Chapter 21
Intravitreal Antibiotics

Sharat Hegde and Avinash Pathengay

Intravitreal antibiotic is the current standard of care in infectious endophthalmitis of any cause. The vitreous is a transparent gelatinous avascular body rich in collagen and hyaluronic acid; it provides a good culture medium for microorganisms to proliferate. In order to eliminate infection in endophthalmitis, antibiotics must reach the intraocular space and adjacent ocular tissues in adequate levels so as to reach above the minimum inhibitory concentration (MIC). Static and dynamic ocular barriers (blood-ocular barrier) that form a part of natural protective mechanisms of the eye impede the penetration of systemically and topically administered antibiotics.

Various factors are responsible for poor penetration of topical and systemic antibiotics: The tear film dilutes topically instilled medicines [1]. Low molecular weight drugs undergo systemic absorption from the conjunctival capillaries, and hence, bioavailability decreases [2]. Tight junctions in corneal epithelium lead to poor paracellular drug penetration especially for ionic drugs [3]. Systemically administered drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the intraocular space via the retinal pigment epithelium (RPE) impedes the further access into the ocular cavity [4]. An intravitreal injection bypasses the blood-retinal barrier as drug is injected directly into the vitreous cavity. Thus, antibiotics delivered through the intravitreal route achieve a higher drug concentration for prolonged periods of time [5].

History of Intravitreal Antibiotics

Injection of intravitreal antibiotics dates back to around 1940s when Sallmann et al. injected penicillin in a rabbit eyes with traumatic endophthalmitis [6]. Intravitreal antibiotic era was heralded when Peyman and associates (1970s) conducted

S. Hegde, M.S. • A. Pathengay, F.R.C.S. (✉)
LV Prasad Eye Institute, Vishakhapatnam, India
e-mail: avinash@lvpei.org

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experimental studies on endophthalmitis-induced rabbits and established the recommended doses of various intravitreal antibiotics [7, 8]. Later, many experimental studies were conducted on small animals and nonhuman primate models to establish the mechanisms of drug clearance and safety doses of intravitreal antibiotics [9]. The class of drug, mechanism of action, and susceptible organisms to the antimicrobials are mentioned in Table 21.1.

Table 21.1 Class of drug, mechanism of action, and susceptibility of the commonly used antimicrobials in endophthalmitis

Drug	Class of drug	Mechanism of action	Susceptible organisms
Amikacin	Aminoglycoside	Inhibits protein synthesis by binding to 30S subunit of ribosomes	Aerobic GNBs, *Pseudomonas aeruginosa*
Amphotericin B	Polyene antibiotics	Binds to ergosterol and alter the permeability of the cell wall	Yeasts, filamentous fungi (resistance for various species of *Aspergillus)*
Ceftazidime	Third-generation cephalosporin	Inhibits peptide cross-linking of polysaccharide chains of peptidoglycan; affects cell wall synthesis	Aerobic GNBs, GPBs including *Pseudomonas*
Cefazolin	First-generation cephalosporin	Inhibits peptide cross-linking of polysaccharide chains of peptidoglycan; affects cell wall synthesis	GPC, GPB, *E. coli*, *Proteus*, *H. influenzae*
Ciprofloxacin	Fluoroquinolones	Topoisomerase II inhibitors (DNA gyrase)	Broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, *Actinomyces*, *Nocardia* sp.
Imipenem	Carbapenem	Inhibits cell wall synthesis, prevents cross-linking of peptidoglycan during cell wall synthesis	MDR GPB, GNBs including *Pseudomonas aeruginosa*, therapeutic option for infections caused by MDR pathogens
Piperacillin/ tazobactam	Beta-lactam antibiotics	Inhibit cell wall synthesis, binding to penicillin-binding proteins	GNBs, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*; therapeutic option for infections caused by MDR pathogens
Vancomycin	Glycopeptide	Inhibits the synthesis of precursor units of bacterial cell wall; inhibits RNA synthesis	GPC—MRSA and MDR *Staphylococcus epidermidis*
Voriconazole	Triazoles	Inhibition of ergosterol synthesis which increases membrane permeability	Broad-spectrum activity against molds and yeasts

GPC Gram-positive cocci, *GPB* gram-positive bacilli, *GNB* gram-negative bacilli, *GNC* gram-negative cocci, *MDR* multidrug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRSA* vancomycin-resistant *Staphylococcus aureus*

Ocular Factors Influencing Intravitreal Antibiotics

Intravitreal injection bypasses the various anatomical and physiological ocular barriers and diffuses freely in the vitreous cavity to reach the retinal surface. The following factors influence the drug distribution, concentration, and clearance from the vitreous cavity [10]:

1. Route of exit: large molecules like vancomycin, aminoglycosides, and macrolides are known to leave the eye predominantly by the passive diffusion through the anterior chamber, while small molecules such as beta-lactams, clindamycin, and fluoroquinolones are cleared by active transport via the blood-retinal barrier [11] (Fig. 21.1).
2. Ionic nature: anionic drugs like beta-lactams, cephalosporins, and clindamycin primarily undergo clearance rapidly via the posterior route across the blood-retinal barrier, while cationic drugs like vancomycin, aminoglycosides, and erythromycin have a comparatively longer half-life as they undergo clearance by passive diffusion into the aqueous and exit via the anterior chamber [9, 12, 13]. Fluoroquinolones which are zwitterions have the shortest half-life as they are cleared via both anterior and posterior routes (Fig. 21.2) [14, 15].

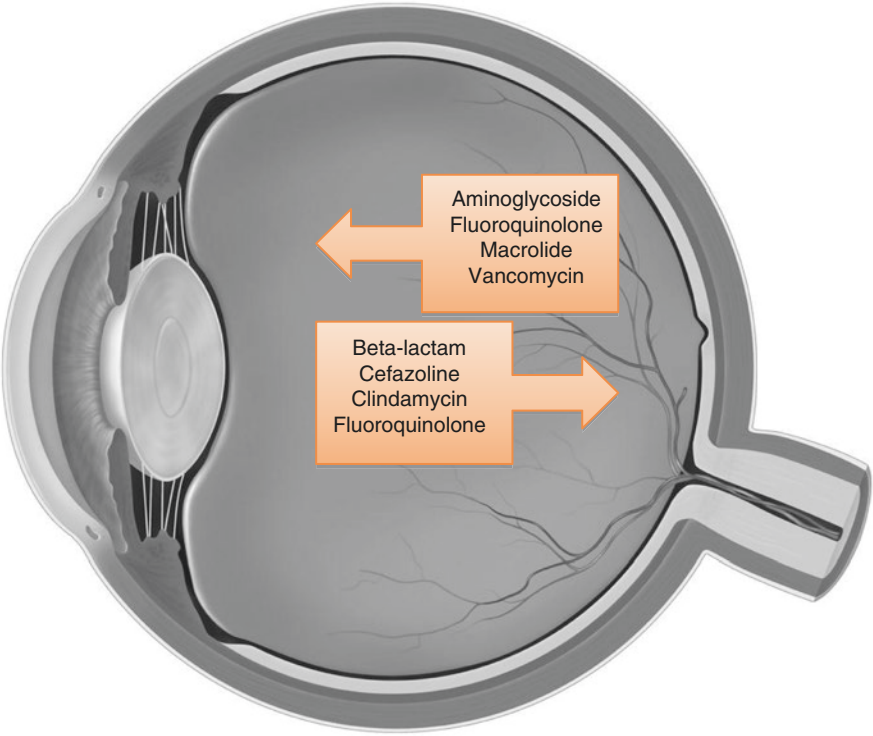

Fig. 21.1 Common antibiotic clearance from the eye

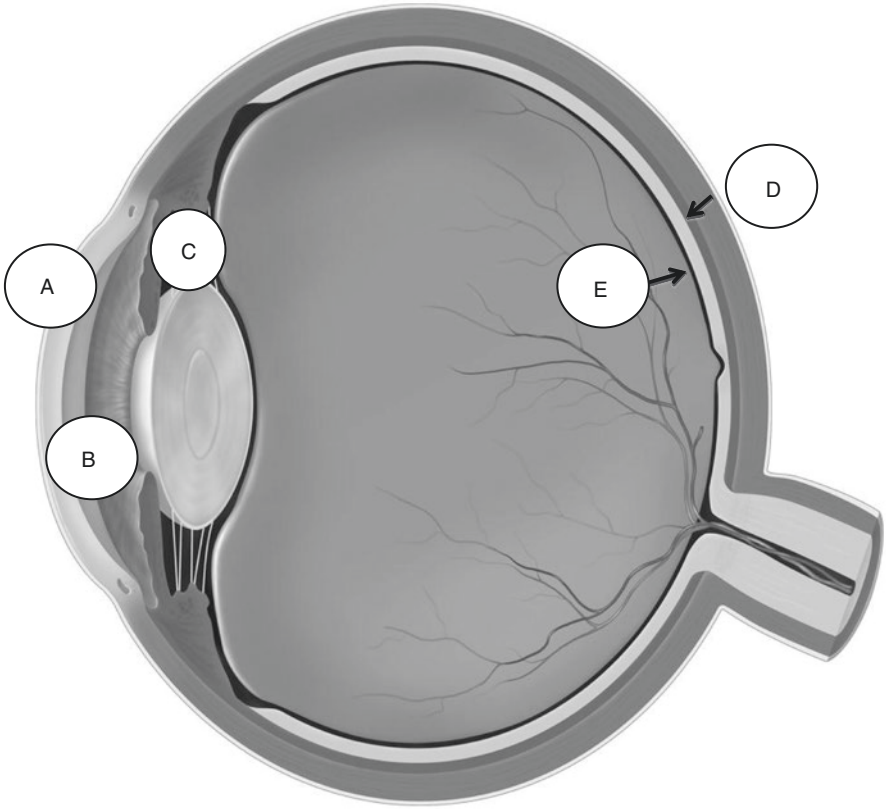

Fig. 21.2 Depicting the routes of exit for various intravitreal antibiotics. (*a*) Epithelial barrier, (*b*) aqueous-vitreous barrier, (*c*) blood-aqueous barrier, (*d*) outer retinal barrier, (*e*) inner retinal barrier (Adapted from Cunha Vaz JG, et al. Doc Ophthalmol 1997; 93:149–57)

3. Solubility coefficient of the drug: lipophilic antibiotics like fluoroquinolones and chloramphenicol are cleared by passive diffusion, while water-soluble antibiotics like beta-lactams leave the eye via active transport [9, 12].
4. Status of ocular inflammation: In an inflamed eye, the drug clearance through the anterior route is faster, while the clearance via the posterior route is delayed due to a compromise RPE pump. Thus in an inflamed eye, antibiotics that are routinely eliminated through the anterior route are cleared faster, while the drug clearance by the posterior route is retarded, thus increasing their half-life [9, 13, 16–18].
5. Surgical status of the eye: In aphakic eyes, the clearance of antibiotics that leave the eye through the anterior route is fast, while in vitrectomized eyes the drugs that leave via the posterior route are increased. In an experimental study, retinal toxicity to routinely used doses of intravitreal antibiotics in silicone oil-filled eyes was noted. This was due to confinement of the drug in the reduced preretinal space causing its delayed clearance [19].

6. Molecular weight: the retention of the drug in the vitreous cavity increases with its increase in molecular weight as it becomes relatively impermeable to the blood-retinal barrier. As most drugs have a molecular weight of <500 Da, their half-life is <72 h [17].
7. Vitreous liquefaction: the half-life of the drug is reduced in presence of liquefied vitreous in the anterior and posterior few millimeters of the globe [17].
8. Solution density: If the density of the injected solution is greater than vitreous, it may settle down with gravity and cause localized retinal toxicity. To avoid this complication, intermittent repositioning of the patients head is required [20].
9. Frequency of intravitreal antibiotic administration: The need for repeated intravitreal antibiotic injection depends on the clinical response, half-life of the drug, and surgical status of the eye. The aim of repeat dosing is to maintain the drug concentrations above the MIC, rather than to attain higher peak levels. Thus, adequate and safe antibiotic levels can be better achieved by frequent rather than higher dosages [16].

Intravitreal Antibiotic Dose

The efficacy of intravitreal antibiotics is based on the duration the intraocular drug level exceeds the MIC of a particular drug against the implicated organism. The safe and therapeutic intravitreal doses of commonly used antibiotics have been determined in experimental and clinical studies. The recommended doses and frequency of repeated injections have been mentioned in Table 21.2.

Preparation of Intravitreal Antibiotics

According to various experimental and clinical studies, the recommended therapeutic dosage of intravitreal antibiotics is very small compared to its systemic dosing and is carefully titrated to prevent retinal toxicity. Thus, it is important that an accurate dose is maintained each time an injection is prepared [21]. The injections should be prepared following standard protocols by trained personnel under strict aseptic conditions in a certified laminar flow area. Also a printed drug preparation reference display sheet should be consulted while preparing injections to prevent dilution errors. Preparation of important intravitreal antibiotics is shown in Table 21.3. Though the expiry of various drugs prepared for intavitreal use is not known, an experimental study reported that vancomycin, ceftazidime, and moxifloxacin when prepared in single-use polypropylene syringes and stored at −20 °C or −80 °C retain their potency, sterility, and stability up to 24 weeks [22].

Table 21.2 Pharmacokinetics of intravitreal antimicrobials: dose, route of exit and half-life in non-vitrectomized and vitrectomized eyes, and frequency of repeated injections

#	Drug	Recommended dose (μg/0.1 ml)	Route of clearance	Half-life ($t_{1/2}$) in vitreous Noninflamed phakic eyes	Aphakic vitrectomized eyes	Frequency of repeat injections (h)
1	Amikacin [25, 49, 50]	400	Anterior	25.5 h	NA	24–48
2	Amphotericin-B [51]	5–10	Posterior	8.9 days	1.8 h	NA
3	Aztreonam [52]	100	Posterior	7.5 h	NA	12
4	Cefazolin [9, 21]	2	Posterior	6.5 h	NA	24
5	Ceftazidime [25, 53]	2	Posterior and anterior	13.8 h	NA	48–72
6	Ciprofloxacin [14, 16]	100	Anterior and posterior	3.5–5.5 h	1.2 h	12
7	Clindamycin [54]	1000	Posterior	40 h	NA	72
8	Daptomycin [55]	200	Posterior	42 h	NA	Single dose
9	Dalfopristin/quinupristin [56]	400	Posterior	NA	NA	48
10	Gentamicin [57, 58]	100	Anterior	40–60 h	<40 h	72–96 h
11	Imipenem [59]	50–100	Posterior	NA	NA	NA
12	Linezolid [60, 61]	400	NA	2 h	NA	NA
13	Moxifloxacin [12]	200	Anterior and posterior	1.72 h	NA	12
14	Ofloxacin [15]	200–500	Anterior and posterior	5.6 h	NA	24
15	Penicillin [6]	2–4000 units	Posterior	NA	NA	48
16	Piperacillin/tazobactam [26–28]	225 <250	Posterior	NA	NA	NA
17	Sulfamethoxazole/trimethoprim [12]	1600 trimethoprim	Anterior	NA	NA	NA
18	Vancomycin [13]	1000	Anterior	25.5–56 h	9.8 h	72
19	Voriconazole [62]	50–200	Posterior	2.5–6.5 h	NA	NA
20	Meropenem [63]		Posterior	2.6 h	NA	NA

Table 21.3 Preparation of intravitreal antibiotics

#	Injection	Add distilled water	Take	Add to Ringer's lactate	Dosage in 0.1 ml
	Antibacterial antibiotic				
1	Amikacin 100 mg		0.1 ml	0.9 ml	400 μg
2	Cefazolin 500 mg	2 ml	0.1 ml	0.9 ml	2.25 mg
3	Ceftazidime 250 mg	1 ml	0.1 ml	0.9 ml	2.25 mg
4	Imipenem 500 mg	NS 10 ml	0.1 ml	0.9 ml double dilution	50 μg
5	Piperacillin and tazobactam 4.5 mg	20 ml	0.1 ml	0.9 ml double dilution	225 μg
6	Vancomycin 500 mg	10 ml	0.2 ml	0.8 ml	1 mg
	Antifungal antibiotics				
7	Amphotericin-B 50 mg	10 ml	0.1 ml	0.9 ml double dilution	5 μg
8	Voriconazole 200 mg	20 ml	0.1 ml	0.9 ml	100 μg

Activity Spectrum and Choice of Antibiotics

Prompt and early clinical, therapeutic, and diagnostic decisions have to be made in cases of endophthalmitis. The initial decision is based on the presenting history and clinical examination and is often empirical, without access to any laboratory or culture results. Ideally an empirical antibiotic combination should cover most common and possible causative agents. Bactericidal agents are preferred over bacteriostatic agents as the eye is an immune-privileged site. The commonly used empirical antibiotic regimen is vancomycin plus ceftazidime or amikacin. Vancomycin is effective against most gram-positive cocci; ceftazidime and amikacin are effective against most gram-negative bacilli. The endophthalmitis vitrectomy study (EVS) used the combination of vancomycin and amikacin though [23] the final recommendation was to use ceftazidime because of reported retinal toxicity of amikacin [24]. The choice of antibiotic can be further modified based on sensitivity spectrum.

The emergence of multidrug-resistant bacteria causing endophthalmitis is a matter of concern in India. Alternative antibiotics like imipenem or fluoroquinolones may be considered for the management of these resistant organisms [25]. In recent times, intravitreal piperacillin-tazobactam has been studied both in animal models and clinically; it is considered a useful alternative to ceftazidime [26–28].

Frequency and Safety of Repeated Intravitreal Injections

Repeat antibiotic injections are required in few circumstances—in persistent endophthalmitis and in fungal endophthalmitis [29]. Decision to repeat intravitreal antibiotic depends on subjective assessment of clinical response, microbiological

results, and toxicity of the chosen drugs. The aim of repeat dosing should be to optimize the duration of drug exposure concentration above the MIC [30, 31]. Retreatment with intravitreal antibiotics with or without vitrectomy should be considered when the treated eye is not stable/not improved after first 36–48 h or there are signs of worsening. Choice of repeat antibiotics should be guided by culture and sensitivity results of vitreous or aqueous tap.

Combination of Drugs

The ideal drug must show a good antibacterial activity against both gram-positive and gram-negative organisms, without being toxic for ocular structures, particularly the retina. Presently, no single antibiotic covers efficiently all organisms that cause endophthalmitis; a combination of at least two drugs is thus required. The practice of combining two drugs for treatment of bacterial endophthalmitis is aimed to provide a broad-spectrum cover for both gram-positive and gram-negative organisms [32]. The most commonly used combination is vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml) or amikacin (0.4 mg/0.1 ml) [33]. Imipenem can also be used with vancomycin as combination therapy in case of fulminant endophthalmitis [25].

Combining drugs may also influence the pharmacokinetics of the drugs. Studies have shown that ceftazidime and vancomycin precipitate if taken in the same syringe [33, 34] but do not lose potency of either antibiotic [35]. There is one report suggesting that adding intravitreal dexamethasone decreases the elimination time of vancomycin in inflamed eyes by stabilizing the blood-retinal barrier [36].

Antibiotic Resistance

Indiscriminate and injudicious use and abuse of antibiotics has led to development of resistant bacterial strains among both ocular and nasopharyngeal flora, as well as pathogenic organisms. Endophthalmitis caused by these organisms is associated with a stormy clinical course and worse visual outcomes [22, 37, 38]. Emerging resistance of organisms to standard antibiotic therapy needs continuous evaluation for the ideal intraocular antibiotics. In such situation, choice of antibiotics is judiciously guided by culture result and sensitivity patterns of the causative organism. But it is also known that resistance found in vitreous does not always correlate with clinical resistance and routinely administered antibiotic doses provide intraocular drug concentration higher than the MICs of most pathogens [37, 38]. A good knowledge of the pharmacokinetics and pharmacodynamics of drug, infection site, and MIC is needed to properly predict in vivo efficacy of antibiotics against target pathogen [39].

Future Trends

A few important factors that increase the therapeutic efficacy of the drug are patient compliance and comfort during drug administration. This can be achieved by various advances in ocular drug delivery such as improved drug bioavailability, prolonged duration of drug action, higher efficacy, improved safety, and less invasive administration [40].

A prodrug is defined a biologically inactive compound which can be metabolized in the body to produce an active drug, essentially in a single step (i.e., enzymatic conversion) [41]. For ocular use, intravitreally administered liposomes containing a lipid prodrug could significantly increase drug half-life and minimize the intraocular side effects of drugs. For example, intravitreal injection of liposomes containing a lipid prodrug of ganciclovir is shown to inhibit CMV retinitis in rabbits [42, 43]. Improvement in drug bioavailability is also seen in the mechanism of iontophoresis where applying an electrical current to an ionizable substance increases its mobility across a surface. A novel iontophoretic system, the EyeGate II Delivery System (EGDS; EyeGate Pharmaceuticals, Inc., Waltham, MA, USA), is designed to achieve optimal therapeutic levels of drug in the eye while simultaneously minimizing systemic distribution [44, 45].

Controlled-release drug delivery in the form of nanoparticles helps in increasing the efficacy and prolonging the duration of drug action. These nanoparticles consist of various biodegradable materials, such as natural or synthetic polymers, lipids, phospholipids, and metals. Studies have shown that nanoparticles of different sizes and electric charges, when injected into the vitreous, migrate through the retinal layers and tend to accumulate in the RPE cells up to 4 months after a single intravenous injection [46]. Also drug delivery systems in the form of nonbiodegradable and biodegradable devices or implants have been investigated [41, 47, 48].

Pharmacokinetics, safety, and efficacy of newer antibiotics and antifungals must be continually explored in view of the emerging multidrug and sometimes pan-drug resistance among organisms causing ocular infections.

Frequently Asked Questions

1. *Which is the most effective modality of antibiotic administration in endophthalmitis?*
   A: Antibiotics in the management of endophthalmitis are administered through three routes—the topical, systemic, and intravitreal. Of these three routes, intravitreal antibiotics provide 10–100-fold concentrations in vitreous; it is greater than MIC level of most organisms. Systemic antibiotics could provide concentration above MIC levels (not as high as intravitreal drug) in vitreous, but it is delayed by 2–3 days. Topical antibiotics fail to reach desired MIC level in the vitreous cavity.

2. *How to select empirical antibiotics in the management of endophthalmitis?*
   A: The need for empirical antibiotics arises because clinical evaluation usually cannot differentiate gram-positive from gram-negative infection. Hence, antibiotics that cover both gram-positive and gram-negative organisms have to be considered for effective management of bacterial endophthalmitis. Additional factors that guide us in selection of these antibiotics include:

   (a) Susceptibility pattern of the bacteria
   (b) Pharmacokinetics of intravitreal antibiotics
   (c) Safety profile of the antibiotics
   (d) Efficacy of the antibiotics

   It is important that every laboratory checks the antibiotic sensitivity of the bacteria causing endophthalmitis; this is the proven way to decide whether to continue or substitute the preinjected antibiotics in the management of endophthalmitis.

3. *When should one repeat intravitreal antibiotics?*
   A: Many times single intravitreal administration of antibiotics may be sufficient in the management of endophthalmitis; there could be certain situation where same or different antibiotics are repeated more than once. These situations include:
   (a) Persistent endophthalmitis
   (b) Recurrent endophthalmitis
   (c) Slow-growing organisms like fungus and mycobacteria
   (d) Resistance to the injected antibiotics

   Care must be taken to understand the pharmacokinetics of intravitreal drugs to prevent drug toxicity due to reinjection.

4. *What is the dose of intravitreal antibiotics in silicon-filled eyes?*
   A: Low concentration, such of one-fourth of the concentration of the antibiotics, is injected over the preretinal surface following which the silicone oil is injected. This concentration is preferred to avoid possible drug-related toxicity.

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