Antibiotic Therapy in Acute Conjunctivitis

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Current evidence indicates that topical antibiotic drops are overprescribed for acute conjunctivitis. Averting this trend of antibiotic overuse and misuse will require a joint effort between physicians, patients, and policymakers.

Acute conjunctivitis, a condition frequently encountered in both primary and eyecare settings, is estimated to affect six million Americans each year. The single most common cause of acute conjunctivitis—in both adults and children—is viral infection, predominantly caused by adenovirus. Usually, viral conjunctivitis is self-limiting and resolves without treatment in less than two weeks.

While the predominant form of acute conjunctivitis has a nonbacterial etiology, today’s physicians seem to have become exceedingly dependent on topical antibiotics in managing the disease. Most recently, a study using data from a large nationwide managed care network found that, of nearly 350,000 enrollees diagnosed with acute conjunctivitis from 2001 through 2014, more than half (58%) filled a prescription for topical antibiotics. The results confirm that antibiotic prescribing for conjunctivitis is commonplace in the US, raising the perplexing question about our current approach to acute conjunctivitis: with most of the cases being viral and little evidence to support the effectiveness of antibiotics, why are the rates of prescribing so high?

Diagnostic Ambiguity

The major driving force behind antibiotic prescribing is the inherent diagnostic uncertainty associated with conjunctivitis. Conjunctivitis, like other common predominantly viral upper respiratory tract infections, is a clinical diagnosis, and few diagnostic tests are available to help determine the underlying cause. The most common types of acute conjunctivitis are viral, bacterial, and allergic, which often produce a similar clinical picture: red eye (conjunctival inflammation), discharge, discomfort, irritation, and sometimes slight blurry vision. Unless there are other clinical symptoms or signs that are more specific, etiology is often not readily apparent (Figure 1).
Among the three types of conjunctivitis, allergic conjunctivitis is rather straightforward to diagnose because patients often have other typical allergy symptoms, such as itchy and puffy eyes, sneezing, and runny or stuffy nose. The presence of cold symptoms is likely an indication of viral infection, but in most cases, it is difficult to clinically distinguish bacterial from viral infection.

Many of us were traditionally taught that a unilateral infection is more likely bacterial. But that criterion is not exclusive—both bacterial and viral conjunctivitis can be unilateral or bilateral. It is also commonly thought that a bacterial etiology is more likely if there is purulent discharge, gluing of the eyelids, or both; but these symptoms can in fact occur in either type of infectious conjunctivitis and therefore do not reliably distinguish one from the other.

A rapid point-of-care immunoassay is available for detection of adenovirus, but it is not widely used in primary care practices, and recent studies have cast doubt on its sensitivity.4 Though several red-eye diagnostic algorithms exist, they are not commonly used in the US, and are not particularly helpful in differentiating between bacterial and viral conjunctivitis. The Edinburgh Red Eye Diagnostic Algorithm, for example, focuses on the diagnosis of more serious conditions like glaucoma and iritis and recommends antibiotic therapy for all cases of infectious conjunctivitis.6

Given this diagnostic uncertainty in patients with red eye and suspected infectious conjunctivitis, many physicians prescribe broad-spectrum antibiotics empirically just to “err on the side of safety.” The rationale is that antibiotic drops will be of benefit if the infection is bacterial, and even if it is not, they should cause little harm. The questions are: What is the treatment benefit of topical antibiotics in bacterial conjunctivitis? And are these topical antibiotics really as benign as we think they are?
Benefits vs Potential Risks

For bacterial conjunctivitis, treatment with topical antibiotics is presumed to speed the resolution of infection. Based on the available evidence, this beneficial effect does not appear to be substantial. A 2012 Cochrane review of 11 randomized, controlled trials involving 3,673 participants found that, compared with placebo, topical antibiotics modestly improved rates of clinical and microbiological remission. The relative risk ratio for clinical remission was 1.36 during days two to five and 1.21 during days six to ten, suggesting a fairly small—20% to 30%—increase in remission over several days.

Another notable finding of this review is that no patients in the placebo arms of these trials had any serious complications. By days six to ten, in fact, 41% of all who received placebo had resolved clinically. This result is in line with the notion that bacterial conjunctivitis in otherwise healthy adults is self-limiting. Most of the time, patients will show good clinical outcome without treatment—perhaps more slowly than with treatment, and with no evidence of serious harm. When a bacterial cause is less certain, as is often the case, the already small benefit of treatment becomes even more diluted. Indeed, bacterial infection is a relatively infrequent cause of acute conjunctivitis in adults. Bacterial conjunctivitis is more prevalent in the pediatric population, but like in adults it tends to be self limited.

If the value of topical antibiotics is debatable even for bacterial conjunctivitis, why prescribe at all? Obviously, prescription antibiotics add unnecessary costs—treating bacterial conjunctivitis alone costs an estimated $377 million to $857 million each year. Less obvious are the nonfinancial impacts. Through extensive studies on gut and skin microbes we have learned that antibiotic exposure influences the composition of human microbiota and promotes antimicrobial resistance and pathogenicity of bacteria. The eye has not been studied as much as other anatomical sites, but recent evidence suggests that repeated use of ophthalmic antibiotics can change the relative populations of ocular commensal species and select for resistant bacterial strains. The clinical implication of such disturbances to ocular microflora is unclear. The key unanswered question is: Do these disturbances constitute greater susceptibility to infections or other diseases?

Evidence-based Prescribing

In our opinion, antibiotics are rarely necessary to treat acute conjunctivitis. Allergic conjunctivitis is usually treatable with antihistamines, mast-cell stabilizers, and rarely with topical corticosteroids. For infectious cases, treatment is primarily supportive and consists of cold compresses and saline drops. Patients who wear contact lenses should be instructed to stop wearing their lenses until resolution of the infection; those who wear makeup should be advised to avoid eye liner or mascara. Topical corticosteroids are thought to be beneficial for patients with decreased vision and severe photophobia from subepithelial corneal infiltrates, but these agents should be used judiciously—particularly in the primary care setting—because they may prolong viral shedding and can lead to worsening of herpes simplex virus (HSV) infection, if present.

This is not to say antibiotics are off limits in the treatment of acute conjunctivitis. Rather, antibiotic therapy should be considered in patients at particular risk for complications of bacterial infection, who are likely to benefit most from treatment. Some high-risk examples include patients who have difficulty in closing their eyelids, patients with diabetes, patients who wear contact lenses, and, rarely seen in primary care, patients with preexisting eye disease or recent eye surgery.

One way physicians can improve the management of acute conjunctivitis is to provide better counseling on an individual level, educating patients on the pros and cons of antibiotics for this self-limiting condition. Once again, the benefit is quite small, even for bacterial infection, whereas the adverse consequences include cost and presumably undesired changes to the ocular microbiota. Meanwhile, it is important for patients to understand that, if they do not use antibiotics, the risk of serious outcome is in fact extremely low. There is a common perception that conjunctivitis is a condition that needs to be treated. Some patients have become so accustomed to an antibiotic prescription for conjunctivitis that they expect to be treated and would otherwise feel at risk for ocular damage.

In many ways this is parallel to what has happened with antimicrobials for conditions such as the common cold and sinusitis: a long process of re-educating patients and their families that antimicrobial therapy is often of little benefit. Only several years ago, primary care physicians were using Tamiflu (oseltamivir phosphate) to treat influenza in...
otherwise healthy patients. Now, thanks to a major shift in thinking, this antiviral agent is reserved only for patients at high risk of complications. If a similar approach were to be adopted for the treatment of conjunctivitis, prescription rates would decrease substantially.

**A Multifaceted Approach**

Changing patients’ perception is not the only hurdle to overcome in curbing antibiotic overprescribing for conjunctivitis. In some states, patients affected by the condition are required to be treated with an antibiotic drop for at least 24 hours before they can return to work or school.13,14 Presumably intended to prevent transmission, such policies are not evidence-based. This requirement of antibiotic therapy can cause patients and parents major inconvenience, and is a driving force behind antibiotic prescription. Those states without statewide rules to exclude children with conjunctivitis also tend to have lower rates of antibiotic prescribing; in contrast, the prescribing rates are much higher in states that have stricter rules.

Policies are generally difficult to change. To modify state- and school-specific policies regarding the requirement for antibiotic treatment, organizations like state health departments, school districts, and childcare centers must reexamine evidence and weigh the benefits against the potential risks. Because the main concern here is the spread of infectious disease, perhaps it is possible to compare teacher absentee rates due to red eye between schools that have the exclusion policy in place and those that do not.

Ultimately, it is up to physicians to adjust their prescribing habits to reduce antibiotic usage, and measures can be taken to encourage evidence-based prescribing for acute conjunctivitis. Because financial incentives have tremendous impact on prescribing practices, a shift to reimbursements based on appropriate use of topical ophthalmic antibiotics, rather than the number of patients seen, could have an immediate effect on prescribing.

**REFERENCES**


Compounded Drugs: Risks and Benefits

Charles Leiter, PharmD

In certain situations, compounded drugs are essential tools but their use is not without risk. Being aware of differences among types of compounding pharmacies, and practicing due diligence in interactions with such facilities, help to ensure optimal patient outcomes.

Pharmacy compounding is the preparation of clinician-prescribed, customized medications that are not available commercially to address individual patient diagnoses. Ophthalmic examples include preservative-free drops for patients allergic to commonly used preservatives, or antibiotics with greater potency than those that are commercially available. Topical ophthalmic tobramycin, for example, is typically manufactured as a 0.3% solution (3 mg/mL), whereas the compounded product may be up to five times more potent, at 12 to 15 mg/mL.

Vancomycin and the cephalosporins are commonly compounded for ophthalmic use, as topical formulations to treat ocular surface infections or for intraocular injection to treat endophthalmitis. The cationic antiseptics chlorhexidine digluconate and polyhexamethylene biguanide (also used to sanitize swimming pools) have been compounded to treat *Acanthamoeba* keratitis. The cysts associated with this condition are responsive only to a limited number of therapies, including these antiseptics; there are no commercially available treatments.1-3

The range and use of compounded drugs for intraocular injection have increased exponentially over the last 10 to 15 years, with one large compounding company reporting that their injectable combination antibiotic and steroid formulations have been dispensed over half a million times in a 3-year period.4,5 Increased adoption by cataract surgeons of intraoperative antibiotic prophylaxis, and requests from retinal specialists for compounded bevacizumab to treat age-related macular degeneration (AMD), have contributed to the growth of this category.6

Risky Business

Compounded drugs are not approved by the FDA, even though they may be prepared in an FDA-approved facility. Inherent risks of compounded drugs may include product contamination (with bacteria, fungi, endotoxins, or even viruses); tonicity, osmolality, and pH being unsuitable for the eye; or reduced antibiotic activity by an adjustment in pH.7 Recently, the FDA received adverse event reports concerning at least 43 patients in Dallas, Texas who had received intravitreal injections of triamcinolone and moxifloxacin after cataract surgery. Symptoms included vision impairment, including decreased night vision and color perception, and many were not exhibited until 1-month postoperatively. Upon examination, patients were found to have diminished vision and macular edema and, after 5 months, a number of patients still exhibited significant visual acuity and visual field impairment.8

Bacterial contamination of off-label bevacizumab produced in compounding pharmacies has also resulted in endophthalmitis outbreaks.6 These examples highlight the significant responsibility of compounding companies to ensure the manufacture of safe medications for patients, particularly where vision is at stake.

Steps to Reduce Risk

The activities of compounding pharmacies came under scrutiny following a 2012 nationwide outbreak of fungal meningitis traced to steroidal injections prepared by one compounding pharmacy. This event led to the development of the Drug Quality and Security Act of 2014.9 Prior to this, traditional compounding companies acted under Section 503A of the Federal Food, Drug, and Cosmetic Act, which distinguished them from drug manufacturers and largely exempted them from further FDA regulations.9

The new Drug Quality and Security Act adds to the provisions of Section 503A for compounding pharmacies with laws under Section 503B. These provide an optional new licensing path for sterile compounders to be called “outsourcing facilities” and adhere to more rigorous FDA standards.9 Traditional compounders (operating under Section 503A) are subject to only state compounding quality standards, and some states do not mandate compliance with the US Pharmacopeia Chapter 797 on sterile compounding.9 Conversely, outsourcing facilities operating under Section 503B must comply with current Good Manufacturing Practices (cGMP), provide production and sales figures to the FDA, and be inspected by the FDA.9 In general, drugs made to cGMP standards are of higher quality.
quality, and both the facilities and the products are subjected to greater testing. Currently there are approximately 70 FDA-approved outsourcing facilities in the US, which represent an important option for healthcare providers keen to reduce risks associated with the use of compounded drugs.10

When purchasing compounded antibiotics, healthcare providers are advised to check the drug certificate of analysis (COA), as well as reports on drug stability, antibiotic culture and sensitivity, and facility testing, licensure, and information on the FDA website. The FDA maintains lists of registered Section 503B outsourcing facilities, as well as compounding inspections, recalls, warning letters, and other actions relating to objectionable conditions.10,11

In general, it is important that healthcare providers practice due diligence when sourcing compounded medicines. Often, for example, products purchased from a Section 503A compounding pharmacy will have specific storage instructions and a very short shelf life, since they may be preservative free and not tested for stability and degradation. As such, strict adherence to storage instructions is recommended. When ordering antibiotics for patients with penicillin allergies, as another example, it is wise to ascertain if the compounding facility prepares β-lactam antibodies in a separate room and, in the case of combination drugs, whether the ingredients have been tested for compatibility and stability together. At the clinic, it is advisable to keep all documentation relating to the compounded drug (source, batch, COA) with the patient’s profile in case complications arise.

Update on Ophthalmic Antibiotic Resistance

An additional risk associated with using antibiotics (whether pharmacy compounded or not) is the emergence of antibiotic-resistant pathogens. The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study is the only nationwide antibiotic resistance surveillance program for ocular isolates currently ongoing in the US.12 Recent updates from ARMOR and the Bascom Palmer Eye Institute in Miami provide information on the frequency of pathogens in ocular isolates and antibiotic resistance trends.13-15 At present, the most prevalent isolates from bacterial keratitis are Pseudomonas aeruginosa, Staphylococcus aureus, and Serratia marcescens; in conjunctivitis, the top isolates are S. aureus, Haemophilus species, P. aeruginosa, Streptococcus pneumoniae, and Streptococcus viridans group; and in endophthalmitis, the top isolates are Staphylococcus epidermidis (a coagulase-negative staphylococci), S. viridans group, S. aureus, S. pneumoniae, and P. aeruginosa.14,15 Both ARMOR and the Miami data concur on the continued high rates of fluoroquinolone and nonsusceptibility for S. aureus and coagulase-negative staphylococci (whether they were methicillin susceptible or resistant) and patterns of multi-drug resistant bacteria.15 There is also the emerging resistant of S. pneumoniae, S. viridans group, haemophilus species and P. aeruginosa.13 Vancomycin (only available from compounding pharmacies) susceptibility remains for most isolates and is considered suitable for infections resistant to other antibiotics.14,15 There are significant differences in fluoroquinolone and aminoglycoside coverage for a coagulase-negative staphylococci, S. aureus and P. aeruginosa between the ARMOR and Miami data, suggesting that knowledge of local area ocular bacterial susceptibility and resistance patterns is important as well as the use of laboratories to target the pathogen appropriately.15,16 In these circumstances, compounding pharmacies have an essential role in providing the desired antibiotic or antibiotic concentration in a suitable formulation to combat these ocular bacterial infections.

Future of Compounding

In the future, compounding pharmacies will continue to support the growing clinical need to improve patient adherence, since the reality is that ocular antibiotics are too often administered using an incorrect technique and/or at the incorrect frequency.17,18 Combination drops and intraoperative delivery of prophylactic antibiotics are helping to mitigate this challenge. In the future, novel delivery methods may also play a role in limiting the role of patient compliance in preventing or treating ocular infection.4,9,20

The preparation of compounded ocular medications in accordance with rigorous cGMP standards, as is the case with the Section 503B-governed outsourcing facilities, has been an important step toward the safe use of compounded drugs. However, this comes at an increased cost, requiring more resources to build and operate such facilities, adequately test and validate drugs, train staff, and keep records. In consequence, the preparation of one-off or small batch drugs may become more expensive, perhaps even prohibitively so, and thus compounding companies may limit their range of products. This would most certainly have a negative impact on those patients requiring customized medications, in the absence of a commercially available product, to treat their condition. The future may see far fewer, but larger, outsourcing facilities to provide compounded medications not only in the US, but perhaps worldwide.

Charles Leiter, PharmD, is the former CEO and chairman of the board of Leiter’s. He is a stock shareholder for Leiter’s. Medical writer Bronwyn E. Brown, PhD, of Markey Medical Consulting Pty Ltd, assisted in the preparation of this manuscript.

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1. Which of the following is NOT a major factor in the use of antibiotics for acute conjunctivitis?
   A. The lack of diagnostic certainty
   B. The perception that antibiotic drops do not cause harm
   C. The tie between prescriptions and reimbursement
   D. The demand for treatment by patients

2. Healthcare providers can practice due diligence when using compounded antibiotics by:
   A. Checking the compounding pharmacy’s registration
   B. Checking and keeping the drug’s COA and other reports
   C. Using the FDA website to search for related alerts or reports
   D. All of the above

3. Antibiotics may influence human microbiota in which of the following ways?
   A. Alter commensal species
   B. Select for resistant strains
   C. Increase pathogenicity of bacteria
   D. All of the above

4. Which of the following statements is true about bacterial conjunctivitis?
   A. It is more common in adults than in children
   B. It is far more common than other types of conjunctivitis in children
   C. It does not require antibiotic therapy in most cases
   D. It is likely to cause serious complications without treatment

5. Ophthalmic antibiotic resistance trends:
   A. Are listed on the FDA website
   B. Are tracked by the ARMOR study group
   C. Are the same all over the US
   D. Are not important in developed countries

6. Incorrectly compounded antibiotics:
   A. May have the wrong pH, tonicity, or osmolality
   B. Could contain bacterial contamination
   C. Both A and B
   D. Might still be well tolerated by patients, but ineffective

7. The most common cause of acute infectious conjunctivitis is:
   A. Adenovirus
   B. HSV
   C. Staphylococcus epidermidis
   D. H. influenzae

8. According to Drs. Keen and Thompson, topical antibiotics are most beneficial for acute conjunctivitis in which of the following patients?
   A. Patients with diabetes
   B. Patients with recent ocular surgery
   C. Patients wearing contact lenses
   D. All of the above

9. Compounding pharmacies, known as outsourcing facilities, under Section 503B:
   A. Must be registered with the FDA and use cGMP
   B. Must be registered with the appropriate state board
   C. Have optional registration
   D. Have the same registration as Section 503A compounding pharmacies

10. Compounded antibiotic drugs:
    A. Must be stored at the correct temperature
    B. Must be used before their expiration dates
    C. May be preservative free
    D. All of the above