Revisiting systemic treatment of bacterial endophthalmitis: a review of intravitreal penetration of systemic antibiotics

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Abstract

Background: Adjunctive systemic antibiotic therapy for treatment of bacterial endophthalmitis is controversial but common practice due to the severity of the disease. In absence of guidance documents, several antibiotic regimens are being used without applying evidence-based prescribing, thus leading to inappropriate treatment of this serious eye condition.

Objectives: To summarize available data on intravitreal penetration of systemically administered antibiotics and to discuss their usefulness from a microbiological and pharmacological point of view.

Sources: We performed a systematic PubMed search of studies investigating antibiotic concentrations in the vitreous after systemic administration in humans, and selected animal models.

Content: The best-documented agents achieving therapeutic levels in the vitreous are meropenem, linezolid and moxifloxacin. Vancomycin, cefazoline, ceftriaxone, ceftazidime, imipenem and trimethoprim-sulfamethoxazole reach levels justifying their use in specific situations. Available data do not support the use of ciprofloxacin, levofloxacin, aminoglycosides, aminopenicillins, piperacillin, cefepime, and clarithromycin. With very limited but available promising data, the use of daptomycin and rifampicin deserves further investigation.

Implications: The choice of the adjunctive systemic antibiotic agent – in situations where considered relevant for treatment - must to date be made on an individual base, considering microbiological aspects as well as operative status and inflammation of the eye. This review gives a systematic overview of antibiotic options and provides guidance to the clinician striving for optimal systemic antibiotic treatment of bacterial endophthalmitis.

Introduction

Vitrectomy and intravitreal antibiotics are nowadays considered as the gold standard treatment of bacterial endophthalmitis [1]. Adjunctive use of systemic antibiotics is controversial but common practice justified by the severity of the disease. Data on intravitreal antibiotic levels reached by systemic administration are sparse and comprehensive recommendations for systemic use have not been established [1–3]. The availability of new antibiotic agents, changing resistance patterns, and new surgical techniques using implants such as keratoprosthesis justify revisiting their systemic use for endophthalmitis.

This review summarizes available data on intravitreal penetration of systemically administered antibiotics and discusses preferred regimens for the treatment of bacterial endophthalmitis from a microbiological and pharmacological perspective.

Definition and commonly isolated microorganisms

Endophthalmitis refers to the inflammation of the internal eye affecting the vitreous cavity and the anterior chamber, resulting from exogenous (mostly surgery related) or, more rarely (5-10%) hematogenous insertion of microorganisms [4].

The most commonly isolated microorganisms are coagulase-negative staphylococci (40-70%), *Staphylococcus aureus* (10-17%), streptococci (5-15%), other Gram-positive cocci including enterococci (5%), as well as Gram-negative bacilli (5-10%) including *Haemophilus influenzae* and *Pseudomonas aeruginosa* [5–8]. The microbiologic spectrum of less common forms like post-traumatic or endogenous endophthalmitis is more varied. For instance, bacillus sp. is regularly found after open-globe injuries [9]. The bacterial spectrum encountered may further vary according to local epidemiology and peri-operative prophylactic regimens [10].

Current treatment recommendations

The current mainstays of bacterial endophthalmitis treatment are vitrectomy and intravitreal antibiotics [1]. Vitrectomy aims to reduce the bacterial load with the intention of a local "source control". Although complete vitrectomy would ensure maximal eradication of the infected tissue, partial vitrectomy is often preferred in clinical practice, because of the lower associated risk of iatrogenic retinal detachment.

Intravitreal antibiotics are injected immediately after vitrectomy and their administration is usually repeated after 48 hours if the clinical course is not favourable. The most commonly used regimens are vancomycin combined with ceftazidime or amikacin. The downside of repeated injections is an increased risk of retinal toxicity.

Intravitreal dexamethasone is often added to reduce intraocular inflammation despite conflicting evidence [1]. Corticosteroids accelerate blood-retinal barrier restitution and thus influence antibiotic penetration.

The role of systemic antibiotics

The single large clinical trial evaluating the role of systemic antibiotics for the treatment of endophthalmitis is the Endophthalmitis-Vitrectomy-Study conducted in the 1990s [11]. In this randomized study, no significant difference in visual acuity was found in patients receiving intravitreal antibiotics followed by intravenous antibiotic therapy compared to patients receiving only intravitreal treatment. However, this finding has been questioned because of the exclusion of patients with severe endophthalmitis and the choice of adjunctive antibiotics: ceftazidime has poor activity against the dominant Gram-positive organisms and amikacin has very limited intraocular penetration. Since then, only small studies have evaluated the efficacy of systemic antibiotic therapy in endophthalmitis with varying methodologies and results [12-13].

Some recommendations advocate the adjunctive use of systemic antibiotics in severe acute purulent postoperative endophthalmitis [1]. Recommended regimens include vancomycin

combined with ceftazidime [14] or imipenem with ciprofloxacin [15]. For the treatment of endogenous endophthalmitis the use of systemic antibiotics is undisputed [2, 4] .

The pharmacokinetic rationale for adjunctive systemic antibiotics is the rapid elimination of intravitreally applied antibiotics, with almost complete removal after 24h [16], whereas systemic administration favors intraocular antibiotic accumulation over time.

Discussing the controversial benefit of adjunctive systemic antibiotics in terms of visual outcome is beyond the scope of this review. The imminent poor outcome constitutes a strong argument for clinicians to use systemic therapy. We strongly believe that adjunctive systemic therapy should not be denied on an individual base, provided that all efforts are made to isolate the causative pathogen and to apply evidence-based prescribing of antibiotic agents.

Intravitreal penetration of systemic antibiotics

Factors determining the penetration of antibiotics into the eye

The penetration of antibiotics into the posterior segment of the eye after systemic administration is limited by two blood-retinal barrier mechanisms (BRB): The retinal pigment endothelial cells located within the retinal cell layers (outer BRB) and the retinal capillary endothelial cells (inner BRB) [17]. Of note, entry into the anterior segment of the eye is limited by the blood-aqueous-barrier characterized by less restrictive properties, thereby resulting in different aqueous and vitreous drug concentrations.

Drug permeability across the blood-retinal barriers depends on drug characteristics such as the molecular size, lipophilicity, ionization and protein binding. Of interest, BRB was shown to be more permeable than the blood-brain-barrier (BBB) owing to morphological differences [17]. As in the BBB, ocular inflammation increases drug permeability across the BRB.

Elimination of antibiotics from the vitreous occurs via two routes: passive diffusion to the anterior chamber and through the Schlemm’s channel (anterior route), and retrograde transport

through the blood-retinal barrier (posterior route). Clearance pathways from the vitreous depends not only on physico-chemical drug properties and ocular inflammation, but also on the surgical status [18]. Post-operative aphakia – after removal of an artificial intra-ocular lens – as well as vitrectomy influence elimination of antibiotics [19].

Pharmacokinetic studies

1) The knowledge of antibiotics pharmacokinetics in the eye is derived from two types of studies: single concentration measurements in human eyes performed at the time of surgery, and rabbit models allowing for repetitive drug measurements. Several limitations should be considered: although single drug measurements are of high value for antibiotics characterized by a concentration-dependent killing effect (aminoglycosides, daptomycin), this approach is less informative for antibiotics with a killing profile that depends on time-above-MIC (beta-lactams) or AUC/MIC (fluoroquinolones, vancomycin, linezolid).
2) Common pharmacodynamic index values (such as Cmax/MIC used in most of the assessed studies) do not necessarily reflect efficacy in the complex microenvironment of the eye.
3) Comprehensive MIC-studies of endophthalmitis isolates are missing. In this review we use EUCAST breakpoints and wild-type distributions (ECOFF) [20] (table 2) as a reference to estimate potential efficacies of antibiotics.
4) Animal studies must be interpreted with caution, as they do not fully reflect the pharmacokinetics in humans.

Suitable publications were identified by a PubMed search using the terms [antibiotic name] and [vitreous] and [systemic/oral/intravenous]. If no publications were found, the search was complemented by the terms [eye] and [penetration]. Rabbit model studies were included for

antibiotics with limited human data or if they provided additional relevant information. Studies are summarized in table 1.

Review of available literature

Vancomycin

Vancomycin did not show any accumulation in phakic (including inflamed) eyes in a rabbit study [21]. Aphakic-vitrectomized eyes showed vitreous levels just above breakpoints of commonly involved Gram-positive organisms after one dose. In aphakic eyes, comparable levels were only reached after prolonged therapy. The poor intravitreal penetration of vancomycin is consistent with the limited CSF penetration [22] and explained by its high molecular weight and hydrophilicity.

The rationale for its continued empiric use [14] despite limited data, is its microbiological spectrum covering almost 100% of Gram-positive organisms causing endophthalmitis [7]. Available data nevertheless suggest that systemic administration should only be considered in aphakic eyes. Given the delay in achieving sufficient concentrations, systemic administration should follow immediately intravitreal injection of the same agent.

Penicillins

Poor vitreal penetration of ampicillin and amoxicillin were demonstrated in rabbit models [23-24]. Similarly, insufficient vitreous concentrations of piperacillin were demonstrated in human eyes with diverse operative status [25]. The vitreal penetration of penicillin G has not been studied but based on CSF penetration data [22] and drug properties, penetration into the vitreous is anticipated to be minimal. Nevertheless, in analogy to CSF infections, high systemic doses might provide effective vitreous levels for streptococcal endophthalmitis.

Available data suggest that systemic administration of most penicillins is not appropriate to treat endophthalmitis. Penicillin G vitreous levels remain to be investigated.

Cephalosporins

Cefazoline vitreous concentrations are issued from a large rabbit study [26] showing levels well above streptococcal breakpoints in aphakic-vitrectomized inflamed eyes but undetectable levels in phakic non-inflamed eyes.

Ceftriaxone was detectable in human phakic non-inflamed eyes after multiple dosing [27] at levels well above streptococci and enterobacteriaceae breakpoints, but below the ECOFF of *S.aureus*. Whether the observed levels result from accumulation after repetitive dosing, or rapid penetration as previously shown in CSF studies [28], is not known.

Vitreous levels of ceftazidime are based on two rabbit studies [29-30]. Levels were above enterobacteriaceae breakpoints in aphakic-vitrectomized inflamed eyes. Only delayed penetration was observed in non-vitrectomized inflamed eyes and undetectable levels were found in phakic non-inflamed eyes [29].

Cefepime showed low vitreous levels in human phakic non-inflamed eyes [31], nonetheless penetration in inflamed eyes have not been studied.

In summary, cefazoline, ceftriaxone and ceftazidime can be considered as targeted therapy when the pathogen is identified and the MIC of the isolate has been determined, yet on a thin evidence base. Ceftazidime is likely to be effective against most enterobacteriaceae in aphakic-vitrectomized eyes. Since it exhibits very limited anti-streptococcal and no anti-staphylococcal activity, it should not be used to cover Gram-positive organisms. Cefepime cannot be recommended as observed levels are clearly below those of other cephalosporins, yet investigation in inflamed eyes is warranted. Neither ceftazidime nor cefepime can be recommended to treat pseudomonas endophthalmitis based on available data.

Carbapenems

Two studies in human phakic non-inflamed eyes showed imipenem vitreous concentrations around 2.0 ug/ml [32-33]. Meropenem was shown to rapidly achieve four-fold higher vitreous

concentrations in a comparable study [34]. This finding is consistent with observed high meropenem levels in CSF [22] and explained by favorable physicochemical properties. Unlike imipenem, the observed levels of meropenem clearly exceed breakpoints for relevant Gram-positive and Gram-negative organisms.

The potential value of carbapenems in empirical treatment – as single agents - is limited by the high prevalence of oxacillin-resistent coagulase negative staphylococci also in ophthalmic isolates [8]. For empiric combination therapy, we would advocate the use of meropenem rather than imipenem based on the above-discussed data. Furthermore, meropenem appears to be the preferred option for targeted Pseudomonas treatment, particularly when considering the insufficient concentrations of ciprofloxacin, piperacillin, ceftazidime and cefepime as discussed above.

Rifampicin

High rifampicin vitreous levels were observed in phakic non-inflamed rabbit eyes [35], however with doses that, corrected for weight, would largely exceed tolerated doses in humans. Human studies are limited to aqueous levels, observed to be 0.2-1.3 ug/ml [36]. As rifampicin vitreous levels were consistently shown to be half of aqueous levels [31], human vitreous levels could be expected to exceed 0.1 ug/ml, which is well above breakpoints for staphylococci.

A role of rifampicin in endophthalmitis after foreign-body implantation, incomplete vitrectomy, and aggressive *S.aureus*-infection deserves further consideration due to its bactericidal and biofilm-active-properties. Importantly, rifampicin has to be combined with an effective second anti-staphylococcal agent to prevent resistance.

Linezolid

Mean vitreous levels of linezolid in phakic non-inflamed human eyes range from 1.2 to 3.7 ug/ml after one dose [37–40], with two studies showing further accumulation after two doses

(4.5 and 5.7 ug/ml) [37, 39]. The good penetration into the vitreous is consistent with CSF penetration [22].

Considering breakpoints of Gram-positive organisms, sufficient vitreous levels are likely to be attained after two doses. The drug, however, is bacteriostatic.

The well documented ocular penetration and comprehensive coverage of Gram-positive germs make of linezolid a potential alternative to vancomycin. Caution is needed due to its toxicity (myelosuppression, peripheral neuropathy, optic neuropathy), although relatively infrequent in short-term administration [41].

Daptomycin

Knowledge of daptomycin penetration is limited to one case report of a patient treated for MRSA-endophthalmitis in a strongly inflamed, phakic, non-vitrectomized eye [42]. Single dose administration (10 mg/kg) resulted in a vitreous concentration of 12.4 ug/ml 42h post administration (patient had renal insufficiency). This finding appears promising considering low staphylococcal breakpoints and the drug's bactericidal properties, but its use remains experimental to date.

Aminoglycosides

Vitreous concentrations far below breakpoints of relevant pathogens were shown after intravenous administration of amikacin and gentamycin in a rabbit study [43], despite study conditions expected to enhance vitreous levels (inflammation, aphakia and vitrectomy).

Given the availability of better alternatives, there is no role for systemic administration of aminoglycosides in endophthalmitis.

Fluoroquinolones

Despite relatively good vitreous/serum (V/S) ratios owing to favourable physicochemical properties, observed concentrations in vitreous proved insufficient for ciprofloxacin [44–50] and levofloxacin [38, 51-52].

Moxifloxacin demonstrated concentrations well above breakpoints of relevant organisms after two doses [53-54], whereas concentrations were significantly lower after a single dose [55-56]. The low concentrations of the Vedantham study can be explained by an inadequate short sampling time of 90 minutes after oral administration [56] . Moxifloxacin maximal CSF levels were shown to occur 2-3 hours after maximal systemic levels [57].

In summary, there are sufficient data to oppose the use of ciprofloxacin and levofloxacin for the treatment of endophthalmitis. Conversely, several studies consistently demonstrating satisfactory moxifloxacin levels are available. Given the observed higher levels with moxifloxacin 800mg, this increased dosage can be considered with a careful monitoring for side effects. Safety data on this dosage are not comprehensive to date [58].

Moxifloxacin lacks activity against most oxacillin-resistant coagulase-negative staphylococci [8]), and streptococci rapidly develop resistance particularly when drug concentrations are low. Therefore, the use of moxifloxacin for empirical treatment of endophthalmitis is limited.

Trimethoprim-Sulfamethoxazole

Sulfonamides and trimethoprim have demonstrated a moderate penetration in the vitreous in one human study [59]. The doses used, however, were below those for the treatment of meningitis [60]. The observed concentrations are not exceeding breakpoints of all relevant organisms although higher concentrations might be reached with increased doses. Concentrations are far below the breakpoint of *Stenotrophomonas maltophilia* (4 ug/ml) suggesting difficulty in treating this pathogen.

Due to limited data and better alternatives for Gram-positive organisms, there is no current role for TMP/SMX in systemic endophthalmitis treatment.

Clarithromycin

Based on one human study of phakic non-inflamed eyes showing insufficient vitreous levels [61], there is no argument to recommend clarithromycin for endophthalmitis treatment. Similarly insufficient levels have been reported in CSF, where the use of clarithromycin is limited to case reports of successful treatment of atypic organisms [22].

Conclusion

Data on the intravitreal concentrations of systemic antibiotics are generally scarce and are based on a single study for many agents. Relatively good evidence exists for therapeutic vitreous levels of meropenem, linezolid and high-dose moxifloxacin. None covers the required bacterial spectrum when used empirically as single agents, but the combination of linezolid with meropenem in empirical treatment of endophthalmitis may offer broad activity against the majority of pathogens. Vancomycin, cefazoline, ceftriaxone, ceftazidime, imipenem, daptomycin and TMP-SMX exhibit levels supporting their use in specific situations for targeted therapy. The operative status of the infected eye needs also to be considered. Available data do not support the use of ciprofloxacin, levofloxacin, aminoglycosides, aminopenicillins, piperacillin, cefepime or clarithromycin. Rifampicin may be considered for combination therapy in complicated staphylococcal infections. Further data on daptomycin vitreous penetration would be valuable.

The choice of the adjunctive systemic antibiotic agent – in situations where considered relevant for treatment - must to date be made on an individual base, taking into account suspected or detected organisms, operative status, intraocular inflammatory activity and drug side effect profiles. Future research should assess the clinical outcome after use of systemic antibiotics with documented good intraocular penetration (e.g. meropenem, linezolid and moxifloxacin), and assess the role of rifampicin for staphylococcal infections.

Transparency declaration

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Access to data

All studies included in this review are publicly available.

Author contributions

LB has done the literature search, analyzed and compiled the data. DG, LE have provided input in relation to ophthalmological and ophthalmo-surgical aspects. CM has contributed to the pharmacological content and analysis of data. SZ has participated in the interpretation of data and revised the manuscript. LB and CM have drafted the manuscript. All authors have revised the manuscript for intellectual content and approved the final submitted version.

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