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REVIEW

The Role of Systemic Antimicrobials in the Treatment of Endophthalmitis: A Review and an International Perspective

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ABSTRACT

Background: The optimal management of patients with endophthalmitis is challenging and includes both intravitreal and, in some cases, systemic antimicrobials. Systemic antimicrobials may be administered either intravenously or orally. In this article we review systemic antimicrobial options currently available for the treatment of types of endophthalmitis and the role of systemic antimicrobials (antibiotics and antifungals) in these treatments.

Review: While systemic antimicrobials are not universally utilized in the management of endophthalmitis, they may be helpful in some circumstances. The blood–retinal barrier affects the penetration of systemic medications into the posterior segment of the eye differently; for example, moxifloxacin and imipenem cross the blood–retinal barrier relatively easily while vancomycin and amikacin do not. However, inflammation, including endophthalmitis, may disrupt the blood–retinal barrier, enhancing the penetration of systemic agents into the eye.

Conclusion: Systemic antimicrobials may be particularly beneficial in patients with certain types of endophthalmitis; as such, they are standard treatment in the management of endogenous endophthalmitis (fungal and bacterial) and also widely used for prophylaxis and treatment of open-globe injuries. Although systemic antimicrobials are used in some patients with acute-onset postoperative endophthalmitis following cataract surgery, the literature generally does not support this practice. It is noted that there are currently no randomized clinical trials demonstrating a benefit of systemic antibiotics for any category of endophthalmitis.

Keywords: Endogenous endophthalmitis; Endophthalmitis; Systemic antimicrobials; Systemic side-effects

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Key Summary Points

The optimal management of patients with endophthalmitis is challenging and includes both intravitreal and, in some cases, systemic antimicrobials.

This article reviews systemic antimicrobial options currently available for the treatment of different categories of endophthalmitis and the role of systemic antimicrobials (antibiotics and antifungals) in these treatments.

INTRODUCTION

Endophthalmitis is an uncommon but potentially devastating disease involving severe inflammation of intraocular tissues and fluids. This inflammatory condition is caused by either bacterial or fungal organisms. Although viruses and parasites may cause similar clinical presentations, these entities are not classically grouped within the traditional categories of endophthalmitis.

Endophthalmitis can be broadly classified as endogenous endophthalmitis or exogenous endophthalmitis. The former results from hematogenous spread from a systemic (non-ocular) infectious source, also when the primary infectious source is never found. In contrast, exogenous endophthalmitis includes post-surgical, post-injection, and post-traumatic endophthalmitis and is associated with microbial keratitis. The causes include bacterial and fungal etiologies.

The optimal management of patients with endophthalmitis is challenging and includes both intravitreal and, in some cases, systemic antimicrobials [1]. Here, we review the role of systemic antimicrobials (intravenous vs. oral administration, and antibiotics vs. antifungals) for different categories of endophthalmitis.

METHODS

We searched the Cochrane Library and PubMed using pre-reported search terms and keywords in combination with both MeSH terms and text words. The search terms included ("endophthalmitis" [MeSH]) AND "systemic antibiotics" OR "systemic antimicrobials" OR "systemic antifungals"). The literature review was concluded 22 May 2020 and included randomized clinical controlled trials (RCTs), prospective and retrospective cohort studies, and case series published in English. All authors then selected the most relevant papers based on their expertise and combined clinical experience in the USA, Europe, and India. Finally, a narrative review was prepared based the authors' consensus opinion, with the ultimate aim to provide a balanced perspective.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

COMMON ORGANISMS IN ENDOPHTHALMITIS

In acute-onset postoperative endophthalmitis, the most common organisms are coagulase-negative *Staphylococci*, followed by *Staphylococcus aureus* and *Streptococci*. In India, fungal endophthalmitis is relatively more common (about 20% of cases) than bacterial endophthalmitis. In delayed-onset (chronic) postoperative endophthalmitis, the most common organism is *Propionobacterium acnes*, followed by fungi. In early-onset bleb-associated endophthalmitis, the most common organisms are coagulase-negative *Staphylococci* and *S. aureus*. In delayed-onset bleb-associated endophthalmitis, the most common organisms are streptococci and Gram-negative organisms, including *Moraxella* catarrhalis. In endophthalmitis following intravitreal injection, the most common causal organisms are coagulase-negative *Staphylococci*, followed by *Streptococci*, *Bacillus cereus*, *Enterococcus faecalis*, and others. Overall, *Streptococci* and other oral flora are relatively more common in these patients than in

postoperative patients. In post-traumatic endophthalmitis, the most common organisms are coagulase-negative *Staphylococci*, *Streptococci*, and *Bacillus*. In endogenous endophthalmitis, the most common organisms vary by geographic location, but overall fungi are more common than bacteria. Common fungal pathogens include *Candida albicans* and *Aspergillus*. In the USA and Europe, common bacterial pathogens include Gram-positive organisms, but in East Asia, Gram-negative organisms (including *Klebsiella*) predominate [2].

SYSTEMIC ANTIMICROBIALS CURRENTLY AVAILABLE FOR THE TREATMENT OF ENDOPHTHALMITIS

The blood–retinal barrier, which includes the retinal pigment epithelium and the walls of retinal capillaries with intercellular tight junctions, limits the penetration of systemic medications into the posterior segment of the eye [3]. In patients with intraocular inflammation, including endophthalmitis, breakdown of the blood–retinal barrier may allow the increased penetration of systemic agents, including antimicrobials [4], reinforcing the importance of understanding the characteristics of and differences between antibiotics.

Glycopeptide antibiotics

Vancomycin

Vancomycin is a glycopeptide antibiotic which acts by binding irreversibly to the D-alanyl-D-alanine moieties of the *N*-acetylmuramic acid and *N*-acetylglucosamine peptides. This binding inhibits the synthesis and cross-linking of the *N*-acetylmuramic acid. Vancomycin has broad-spectrum coverage against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), and is very effective when administered intravitreally, but penetration of the drug from the systemic cirulation into the posterior segment of the eye is poor. In a rabbit model, intravenous administration of vancomycin resulted in detectable amounts of drug in the aqueous, but not the vitreous, humor in both normal and inflamed eyes [5]. In another rabbit model, intravitreal vancomycin levels after systemic administration did not reach the minimum inhibitory concentration (MIC90) for Gram-positive organisms commonly causing intraocular infection even in those eyes with scleral or corneal perforating injury [6]. Systemic vancomycin must be administered intravenously (not orally) to have a therapeutic effect in patients with eye diseases. The risks associated with vancomycin include nephrotoxicity, "red man" syndrome, thrombocytopenia, neutropenia, fever, and dermatitis.

Alternative antibiotic options for the management of infections due to vancomycin-resistant organisms include linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline, among others. There is limited published information on the intraocular penetration of these alternative drugs when used in systemic treatments [7].

Cephalosporins

Third-Generation (Ceftriaxone, Ceftazidime) and Fourth-Generation (Cefepime) Cephalosporins

Third- and fourth-generation cephalosporins interrupt cell-wall synthesis via their affinity for penicillin-binding proteins (PBP). They have broad-spectrum coverage against Gram-negative organisms and show some activity against Gram-positive organisms, including methicillin-sensitive staphylococci, *Streptococcus*, *Propionibacterium acnes*, and others. In a rabbit model, ceftazidime was found not to penetrate into the vitreous humor after intravenous injection in noninflamed phakic and aphakic rabbit eyes, but there was effective penetration in inflamed rabbit eyes [8]. The vitreous levels of cefepime, a fourth-generation cephalosporin, after intravenous injections were reported to be above the MIC90 against *Proteus mirabilis*, Klebsiella species, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *S. pyogenes* and Enterobacter species, but below the MIC90 against *Staphylococcus aureus*, *S. epidermidis* and

Pseudomonas aeruginosa. Risks associated with ceftazidime include nausea, vomiting, diarrhea, and cross-allergy with other antibiotics.

Beta-Lactams

Imipenem

Systemic imipenem, a carbapenem beta-lactam antibiotic, shows good vitreous penetration into the posterior segment of the eye after intravenous infusion [9]. Carbapenems have a wide spectrum of antibacterial activity and are generally resistant to beta-lactamases. They are active against both Gram-positive and Gram-negative bacteria, including *Propionobacterium acnes*. Moreover, imipenem is reported to be nontoxic to ocular structures [10]. Despite these apparent advantages, imipenem is rarely used in the treatment of patients with endophthalmitis. Risks associated with imipenem include seizures and nephrotoxicity.

Aminoglycosides

Amikacin

Amikacin, an aminoglycoside antibiotic, has bactericidal activity against a broad spectrum of aerobic Gram-negative bacteria as well as activity against some Gram-positive bacterial species, but acquired resistance is a concern. Amikacin is poorly effective against enterococci and most anaerobic bacteria. Several studies have reported that intravenously administered aminoglycosides penetrate the blood-retinal barrier poorly and do not achieve therapeutic intraocular concentrations in the vitreous cavity [11, 12]. Risks associated with amikacin include nephrotoxicity, ototoxicity with deafness, and vertigo.

Macrolides

Clarithromycin

Clarithromycin, a semisynthetic macrolide antibiotic, has 50% bioavailability and an antibiofilm action. It can be used as adjunctive therapy, but not as monotherapy, in patients with mycobacterial infections. In a case series of 19 patients with delayed-onset postoperative endophthalmitis caused by nontuberculous mycobacteria, systemic antibiotics were used for the management of 12 patients, with oral clarithromycin administered to seven of 12 patients for 1–4 weeks [13]. Risks associated with clarithromycin include cardiac toxicity, rhabdomyolysis, and renal failure.

Fluoroquinolones

Fluoroquinolones are bactericidal antibiotics that inhibit the bacterial enzymes DNA gyrase and topoisomerase IV, both of which are required for bacterial DNA replication, transcription, repair, and recombination. Fourth-generation fluoroquinolones have a broad spectrum of coverage that includes both Gram-positive and Gram-negative bacteria, many anaerobes, and obligate intracellular bacteria (chlamydia, mycoplasma, and some mycobacteria infections). However, fluoroquinolone resistance rates among coagulase-negative *Staphylococcus endophthalmitis* isolates have been reported to be as high as 40–60% [14]. Several studies have confirmed that fluoroquinolones administered orally (moxifloxacin and gatifloxacin) [15, 16], or even topically every 2 h (moxifloxacin), achieve adequate MIC in the aqueous and vitreous humor, respectively [17]. Additionally, the maximum intraocular levels are achieved in 1–2 days. Fluoroquinolones are generally well-tolerated, although systemic administration may cause serious side effects involving the tendons, muscles, joints, nerves, and central nervous system [18, 19]. However, a rapid development of ocular isolates showing fluoroquinolone resistance has been observed recently, which is concerning [20, 21]. Risks associated with fluoroquinolones include tendinopathy, dysglycemia, thrombocytopenia, and cardiac toxicity.

Antibiotic Combinations

Trimethoprim–Sulfamethoxazole

Trimethoprim–sulfamethoxazole is a combination antibiotic formulation that is commonly used as an oral antibiotic. Its action includes blocking microbial folic acid synthesis [22]. This agent does achieve therapeutic levels in the vitreous

following oral administration [1]. Oral administration of trimethoprim–sulfamethoxazole as adjunctive therapy has been reported in the treatment of endogenous endophthalmitis with subretinal abscess due to *Nocardia* [23, 24], MRSA [25], and other organisms. Risks associated with trimethoprim–sulfamethoxazole include nausea, vomiting, peripheral neuritis, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

Antifungals

Amphotericin B

Amphotericin B is a member of the polyene class of antifungal drugs which bind with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of intracellular material and subsequent fungal cell death. Amphotericin B administered intravenously seems to work efficiently in patients with *Candida* endophthalmitis, but due to its propensity to cause systemic toxicity, it generally should be used under the supervision of an internal medicine or infectious disease specialist. Close monitoring is necessary, as the risks associated with amphotericin B include fever, chills, renal toxicity, electrolyte imbalances, cardiac arrythmias, and hepatotoxicity.

Voriconazole

Voriconazole is a member of the azole class of antifungal drugs that causes inhibition of cytochrome P450-dependent 14a-lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi. Voriconazole was first introduced in 2002 and shows good oral bioavailability and intraocular penetration. Its use has been increasing more recently, and it may have a broader spectrum of coverage against various fungi (filamentous as well as yeast) than originally thought [26, 27]. Similar to systemic amphotericin B, patients receiving voriconazole require close monitoring because risks associated with voriconazole include hepatic toxicity, cardiac arrythmias, fever, and hypertension.

Caspofungin

Caspofungin is a lipopeptide antifungal that belongs to the echinocandin class of antifungal drugs. Intravitreal caspofungin has been reported to be helpful in the management of fungal endophthalmitis [28, 29]. Systemic caspofungin also has been reported to be successful in the treatment of endogenous candidal endophthalmitis [30, 31]. However, other investigators have reported systemic caspofungin to be ineffective as monotherapy [32]. Risks associated with caspofungin include hepatotoxicity, Stevens–Johnson syndrome, and toxic epidermal necrolysis.

ROLE OF SYSTEMIC ANTIMICROBIALS (ANTIBIOTICS AND ANTIFUNGALS) IN THE MANAGEMENT OF DIFFERENT ETIOLOGIES OF ENDOPHTHALMITIS

Systemic antimicrobials are useful in the management of endophthalmitis due to certain etiologies (Table 1). In this section we discuss their role in different categories of endophthalmitis. Although the use of adjunctive systemic antibiotics would seem to be beneficial in patients with endophthalmitis, the empirical findings do not support their use in most categories of infection, possibly related to the concentration of antibiotics achieved inside the eye. In general, much higher doses may be achieved with intravitreal, rather than systemic, administration, and the effectiveness of antibiotics may greatly increase with increasing doses.

Further, the systemic administration of antimicrobials is associated with systemic toxicities; in contrast, the intravitreal administration of antimicrobials is associated only with ocular toxicities. Perhaps the most potentially toxic agents are vancomycin and the aminoglycosides; fortunately, these agents are easy to obtain for intravitreal use.

Endophthalmitis After Open-Globe Injuries

Early wound closure and prophylactic use of systemic levofloxacin was associated with a very low endophthalmitis risk in a large series of

Table 1 Role of systemic antimicrobials (antibiotics and antifungals) in the management of different etiologies of endophthalmitis

Type of endophthalmitis	Role of systemic antimicrobials
Endophthalmitis after open-globe injuries	Usually given for endophthalmitis prophylaxis or treatment
Endogenous fungal endophthalmitis	Yes (antifungals)
Endogenous bacterial endophthalmitis	Yes (antibiotics)
Post-cataract surgery endophthalmitis	Rarely in USA but frequently in other countries
Post-intravitreal injection endophthalmitis	Rarely in USA but more frequently in other countries
Filtering bleb-associated endophthalmitis	Rarely in USA but more frequently in other countries
Post-keratitis endophthalmitis	Rarely in USA but more frequently in other countries

patients with open-globe injuries without endophthalmitis at initial presentation [33]. Prophylactic systemic antibiotics are often utilized in such cases with open-globe injuries, although no results from randomized clinical trials are available that support their use in this situation. The use of systemic antimicrobials in this situation is consistent with the widespread use of systemic antibiotics in patients with penetrating injuries to other body parts.

Pars plana vitrectomy (PPV) with the injection of intravitreal antibiotics is a standard treatment for the management of established post-traumatic endophthalmitis. The benefits of systemic antimicrobials in these patients are unknown.

Endogenous Fungal Endophthalmitis

In patients with endogenous fungal endophthalmitis, systemic antifungals (amphotericin B or voriconazole) are generally used in consultation with an infectious disease or internal medicine specialist. The underlying rationale is that patients with endogenous endophthalmitis have, by definition, a systemic (non-ocular) source of infection, even if that source is never found. Systemic antifungals are beneficial not only in the treatment of the ocular infection but also in the treatment of the widespread infection throughout the body or other organ systems. In addition, intravitreal antifungal agents are usually employed and PPV can be considered [34–36].

Endogenous Bacterial Endophthalmitis

In patients with endogenous bacterial endophthalmitis, systemic antibiotics are necessary and are generally used in consultation with an internist. Again, these patients by definition have a systemic (non-ocular) source of infection, even if it cannot be identified. In some patients with severe intraocular infection, adjunctive PPV can be considered [36–38]. As an illustration of the effectiveness of systemic antibiotics in this condition, in a series of 40 eyes (35 patients) with endogenous endophthalmitis from the University of Florida, the authors reported positive intraocular cultures in 28.6% of patients before initiation of treatment with systemic antibiotics and in 0% after initiation [39].

Post-Cataract Surgery Endophthalmitis

The Endophthalmitis Vitrectomy Study (EVS) was a large randomized clinical trial conducted in the early 1990s that evaluated the role of early PPV and systemic antibiotic treatment in the management of acute-onset postoperative endophthalmitis following cataract surgery or secondary intraocular lens (IOL) implantation [40]. The authors of this study reported no significant difference in visual acuity outcomes and complication rates with or without systemic antibiotics (intravenous ceftazidime and amikacin). These two agents have limited effectiveness against coagulase-negative staphylococci, which was responsible for 80% of

culture-positive cases in the EVS. Many newer antimicrobials, including fourth-generation fluoroquinolones (gatifloxacin or moxifloxacin), have been reported to achieve therapeutic levels of intravitreal drug with systemic use, but there is currently relatively little evidence to support their use in modern clinical practice. As per the EVS, systemic antibiotics may be considered in selected patients with more severe signs and symptoms, such as panophthalmitis, presenting visual acuity of light perception or large hypopyon or lack of red reflex.

Systemic antibiotics appear to be used more commonly in Europe than in the USA for these patients. The European Society of Cataract and Refractive Surgeons (ESCRS) published consensus guidelines in 2013 which recommend—for patients with severe acute-onset postoperative endophthalmitis for which the treating physician is considering systemic antibiotics—using the same antibiotics as those given intravitreally (i.e., vancomycin and ceftazidime rather than amikacin and ceftazidime). These guidelines also recommend clarithromycin taken orally and possibly additional moxifloxacin taken orally in patients with chronic (delayed-onset) postoperative endophthalmitis following cataract surgery [41]. More recently, the European Vitreo-Retinal Society reported a retrospective series of 237 eyes with acute endophthalmitis following intraocular surgery or intravitreal injections. Of this group, the majority (153 eyes, 64.6%) had undergone cataract surgery or secondary lens implantation. The investigators reported the use of systemic antibiotics in 66.6% of eyes [42].

Post-Intravitreal Injection Endophthalmitis

The treatment includes vitreous tap or PPV with intravitreal antimicrobials. Systemic antimicrobials are generally not used for the management of post-intravitreal injection endophthalmitis, either in Europe or in the USA [43, 44].

Filtering Bleb-Associated Endophthalmitis

The treatment is similar to the management of post-intravitreal injection endophthalmitis and includes vitreous tap or PPV with intravitreal antimicrobials. Systemic antimicrobials are generally not used for the management of filtering bleb-associated endophthalmitis [45–49].

Post-Keratitis Endophthalmitis

Treatment of post-keratitis endophthalmitis includes corneal scraping or biopsy which may be followed by therapeutic keratoplasty in addition to the pars plana vitrectomy and injection of intravitreal antimicrobials (antibiotics or antifungals). Frequent applications of topical antimicrobials are utilized in the follow-up course. Systemic antimicrobials are generally not utilized for the management of post-keratitis endophthalmitis [50–53].

COMPLICATIONS AND SIDE-EFFECTS OF SYSTEMIC ANTIMICROBIALS

Knowledge of the potential side-effects and complications of administering systemic antimicrobials is very important (Table 2) [54]. The role of an infectious disease consultant or internist is invaluable in those cases requiring multi-specialty care.

Table 2 Systemic antimicrobials with potential use in the management of patients with endophthalmitis

Type of endophthalmitis	Systemic antimicrobial	Recommended dose	Side-effects and potential complications
Endogenous fungal endophthalmitis, endophthalmitis associated with open-globe injury with organic matter (fungal or suspected fungal etiology)	Voriconazole (Vfend®; Pfizer Ltd.)	200 mg PO bid for 2–4 weeks	Hepatitis, cholestasis, fulminant hepatic failure, photosensitivity, skin cancer, hallucinations, anaphylactoid reactions with fever and hypertension, QT prolongation with ventricular tachycardia, transient visual disturbance (altered/enhanced visual perception, blurred or colored visual change or photophobia), hypoglycemia, electrolyte disturbance and pneumonitis
	Fluconazole (Diflucan®; Pfizer Ltd.)	200 mg PO bid for 2–4 weeks	Vomiting, diarrhea, rash, abdominal pain, headache, skin rash, alopecia, increased liver enzymes, severe hepatotoxicity, exfoliative dermatitis, QT prolongation, and seizures
	Itraconazole (Sporanox®; Janssen)	200 mg PO bid for 2–4 weeks	Nausea, vomiting, diarrhea, abdominal discomfort, constipation, allergic rash, hepatitis, edema, hypokalemia, hypertension, headache, delirium, peripheral neuropathy, tremors
	Ketoconazole (Nizoral®; Janssen)	200 mg PO bid for 2–4 weeks	Mild nausea, vomiting, or stomach pain, skin rash, headache, dizziness, breast swelling, impotence, hepatotoxicity, adrenal crisis
	Amphotericin B (Fungizone®; ER Squibb & Sons)	0.25–1.0 mg/kg IV every 6 h as tolerated	High fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, dyspnea and tachypnea, drowsiness, and generalized weakness, renal toxicity, electrolyte imbalances (hypokalemia and hypomagnesemia), hepatotoxicity, cardiac arrhythmias, blood dyscrasias (leukopenia, thrombopenia)
	Caspofungin (Cancidas®; Merck & Co., Inc.)	70 mg daily loading dose, followed by 50 mg daily	Hepatotoxicity, Stevens–Johnson syndrome, toxic epidermal necrolysis

Table 2 continued

Type of endophthalmitis	Systemic antimicrobial	Recommended dose	Side-effects and potential complications
Endogenous bacterial endophthalmitis, Endophthalmitis associated with open-globe injury with non-organic matter (bacterial or suspected bacterial etiology)	Vancomycin (Vancocin®; Pfizer)	1 g IV bid	Nephrotoxicity, "red man" syndrome, rash, immune thrombocytopenia, fever, neutropenia, dose dependent decrease in platelet count, IgA bullous dermatitis
	Ceftazidime (Fortaz®; GlaxoSmithKline)	1 g IV bid	Nausea, vomiting, diarrhea, risk of cross-allergenicity with aztreonam
	Amikacin (Amikin®; Taj)	7.5–15 mg/kg/day IV/IM divided q8–12h	Allergic reaction, tubular necrosis, renal failure, deafness due to cochlear toxicity, vertigo due to damage to vestibular organs, rarely neuromuscular blockade
	Gentamicin (Garamycin®; Taj)	2 mg/kg load then 1.7 mg/kg q8h	Same as amikacin
	Imipenem[a] (Primaxin®; Merck & Co., Inc.)	0.5–1.0 g q6–q8h	Seizures, renal tubular toxicity
	Gatifloxacin (Tequin®; Bristol-Myers Squibb (no longer manufactured))	200–400 mg IV/PO q24h	False positive urine drug screen for opiates, not approved for use under age 16 years based on joint cartilage injury in immature animals, CNS toxicity, skin rash, dysglycemia, thrombocytopenia, photosensitivity, QT prolongation
	Ciprofloxacin (Cipro®; Bayer)	750 mg PO q12h	Same as gatifloxacin
	Moxifloxacin (Avelox®; Bayer)	400 mg IV/PO q24h	Tendinopathy, Achilles tendon rupture, allergic reactions, myasthenia gravis
	Levofloxacin (Levaquin®; Janssen)	250–750 mg IV/PO q24h	Same as moxifloxacin
	Linezolid (Zyvox®; Pharmacia and Upjohn)	600 mg IV/PO q12h	Reversible myelosuppression, lactic acidosis, peripheral neuropathy, optic neuropathy, risk of severe hypertension if taken with foods rich in tyramine, rhabdomyolysis
	Trimethoprim–sulfamethoxazole (Bactrim DS®; Sun Pharmaceuticals)	160 mg/800 mg PO bid	Nausea, vomiting, vertigo, peripheral neuritis, Stevens–Johnson syndrome, toxic epidermal necrolysis

Table 2 continued

Type of endophthalmitis	Systemic antimicrobial	Recommended dose	Side-effects and potential complications
Chronic endophthalmitis caused by non-tuberculous mycobacteria	Clarithromycin (Biaxin®; Abbott)	250–500 mg PO BID for 2–4 weeks	QT prolongation, rhabdomyolysis if given with statins, fatal pancytopenia/renal failure if given with colchicine, hypotension/renal injury if given with calcium channel blockers

bid Twice daily, *CNS* central nervous system, *IM* intramuscular, *IV* intravenous, *PO* per oral route of administration, *q* every

[a] Given with cilastatin

CONCLUSIONS

We have reviewed the current usage of systemic antimicrobials in different types of endophthalmitis. Our combined clinical experience in the field encompasses clinical practice in the USA, Europe, and India, and we have attempted to provide a consensus opinion. There is considerable uncertainty on this topic because, other than the EVS, there is no evidence from relevant randomized clinical trials to provide guidance. The EVS reported that ceftazidime and amikacin had no benefit in the treatment of acute-onset postoperative endophthalmitis following cataract surgery or secondary IOL implantation. Therefore, in our review, we have used a consensus approach based on lower-quality evidence.

Systemic antimicrobials are considered to be beneficial in the management of endogenous (fungal and bacterial) endophthalmitis and as endophthalmitis prophylaxis in open-globe injury. The benefits of systemic antimicrobials for any other category of endophthalmitis (especially following cataract surgery) are generally not supported by the literature. Certain patients with severe disease may benefit on a case-by-case basis, but the increased costs of systemic agents and possible related systemic toxicity remain important considerations. Consultation with an infectious disease specialist or internist when the initiation of systemic antimicrobial agents is being considered is important, as is the subsequent monitoring for possible systemic side effects.

It is possible that there is a potential role for some systemic antimicrobials, especially in patients with severe or nonresponsive disease. For example, imipenem has activity against many bacterial species and is relatively nontoxic to the eye. Further investigation of this agent would appear warranted. Further, continued systemic antibiotics are easier to administer than repeated intravitreal injections. Achieving sufficient and sustained intraocular therapeutic levels of drug is essential for the effective management of endophthalmitis. Currently, the most effective way to achieve

therapeutic drug levels in the vitreous humor is by way of intravitreal administration.

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