présumé comme secondaire à des pathogènes transmis sexuellement et en cas de flambées. Règle générale, la conjonctivite est une maladie bénigne et résolutive, mais les antibiotiques topiques donnent de meilleurs résultats qu'un placebo pour réduire la durée et la gravité des symptômes. La plupart des agents topiques sont d'une efficacité équivalente. Par conséquent, les agents de première ligne devraient être sélectionnés parmi les médicaments peu coûteux aux effets secondaires rares. Parmi les choix judicieux, soulignons la polymyxine et la gramicidine, la polymyxine et le triméthoprime, ou la sulfacétamide. Il faut envisager une consultation avec un ophtalmologiste lorsque le diagnostic de conjonctivite simple est mis en doute ou que le traitement ne procure pas une amélioration rapide de l'état du patient.

Acute conjunctivitis may be defined as conjunctival redness with or without increased tearing or discharge that is less than 14 days in duration (1). Acute infectious conjunctivitis is a common problem in childhood, and is the most common acute eye infection treated by primary care physicians and paediatricians. The present paper reviews the etiology, clinical features and diagnosis of acute infectious conjunctivitis. Data from clinical trials of conjunctivitis treatment are summarized and presented to aid readers in making evidence-based treatment decisions. Neonatal conjunctivitis is not discussed.

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TABLE 1: Clinical features of bacterial and viral conjunctivitis

Clinical feature	Bacterial conjunctivitis	Viral conjunctivitis
Bilateral at onset	In 75% of cases	In 35% of cases
Conjunctival discharge	Mucopurulent	Watery
Conjunctival membrane apparent	Late onset	Early onset
Preauricular nodes and/or pharyngitis	No	Yes
Concurrent otitis media	In 20% to 75% of cases	In 0% of cases
Slit lamp conjunctival findings	Mixed and/or nonspecific	Follicular

Figure 1) *Typical appearance of bacterial conjunctivitis*

Figure 2) *Typical appearance of viral conjunctivitis (upper eyelid everted)*

ETIOLOGY

Acute conjunctivitis is almost always caused by bacteria or viruses. One study showed that bacteria caused acute conjunctivitis in 80% of cases, viruses in 13% of cases and allergy in 2% of cases; no etiology was identified in 5% of cases (1).

Several bacterial pathogens may cause conjunctivitis. In acute, uncomplicated purulent conjunctivitis, approximately 50% of cases are caused by nontypable *Haemophilus influenzae*, approximately 25% of cases are caused by *Streptococcus pneumoniae* and less than 5% of cases are caused by *Moraxella catarrhalis* (1,2). Other less common organisms include *Staphylococcus* species, Gram-negative

bacilli, other Gram-positive bacteria and *Chlamydia* species. All of these organisms have been found in conjunctival and lid cultures from children with conjunctivitis but not in matched controls without conjunctivitis (1,2). The combination of conjunctivitis and acute otitis media is most commonly caused by nontypable *H influenzae,* and occasionally by *S pneumoniae* (3-9).

Other bacteria can cause conjunctivitis in specific settings. *Niesseria gonorrhea* causes conjunctivitis in sexually active adolescents and in individuals who are victims of sexual abuse. It is rarely, if ever, acquired in a nonsexual manner, except when it is acquired at birth (9,10). *Niesseria meningiditis* is a rare cause of bacterial conjunctivitis (2,10,11). Enteric Gram-negative bacteria are a rare cause of conjunctivitis that may be acquired nosocomially due to poor hygiene and after antimicrobial therapy (2,10). *Staphylococcus aureus* and coagulase-negative staphylococci are often recovered from lid cultures but not from the conjunctiva (1,2). The organisms have been associated with blepharitis and are perhaps more common in adults. Viridans streptococci and other Gram-positive bacteria have been cultured from eye swabs, but their role as a cause of conjunctivitis is unproven (1,5,11). The clinical conjunctivitis syndromes of trachoma and adult inclusion conjunctivitis are caused by *Chlamydia trachomatis* (11).

Several viruses cause conjunctivitis. Adenoviruses (types 3, 4, 5 and 7) cause pharyngoconjunctival fever (2,7,11). Other adenoviruses (types 8, 19 and 37) cause keratoconjunctivitis (2,11). Herpes simplex virus (HSV) also causes keratoconjunctivitis (2,7,11). Enteroviruses (coxsackie A24 or enterovirus 70) cause an acute hemorrhagic conjunctivitis (11). Other viruses that may cause conjunctivitis include measles, influenza, molluscum contagiosum and rubella (11).

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

There are certain clinical features that help distinguish the etiology of conjunctivitis. Infectious conjunctivitis (bacterial or viral) is associated with conjunctival hyperemia and ocular discharge (7). The palpebral involvement is typically much greater than the bulbar involvement. Clinical features can sometimes be used to distinguish bacterial from viral conjunctivitis, as outlined in Table 1 (1,2,7). The typical appearance of bacterial and viral conjunctivitis is shown in Figures 1 and 2. As noted above,

TABLE 2: Clinical features of infectious conjunctivitis, allergic conjunctivitis and systemic disorders with conjunctivitis			
Clinical feature	Infectious conjunctivitis	Allergic conjunctivitis	Systemic disorders with conjunctivitis
Conjunctival involvement	Palpebral greater than bulbar	Papillary changes on palpebra	Bulbar greater than palpebral
Eye discharge	Watery to mucopurulent	May be stringy	Often absent
Eye itchiness	No	Yes	No
Acute triggers, seasonal variation and history of atopy	No	Yes	No

there is a connection between bacterial conjunctivitis and acute otitis media, and therefore, physicians should examine the ears of all children who have conjunctivitis.

There are unique clinical features associated with some bacteria and viruses. *N gonorrhea* causes 'hyperacute' conjunctivitis with abrupt onset, rapid progression, prominent lid edema, excessive purulent discharge and a tender globe (2,7,10,11). *N meningiditis* conjunctivitis is generally unilateral with purulent discharge (2,10,11). In approximately 20% of patients with *N meningiditis* conjunctivitis, systemic disease develops later. Chlamydia conjunctivitis is associated with urethritis and cervicitis. It causes a subacute infection that is follicular in nature. Inclusion conjunctivitis is a sexually transmitted disease with ocular signs of a chronic conjunctival reaction that is most prominent in the lower lid, with a scant mucopurulent discharge (11). It is usually found in teenagers and young adults, but it can also be seen in neonates infected at delivery. A significant percentage of patients with chlamydia conjunctivitis also have concomitant asymptomatic gonococcal infection (11). Trachoma affects about 400 million individuals worldwide and is the leading cause of preventable blindness (11). It mostly occurs in underprivileged countries with inadequate sanitation (11). The hallmark finding is a follicular conjunctivitis, and blindness is caused by a process of progressive scarring and cicatrisation of the eyelids and adnexa.

Adenoviruses (types 3, 4, 5 and 7) cause conjunctivitis in patients younger than 10 years of age, and outbreaks of conjunctivitis do occur (2,7,11). The viral infection causes the conjunctivitis, and also leads to pharyngitis and fever. Other adenoviruses (types 8, 19 and 37) more commonly cause epidemics in older children and adults (2,11). Infections caused by these types of adenoviruses are not associated with upper respiratory symptoms or fever. The predominant finding is corneal involvement with the sensation that a foreign body is present and photophobia. The illness evolves over seven to 10 days, but local discomfort can continue for weeks to months. One may see marked eyelid swelling with this type of infection.

HSV can cause serious illnesses with vision-threatening complications with or without systemic manifestations. Herpes simplex infection is usually seen in the one- to five-year-old patient and is usually unilateral (2,7,11). Infection with HSV should be considered in any child with an acute follicular conjunctivitis and watery discharge. This type of infection can also be seen in neonatal herpes infection, with the disease involving the skin, eyes and mucous membranes. There may be vesicular lesions on the eyelids and a keratitis (dendritic). Enteroviral conjunctivitis is of abrupt onset, bilateral, with lid edema and profuse watery discharge (11). There often is pinpoint or confluent subconjunctival hemorrhage. Associated neurological involvement in the form of neuropathies may be present.

The differential diagnosis of acute conjunctivitis includes systemic diseases that have associated conjunctivitis and allergic conjunctivitis. Systemic disorders that are associated with conjunctivitis include Kawasaki syndrome, Stevens-Johnson syndrome, ataxia-telangiectasia, Lyme disease and juvenile rheumatoid arthritis (7). In patients with the above disorders, the bulbar involvement is much greater than the palpebral involvement, and there is no eye discharge. In allergic conjunctivitis, patients have prominent itching as a symptom and may have a stringy discharge (7). In allergic conjunctivitis, acute triggers, seasonal variation or evidence of atopy may be present. Allergic conjunctivitis and vernal keratoconjunctivitis share many of the signs and symptoms of infectious conjunctivitis, but the presence of itchiness as a symptom and papillary changes on the palpebral conductive should help differentiate this from infectious causes. Episcleritis, scleritis and anterior uveitis, all of which may have associated rheumatological findings, can also mimic infectious conjunctivitis. Scleritis and anterior uveitis are more ominous disorders that may have ramifications for sight if not diagnosed early. The clinical features of infectious conjunctivitis compared with systemic diseases with associated conjunctivitis and allergic conjunctivitis are summarized in Table 2.

In addition, more serious ocular conditions can mimic infectious conjunctivitis. When these more ominous disorders are not diagnosed appropriately, they can lead to permanent vision loss. Acute angle closure glaucoma and congenital glaucoma can mimic infectious conjunctivitis. Both disorders can lead to permanent vision loss if they are not appropriately diagnosed. Orbital cellulitis can be misdiagnosed early in its evolution, and retinoblastoma can mimic conjunctivitis and orbital cellulitis. Whenever
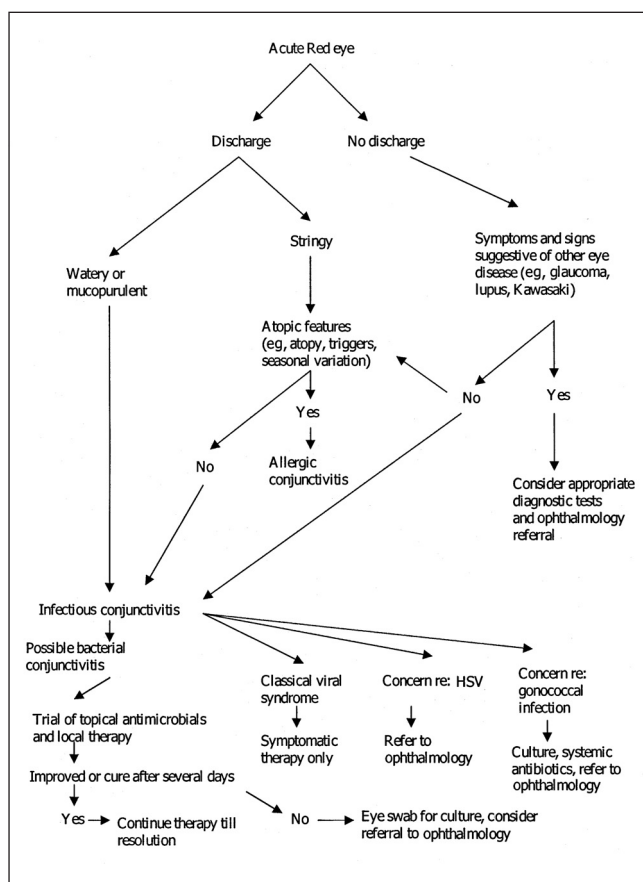
Figure 3) *Algorithm for the management of acute conjunctivitis in children. HSV Herpes simplex virus*

a patient does not respond rapidly to therapy for infectious conjunctivitis; has evidence of HSV, gonococcal or chlamydia infection; or has evidence of a noninfectious systemic disorder, a referral to an ophthalmologist should be made.

DIAGNOSTIC TESTS

Diagnostic microbiological testing for acute infectious conjunctivitis is not routinely indicated. Most cases are readily diagnosed on the basis of clinical features, and effective empirical therapy can be provided without a microbiological diagnosis. In the majority of cases, cultures do not provide clinically important information. Indications for performing stains and a bacterial culture include the following: age younger than two months; a very ill patient; a lack of response to initial therapy; nosocomial infections; sexual abuse; and outbreaks of conjunctivitis (2,11). If bacterial cultures are taken, culture swabs and two smears for Gram and acridine orange stains should be collected, and the swabs should be cultured on blood and chocolate (12,13). The most appropriate sample is obtained with a conjunctival scraping using an appropriate swab (12,13). Testing for chlamydia conjunctivitis is performed by identifying the antigen from a monoclonal antibody test (12,13). The conjunctivae are scraped for cells using a spatula, and the sam-

ple is then placed on a special slide that is provided with the testing kit.

Viral cultures are not useful unless HSV is considered or during an outbreak investigation because no effective treatment is available, except for HSV (12,13). If HSV is thought to be the causative agent, an urgent eye examination by an ophthalmologist is necessary. A swab stick or spatula is rubbed firmly against the conjunctiva, and to maximize the yield of cultures, the culture media should be inoculated directly or the sample should be immediately taken to the laboratory in viral transport media (13). The swabs are then either inoculated directly into tissue culture, used in immunoflourescence tests for a particular viral antigen or used for a nucleic acid, amplification-based (eg, polymerase chain reaction) diagnosis. A combination of these techniques can be used to provide a rapid and sensitive result (12,13).

MANAGEMENT

An algorithm for the diagnosis and treatment of acute conjunctivitis is presented in Figure 3. The initial step in the management of both bacterial and viral conjunctivitis is the use of symptomatic measures to both control symptoms and prevent the spread of the conjunctivitis. Important symptomatic treatments include the use of an eye toilette, warm compresses, artificial tears, strict hand washing and the avoidance of bright lights (if photophobia is present).

Acute bacterial conjunctivitis is mostly a self-limited illness that lasts seven to 14 days, but antimicrobial treatment will reduce symptoms and shorten the duration of the clinical disease (2,14). Topical antimicrobial agents are the usual method of treating bacterial conjunctivitis. Numerous placebo controlled trials have shown both statistical and clinical benefit from topical antimicrobial agents (Table 3) (14-16). The topical antimicrobial selection for the treatment of bacterial conjunctivitis includes aminoglycosides (gentamycin, tobramycin, neomycin and framycetin), fluoroquinolones (ciprofloxacin, ofloxacin and norfloxacin), sulfacetamide, chloramphenicol, erythromycin and combination agents, including neomycin and polymyxin with bacitracin or gramicidin, and polymyxin and trimethoprim or bacitracin or gramicidin.

In choosing a topical antimicrobial agent, certain factors need to be considered, including the efficacy, the route of administration (ointment versus drops), dose interval and duration of therapy, side effects, and cost (2,7,11,17). Any antimicrobial agent combined with a steroid should be avoided. The corticosteroid in these combination topical agents may hinder the eradication of the organism. In addition, steroids can cause the dendritic ulcer of herpes keratitis to worsen (this condition may be mistaken for acute bacterial conjunctivitis), and prolonged use leads to increased intraocular pressure (17). Limited data exist about the susceptibility of the most common organisms that cause acute conjunctivitis to the antimicrobial agents that are routinely used (Table 4).

TABLE 3: Placebo controlled clinical trials for drug treatment of acute bacterial conjunctivitis

Study	Number enrolled	Age range (years)	Study drug	Outcome(s) compared	Outcome measure day*	Result (drug versus placebo) (%)[†]	P
Gigliotti et al, 1984 (14)	66	Birth to 18	Polysporin (Warner-Lambert Consumer Healthcare, Canada)	Clinical cure	3 to 5	62 versus 28	<0.02
				Clinical improvement	8 to 10	91 versus 72	NS
				Bacteriological cure	3 to 5	71 versus 19	<0.001
					8 to 10	79 versus 31	<0.001
Leibowitz, 1991 (15)	288	Not stated	Ciprofloxacin	Bacteriological cure	3	94 versus 60	<0.001
Miller et al, 1992 (16)	284	At least 18	Norfloxacin	Clinical cure or improvement	5	88 versus 72	<0.01
				Bacteriological cure	2 to 3	65 versus 26	<0.01

*Day after onset of study that outcomes were measured; [†]Percentage of patients in each study group (study drug versus placebo) that achieved a beneficial outcome; NS Not significant

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TABLE 4: In vitro antimicrobial susceptibility (%) of topical antimicrobial agents to common pathogens causing bacterial conjunctivitis

	Estimated percentage of antimicrobial susceptibility			
Drug	Haemophilus influenzae	Streptococcus pneumoniae	Moraxella catarrhalis	Streptococcus aureus
Neomycin	85	<5	Most	95
Polymyxin	83	0	Not reported	11
Bacitracin	0	100	Not reported	99
Gramicidin	0	Most	Not reported	50
Sulfacetamide	70	75	Most	96
Trimethoprim	95	64	0	91
Gentamicin and other aminoglycosides	85	<5	Most	95
Ciprofloxacin	100	90	100	90
Ofloxacin	100	90	99	90
Chloramphenicol	95	95	100	Most
Neosporin (Glaxo Wellcome Inc, Canada)				
Neomycin *and*	85	<5	Most	95
Bacitracin *or*	0	100	Not reported	99
Gramicidin	0	Most	Not reported	50
Polysporin (Warner-Lambert Consumer Healthcare, Canada)				
Polymyxin *and*	83	0	Not reported	11
Bacitracin *or*	0	100	Not reported	99
Gramicidin	0	Most	Not reported	50
Polytrim (Allergan Inc, Canada))				
Polymyxin *and*	83	0	Not reported	11
Trimethoprim	95	64	0	91

Data from multiple sources

Few clinical trials have been performed to compare two or more antimicrobial agents. Lohr et al (18) studied 158 patients from two months to 21 years of age (88% of patients were 12 years of age or younger). All patients had culture-proven bacterial conjunctivitis (*S pneumoniae* or *H influenzae*), and all were given polymyxin/trimethoprim (Polytrim, Allergan Inc, Canada), sulfacetamide or gentamicin drops, one drop to each eye every 3 h while awake.

After 10 days, the clinical cure rates of polymyxin/trimethoprim, sulfacetamide and gentamicin were 93%, 93% and 97%, respectively (P was not significant), and the bacteriological cure rates were 83%, 72% and 68%, respectively (P was not significant) (18). Gross et al (19) studied 141 children aged 12 years or younger with culture-proven bacterial conjunctivitis (45% with *H influenzae*, 30% with *S pneumoniae* and 25% with another

infection) and compared ciprofloxacin with tobramycin drops, one to two drops every 2 h while awake for two days and then every 4 h for another five days. After seven days, the clinical cure rates of ciprofloxacin and tobramycin were 99% and 97%, respectively, and the bacteriological cure rates were 90% and 84%, respectively.

Many other comparison studies involving adults have compared aminoglycosides, quinolones, chloramphenicol, combination antibiotics and other agents (16,20-38). In almost all of the studies, no differences were found in the clinical or bacteriological cure rates. One study found that trimethoprim/polymyxin was superior to chloramphenicol (39), another study found that ciprofloxacin was superior to rifamycin (36) and a different study found that fusidic acid was superior to chloramphenicol or framycetin (40).

Side effects of topical ophthalmic antimicrobial agents are common, but, fortunately, they are mostly minor. Local irritation is the most commonly reported adverse effect (sulfacetamide, especially burns with instillation) (17). Moderate to severe drug side effects are rare and drug specific. Neomycin may cause allergic reactions, especially five to six days after use (2,41). All aminoglycosides can cause corneal toxicity, and it is not clear whether this is due to prolonged use or other factors (2,11,17). There have been reported cases of idiosyncratic aplastic anemia with topical chloramphenicol use (11,42). Cases of Stevens-Johnson syndrome have been reported with the use of sulfacetamide (43,44). Arthropathy has not been reported with the topical use of fluoroquinolones.

Because clinical efficacy is more or less equivalent among many topical antimicrobial agents, the important factors in choosing a first-line topical antimicrobial agent are convenience, side effects and cost. Brand name antimicrobial agents are more expensive than generic formulations but are not routinely more effective. The least expensive antimicrobial agents include polymyxin/gramicidin (Polysporin, Warner-Lambert Consumer Healthcare, Canada), sulfacetamide and gentamicin. Thus, appropriate first-line agents include polymyxin/gramicidin (Polysporin), polymyxin/trimethoprim (Polytrim) or sulfacetamide. In Canada, the first two formulations are available over the counter, but sulfacetamide requires a prescription. Alternative agents include aminoglycosides and neomycin/gramicidin (Neosporin, Glaxo Wellcome Inc, Canada) or fluoroquinolones. Although effective, there is no role for chloramphenicol in the treatment of conjunctivitis because of the small risk of serious hematological toxicity.

Systemic antimicrobial agents have also been found to be effective in the treatment of conjunctivitis and the prevention of otitis media, but the routine use of systemic antimicrobial agents in the treatment of bacterial conjunctivitis is not recommended (2,9,11,41). There may be a role for systemic antibiotics in the treatment of conjunctivitis in the otitis-prone child. Systemic antimicrobial agents are also indicated for the therapy of neonatal conjunctivitis due to *N gonorrhea* or *C trachomatis* (45). The incidental benefit of treating a focal or systemic infection with systemic antimicrobial agents is that, if bacterial conjunctivitis is present, it also will be treated (2). Therapy with intravenous antimicrobial agents provides levels of antibiotic in the conjunctiva that are more than sufficient to eradicate bacterial pathogens. With oral therapy, the levels of antibiotic in the conjunctiva are more likely to be considerably lower but still adequate (2).

For the treatment of viral conjunctivitis, the mainstay of management is symptomatic control. There is no evidence to support the use of topical antimicrobial agents. For herpes keratoconjunctivitis, the topical medications that are used are trifluridine (Viroptic, Glaxo Wellcome Inc) and idoxuridine (Herplex, Allergan Inc) (11,13). Currently, there are no other topical or systemic antimicrobial agents available for the management of viral conjunctivitis.

Finally, any patient treated for suspected bacterial or viral conjunctivitis that does not improve significantly with initial therapy should be referred to an ophthalmologist for further evaluation. As an example, HSV, varicella, epidemic keratoconjunctivitis and chlamydia infections should be followed by an ophthalmologist because these diseases can have significant vision-threatening corneal complications associated with them. Severe bacterial conjunctivitis can also be associated with bacterial keratitis and corneal ulcers, which may not respond to standard antibiotic therapy.

A review of the management of 'the red eye' was recently published (46). The review presented several helpful practical pointers; however, it focused on the management of adults and did not critically review clinical trials of drug therapy. In addition, the author recommended the use of antibacterial drops for the management of presumed viral conjunctivitis because "in many cases … the patient will not accept a recommendation that no therapy be administered" (46). In the opinion of the authors of the present paper, this belief conflicts with the rapidly changing beliefs and behaviours of physicians, and the public in Canada toward the acceptance of more appropriate use of antibiotics in children.

SUMMARY

Acute conjunctivitis is a common childhood condition and is most frequently infectious. A diagnosis can usually be made on the basis of clinical features, but laboratory testing may be necessary in complicated or severe cases. Most cases of viral and bacterial conjunctivitis are self-limited. Symptomatic measures may reduce symptoms and prevent the spread of the infection. Topical antimicrobial therapy is effective to reduce symptoms and eradicate bacterial pathogens. Inexpensive topical antimicrobial agents, such as sulfacetamide, are appropriate first-line agents with few side effects. Referral to an ophthalmologist is indicated in severe cases, in cases with unusual clinical features or in cases that do not respond to appropriate therapy.

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