CHOOSING WISELY: ANTIBIOTIC USE IN OPHTHALMIC SURGERY

Rethinking the use of antibiotics before and after surgery.

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Ophthalmic surgery is thought to be a "clean" surgery and, as a result, antimicrobial prophylaxis for ophthalmic surgery is not discussed in prominent infectious disease textbooks.[1]

In a recent review, we coined the term *odontoiatric model*, based on the Italian *odontoiatria*—in English, *dentistry*. We aimed to emphasize that modern ophthalmic surgery, like dental surgery, can be 1-day or office-based surgery. We noted the incidence of endophthalmitis (nosocomial infection) has remained stable for the past 5 years.[2]

For years, the ocular surface was thought to be sterile due to the presence of lysozyme, antimicrobial peptides, immunoglobulin A complement, and other substances. A group led by Rachel Caspi at the US National Eye Institute, using an animal model, found that local bacteria on the ocular surface maintain ocular immunity and that transient disruption of bacteria via antibiotics results in a reduction in immune-related mechanisms.[3] These authors demonstrated that a specific commensal organism, *Corynebacterium mastitidis*, stably colonized the ocular surface and stimulated the host's ability to resist pathogenic fungal and bacterial infections. This demonstration of the role of a living, resident ocular microbiome will, hopefully, lead to more appropriate and judicious prescription of antibiotics.[3,4]

ANTIBIOTIC PROPHYLAXIS IN OPHTHALMIC SURGERY

Some principles regarding antibiotic prophylaxis in ophthalmic surgery are well established. First, microbiologic surveillance should guide the choice of antibiotics.[5,6] That is, knowing the organisms that are highly prevalent in one's region can help determine which agents will be most effective as infection prophylaxis.

Second, topical povidone-iodine is an effective monotherapy against infection for intravitreal injections and vitreoretinal surgery. It has broad-spectrum microbicidal activity (against bacteria, viruses, spores), no reported resistance, and a fast kill time. All physicians should perform surgical prophylaxis with povidone-iodine preparation. Ocular surface preparation for intravitreal injection using 5% povidone-iodine alone, in the absence of postinjection topical antibiotics, does not seem to induce bacterial resistance

AT A GLANCE

- Bacteria on the ocular surface help to maintain ocular immunity. Transient disruption of bacteria via antibiotics results in a reduction in these immune-related mechanisms.
- If a patient's own eye flora are the source of most postprocedural endophthalmitis, and the use of postinjection antibiotics leads to increased resistance, then the indiscriminate use of antibiotics will lead to more resistant organisms in endophthalmitis.
- The natural history of endophthalmitis suggests that we should rethink the scheduling of postoperative visits in routine cases. Postoperative visits on day 2 or 3 after the injection, if performed at all, may make more sense than a return the next day.

or change conjunctival flora.[7-10]

Third, antibiotic resistance is a global public health issue. Ocular surface organisms are becoming more resistant (with increased minimum inhibitory concentration [MIC] values based on systemic susceptibility standards) to antibiotics. Up to 30% of cultured ocular isolates now demonstrate resistance to fluoroquinolones.[11-16]

MICROBIOLOGIC EPIDEMIOLOGY

We have analyzed 10 years of microbiologic data (2003-2013) from the Torino Eye Hospital. The top five bacteria isolated in the hospital's territory after postsurgical endophthalmitis were as follows:

- coagulase-negative *staphylococci*
- *Staphylococcus aureus*
- viridans group *streptococci*
- *Pseudomonas aeruginosa*
- *Streptococcus* pneumonia

Interestingly, 3 cases of *Acinetobacter lwoffii* and 23 cases of *Peptostreptococcus spp.* were also reported.

There is increasing evidence that coagulase-negative *staphylococci* show multiple antibiotic resistance mechanisms. The *Bacillaceae* deserve special attention because, compared with the past, this family of Gram-positive bacteria have become more aggressive, they grow rapidly, and they cause colliquative necrosis in tissues.[5,6,17-19]

Sometimes, it seems that microbiologic surveillance does not help physicians make appropriate choices of antibiotics. Up to 30% of vitreous taps are negative. However, in an apparently culture-negative endophthalmitis, it may be that *S. epidermidis* or some other indolent organism, including a virus that has already been sterilized by the body, is present. In rabbit eyes with experimental *S. epidermidis* endophthalmitis, culture results were negative after 48 to 72 hours, even though the entire vitreous of the enucleated eyes was cultured.[20]

We have tested in vitro susceptibility to different topical ophthalmic antibiotics of bacteria isolated from patients with endophthalmitis (Table) with the following findings:

- Fusidic acid is effective only against *Staphylococcaceae*;
- Tobramycin shows a high profile of resistance;
- Netilmicin is effective against a wide spectrum of bacteria, with the exception of *Streptococcaceae* (*S. pneumoniae* and alpha-hemolytic *Streptococcus*);
- Fluoroquinolones are effective, except against coagulase-negative *staphylococci*;
- Moxifloxacin shows only moderate effectiveness against prevalent bacteria; and
- Chloramphenicol is a static antibiotic that is effective against all bacteria with the exception of Gram-negatives.

Bacteria can gain access to the anterior chamber during the perioperative period. If this happens, it is important to choose an antibiotic that can penetrate the cornea and achieve levels in the aqueous high enough to eliminate the bacteria. Fluoroquinolones can penetrate tissue, but are concentration-dependent, require frequent dosing, and bacteria are becoming more resistant to them.

Choices for prophylaxis vary by region. In Italy, chloramphenicol is used topically but not systemically. Across Europe, broad-spectrum topical antibiotic therapy is the convention following surgery (cataract and vitreoretinal surgery, and post-injection). A fluoroquinolone plus netilmicin or a fluoroquinolone plus chloramphenicol are the most commonly used combinations.

Over the past 5 years, there has been reduced susceptibility of Gram-positive bacteria to levofloxacin (75%), although levofloxacin remains effective against Gram-negative bacteria (95%).

It is important to understand how different antibiotics work. Fluoroquinolones and netilmicin are concentration-dependent. Fluoroquinolones are bacteriocidal, unlike bacteriostatic antibiotics, which only inhibit bacterial growth. A fluoroquinolone's efficacy is dependent upon its concentration. The higher the concentration, the greater the kill rate. Frequent dosing during a short period of time may be more appropriate than infrequent long-term use.

Chloramphenicol can also be concentration-dependent, depending on the type of bacteria.

The addition of benzalkonium chloride as a preservative may facilitate more rapid killing of bacteria compared with antibiotics without benzalkonium chloride.[21-24]

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE

Most studies of antibiotic use in ophthalmology do not have proper controls because we do not know how many patient eyes are really challenged by bacteria. Also, because endophthalmitis is uncommon, studies must be very large to be adequately powered to detect a change in the rate of endophthalmitis with different regimens.

The problem with studying antibiotic resistance against the topical antibiotics used in ophthalmology is that it may not be directly analogous to antibiotic resistance against their systemic use. Topical antibiotics can obtain very high concentrations compared with systemic antibiotics; therefore, even when an antibiotic may be considered resistant, it may still be effective at killing bacteria, given the high levels of the medication present in the tear film and tissue.

All susceptibility and resistance data are based on systemic treatment standards, so they may not correspond to topical, intracameral, or intravitreal treatments.

True resistance in ophthalmology occurs when (1) an isolate has increased MIC that cannot be treated,

TABLE. IN VITRO SUSCEPTIBILITY TO DIFFERENT TOPICAL OPHTHALMIC ANTIBIOTICS OF BACTERIAL ISOLATES FROM PATIENTS WITH ENDOPHTHALMITIS (ROUNDED TO THE NEAREST WHOLE NUMBER).

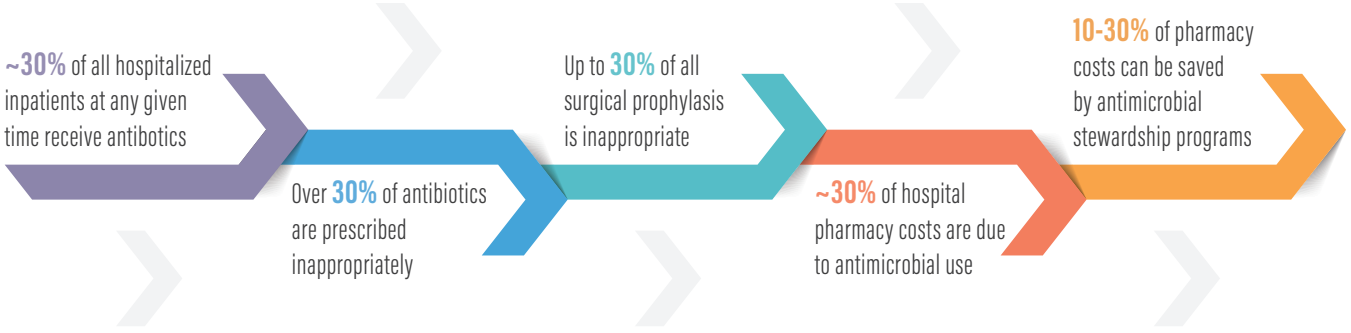
	Antibiotic							
Germ		Ampicillin	Chloramphenicol	Tetracycline	Neomycin	Netilmicin	Amikacin	Ciprofloxacin	Moxifloxacin
	Bacillaceae	20%	60%	53%	47%	60%	53%	93%	100%
	Moraxella	50%	92%	90%	42%	77%	42%	95%	98%
	Pseudomonas aeruginosa	0%	2%	2%	38%	77%	80%	95%	73%
	Serratia liquefaciens	8%	68%	23%	55%	77%	55%	92%	92%
	Serratia marcescens	8%	75%	8%	58%	58%	67%	75%	83%
	Stafilococchi coagulasi negativi	36%	75%	39%	71%	79%	57%	46%	86%
	Stphaylococcus aureus	30%	84%	76%	74%	85%	67%	73%	88%
	Streptococcus pneumoniae	95%	99%	86%	1%	47%	7%	85%	98%
	Streptococcus α-emol	90%	97%	68%	2%	30%	3%	60%	96%
	Streptococcus ß-emol	100%	100%	100%	0%	25%	13%	75%	100%

	Antibiotic							
Germ		Ofloxacin	Gentamicin	Fusidic Acid	Tobramycin	Norfloxacin	Lomefloxacin	Vancomycin	Levofloxacin
	Bacillaceae	93%	40%	40%	20%	53%	80%	80%	93%
	Moraxella	100%	45%	15%	31%	92%	92%	97%	98%
	Pseudomonas aeruginosa	79%	68%	2%	80%	80%	80%	4%	89%
	Serratia liquefaciens	87%	58%	6%	38%	84%	91%	4%	94%
	Serratia marcescens	83%	58%	0%	17%	75%	75%	0%	83%
	Stafilococchi coagulasi negativi	43%	50%	61%	36%	39%	43%	75%	46%
	Stphaylococcus aureus	75%	57%	84%	50%	67%	69%	91%	79%
	Streptococcus pneumoniae	88%	5%	50%	2%	60%	57%	88%	96%
	Streptococcus α-emol	68%	4%	23%	1%	19%	21%	85%	91%
	Streptococcus ß-emol	75%	13%	50%	0%	75%	63%	88%	63%

Data courtesy Franco Giardini, Turin Eye Hospital Microbiological Laboratory, Italy

ANTIMICROBIAL STEWARDSHIP

Antimicrobial Prescribing Facts: The **30%** Rule



Sidebar courtesy R. Murri and M. Fantoni, Fondazione Policlinico Gemelli, Italy

topically or by injection; (2) bacteria with elevated MIC are spread to other patients; and (3) the isolate with elevated MIC cannot be treated with antibiotics. No bacterium has met these three conditions in ophthalmology.[19]

Another limitation to studying antibiotic resistance is the variation in resistance patterns based on geographic location. The TRUST study is a surveillance report of more than 70,000 isolates collected from more than 200 institutions since 1999. This ongoing study does not include important antibiotics that are used in ophthalmology (ie, cephazolin, bacitracin, polymyxin B, neomycin, and sulfacetamide).[25]

If the patient's own flora are the source of most postprocedural endophthalmitis, and if the use of postinjection antibiotics leads to increased resistance, then use of topical antibiotics will lead to more resistant organisms in endophthalmitis events. This has been shown in the ARCANE study.[14]

Schimel et al studied bacterial isolates from endophthalmitis and found a tenfold increase over 10 years in resistance to topical fluoroquinolones and an additional doubling of resistance over a 1-year period as the use of intravitreal injections increased.[26]

Another study by Milder et al demonstrated that even one drop of peri-injection antibiotics increased the development of bacterial resistance.[27]

ANTIMICROBIAL STEWARDSHIP

What can be done to stem the rising time of antibiotic resistance? More than 30% of antibiotics are prescribed inappropriately in the community and up to 30% of all surgical prophylaxis is inappropriate (see *Antimicrobial Stewardship* sidebar).[28] The main areas of antibiotic use that seem to affect selection and diffusion of antibiotic resistance are in the food industry and in family medicine.[29-31]

From a public health perspective, certain processes may help limit unnecessary antibiotic use, thus limiting development of resistance. These targets include conversion from intravenous to oral antibiotic use, batching of intravenous antimicrobials, therapeutic substitutions, and formulary restriction. These strategies require fewer resources and less effort than other stewardship activities; are applicable to a variety of health care settings, including limited-resource hospitals; and have demonstrated significant financial savings.[32]

CHOOSING WISELY

According to the principles of the Choosing Wisely campaign (choosingwisely.org), we should not routinely use antibiotics before or after intravitreal injections. It is quite surprising that we are still talking about issues raised in 2004, with no clear consensus in 2019.[33]

In a 2004 report, Aiello et al found that postinjection topical antibiotics did not decrease endophthalmitis incidence.[33] The clinical presentations and visual outcomes of patients with endophthalmitis were similar, regardless of whether postinjection antibiotics were used. Greater incidence of endophthalmitis with the use of topical antibiotics was also demonstrated.

Regarding vitreoretinal surgery, no antibiotics should be given preoperatively. Routine antibiotics are unnecessary postoperatively after routine (ie, uneventful or uncomplicated) surgery.[7,34-37] The guidelines in Europe leave the use of antibiotic prophylaxis to the discretion of the surgeon.

Choosing wisely is also a patient-specific choice. Complicated surgery has a higher risk of postprocedure infection, so antibiotic use should still be considered for selected cases such as: elderly patients with blepharitis; patients with a poor tear film; monocular patients or those with a prothesis in the fellow eye, a history of ocular trauma, or previous surgery; immunosuppressed patients for local or systemic reasons; and patients with diabetes, multiple diseases, multiple medications, or

cancer. These patients may be more prone to infection and, therefore, good candidates for additional preventive measures, such as use of intracameral or preoperative antibiotics.

HOW DO THESE DATA AFFECT CLINICAL PRACTICE?

The natural history of endophthalmitis suggests that we should rethink the scheduling of postoperative visits in routine cases. We must shift the standard of care in a more patient-friendly direction without compromising safety.

Regarding injections, in many parts of the world, patients do not return for safety monitoring in the days following an injection. Instead, patients are given written instructions to call immediately if redness, pain, decreased vision, or other issues develop.

Regarding vitreoretinal surgery, while many routine cases should be reviewed on day 2 or 3 postoperative, it is the general legal consensus that a postoperative day 1 visit is required.[38]

MEDICOLEGAL CONSIDERATIONS

From a medicolegal standpoint, we are safest when we adhere to the community standard. Unfortunately, the standard of care in many communities requires antibiotic use, even though, as suggested above, it may not be necessary. This makes it difficult for surgeons to go against the current standard.

It is difficult to prove definitively that antibiotics are unnecessary. For postinjection antibiotics, there are good data from both prospective and large retrospective trials that topical antibiotics are not helpful and may even be harmful particularly because, unlike cataract surgery or vitrectomy, which are likely to be performed only once per eye, intravitreal injections are often repeated numerous times per eye. There is little data to suggest that use of antibiotics before or after injection reduces endophthalmitis risk. Nonetheless, use of antibiotics in these situations may continue to be the standard of care until better data are obtained.

KEY MESSAGES

A multidisciplinary approach is important, and local microbiologic surveillance is mandatory. We should not give topical or oral antibiotics for intravitreal injection. We should prescribe broad-spectrum topical therapy following surgery based on local microbiologic surveillance. Antibiotic resistance in ophthalmology is necessarily applicable to systemic resistance defined because topical antibiotics obtain concentrations higher than oral antibiotics. Risk assessment is the key process to combat defensive medicine. In selected patients, additional preventive measures may be necessary. ■

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