Pediatric Acute Bacterial Conjunctivitis: An Update

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Pediatric acute bacterial conjunctivitis is a microbial infection involving the bulbar/palpebral conjunctiva of the eye. This infection is usually self-limited, and is most frequently observed among infants, toddlers, and preschool-aged children. Acute bacterial conjunctivitis affects approximately 1 of every 8 children each year and 5 million cases occur in the United States annually.[1-3] Bacterial conjunctivitis accounts for up to 1% of all consultations in primary care.[4] The most common causative pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and, occasionally, *Streptococcus pyogenes*. The characteristic signs and symptoms of bacterial conjunctivitis and periorbital cellulitis are similar regardless of the causative micro-organism, and although rarely performed, bacterial culture is required to definitively identify the specific pathogen. Polymerase chain reaction (PCR) testing for adenoviral infection is also available.

Management of acute bacterial conjunctivitis in young children raises a number of important questions, including:

- the epidemiology of bacterial conjunctivitis for patients of different age groups;
- differences in management between newborns, toddlers, young children, and adolescents;
- the use of standardized in-office treatment algorithms or guidelines;
- the role of bacterial culture and testing for adenovirus;
- the relative efficacy and cost-effectiveness of different topical antibiotics;
- the incidence of co-infection with otitis media and the treatment options for children with co-infection;
- the role of bacterial vs. viral infections;
- changes in conjunctivitis epidemiology following the introduction of the pneumococcal conjugate vaccine (PCV13).

In addition, a number of factors must be considered when evaluating the results of clinical trials that have compared different treatment approaches for bacterial conjunctivitis, including the median age of participating patients, the number of young children enrolled, and differences between natural history observational studies and those that have randomized patients with bacterial conjunctivitis to different topical antibacterial agents.

Diagnosis of Pediatric Acute Conjunctivitis

The presenting symptoms may suggest whether conjunctivitis is bacterial, viral, or allergic (Table 1). Patients with bacterial conjunctivitis tend to have bilateral involvement (present in 50% to 74% of cases) and mucopurulent discharge.5 Conjunctival redness is common in older children and less common in infants and toddlers. Studies have shown that approximately 50% of children with bacterial conjunctivitis have redness with discharge.[5] Sometimes, however, the redness is experienced in the absence of discharge. The combination of conjunctivitis and acute otitis media (conjunctivitis-otitis syndrome) occurs in 32% to 39% of cases, mostly in children aged 6 to 36 months.[5] Viral disease is less often bilateral (approximately 35% of cases),[6] is associated with a milder, more watery conjunctival discharge, and is usually associated with conjunctival redness.[7] Acute otitis media is uncommon in patients with viral conjunctivitis, and the eyes are generally not pruritic. Allergic conjunctivitis is typically bilateral and associated with conjunctival redness. Edema palpebral or bulbar discharge is rare.[7] Pruritus is common and can be severe.

Table 1. Bacterial vs. Viral vs. Allergic Conjunctivitis

Clinical Finding	Bacterial	Viral	Allergic
Bilateral eyes	50% to 74%	35%	Mostly
Discharge	Mucopurulent in younger children	Mild, watery, or "sleepers" only	Rare
Redness	Common in older children, uncommon in infants and toddlers	Usually	Usually
Acute otitis media	32% to 39%	10%	No
Pruritic	No (but many rub eyes)	No	Major

Sources: Block SL, et al. *Antimicrob Agents Chemother.* 2000;44:1650-1654; Bodor FF, et al. *Pediatrics.* 1985;76:26-28; Gigliotti F, et al. *J Pediatr.* 1981;98:531-536; Tarabishy AB, et al. *Cleve Clin J Med.* 2008;75:507-512.

Click here for larger version of Table 1.

Acute conjunctivitis is primarily diagnosed clinically, and treatment is nearly always empiric. Bacterial cultures are rarely obtained because of the relatively high cost and the 4 to 5 days before results become available. Bacterial cultures may be obtained for refractory cases, neonates, and patients with periorbital cellulitis. Viral cultures are rarely performed. When herpes or adenovirus is suspected, PCR testing may be performed to confirm the presence of these pathogens.[8] Wood's lamp examination in the office setting may help to differentiate bacterial conjunctivitis from suspected corneal abrasion or herpes virus. Very rare conditions that may resemble acute conjunctivitis include ophthalmologic manifestations of Kawasaki disease, measles, or herpes infection.

Although many clinicians believe that acute conjunctivitis accompanied by purulent discharge is not caused by bacterial infection, several studies have confirmed the presence of bacterial infection in the majority of these cases. In a study published in 1981, Gigliotti and colleagues examined 99 cases of pediatric acute conjunctivitis and found that bacterial infection accounted for 65% of the cases, with viral infection accounting for 20%.[6] Several subsequent studies reported rates of bacterial infection between 55% and 80% among children with conjunctivitis accompanied by purulent discharge.[5,9-12]

Patel and colleagues evaluated the usefulness of clinical signs and symptoms to distinguish bacterial from viral conjunctivitis in 111 pediatric patients.[12] The mean age of the patients was 33 months, 78% had positive bacterial cultures, and nontypeable *H influenzae* accounted for 82% of bacterial infections. A history of glued or sticky eyelids, in combination with a physical finding of mucoid or purulent discharge, was attributable to bacterial infection in 95% of cases.

These observations were confirmed in a more recent study of 368 patients with conjunctivitis who were between 6 months and 17 years of age.[13] Four factors were associated with bacterial infection: age less than 6 years, onset of symptoms between December and March, "glued eye" in the morning, and the absence of eye watering. For patients with all 4 of these factors, 88% had a positive bacterial culture. The most common causative organisms included H influenzae and *S pneumoniae* (Table 2). The relatively low rate of S pneumoniae

in this study (approximately 20%) is likely due to the fact that the patients were enrolled in 2007 and 2008, when most of the population had received the highly effective pneumococcal conjugate vaccine (PCV7).

Table 2. Causes of Bacterial Conjunctivitis in 238 Culture-positive Patients

Bacteria	Patients (%)
Haemophilus influenzae	67.6
Streptococcus pneumoniae	19.7
Staphylococcus aureus	8.0
Haemophilus parainfluenzae	2.5
Other bacteria	2.2

Source: Meltzer JA, et al. *Arch Pediatr Adolesc Med*. 2010;164:263-267.

Click here for larger version of Table 2.

A third study, conducted in rural Kentucky between 1997 and 1998, examined factors associated with bacterial eye infection in 250 children with acute conjunctivitis.[5] The mean age of the children was 24 months. Bacterial cultures were positive for *H influenzae* in 42% of cases (69% of which produced ß-lactamase), *S pneumoniae* in 30% of cases, and were negative in 32% of cases. Erythema was present in 53% of cases, and purulent discharge in 83%. Many children had erythema alone, therefore redness of the eye does not definitively indicate viral conjunctivitis. In addition, bacterial otopathogens were recovered from the eyes of 60% of patients between the ages of 2 weeks and 2 months. Together, the results of these studies show that the presence of purulent discharge is usually associated with bacterial conjunctivitis even in patients as young as a few weeks of age.

Microbiology of Acute Bacterial Conjunctivitis

Nontypeable *H influenzae* accounts for approximately 50% to 80% of cases of bacterial conjunctivitis after the newborn period.[5,13] These cases are not preventable by *H influenzae* type B (Hib) vaccination. ß-lactamase-producing bacteria are identified in approximately 50% to 60% of cases attributed to *H influenzae*. Pneumococcal infections account for approximately 20% to 30% of cases.[5] The proportion of conjunctivitis cases attributable to pneumococcal infection varies with age and also with PCV7/13 status, which likely reduces

rates of penicillin-nonsusceptible pneumococcus (PNSP). Moraxella catarrhalis is present in 0% to 10% of children, and 100% of these infections are ß-lactamase producers (ie, relatively weak). Group A streptococcal infections (eg, *S pyogenes*) are rare, and mostly occur in school-aged children. *Staphylococcus aureus*, gonorrhea, and meningococcus are rare causes of conjunctivitis in young children.

In neonatal patients, infection with vaginal flora (eg, *Escherichia coli, Klebsiella pneumoniae, Staphylococcus epidermidis*) is a common cause of bacterial conjunctivitis. As with older children, pediatric respiratory bacterial pathogens (eg, *H influenzae*, *S pneumoniae*) are also common causes of acute conjunctivitis in the newborn population.[14] Although chlamydial conjunctivitis is thought to be common, in fact it is a rare cause of conjunctivitis in most pediatric populations. Approximately 2% to 15% of mothers have chlamydia, with a 50% risk of vertical transmission.[15] Prophylactic ointments applied at birth protect against gonorrhea but not chlamydia. In cases where chlamydia is strongly suspected as the causative pathogen, treatment typically consists of oral erythromycin or the better-tolerated but less well-studied azithromycin.[16] In addition to its propensity to cause notable gastrointestinal distress, the use of erythromycin in the neonatal period is associated with a risk of pyloric stenosis in infants, and many experts recommend avoiding its use.[17] Herpes simplex infection is a rare cause of neonatal conjunctivitis, but should prompt an immediate referral to an ophthalmologist.[18]

Treatment of Pediatric Acute Conjunctivitis

A Cochrane Collaboration review and meta-analysis examined the efficacy of topical antibiotic therapy for the treatment of pediatric conjunctivitis. Data from 5 clinical trials in which 1,034 patients were randomized to either topical antibiotics or placebo were included in the analysis.[4] The meta-analysis demonstrated higher rates of clinical remission (relative risk [RR], 1.24; 95% confidence interval [CI], 1.05-1.45) and microbiological cure (RR, 1.77; 95% CI, 1.23-2.54) after 2 to 5 days for children assigned to topical antibiotics. At 6 to 10 days, the effects of topical antibiotic therapy were smaller but remained statistically significant for clinical remission (RR, 1.11; 95% CI, 1.02-1.21) and microbiological cure (RR, 1.56; 95% CI, 1.17-2.09). After 10 to 14 days, response rates were similar for the antibiotic and placebo groups. The authors concluded that pediatric conjunctivitis is self-limited in most cases, generally

resolves spontaneously after 10 to 14 days, and that the use of topical antibiotics significantly increases the number of patients with early clinical and microbiological remission.

Although acute bacterial conjunctivitis may resolve without therapy in 10 to 14 days, treatment may permit earlier return to daycare for the child and to work for the child's parents, reduce the likelihood of transmission to other children, and prevent relapse. In many cases, children with conjunctivitis are required to avoid school or daycare settings until symptoms subside, and treatment may therefore help to minimize the socioeconomic impact of ocular infection. In addition, untreated bacterial conjunctivitis may be associated with complications such as keratitis and periorbital cellulitis. As noted previously, acute otitis media is among the most common bacterial co-infections of acute conjunctivitis, occurring in approximately 32% to 39% of cases.[5,10] Periorbital cellulitis is less common, is usually associated with ethmoid sinusitis or trauma, and may be associated with dacryostenosis in older children.[19] Methicillin-resistant *S aureus* (MRSA) is rarely found in acute bacterial conjunctivitis cultures of children younger than 4 years of age, and is most often encountered in association with traumatic eye infection or skin infection. Potential viral complications include keratitis and pre-auricular lymphadenitis. Adenovirus conjunctival infection usually presents with pharyngitis, fever, and a negative streptococcal test.[20]

A number of antibacterial agents are available for the treatment of acute bacterial conjunctivitis, most of which are only approved for patients aged 12 months and older (**Table 3**). Topical sulfonamides should not be used to treat pediatric patients. Although inexpensive, these agents often cause burning of the eye, provide minimal coverage against ocular pathogens such as *H influenzae* or pneumococci, and may cause hypersensitivity reactions. Topical aminoglycosides (eg, tobramycin, gentamicin, or neomycin) are also relatively inexpensive, but are often not effective against *S pneumoniae* and group A streptococcus. These topical agents may also cause chemical conjunctivitis. Topical macrolides (eg, azithromycin, erythromycin) are generally well-tolerated, are available as ointments, but they are bacteriostatic and provide relatively weak antibacterial effects against *H influenzae*, pneumococcus, and staphylococcus. Azithromycin is relatively expensive but has a long half-life, allowing once-daily dosing.[21] Polymyxin B/trimethoprim provides reasonable coverage against ocular pathogens, especially for patients vaccinated with PCV7/13. However, polymyxin B/trimethoprim is a bacteriostatic agent and is

therefore associated with slow clinical resolution.[22] Older fluoroquinolones (eg, ciprofloxacin, ofloxacin) are available as low-cost generics and provide good coverage against *H influenzae* but only fair coverage against *S pneumoniae*.[23] Newer fluoroquinolones (eg, moxifloxacin, gatifloxacin, besifloxacin, levofloxacin) are more expensive, but provide excellent coverage against most ocular pathogens.

Table 3. Treatment Options for Acute Bacterial Conjunctivitis

Macrolides	Miscellaneous
Azithromycin (Azasite)	Polymyxin B/ trimethoprim (Polytrim)
Erythromycin	Sulfacetamide (Bleph-10)
	Bacitracin ointment
Quinolones	**Aminoglycosides**
Besifloxacin (Besivance)	Tobramycin (Tobrex)
Ciprofloxacin (Ciloxan)	Gentamicin (Garamycin)
Ofloxacin (Ocuflox)	Neosporin (Neomycin combo)
Moxifloxacin (Vigamox)	
Gatifloxacin (Zymar)	

Source Tarabishy AB, et al. *Cleve Clin J Med*. 2008;75:507-512.

Click here for larger version of Table 3.

Several studies have compared treatment outcomes for pediatric patients receiving different topical antibiotics for acute conjunctivitis. Bremond and colleagues compared the efficacies of azithromycin and tobramycin in 150 patients with acute conjunctivitis.[24] The average age of the patients was 7 years, which is a much older population with acute bacterial conjunctivitis than customarily seen in routine pediatric practice. The principal pathogens identified included *H influenzae* (n = 22), staphylococcus species (n = 34), and *S pneumoniae* (n = 6). The clinical cure rates were 48% vs. 27% for the azithromycin and tobramycin groups, respectively, at 3 days ($P < .001$), but were similar after 9 days (80% vs. 82% for the azithromycin and tobramycin groups, respectively; not statistically significant). Limitations of this study included the relatively small sample size, the limited enrollment of younger children, and the

fact that few pathogens were recovered due to the small sample size. In addition, staphylococcal species are often commensals in eyes, and few patients had typical conjunctival pathogens.

A second study compared the effectiveness of bactericidal therapy with topical moxifloxacin 3 times daily vs. bacteriostatic therapy with polymyxin B/trimethoprim 4 times daily in 56 pediatric patients with conjunctivitis, most of whom were between 6 and 18 years of age.[22] At 48 hours, cure rates were 81% with moxifloxacin and 44% with polymyxin B/trimethoprim (P = .001), suggesting a more rapid early response with bactericidal treatment compared with bacteriostatic treatment. Limitations of this study included the enrollment of primarily older children, a very small sample size, and minimal differences in outcome at final end-of-treatment visit.

A third study compared besifloxacin with moxifloxacin in 1,161 patients aged 1 year and older (mean age, 31.6 ± 26.2 years).[25] Besifloxacin was noninferior to moxifloxacin for clinical resolution on day 5 (58.3% vs. 59.4%, respectively) and day 8 (84.5% vs. 84.0%, respectively) and for microbial eradication on day 5 (93.3% vs. 91.1%, respectively) and day 8 (87.3% vs. 84.7%).

Oral antibiotics may be helpful for patients with conjunctivitis-otitis syndrome. *H influenzae* is the causative pathogen in as many as 80% of these cases, and approximately 60% to 65% are ß-lactamase producers.[26] In most cases, conjunctivitis and otitis media are caused by the same pathogen.[26] Oral antibiotics with ß-lactamase stability are preferred such as cefdinir, amoxicillin/clavulanate, cefpodoxime, and cefixime. In contrast, drugs with poor ß-lactamase coverage should be avoided in these patients, including amoxicillin, azithromycin, cefprozil, and cefaclor. Trimethoprim/sulfa may also be reasonable, but it lacks adequate pneumococcal coverage.

Summary and Conclusions

In pediatric patients younger than 4 years of age, purulent discharge, rather than redness, is the most common sign of bacterial conjunctivitis, and H influenzae is the most common causative organism. The incidence of *S pneumoniae* infection increases with age, and routine PCV13 vaccination may prevent most cases of PNSP. As many as one-third of younger children with acute bacterial conjunctivitis have concomitant acute otitis media. A thorough ear, throat, and lung exam is important in children with acute bacterial conjunctivitis. Topical

therapy is warranted in most cases, and topical fluoroquinolones are more potent than other classes of topical agents. Cost and formulary restrictions may encourage clinicians to use polymyxin B/trimethoprim or neomycin combinations as first-line agents. Sulfa drugs, aminoglycosides, and erythromycin should not be used for the treatment of pediatric conjunctivitis. Azithromycin may be considered for patients with hypersensitivity reactions to other agents.

Discussion

Would you advocate the use of antibiotics in children younger than 12 months of age, even if most of them have not been approved for this age group?

Stan L. Block, MD, FAAP: I would argue that any of the antibiotics I discussed could be used in younger children despite the fact that most are not specifically approved for children who are younger than 1 year of age. With regard to safety issues with the fluoroquinolones, I think most clinicians are becoming more comfortable with the use of topical fluoroquinolones in children under the age of 12 months. Oral ciprofloxacin is approved for children older than 12 months of age for recurrent or refractory urinary tract infections, and its safety has not been an issue.

Please comment on the frequency of MRSA as a causative pathogen for bacterial conjunctivitis.

Block: MRSA is rare among the children who are typically seen in primary care — those with purulent discharge, rather than those with contacts, eye surgery, or similar conditions.

Sean P. Donahue, MD, PhD: I would say that MRSA is rare among patients in the community setting who are presenting to the primary care pediatrician's office. MRSA is observed somewhat more often with orbital signs or in patients with markedly red eye and minimal discharge. We did not really see MRSA around the eye 5 to 10 years ago. In the pediatrician's office or primary care, purulent discharge from an eye is probably not caused by MRSA. However, MRSA may be something to consider if conjunctivitis does not resolve.

Do your patients with preseptal or orbital cellulitis have MRSA very often?

Donahue: That is what we are seeing, including severe orbital cellulitis in patients who have few of the typical risk factors for orbital cellulitis. They may have a family member who had MRSA a few months ago.

Regarding preseptal cellulitis, we are observing MRSA not as often as we do with orbital cellulitis, but it is becoming a concern. These are children with typical bacterial conjunctivitis with purulent discharge in a relatively white eye.

Block: My contention would be that most nontraumatic preseptal periorbital cellulitis is pneumococcal despite PCV7/13 vaccination.

Donahue: We reported data on this approximately 8 to 10 years ago. We found that *H influenzae* type B was virtually eliminated by routine Hib vaccination in orbital cellulitis, although we still saw some in preseptal cellulitis. The nontypeable Haemophilus seems to be prominent in both preseptal and orbital patients, although we do not culture many patients because the majority responds to oral antibiotics, intravenous antibiotics, or intramuscular injections of antibiotics without the need to obtain a culture. These children usually do not have extensive sepsis.

How do the pathogens we see in children with conjunctivitis change with age?

Block: I think more staphylococcal infections are observed in children older than 5 to 7 years of age. In my practice, 90% to 95% of the patients I see with purulent discharge are younger than 3 years of age. Red eyes are more common in children older than 3 years, who are more likely to have staphylococcal infection or, less often, streptococcal infections, pneumococcus, or *H influenzae*. Pathogens become more diverse as children enter school, and gram-positive pathogens are more likely.

Which is more important, the end-of-treatment assessment or the 24- to 48-hour assessment?

Block: I think the critical time is the 2- to 4-day period, and many studies show differences when evaluated at those time points. Conjunctivitis will usually resolve eventually, but 7 days of purulent discharge and the risk of infecting other children are usually not acceptable for most parents, teachers, and daycare workers. Having that more rapid response is important.

Michael E. Pichichero, MD: When patients present with pink eye, I do not watch and wait. I administer a topical antibiotic.

Considering your observations from your own patients, the literature, and the types of pathogens that may be involved, what is your approach to first-line therapy of pediatric conjunctivitis?

Block: My first-line option is usually the polymyxin B/trimethoprim combination. In some cases, I may administer neomycin combinations. I never use amoxicillin for patients with concomitant acute otitis media, but will select either cefdinir or amoxicillin-clavulanate. I would expect a 70% to 80% cure rate with those options. For second-line therapy, I usually prescribe the fluoroquinolones. Which fluoroquinolone I choose depends on the patient's insurance status. For patients on Medicaid, we are required to use ofloxacin or ciprofloxacin for cost reasons. Options for patients not on Medicaid include broad-spectrum antibiotics such as levofloxacin, besifloxacin, or moxifloxacin. I do not implement tobramycin or gentamicin because we have published data showing that the MIC_{90} values for *H influenzae* and *S pneumoniae* were µg/mL and 16 µg/mL, respectively.[5] I avoid azithromycin except for true allergies to multiple agents.

Donahue: I usually start with gentamicin, which provides approximately 99% coverage for *H influenzae* and about 90% coverage for staphylococcus species, although streptococcus species are not well-covered.[27] The limited coverage of pneumococcal species may not be a significant issue, however, due to the availability of pneumococcal immunization. When choosing a second-line agent, I usually look at the treatment history to see what the patient has already received. Usually by the time they are referred to me they have been to a pediatrician and had 1 or 2 antibiotics and they have had conjunctivitis for 10 to 12 days. I typically reserve fluoroquinolones for more severe cases (ie, for those who have already had several antibiotics, or for cases where vision is threatened). I would usually choose a newer fluoroquinolone to avoid the possibility of resistance. Many of the patients I treat have some toxic conjunctivitis from medication or from allergic responses. For a patient with some purulent discharge, red eye, and light sensitivity, I may consider stopping the medications or replacing it with artificial tears.

Block: In a study that my colleagues and I published in which we examined the susceptibility of commonly encountered micro-organisms to different antibiotics, we found that the MIC_{90} for *H influenzae* was 8 µg/mL with

gentamicin/tobramycin vs. 1 µg/mL with polymyxin B/trimethoprim.[5] Although there may be differences in the antibiotic concentration delivered with different eye drop formulations, we felt that this greater susceptibility of *H influenzae* made polymyxin B/trimethoprim a reasonable option for first-line treatment.

When do you obtain cultures?

Block: I will obtain a culture for a small percentage of patients who fail first-line or second-line therapy and have an eye that appears severely affected. I obtain cultures for children younger than 2 weeks of age, or for children with any kind of periorbital cellulitis.

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