Atypical Organisms in Postoperative Infections

Virender Singh Sangwan, MD

The infrequency of atypical postoperative infection makes awareness of the signs and symptoms all the more critical.

Atypical postoperative infections are estimated to occur at a rate of 2 to 5 per 10,000 ocular surgeries, comprising roughly 7.2% of all ocular postoperative infections. Although the incidence is low, the sheer volume of intraocular surgery in the developed world—upwards of 4,000 cataract surgeries per million persons per year—makes atypical infection an important postoperative complication and one that clinicians should be prepared to investigate in any patient with an unusual postoperative course.

What is Typical?

Several endophthalmitis reviews make distinction between typical and atypical postoperative infections. Generally speaking, "typical" infections present within the first 6 weeks following intraocular surgery (acute-onset) and are caused by common ocular and periorbital flora, namely Gram-positive bacteria such as coagulase-negative Staphylococcus, Staphylococcus aureus, and Streptococcus species. Presentation is typically overt; a majority of patients complain of moderate to severe eye pain, conjunctival injection, and/or decreased visual acuity. Many also have eyelid edema. Hypopyon, which may also be present with atypical infection, is more commonly associated with typical infection.

What distinguishes atypical infections as a group is an indolent course—due to lower virulence and less toxic reactions by the retina and macula. Often they are mistaken for noninfectious conditions (Figure 1). Because of their slow progression, atypical postoperative infections commonly present 6 or more weeks after surgery (delayed-onset). And the presentation is less remarkable: vision is less severely impacted, complaints of photophobia, pain and redness are generally less pronounced. Topical corticosteroids tend to mask the symptoms, which then flare when...
corticosteroids are stopped and quiet down when restarted. Improvement on corticosteroids can reinforce an erroneous impression of chronic low-grade inflammatory uveitis, when in fact, an atypical intraocular infection is smoldering under the radar.

Common Atypicals

In postoperative ocular infection, *atypical* describes a range of microorganisms, from bacteria to mycobacteria to fungi, and varies by geography. The most common atypical pathogen responsible for delayed onset postoperative infection is *Propionibacterium acnes*, a periocular skin and conjunctiva commensal.1,4 In one review of delayed postoperative endophthalmitis cases, the hallmark of *P. acnes* infection—a white capsular plaque—was observed in 28.5% of cases. (Note: A white capsular plaque may also be observed in infections caused by other pathogen as well.)3 Other atypical pathogens include fungi, tubercular and nontubercular mycobacteria, and less common bacterial species including *Enterococcus, Bacillus,* and *Serratia* species. Fungal endophthalmitis, including disease caused by *Candida, Aspergillus, Fusarium,* and *Cryptococcus,* and others, is far more common in tropical climates, such as parts of Asia, Africa, South America, and certainly, where I practice in India, accounting for up to a quarter of causative pathogens in some series.2 The clinical picture in these cases is variable and may bear a strong resemblance to bacterial endophthalmitis.5 Fluffy white deposits that appear like a string of pearls within the capsule are characteristic of some forms of fungal infection.

FACULTY AND DISCLOSURE STATEMENTS

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the posterior capsule or on the anterior hyaloid membrane, similar to lesions associated with *P. acnes*. Mycobacterium, *tuberculosis* is a very rare but severe cause of postoperative infection. In the mid-2000s, atypical mycobacteria were reported as the cause in a surprisingly large proportion of cases of post-LASIK keratitis. However, after several years the proportion of post-LASIK keratitis caused by mycobacteria decreased markedly, possibly as a result of more widespread use of later generation fluoroquinolones to which many mycobacterial species are susceptible. Better surgical techniques that have decreased instrumentation and surgery time have also likely contributed to declining rates of postoperative infection with mycobacteria. Although mycobacterium-associated infections have declined, the incidence of postoperative infection with methicillin-resistant *S. aureus*—increasingly resistant to fluoroquinolones—has coincidentally risen.

**Postoperative Infection Risk**

Patient, procedural, or environment factors may increase risk of atypical postoperative infection. Patients with immunosuppression or comorbidities such as uncontrolled diabetes mellitus, malignancy, cardiac disease, or renal failure are at increased risk, as are those who abuse intravenous drugs or have impaired personal hygiene. Surgeries that are prolonged, complicated for any reason, or involve a breach in sterility protocol also increase infection risk.

**Timely Diagnosis**

The longer it takes to diagnose a postoperative infection of any kind, the worse the patient experience and potential outcome. A careful clinician will not miss the rare case of atypical postoperative infection if she or he takes these three steps:

**Suspect** As discussed above, atypical postoperative infections can closely mimic typical infections as well as noninfectious processes. One of the most common mistakes I see among clinicians is not considering the possibility of infection in a postoperative patient with mild, steroid-responsive or unusual complaints. When a patient’s symptoms are initially—and then repeatedly—attributed to a certain diagnosis (eg, uveitis), the patient and medical team can become attached or cognitively “anchored” to that diagnosis and lose sight of other considerations, delaying the diagnosis. An example of how the “anchoring heuristic” can contribute to a delayed diagnosis and considerable patient distress is presented below.

Operating surgeons should be aware of mental reasoning traps that introduce bias to their own logic and entertain alternative diagnoses, including infection, when patients have a questionable postoperative course or unusual clinical appearance.

**Collaborate** Even in the course of a long career, most surgeons will not have an opportunity to see very many atypical postoperative infections—they are too rare and there are too many types. Luckily, they do not have to navigate this territory alone. In the best interest of the patient, clinicians should not hesitate to call in an experienced colleague who was not a part of the surgical team to be of assistance.

**Test** Increasing availability of reverse-transcriptase polymerase chain reaction has made identifying slow-growing atypical pathogens far easier. When collecting specimens, submit tissue for both routine microbiologic and molecular testing to cover a range of likely and less likely pathogens.

**A Parable**

Several months ago, a retired psychologist underwent cataract surgery at another institution and subsequently developed mild, but unremitting conjunctival injection and photophobia. She sought out numerous surgeons in Bombay, where she lived, and elsewhere, each of whom told her that she had inflammatory uveitis. One of the surgeons referred her to me; she came in expecting me to confirm the diagnosis and find a way to resolve her uveitis symptoms.

I reviewed her history and performed an examination and suspected not uveitis but an atypical infection. After discussing it with a colleague, I suggested a course of action to obtain ocular material for diagnostic testing. Naturally she was incredulous and highly resistant to the plan I proposed. She had seen perhaps ten other doctors and my diagnosis was the outlier! Later she went through with the operation in Bombay; when her lab results came back, she called and informed me that...
she did in fact have an atypical infection—*P. acnes* endophthalmitis—and was grateful for my assessment.

I share this case synopsis to underscore the importance of staying suspicious, keeping an open mind, and letting go of bias that can be introduced by prior clinical assessments, patients’ beliefs, and a very natural desire to want the worst not to be true. Patients crave answers; but sometimes our job is to help patients hang out with uncertainty while appropriate diagnostic considerations are being explored.

**Conclusion**

Vigilance on the part of the postsurgical care team and generous use of colleague consultation and molecular testing will help diminish delays in diagnosis and improve outcomes for patients with atypical postoperative infection.

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**REFERENCES**

The Quinolone Antibiotics: Past, Present, and Future

Christopher N. Tu, MD

Excessive antibiotic use inevitably creates selection pressures that favor the rise of resistant strains. Having for years dominated the management of ocular infection, the quinolones are now challenged by a trend of rising resistance, most notably in the rise of methicillin-resistant staphylococci. While the bacteria may win out in the long run, shrewd use of the quinolone antibiotics should extend their clinical utility.

Nalidixic acid, the first quinolone antibiotic, was discovered accidentally in 1962 by George Lesher and coworkers while they were working on the synthesis of the antimalarial drug chloroquine. Nalidixic acid had modest efficacy against gram-negative bacteria and was used for the treatment of urinary tract infections. Since then, ongoing modifications to the chemical structure of the quinolone backbone has led to the development of a group of quinolone compounds, that has given us a second, third, and fourth generation of fluoroquinolones (Figure 1).

Fluoroquinolones, quinolones in which a fluorine atom is added to the core ring structure, are generally broad spectrum and make up the majority of quinolones in clinical use today. These drugs work by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, enzymes essential for replication and transcription of bacterial DNA. This mechanism of action makes the fluoroquinolones bactericidal.

Ophthalmic fluoroquinolones, including both the older generations (ciprofloxacin, ofloxacin) and the newer fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin, and besifloxacin), are now the most frequently used antibiotics for both the prevention and treatment of ocular infection. But, like their systemic counterparts, these agents are faced with a rising tide of bacterial resistance that poses a serious threat to our ability to treat infection and has brought the future role of the fluoroquinolones into question.

The Evolution of Quinolones

The determination of quinolone “generations” has been somewhat arbitrary and no doubt influenced by marketing as well as scientific considerations. Nonetheless, it is fair to say that, in general, the higher the generation, the broader the spectrum of activity and the better the pharmacokinetic properties.

Extending coverage to a wider range of organisms is a major goal of antibiotic development. For quinolones, the goal has been to expand gram-positive coverage without losing potency against gram-negative bacteria. The newer generation fluoroquinolones cover a variety of common pathogens, including gram-positive, gram-negative, and anaerobic bacteria. The most recent fluoroquinolones also tend to possess greater potency and longer elimination half-life.

Structural Modifications

Unlike some older antibiotic classes that were natural byproducts of living organisms, the quinolones are completely synthetic products. By changing substituents to the quinolone backbone, it has been possible to alter the antimicrobial activity and metabolic properties of these antibiotics—in effect, creating designer drugs. Although limited by the possibility of creating unwanted side effects, structural modifications have been very successful in improving quinolone potency and efficacy and, thus, driving forward their evolution as

Figure 1 Structure of quinolones and (as denoted by –F) fluoroquinolones.
an antibiotic class.

A few of the key substitutions include those at positions C-6, C-7, and C-8. The addition of a fluorine atom at position C-6 increased topoisomerase II activity and gave the quinolones greater ability to penetrate bacterial cells. The fluorine substitution also increased activity against staphylococci. At position C-7, the addition of a piperazine ring, a 6-member organic ring with 2 nitrogen, resulted in enhanced gram-negative coverage and enabled increased activity against species of staphylococci and *Pseudomonas*. Alkylation (addition of an R-group made up of carbon and hydrogen atoms, such as a methyl group) of the C-7 ring, on the other hand, provided greater activity against gram-positive bacteria and increased elimination half-life.

Modifications at the C-8 position helped in achieving some desirable characteristics. The C-8 methoxy-fluoroquinolones (gatifloxacin and moxifloxacin) have a methoxy substituent (an oxygen connected to a methyl group) at the C-8 position and, consequently, enhanced effect on topoisomerases II and IV and increased activity against gram-positive bacteria.

Beslfloxacin, the newest member of the class, is a “chloro-fluoroquinolone” thanks to the substitution of a chlorine atom at the C-8 position. Developed specifically for ophthalmic use, beslfloxacin has balanced activity, inhibiting both topoisomerase II and topoisomerase IV. The addition of a second halogen to the quinolone molecule further broadens the drug’s spectrum of coverage and makes it highly potent against gram-positive bacteria.

**Advantage of Topical Application**

The quinolones, and later the fluoroquinolones, have been associated with severe systemic side effects, such as photosensitivity, central nervous system toxicity, and arrhythmia. More recently, they have been linked to tendon rupture, particularly in older patients and those who take corticosteroids. Such safety concerns have resulted in the removal of a number of potential quinolone agents from development; and some marketed drugs have been withdrawn. Systemic gatifloxacin, for example, is no longer on the market because it causes hypoglycemia and other diabetic complications. And sparfloxacin, a systemic fluoroquinolone, can cause phototoxicity and arrhythmia. It is unavailable in the US and Canada.

Topical fluoroquinolones—even some that can’t be used systemically—are generally safe and well tolerated, without the toxicity seen in some of their systemic counterparts. Relatively small amounts of ophthalmic antibiotic can be used to achieve high local drug concentrations at the infection site—without systemic consequences. Thus, some compounds that are too toxic to be used systemically can be safely used as topical ophthalmic agents. Gatifloxacin, for instance, is safe in its ophthalmic form, although the systemic drug has been taken off the US market.

**Role in Ophthalmology**

Following the introduction of ciprofloxacin 0.3% and ofloxacin 0.3%, clinical use of the ophthalmic fluoroquinolones increased rapidly. In large part this has been the result of the continuous expansion of the fluoroquinolones’ spectrum of coverage. Topical fluoroquinolones are most commonly prescribed as off-labeled use to prevent postoperative infection. This is critical in ophthalmology because both gram-positive and gram-negative bacteria can cause infection. Furthermore, when a patient presents with an infection, such as conjunctivitis or a cornea ulcer, the causative organism can’t be known until it has been identified, generally by culturing. Culture, however, requires time, but corneal infections can progress rapidly. For small peripheral corneal ulcers, empiric treatment with a broad-spectrum fluoroquinolone is usually safe and effective. Many ophthalmologists still recommend the use of fortified antibiotics for severe sight-threatening corneal ulcers.

Thanks to their broad spectrum of activity, current-generation fluoroquinolones allow physicians to cover nearly the full spectrum of common bacterial ocular pathogens with a single drug, making them an attractive choice for empirical treatment. The newer fluoroquinolones can also achieve effective concentrations in the tear film, the conjunctiva, the cornea, and, in some cases, the aqueous humor.

Other beneficial properties of fluoroquinolones that have contributed to their popularity in ophthalmology include excellent clinical efficacy, fast killing time, and ready availability without compounding. Additionally, fluoroquinolone drops are more comfortable than many other topical ocular antibiotics; and it is rare for patients to have allergic or other adverse reactions, such as inflammation or hyperemia. Perhaps the best known side effect of ophthalmic fluoroquinolones is ciprofloxacin’s tendency to cause benign white deposits on the cornea in patients with epithelial defects. While in vitro studies have suggested that fluoroquinolones have at least the potential to cause epithelial toxicity on the ocular surface, the clinical relevance of those findings remains controversial.

With little need to worry about severe systemic or local toxicities, ophthalmic fluoroquinolones can be applied frequently and at high concentrations to achieve high levels on the ocular surface. For concentration-dependent agents like fluoroquinolones, high concentration at the infection site implies more efficient killing and greater clinical potency.

**Considerations in Drug Selection**

Although the newer fluoroquinolones have improved significantly in terms of potency and spectrum of activity, they do not entirely replace the older generation agents, which still play an important role in the management of ocular infection. Generic ciprofloxacin and ofloxacin can be cost-effective choices for some patients; and, under certain circumstances, the older genera-
tion fluoroquinolones may even be more effective.

Because potency and broad spectrum coverage are critical requirements for agents selected for empirical therapy, fourth-generation fluoroquinolones remain the agents of choice for that application. However, once a pathogen has been identified, another drug may be selected. For example, if one is dealing with a gram-negative bacterium like Pseudomonas aeruginosa, a second-generation fluoroquinolone may be the most effective agent available thanks to its excellent gram-negative activity.

The Threat of Resistance

In recent years, surveillance studies have found a notable increase in the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE), pathogens that are capable of causing severe ocular infections but which have reduced susceptibility to commonly used antimicrobials, including the fluoroquinolones.8-10 The widespread clinical use of fluoroquinolones provides one explanation for increasing bacterial resistance, since extensive use of antibiotics selects for resistant organisms. Massive overuse of fluoroquinolones in the raising of poultry is another source of resistant organisms. The degree to which a drug is likely to provoke resistance is also related to its mechanism of action. Fluoroquinolones that offer balanced inhibition of both topoisomerases should be less prone to resistance than agents that have greater activity against one topoisomerase, because, in theory, with balanced activity a bacterium must acquire two mutations to become resistant.11,12

One major advantage that topical antibiotics have over systemic medications is the level of local drug concentration. Whether or not an organism is considered resistant is based on systemic serum drug level. There is no standard for testing drug resistance for ocular infections. Therefore, resistance can be overcome by frequent topical dosing of the medications such that the drug concentration is above the minimal inhibitory concentration.

It is hoped that the newer generation fluoroquinolones, particularly those that, like besifloxacin, have never been used in systemic medicine, will be able to circumvent the quick development of resistance that took place with earlier generation agents. Nonetheless, it is likely only a matter of time before the bacteria develop resistance to all these agents.

Looking Forward

In ophthalmology, one potential approach to counter increasing MRSA and fluoroquinolone resistance is to expand the antibiotic pipeline by developing ophthalmic preparations of current systemic agents. Fortified antibiotics are already being used to treat patients who suffer serious ocular infections, but they have to be compounded and are not commercially available.

Tigecycline, a later-generation tetracycline that has good coverage of both gram-positive and gram-negative bacteria, including MRSA, is one systemic agent that could be considered for future ophthalmic use. The class of glycopeptide antibiotics, which includes vancomycin and daptomycin, offers additional potential candidates. Covering gram-positive bacteria—including MRSA—but not gram-negatives, the glycopeptides could be used in combination with a second antibiotic with gram-negative coverage. Most recently, oritavancin, dalbavancin, and tedizolid received FDA approval for the treatment of skin infections caused by MRSA.

Bringing a new antibiotic to market takes a tremendous research and development effort that spans many years and consumes millions of dollars. Until the emergence of novel agents that are effective against MRSA, the best strategy for preventing resistance selection and protecting the clinical effectiveness of fluoroquinolones is appropriate antibiotic use. Clinicians should avoid unnecessary use, and, whenever fluoroquinolones are used, they should be dosed frequently and at the highest concentration possible. Antibiotics should never be tapered.

REFERENCES

1. The estimated incidence of atypical infection as a complication of intraocular surgery is approximately:
   A. 2 to 5 in 10,000 surgeries
   B. 5 in 1000 surgeries
   C. 7% of surgeries
   D. None of the above

2. Which of the following steps would be helpful in preventing development of bacterial resistance to fluoroquinolones?
   A. Avoid overuse of fluoroquinolones
   B. Use higher drug concentrations
   C. More frequent dosing
   D. All of the above

3. Which of the following is NOT a risk factor for atypical postoperative infection?
   A. Uncontrolled diabetes
   B. IV drug abuse
   C. Prolonged surgical procedure
   D. Surgery performed in Canada

4. Fluoroquinolone resistance has grown in parallel with the rise of:
   A. Methicillin-resistant Staphylococcus aureus
   B. Methicillin-susceptible Staphylococcus aureus
   C. Methicillin-susceptible Staphylococcus epidermidis
   D. Both A and B

5. Which of the following properties has NOT been associated with topical ocular fluoroquinolones?
   A. Activity against common ocular pathogens
   B. High potency
   C. Rapid bacterial killing
   D. Severe ocular toxicity

6. Compared to “typical infections” atypical infections tend to:
   A. Cause more severe visual complaints
   B. Cause greater pain and visual impairment
   C. Have earlier onset
   D. Are more easily mistaken for noninfectious inflammatory conditions

7. The quinolone antibiotics kill by:
   A. Disrupting the replication of bacterial DNA
   B. Blocking bacterial protein synthesis
   C. Interfering with bacterial cell wall synthesis
   D. All of the above

8. As experienced within the medical profession, which of the following best describe(s) the phenomenon of anchoring?
   A. Anticipation of the worst possible outcome
   B. Mental attachment to an initial answer or diagnosis
   C. Cognitive shortcut in reasoning
   D. Both B and C

9. In the context of postoperative infection, which of the following is NOT an atypical causative organism?
   A. Propionibacterium acne
   B. Staphylococcus aureus
   C. Candida albicans
   D. Aspergillus niger

10. Fluoroquinolones with enhanced activity against gram-positive bacteria include:
    A. Ofloxacin, gatifloxacin, and moxifloxacin
    B. Gatifloxacin, moxifloxacin, and besifloxacin
    C. Ciprofloxacin, ofloxacin, and moxifloxacin
    D. Ciprofloxacin, ofloxacin, and besifloxacin

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