Overcoming Antimicrobial Resistance in Endophthalmitis

Subjects: Ophthalmology
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Endophthalmitis is a rare but vision-threatening infection characterized by marked inflammation of intraocular fluids and tissues, uncommonly seen following surgery and intravitreal injection. Antimicrobials are used worldwide in the prophylaxis and treatment of bacterial and fungal infections of the eye and are standard treatment in the preoperative and postoperative care of surgical patients. However, antimicrobials are reported to be overprescribed in many parts of the world, which contributes to antimicrobial resistance (AMR). AMR complicates the prophylaxis and treatment of endophthalmitis.

endophthalmitis | cataract surgery prophylaxis | intracameral antibiotics | antimicrobial resistance | stewardship

1. Current Prophylactic Measures and Management Approaches

Patients with endophthalmitis may have very unfavorable clinical outcomes in spite of prompt diagnosis and proper therapy. This highlights the importance of prophylaxis. Endophthalmitis cannot be "prevented" but its incidence can be reduced using various techniques. Prophylaxis includes more than the use of antibiotics; it encompasses preoperative patient evaluation, the surgical "prep", antisepsis, and meticulous surgical techniques in addition to the judicious administration of antimicrobial agents. Important steps include antisepsis with topical povidone-iodine, hand hygiene, sustaining a sterile procedure field, and a highly selective protocol for the use of pre- and postoperative prophylactic antibiotics [1].

The goal of preoperative antisepsis is to minimize the pathogen load in the conjunctiva and eyelids, since ocular flora is the most common source of infection [2]. The use of preoperative povidone-iodine antisepsis is well established [3][4]. Povidone-iodine has broad-spectrum antimicrobial activity against bacteria, fungi, protozoa, and viruses and has limited reported adverse effects. It is inexpensive and has a rapid onset of action, with effectiveness starting as soon as one minute upon skin contact. It also decreases bacterial growth from the conjunctiva without inducing antibiotic resistance, achieving a significant reduction in culture positivity rates [4][5][6]. The recommended povidone-iodine concentration varies. Numerous studies have supported the use of 5% povidone-iodine on the ocular surface [7][8]. The European Society of Cataract and Refractive Surgery (ESCRS) recommends 5–10% povidone-iodine prior to cataract surgery, with an alternate of 0.05% aqueous chlorhexidine in case of iodine allergy or hyperthyroidism [7][8]. The American Academy of Ophthalmology (AAO) also recommends 5% povidone-iodine but does not recommend chlorhexidine due to reports of corneal surface toxicity causing irreversible keratitis [9][10].

In a RCT comparing povidone-iodine 5%, polyhexanide biguanide (PHMB) 0.02%, and chlorhexidine 0.02% in cataract surgery, there were no significant differences between the three agents in reducing the numbers of colony-forming units [11]. Another RCT reported no additional efficacy with adding topical 0.5% moxifloxacin to 5% povidone-iodine [12].

The prophylactic use of antibiotics perioperatively to reduce endophthalmitis remains controversial and uncertain and varies geographically around the world. The AAO and the ESCRS have both reported that the use of preoperative topical antibiotics is unnecessary and not cost-effective [13]. Postoperatively, there were no differences in prophylaxis efficacy among various classes of topical antibiotics, including gatifloxacin, ofloxacin, and polymyxin/trimethoprim. However, topical postoperative aminoglycosides were reported to be ineffective [14]. There has been a trend of decreasing utilization of postoperative topical antibiotics [15][16][17]. Techniques such as intraoperative injections offer the benefit of assured delivery of drugs and avoidance of patient-related complications. Patient-dependent topical administration of eye drops carries the risk of poor patient compliance, microtrauma to eye, contamination of the bottle, and insufficient or prolonged administration of drops, which carry a risk of AMR [15].

There is an increasing use of routine prophylactic intracameral antibiotics around the world [18]. The ESCRS published a RCT of over 16,000 patients, randomized to receive intracameral cefuroxime 1 mg/0.1 mL with or without topical levofloxacin, and reported that intracameral cefuroxime was associated with an approximate five-fold reduction in the rate of endophthalmitis after cataract surgery [19]. Another RCT studied intracameral 0.5% moxifloxacin and reported that intracameral moxifloxacin was associated with a reduced rate of endophthalmitis [20]. In addition, many retrospective series and prospective studies have reported benefits with intracameral antibiotic prophylaxis in cataract surgery [14][21][22][23][24][25][26][27][28][29][30]. Further, several meta-analyses have also supported the use of intracameral antibiotics, highlighting a greater effectiveness of this route as a prophylactic measure and a lack of additional benefits from topical antibiotic administration [26][31][32]. Although intraoperative complications such as posterior capsular rupture and vitreous loss are associated with a more than three-fold increase in endophthalmitis, intracameral antibiotics have demonstrated marked efficacy as prophylaxis in these complicated cases [33][34][35].

There are several concerns regarding these studies. Cefuroxime is a second-generation cephalosporin mainly active against gram-positive organisms but does not provide coverage against gram-negative bacteria and is ineffective against MRSA and enterococci. Additionally, the effectiveness of intracameral cefuroxime is time-dependent with concentrations above the MIC only for about 5 h, which suggests a short-term benefit [36]. Vancomycin is very effective against gram-positive organisms, including MRSA, but less effective against common gram-negative organisms. Intracameral vancomycin remains above the MIC for about 32 h after administration [37]. Moxifloxacin is a fourth-generation fluoroquinolone that has a broader spectrum against both gram-positive and gram-negative isolates and is able to achieve a greater concentration than the MIC for a longer time than cefuroxime. The effectiveness of this medication is dose-dependent, and there have been reports of bacterial resistance to moxifloxacin being overcome by administering higher, yet safely tolerable, doses [38][39][40].

Although intracameral antibiotics have the benefit of greater intraocular concentrations, their use is not innocuous [41]. Preservative-free intracameral moxifloxacin is associated with decreased corneal cell density and increased apoptotic markers of the cornea as well as two case reports of uveitis [26][34][42][43][44][45][46]. Intracameral cefuroxime also seems to have a favorable safety profile, but overdoses due to compounding mistakes have been associated with uveitis, macular and corneal edema, and toxic anterior segment syndrome, and patients with penicillin allergies may have an anaphylactic reaction [26][45][46][47]. Vancomycin use has been associated with ischemic retinal vasculitis and hemorrhagic occlusive retinal vasculitis (HORV) [48][49][50].

In response to a 2021 survey from the American Society of Cataract and Refractive Surgery (ASCRS), about 66% of respondents reported the prophylactic use of intracameral antibiotics, representing an increasing trend from previous reports published in 2014 (50%) and 2007 (30%). Moxifloxacin was the most commonly used, as reported by 83% of the respondents [18]. Of those not using intracameral antibiotics, a majority responded that they would use an affordable and approved product if one were available in the US [18]. Currently, there is a packaged formulation of cefuroxime approved in Europe (Aprokam®, Laboratories Théa, Clermont-Ferrand, France). In the US, there is no approved medication and no universally accepted dose of “off-label” medication, although 500 µg of the preservative-free formulation of moxifloxacin (Vigamox®, Alcon, Fort Worth, TX, USA) is widely used [51][52].

An approved, affordable product would increase utilization in the US, as has occurred in India with intracameral moxifloxacin [53]. Another proposed technique is to use an IOL loaded with antibiotics (moxifloxacin, gatifloxacin) and anti-inflammatories (ketorolac). The latter would allow a sustained and extended drug release with the challenge of avoiding a negative effect on the lens’ physical properties or on the surrounding ocular tissues [54][55][56][57][58][59].

Most patients only undergo cataract surgery once per eye per lifetime, so the cumulative risk of endophthalmitis after cataract surgery is limited. However, intravitreal injections are generally performed repeatedly over a period potentially lasting many years. This cumulative risk may be mitigated by using newer intravitreal medications with longer durations, thus requiring fewer injections. These include newer anti-VEGF agents faricimab (Vabysmo®, Genentech, South San Francisco, CA, USA) and high-dose aflibercept (Eylea HD®, Regeneron, Tarrytown, NY, USA); the dexamethasone delivery system (Ozurdex®, Allergan, Inc., Irvine, CA, USA); and the fluocinolone acetonide intravitreal insert (Iluvien®, Alimera Sciences, Alpharetta, GA, USA) [60].

2. Stewardship in Ophthalmology

Antibiotic stewardship initiatives promote a collaborative, multidisciplinary approach aimed at fostering the judicious use of antimicrobial agents. Key strategies to reduce antimicrobial resistance are described in this section and summarized in **Table 1**. The primary goal is to ensure that antibiotics are prescribed correctly, including selecting the appropriate drug and determining the correct dosage, route, and treatment duration in relation to local resistance patterns. Such programs have been reported to mitigate the emergence of resistant organisms and reduce healthcare costs without compromising clinical outcomes [61][62][63][64]. Stewardship programs depend on awareness, research, policies, and targeted (rather than widespread and broad-spectrum) antibiotic use [65].

Table 1. Key strategies to reduce antimicrobial resistance.

CLINICAL STRATEGIES
Strict adherence to sterile surgical protocols.
Use of povidone-iodine as an antiseptic.
Minimizing polypharmacy when feasible.
Obtaining early culture samples in cases of clinically suspected infection.
Tailoring antibiotic therapy based on culture results and de-escalation of antibiotic regimen.
Avoiding long-term use of antimicrobials.
Reducing the prophylactic use of antimicrobials in uncomplicated procedures.
Developing specific guidelines for antimicrobial use in ophthalmic conditions to promote evidence-based prescribing practices.
PUBLIC HEALTH STRATEGIES
Identifying region-specific bacterial susceptibility and local antimicrobial resistance patterns for ocular infections.
Analyzing current prescription trends (from eye-care providers, primary physicians, and pharmacies) to identify areas for intervention.
Investing in research for alternative non-antibiotics antimicrobial strategies (bacteriophages, antimicrobial peptides, gene-targeting strategies).
Establishing antimicrobial stewardship programs.
Educating patients about the importance of completing prescribed antimicrobial courses, avoiding self-medication, and adhering to hygiene practices to help in preventing the spread of resistant strains.
Encouraging global collaboration to implement effective antibiotic stewardship programs and combating antimicrobial resistance worldwide.

The US CDC has outlined the Core Elements of Outpatient Antibiotic Stewardship to provide a framework for antibiotic stewardship for healthcare departments and outpatient clinicians that routinely provide antibiotic treatment. The key elements emphasize leadership commitment, accountability, stewardship expertise, action for policy and change, tracking, reporting, and education in acute care and long-term care settings. The CDC actively tracks data on outpatient antibiotic prescriptions from various sources to gain insights into prescribing patterns, identify areas requiring interventions, and gauge improvement. The most recent report indicates that, as of 2022, 97% of hospitals have successfully implemented all Core Elements [66]. Stewardship programs have led to a decrease in infections caused by drug-resistant pathogens, along with 18% fewer deaths from antibiotic resistance overall [67].

Specific stewardship recommendations stipulate that the concentration of antibiotics must be greater than or equal to the MIC and preferably the minimum bactericidal concentration at the infection site, as using lower concentrations than the MIC90 may select for resistant organisms. Other recommendations also emphasize the use of appropriate dosages and durations of therapy and the limiting of the use of multiple agents [65]. Empiric broad-spectrum treatment is useful in many situations (such as in the initial management of most patients with endophthalmitis), but, ideally, the antibiotic regimen will be de-escalated and tailored as diagnostic culture results become available. In empiric treatment, the option of combination therapy can be considered to improve therapeutic efficacy or expand the range of targeted pathogens [65][68].

Antibiotic stewardship programs have been successfully implemented in various healthcare settings, but they have not been widely adopted within ophthalmology. There are no specific guidelines for antimicrobial prescription in ophthalmology which result in widely used treatments for minor and self-limiting conditions as well as pre- and postsurgical prophylaxis [63]. The principles of stewardship suggest that, ideally, antimicrobials should be used only when medically needed to treat established infections and not for prophylaxis. However, the specific agents, doses, durations, and clinical indications are generally undetermined in eye conditions [63].

The use of routine prophylactic intracameral antibiotics contradicts the principles of antibiotic stewardship [69]. It has been recommended not to prescribe fluoroquinolones as monotherapy since this is associated with increased risks of selecting for resistant organisms and encouraging MRSA colonization [70][71]. As a potential mitigating factor, the high concentrations of medications instilled via intracameral administration usually exceed the MIC, which reduces the risk of drug resistance [71]. The use of intracameral vancomycin defies multiple CDC recommendations to reserve the use of vancomycin for life- or organ-threatening infections, rather than for prophylaxis [72][73]. Vancomycin remains the most important agent against gram-positive organisms in patients with established endophthalmitis, so the use of vancomycin for prophylaxis undermines its effectiveness by promoting resistant organisms [49][50].

The ideal broad-spectrum antibiotic is yet to be established. AMR is an increasing worldwide clinical challenge. One possible strategy involves the use of known antimicrobial agents that develop resistance less frequently due to the specificity of their mechanism of action. One example is polymyxins, which have demonstrated efficacy against multi-drug resistant gram-negative organisms. However, the safety and efficacy of intravitreal polymyxins remain unestablished at this time [74][75][76].

When evaluating any intracameral antibiotic, one should consider a number-needed-to-treat analysis, which represents the average number of patients who must be exposed to the antibiotic in order to “prevent” one case of endophthalmitis. Antisepsis is clearly more cost-effective than antibiotic treatment [69].

Future advancements in the field may explore the utilization of bacteriophages and antimicrobial peptides to combat bacterial ocular infections, the integration of hydrogels in contact lenses for biofilm prevention, the development of liposomal-lactoferrin-based eye drops to diminish pathogen presence, and the implementation of gene-targeting strategies to address antimicrobial resistance [77][78][79][80][81][82]. There is also ongoing research exploring the potential of stem cells as adjuncts to antimicrobial treatments to aid in the repair of damaged ocular tissues and combating septic infections [83].

Additionally, efforts are being made to investigate plant-based methods and natural products as potential solutions to antimicrobial resistance. It has been proposed that naturally occurring compounds (including plant metabolites), rather than fully synthetic molecules (such as sulfonamides, fluoroquinolones, and oxazolidinones) would be better suited to overcome AMR [84][85]. However, none of these strategies are in current widespread clinical use.

Guidelines for the judicious use of antibiotics include monitoring and providing specific feedback regarding prescribing patterns specific to different ocular infections [63][65][69]. Large scale surveillance for ocular infections is important. Active surveillance programs in the United States gather country and world-wide data to track drug resistance in ophthalmology through the Ocular Tracking Resistance in the U.S. Today (TRUST) and ARMOR programs [71][86]. Promoting such programs may aid studying the local patterns of AMR and in allowing effective implementation of antibiotic stewardship programs both nationally and globally [65][87].

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