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Emerging Worldwide Antimicrobial Resistance, Antibiotic Stewardship and Alternative Intravitreal Agents for the Treatment of Endophthalmitis

Nidhi Relhan, MD¹, Avinash Pathengay, MD², Stephen G Schwartz, MD, MBA¹, and Harry W Flynn Jr., MD¹

¹Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA.

²Retina and Uveitis Department, L V Prasad Eye Institute, GMR Varalakshmi Campus, Visakhapatnam, Andhra Pradesh, India.

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Intravitreal antimicrobials are essential in the treatment of all categories of endophthalmitis including the most common category, acute-onset endophthalmitis, generally defined as presenting within 6 weeks after cataract surgery. The purpose of this editorial is to address the issue of emerging worldwide antimicrobial resistance and the importance of antibiotic stewardship. In addition, current first-line intravitreal antimicrobial as well as alternative agents used for the management of endophthalmitis are discussed.

Emerging Worldwide Antimicrobial Resistance

Emergence of resistance to commonly used antimicrobial agents is a great challenge in health care. The overuse of antibiotics in hospitals and outpatient clinics, widespread agricultural use of antibiotics, and intrinsic genetic factors may all contribute to increasing antimicrobial resistance. Approximately 80%¹ of total antibiotic consumption in the United States is for uninfected animals raised for food and 62%² of these antibiotics are drugs also used to treat human diseases. In 2013, the Centers for Disease Control and Prevention (CDC)³ reported that 2 million people in the United States every year become infected with bacteria that are antibiotic-resistant resulting in approximately \$20 billion in excess direct health care costs and \$35 billion per year in lost productivity. In a recent review (2016),

Corresponding Author/Address for reprints – Harry W Flynn Jr. MD., Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, 900 N.W. 17th Street, Miami, Florida 33136, USA, Phone Number +1-305-326-6118, Fax - 305-326-6417 – hflynn@med.miami.edu.

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Marston et al reported that infections caused by antimicrobial-resistant organisms lead to >20000 deaths every year in the United States and Europe.⁴

Concern about emerging antimicrobial resistance has caused regulatory consequences. To minimize antimicrobial resistance, a bill was introduced by the United States Congress on March 2, 2015 entitled “Preventing Antibiotic Resistance Act of 2015”. This bill proposed a plan for the Food and Drug Administration (FDA) to determine the judicious use of antibiotics in food-producing animals but this bill did not pass as the pharmaceutical industry opposed it. The National Action Plan, an Obama administration initiative, provides guidelines for federal activities over the next 5 years to address this challenge of emerging antimicrobial resistance. The amount of annual federal funding for antibiotic resistance research and surveillance was doubled to more than \$1.2 billion in the fiscal year 2016 budget.

The issue of antimicrobial resistance is a worldwide problem and highlights the need for antibiotic stewardship. In the field of ophthalmology, endophthalmitis is a potentially sight-threatening disease and, in general multiple agents are required for effective therapy. For example, in one series of 350 isolates from eyes with endophthalmitis, no single antimicrobial agent provided universal coverage for gram-positive, gram-negative and fungal isolates.⁵

Among the 291/420 culture positive cases in the Endophthalmitis Vitrectomy Study (EVS), gram-positive and gram-negative bacteria were isolated from 274 (94.2%) and 19 (5.5%) patients respectively.⁶ All patients in the EVS were treated with intravitreal vancomycin (1.0 milligram/0.1cc) and amikacin (0.4 milligrams/0.1cc). The EVS excluded cases of suspected fungal endophthalmitis.

As reported in the EVS⁶ in 1994 and the Antibiotic Resistance Monitoring in Ocular microorganisms (ARMOR) 2009 surveillance study,⁷ 100% of the gram-positive isolates were susceptible to vancomycin. However, a more recent PubMed-based data review (1990-2015) reported 27 cases of endophthalmitis caused by gram-positive organisms with reduced vancomycin susceptibility or vancomycin resistance.⁸ Visual acuity outcomes were generally poor in these cases. A visual acuity of 20/400 or better at the final follow-up was reported in 10/26 patients (38.5%, data not available for one patient).⁸

Studies from the United States report that the overall antibiotic susceptibility pattern of gram negative bacteria from vitreous isolates has not changed.^{7,9} However, increasing degrees of antimicrobial resistance in gram-negative organisms is a concern in other parts of the world. In the EVS, 89.5% of gram-negative bacteria were sensitive to both amikacin and ceftazidime. Among gram-negative isolates, 2/19 (one *Pseudomonas vesicularis* and one *Flavobacterium*, not speciated) were resistant to both amikacin and ceftazidime.⁶ In 1999, Kunitomo et al from India reported incomplete susceptibility of gram-negative isolates for ciprofloxacin (87.5%), amikacin (82.1%) and ceftazidime (60.9%).⁹ Also Dave et al in 2016 reported 11 cases of endophthalmitis from India caused by ceftazidime-resistant gram-negative organisms. These cases were subsequently managed with intravitreal imipenem.¹¹

Emerging resistant isolates further complicate management decisions, and this problem is, perhaps, exacerbated by the increasing utilization of preoperative, intraoperative, and postoperative antibiotics associated with cataract surgery.¹² Practice patterns vary throughout the world, but antimicrobials are almost universally employed in the perioperative period.¹³ With the increasing use of prophylactic intracameral antibiotics during cataract surgery, it is reasonable to suspect that antibiotic-containing irrigating solutions represent yet another potential contributor to emerging resistance.

As a caveat, laboratory results of antimicrobial resistance do not always correlate with clinical outcomes. Management decisions are generally driven by clinical response rather than laboratory results; patients may improve despite partial or complete antimicrobial resistance. Antimicrobial susceptibility levels are continuously reviewed and updated frequently by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.^{14, 15} Interpretive criteria of minimal inhibitory concentrations (MIC) of any antimicrobial agent are established by microbiological, pharmacokinetic, and pharmacodynamic data as well as clinical studies results.¹⁴ As per CLSI (M100-S25) guidelines, the antimicrobial susceptibility tests are applicable to both blood and tissue levels of the drugs.¹⁶

Antibiotic Stewardship

In order to address emerging antimicrobial resistance, the US CDC recommends antibiotic stewardship programs to optimize antibiotic selection and reduce the inappropriate use of broad-spectrum antibiotics. As part of the Centers for Medicare and Medicaid Services (CMS) mandated strategies in 2017, these measures include immunization, infection control actions in healthcare settings, safe food preparation and handling, general hand washing, tracking clinical data on antibiotic-resistant infections, tracking causes of infections, performing root cause analyses and initiating antibiotic stewardship programs.¹⁷ The new medication management standards (MM.09.01.01) for hospitals, critical access hospitals, and nursing care centers became effective January 1, 2017 (https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf). Features of this new antimicrobial stewardship standard include elements of leadership commitment (accountability documents, budget plans, performance improvement plans, strategic plans, use of electronic health records), education of staff and patients, multidisciplinary teams, analysis of individual medical center data, and applying these results towards improvement in treatment outcomes.

In ophthalmology, antimicrobial use is mostly prophylactic, with little peer-reviewed evidence to support its use. With regards to elective intraocular procedures, antisepsis, rather than antibiotics, may be more important.¹⁸ In cataract surgery, there is no worldwide consensus regarding antibiotic prophylaxis in general and intracameral antibiotics in particular. Intracameral antibiotics are used more commonly in Europe than in the US.¹⁹ However, many US cataract surgeons currently use “off-label” intracameral antibiotics, and others would use an approved, prepackaged antibiotic solution if one became available.²⁰ Prophylactic antibiotics are associated with increased costs, risks to the individual patient, and risks to society as a whole by contributing to emerging antimicrobial resistance.

An online survey of the American Society of Cataract and Refractive Surgery members in 2014 reported increasing use of intracameral antibiotic injection prophylaxis. The use of intracameral antibiotics – at this time, primarily cefuroxime, moxifloxacin and vancomycin – is supported by one randomized controlled trial from 2007²¹ and about a dozen more recent retrospective “big data” series.²² These studies reported that intracameral antibiotics are associated with lower endophthalmitis rates, but a “number needed to treat” analysis suggests that in order to avoid one case of endophthalmitis (considering a rate of endophthalmitis without intracameral antibiotics of 0.02-0.04%), approximately 2499-4999 cases must be treated with intracameral antibiotics.

Intracameral antibiotics have disadvantages, including failure to adequately eliminate common ocular surface bacteria that may enter the eye during surgery. In the US, fluoroquinolone resistance rates among coagulase-negative *Staphylococcus* endophthalmitis isolates (the most common cause of endophthalmitis) have been reported as high as 50-60%.²³ In addition, intracameral antimicrobials are associated with complications including dilution errors, contamination during compounding, toxic anterior segment syndrome (TASS), corneal endothelial toxicity, toxic effects on the retina and others.^{20, 24-27} Hemorrhagic occlusive retinal vasculitis (HORV) is a poorly understood but potentially devastating complication associated with intracameral vancomycin.²⁸ Antibiotic stewardship programs seek to mitigate these concerns.

Another important category of endophthalmitis is that associated with intravitreal injections. Again, there is no worldwide consensus but it appears that topical antibiotics do not decrease rates of infection.²⁹ A prospective, nonrandomized cohort study by Yin et al (2013) reported that there was an increased antibiotic resistance of ocular surface flora with repeated use of topical moxifloxacin after intravitreal injections.³⁰ With an ever-increasing number of intravitreal injections performed for retinal pathologies including age related macular degeneration, diabetic macular edema, branched retinal vein occlusion etc. retina specialists are moving away from the use of prophylactic preoperative topical antibiotics.³¹⁻³³

Current Intravitreal antimicrobials

While intracameral antibiotics are generally used for prophylaxis, intravitreal antibiotics are used in the treatment of clinically suspected endophthalmitis. Various factors including aphakia, degree of ocular inflammation, frequency of doses, surgical status of the eye (vitrectomized versus non-vitrectomized) may affect the pharmacokinetics and pharmacodynamics of the intravitreal agents.³⁴

Intravitreal antimicrobials are all used “off-label” and must be prepared by compounding which entails a risk for contamination or dilution error. However, several intravitreal agents have been used for decades in treating endophthalmitis and are considered first-line therapy (Table 1).

Vancomycin (a glycopeptide antibiotic) is commonly utilized as a first-line treatment and is usually effective for gram-positive isolates. Vancomycin was approved for human use by the United States Food and Drugs Administration in 1958. It acts by binding irreversibly to D-

alanyl-D-alanine moieties of the N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) peptides. This inhibits synthesis and cross-linking of the NAM/NAG polymers that form the backbone of the bacterial cell wall. Intravitreal injection of vancomycin has been reported in literature to be non-toxic at dose of up to 2 milligrams in phakic- and aphakic-vitreotomized eyes.³⁵⁻³⁷

Amikacin (aminoglycoside antibiotic) is frequently utilized for coverage of gram-negative organisms. It interrupts bacterial protein synthesis by binding to the 30S ribosome of susceptible organisms. The dose of intravitreal injection 0.4 milligram/0.1ml is considered safe. However, in 1991 Campochiaro and Conway did a survey of members of the Retina, Macula, and Vitreous Societies and reported 5 cases of macular infarction which were believed to be related to administration of amikacin sulfate and later many others also reported similar macular toxicity.^{38, 39}

Ceftazidime (Beta-lactam antibiotic, 3rd generation cephalosporin) is commonly utilized as a first-line treatment and is highly effective in treating endophthalmitis caused by gram-negative bacteria. Because of toxicity concerns with aminoglycosides, ceftazidime is generally used for empiric treatment of endophthalmitis with suspected bacterial etiology. It interrupts cell wall synthesis via affinity for penicillin-binding proteins (PBPs). The dose of intravitreal injection of ceftazidime at 2.25 milligrams/0.1ml is considered safe.

Amphotericin B (Polyene class of antifungal drugs) is a traditionally used antifungal agent effective in the treatment of endophthalmitis due to *Candida*,⁴⁰ *Aspergillus*,⁴¹ *Blastomyces*,⁴² *Coccidioides*,⁴³ and other fungi. Amphotericin B binds with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of intracellular material and subsequent fungal cell death. An intravitreal dose of 5-10 micrograms/0.1 ml of amphotericin B is reported to be safe in animal experiments.⁴⁴

Voriconazole (Azole class of antifungal drugs) is a triazole first introduced in 2002 with good oral bioavailability and intraocular penetration. It has been utilized more recently and may have a broader spectrum of coverage for various fungi. Voriconazole causes inhibition of cytochrome P450 (CYP 450)-dependent 14 α -lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi. Retinal pigment epithelial damage occurs at concentrations >250 micrograms/mL, and focal retinal necrosis of the outer retina (with no electroretinographic changes) occurs at levels >50 micrograms/mL.⁴⁵ It is notable that voriconazole has a higher safety index as compared to those of intravitreal amphotericin B. Intravitreal dose is 50-100 micrograms/0.1ml. Silva et al (2015) reported that intravitreal voriconazole provided the broadest spectrum of antifungal coverage based on a laboratory study of isolates, and suggested it as empiric therapy of suspected fungal endophthalmitis.⁴⁵

The importance of antibiotic synergy is an interesting concept but has not been well studied among intravitreal antimicrobial agents.⁴⁶

Alternative Intravitreal Antimicrobials

Although the previously described antimicrobials comprise the mainstay of therapy, there are increasing reports of antimicrobial resistance (intrinsic or acquired). In the setting of

endophthalmitis caused by resistant organism alternative antimicrobial options are discussed (Table 2).

Alternative antibiotics for gram-positive organisms

Alternative antibiotic options include linezolid, quinupristin/dalfopristin, daptomycin, tigecyclin or other antibiotics to which the organism is susceptible on sensitivity testing.⁴⁷⁻⁵² Hernandez-Da Mota et al (2011) and Stroh et al (2012) reported cases of endophthalmitis caused by vancomycin-resistant *Staphylococcus aureus* which were successfully treated with intravitreal quinupristin/dalfopristin.^{47, 48} A literature review showed two case reports (Buzzaco et al, 2012 and Sim et al, 2016) of endophthalmitis caused by vancomycin-resistant gram-positive cocci which resolved completely with the use of intravitreal daptomycin.^{50, 51} Studies regarding safety, efficacy and effectiveness of intravitreal linezolid and tigecycline are currently ongoing in rabbit models of endophthalmitis.^{53, 54} Preservative-free linezolid was found to be nontoxic to the retinas of rabbits when injected intravitreally while hypersensitivity-like reaction due to intravitreal application of tigecycline has been reported in the rabbits.

Alternative antibiotics for gram-negative organisms

In isolated resistance to ceftazidime, other drugs such as imipenem or fluoroquinolones (ciprofloxacin/moxifloxacin) can be considered based on antibiotic susceptibility, availability and affordability. Fluoroquinolones and imipenem have been reported to be highly effective against these gram-negative organisms. In a case series of endophthalmitis caused by multi-drug resistant gram-negative organism in 3 patients, isolates were found to be susceptible only to imipenem.⁵⁵ The visual outcomes were generally poor (phthisis bulbi in 2 patients and optic atrophy in one patient). Dave et al¹¹ recently reported 11 cases of endophthalmitis with ceftazidime resistant gram-negative organisms which were managed by intravitreal imipenem. The clinical efficacy of ciprofloxacin for gram-negative organisms including *Pseudomonas* species has been demonstrated in many clinical series. Ciprofloxacin is considered as a better alternative to ceftazidime and amikacin for coverage of gram-negative organisms with low chances of precipitation, higher efficacy and possible synergistic effects with vancomycin.⁵⁶ Levofloxacin is another fluoroquinolone which has been used in experimental models of *Pseudomonas aeruginosa* endophthalmitis.⁵⁷ Jacobs et al reported a case of persistent endophthalmitis due to multidrug-resistant gram-negative bacteria (*Ochrobactrum intermedium*) which resolved successfully after administration of intravitreal moxifloxacin.⁵⁸ Moxifloxacin has a broader coverage for both gram-positive and gram-negative organisms but when compared to ciprofloxacin, the coverage by moxifloxacin for gram-negative organisms is less. Third generation cephalosporins (cefotaxime and ceftriaxone) are effective for most gram-negative organisms but lack coverage for *Pseudomonas* species.

Alternative Antifungals

Amphotericin-B and voriconazole comprise the mainstay of treatment for endophthalmitis caused by fungi. Intrinsic and acquired resistance to amphotericin-B has been reported. Alternative treatment options include miconazole and echinocandins.⁵⁹⁻⁶¹ Intravitreal miconazole was used to treat endophthalmitis caused by amphotericin-B resistant

Paecilomyces lilacinus successfully.⁶⁰ In 2014, Shen et al reported intravitreal caspofungin injection (in rabbit model of endophthalmitis) has low retinal toxicity and has a potential to be used as an alternative antifungal agent.^{59, 61}

Conclusion

A major challenge to ophthalmologists is that, in the clinical setting, a patient with drug-resistant endophthalmitis appears indistinguishable from a patient with drug-sensitive endophthalmitis at initial presentation. Treatment with traditional first-line agents is still recommended but may be inadequate in some patients. In the setting of resistance to first-line agents, the clinician can consider alternative agents during retreatment. A sensitivity report indicating that an isolate is resistant to a certain antimicrobial may not be relevant if clinical improvement occurs. However, a failure to improve within 48-72 hours, even before sensitivity reports are available, should prompt the clinician to consider the possibility of a drug-resistant organism.

Although traditional antimicrobials are usually effective, clinical experience with alternative intravitreal agents for resistant organisms continues to evolve. Various studies using experimental animal models (rabbits and mice) have provided some information on alternative antimicrobial drugs but experience is limited in treating patients with endophthalmitis.

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Summary Statement

Emerging worldwide antimicrobial resistance is a significant medical concern. Antibiotic stewardship programs to optimize antibiotic selection are important. The options of alternative intravitreal agents for the treatment of endophthalmitis caused by resistant microorganisms are discussed.

Table 1

First-line intravitreal antimicrobial agents for management of endophthalmitis.

Antimicrobial agent	Name of drugs	Class of drugs	Mechanism of Action	Intravitreal dose
Antibiotics	Vancomycin (Vancocin®)	Glycopeptide	Vancomycin acts by binding irreversibly to D-alanyl-D-alanine moieties of the N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) peptides. This inhibits synthesis and cross-linking of the NAM/NAG polymers that form the backbone of the bacterial cell wall.	1 milligram/0.1ml
	Ceftazidime (Fortaz®)	Cephalosporin (3 rd generation cephalosporin)	Ceftazidime interrupts cell wall synthesis via affinity for penicillin-binding proteins (PBPs).	2.25 milligrams/0.1ml
	Amikacin (Amikin®)	Aminoglycoside	Amikacin interrupts bacterial protein synthesis by binding to the 30S ribosome of susceptible organisms.	0.4 milligram/0.1ml
Antifungals	Amphotericin-B (Fungizone®)	Polyene	Amphotericin B binds with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of intracellular material and subsequent fungal cell death.	5-10 micrograms/0.1ml
	Voriconazole (Vfend®)	Azole	Voriconazole causes inhibition of cytochrome P450 (CYP 450)-dependent 14 α -lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi.	50-100 micrograms/0.1ml

Table 2

Alternative intravitreal antimicrobial agents for potential use in management of endophthalmitis caused by organisms resistant to standard antimicrobials.

Organisms	Name of drugs	Class of drugs	Mechanism of Action	Intravitreal dose
GPO	Linezolid (Zyvox®)	Oxazolidinone (fermentation byproduct of <i>Streptomyces roseosporus</i>)	Inhibits initiation of protein synthesis by binding 23S rRNA of the 50S subunit of bacterial ribosome.	300 micrograms/0.1ml ⁵³ (rabbits)
	Quinupristin/dalfopristin (Synercid®)	Streptogramin (isolated from <i>Streptomyces pristinaspiralis</i>)	Inhibits bacterial protein synthesis by interfering with function of 23S RNA (quinupristin:dalfopristin=3:7)	0.4 milligram/0.1ml ⁴⁷⁻⁴⁹ (rabbits and case reports in humans)
	Daptomycin (Cubicin®)	Cyclic lipopeptide	Terminates bacterial DNA, RNA and protein synthesis and cell death by forming transmembrane channels in cell membrane and depolarization of membrane potential.	200 micrograms/0.1ml ⁵⁰⁻⁵² (case report in humans)
	Tigecycline (Tygacil®)	Glycylcycline (a derivative of minocycline)	Inhibits bacterial protein synthesis by irreversibly binding to 30 S ribosomal unit	0.5-1 milligrams/0.1ml ⁵⁴ (rabbits)
GNO	Imipenem (Primaxin®)	Carbapenem	Interrupts cell wall synthesis of various GPO & GNO and is a strong inhibitor of β -lactamases from some GNO that are resistant to most β -lactam antibiotics.	50 micrograms/0.1 mL ^{11,55} (case series in humans)
	Ciprofloxacin (Cipro®)	Fluoroquinolones	Inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination.	0.1 milligrams/0.1ml
	Levofloxacin (Levaquin®)	Fluoroquinolones	Same as above	0.1ml of 0.5% ophthalmic solution ⁵⁷ (rabbits)
	Moxifloxacin (Avelox®)	Fluoroquinolones	Same as above	0.2 milligrams/0.1ml ⁵⁸ (case report in humans)
Fungi	Miconazole	Azole	Effects on respiration and cell permeability. It inhibits the growth of several species of Candida.	25 micrograms/0.1ml ⁶⁰ (case series in humans)
	Caspofungin (Cancidas®)	Echinocandin	Blocks the synthesis of $\beta(1,3)$ -d-glucan of the fungal cell wall, by non-competitive inhibition of the enzyme $\beta(1,3)$ -d-glucan synthase. $\beta(1,3)$ -d-Glucan is an essential component of the cell wall of numerous fungal species.	50 micrograms/0.1 ml ^{59,61} (rabbits and mice)
	Micafungin (Mycamine®)	Echinocandin	It inhibits an enzyme essential for fungal cell-wall synthesis.	0.025 milligrams/0.1 ml (rabbits) *

GPO-gram-positive organisms, GNO-gram-negative organisms

* ARVO Annual Meeting Abstract, April 2010 - Kapur R; Kim B; Tu EY; Birnbaum A; Fiscella R; Navare S; Blair MP; Edward DP; Carroll J; Lim JI. The Safe and Non-Toxic Dose of Intravitreal Micafungin and Caspofungin in a Rabbit Model.