The increasing problem of antibiotic resistance

There is nothing that a good defense cannot beat a better offense.

Bobby Knight

The new generation of fluoroquinolones has gained widespread use in the prophylaxis of endophthalmitis and postoperative infections in both cataract and refractive surgeries. With older fluoroquinolones such as ciprofloxacin and ofloxacin, a marked increase in the resistance of many gram-positive bacteria was seen, including coagulase-negative *Staphylococcus*, which accounts for most cases of endophthalmitis following cataract surgery. The so-called fourth-generation fluoroquinolones gatifloxacin and moxifloxacin have an enhanced spectrum of activity against many bacteria due to a fluorine substitution at the C6 position on the drug backbone, as well as a methoxy group at the C8 position. These new agents gain their increased antibacterial activity from the formation of complexes with 2 enzymes that are critical to the ability of bacteria to super coil their DNA and induce cell death or apoptosis: DNA gyrase and topoisomerase IV.

The alterations in the structure of the fourth-generation fluoroquinolones have enhanced their spectrum of activity against many gram-positive bacteria, especially compared with the spectrum of older generations of fluoroquinolones. The fourth-generation agents seem to maintain the gram-negative coverage found in early generations and are also effective against other types of organisms, especially atypical mycobacteria, that are sometimes noted following refractive surgery. It was generally thought that the fourth-generation fluoroquinolones would reduce the risk for postoperative endophthalmitis following cataract surgery as well as for postsurgical infectious keratitis.

Unfortunately, resistance has again reared its head regarding prophylactic antibiotic treatments. Similar to the issue of offensive and defensive weapons in warfare, the increase in bacterial resistance to an antibiotic and the subsequent need for a stronger or more potent antibiotic to treat the bacteria is an ongoing battle. The example of simple roadside explosives leading to the need for armor on military vehicles is an appropriate analogy. The increasing use of armor in defense of simple roadside explosives leads to the development of shaped projectile explosives, which then require more cumbersome and expensive redesign of armored vehicles to resist the new weapons. Bacteria have the ability to evolve rapidly and develop mechanisms for resistance to more elaborate and expensive antibiotic agents, which leads to the need to develop even more sophisticated antibiotic agents.

In addition to the development of resistance to one type of antibiotic, changes in bacteria may cross over and lead to simultaneous resistance to multiple agents. A classic example is the development of methicillin-resistant *Staphylococcus aureus* (MRSA). The MRSA bacteria are now showing multi-drug resistance, with high levels of resistance to older and newer fluoroquinolones. The ocular Tracking Resistance in the US Today (TRUST) program monitors trends in antibiotic resistance with susceptibility data. This ocular TRUST program has confirmed that MRSA shows high-level resistance to fluoroquinolones, including the latest generation.

Because fluoroquinolones act by inhibiting DNA gyrase and topoisomerase IV, the enzymes involved in bacterial DNA synthesis, bacterial resistance to these antibiotics can develop through alteration in the actual target enzyme or in access to the target enzymes. These alterations can include mutations that develop in the DNA gyrase itself or mutations in topoisomerase IV, which have been noted to occur in fluoroquinolone-resistant gram-positive bacteria. In addition, alterations in the actual access of the antibiotic to the target enzymes may prevent the fluoroquinolone antibiotic from crossing the bacterial cell wall. This mechanism of bacterial resistance involves the expression of membrane-associated efflux pumps that may actively pump the antibiotic out of the bacteria.

The incidence of postoperative endophthalmitis increased after the introduction of clear corneal incisions and the use of second-generation fluoroquinolones postoperatively.[1] The use of fourth-generation fluoroquinolones as well as proper construction of clear corneal wounds following uneventful cataract surgery has lead to a decrease in the incidence over the past few years. In a recent retrospective study[2] from 2 major eye centers, the rate of postoperative endophthalmitis was 0.07% overall in patients who received postoperative antibiotic treatment with moxifloxacin or gatifloxacin. However, reports of endophthalmitis following cataract surgery with bacteria that are resistant have begun to appear. A study of acute postoperative endophthalmitis from a retinal referral practice found that 31 of 42 patients were treated with perioperative gatifloxacin or moxifloxacin.[3] Sensitivities done on gram-positive organisms found sensitivities to gatifloxacin or moxifloxacin of only 38%.

In addition to infections with resistant bacteria following cataract surgery, case reports of fourth-generation-fluoroquinolone–resistant bacterial keratitis in

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general[4] as well as infections with bacteria resistant to fourth-generation fluoroquinolones following refractive surgery[5] are now appearing. Along with reports of resistant bacteria occurring after refractive surgery, reports of fourth-generation-fluoroquinolone–resistant mycobacterial keratitis following LASIK are surfacing. In this issue, Moshirfar et al. (pages 1979–1982) report a case of mycobacterial keratitis following uneventful LASIK. Cultures revealed a mycobacterium chelonae isolate that was resistant to moxifloxacin and gatifloxacin. Cases such as this demonstrate the potential problems and limitations of postoperative antibiotic coverage against resistant organisms.

The important issue is what ophthalmic surgeons can do to limit the development of antibiotic resistance. First and foremost is the use of the correct antibiotic agent for the correct situation. Use of a powerful broad-spectrum antibiotic such as the fourth-generation fluoroquinolones is appropriate for the treatment and prophylaxis of serious infections such as postoperative endophthalmitis and post-refractive surgery keratitis or bacterial keratitis. However, the use of these agents as a first-line treatment for relatively mild infections such as uncomplicated conjunctivitis or chronic infections such as blepharitis should be discouraged. This will help decrease the widespread use of these medications in inappropriate situations that may lead to the development of resistance.

It is also important that antibiotic agents be used in a concentration and regimen that allows a high tissue concentration compared with the minimum inhibitory concentration required to kill a bacterium for maximum possible response to the antibiotic and a lower risk for developing resistance. Finally, the correct dosage of these antibiotics is critically important. These medications should not be prescribed at a frequency fewer than 4 times per day. In addition, use of the antibiotics should be for only the prescribed period of time necessary to kill bacteria or provide adequate prophylaxis against bacteria. An example is the use of fourth-generation fluoroquinolones following routine cataract surgery. These medications should be used 4 times per day for approximately 7 days and discontinued abruptly. There should be no tapering or long-term use of these agents because low level, long-term exposure is a recipe for the development of bacterial resistance. The use of the optimal antibiotic in the optimal dose for the optimal period of time is essential to prevent the development of resistance to these fluoroquinolone antibiotics and hopefully extend the useful lifeline of these medications.

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