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Endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility: literature review and options for treatment

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Abstract

Background—Endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility and/or resistance is an important clinical issue worldwide.

Purpose—To review the published literature on endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance.

Methods—The data were analysed from a PubMed search of endophthalmitis cases caused by Gram-positive organisms with reported reduced vancomycin susceptibility and/or vancomycin resistance from 1990 to 2015.

Results—From 18 publications identified, a total of 27 endophthalmitis cases caused by Gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance were identified. The aetiologies of endophthalmitis were exogenous in 19/27 cases (11 post-cataract surgery, 2 post-penetrating keratoplasty, 1 post-glaucoma surgery, 4 post-open globe injury, 1 post-intravitreal injection of ranibizumab), and endogenous in 4/24 cases; no details were available about the four remaining patients. The causative organisms included *Enterococcus* species (7/27), coagulase-negative staphylococci (4/27), *Staphylococcus aureus* (4/27), *Bacillus* species (4/27), *Streptococcus* species (3/27), *Leuconostoc* species (3/27), *Staphylococcus hominis* (1/27), and unidentified Gram-positive cocci (1/27). Visual acuity of 20/400 or better at the final follow-up was recorded in 10/26 patients (38.5%; data were not available for one patient). Treatment options include fluoroquinolones, penicillin, cephalosporins, tetracyclines, and oxazolidinones.

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Contributors

NR collected the data and drafted the manuscript. TAA, AP, AEK, DM and HWF helped to look for relevant literature, understand the concept better and did the critical revision of manuscript. All the authors have read and approved the manuscript submitted.

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Conclusions—In the current study, visual acuity outcomes were generally poor. *Enterococcus* and *Staphylococcus* species were the most common organisms reported and postoperative endophthalmitis after cataract surgery was the most common clinical setting.

INTRODUCTION

Infectious endophthalmitis is a rare but potentially blinding disease caused by bacterial or fungal microbes involving intraocular fluids and tissues of the eye. Gram-positive organisms are the most common cause of postoperative endophthalmitis.[1] Intravitreal antibiotics (broad spectrum drugs covering Gram-positive and Gram-negative organisms) with or without vitrectomy remain standard treatment in suspected bacterial cases.

Vancomycin, a glycopeptide antibiotic, is usually effective against most Gram-positive organisms (*Streptococcus*, *Staphylococcus*, and *Bacillus* species). Vancomycin was discovered in the 1950s and approved for human use by the US Food and Drug Administration (FDA) in 1958, for the management of severe life threatening and organ threatening infections caused by susceptible organisms.[2] 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. Intravitreal injection of vancomycin has been reported in the literature to be nontoxic.[3,4] For ocular use, both intravitreal and topical vancomycin are prepared by compounding. The risk of contamination during compounding is very low in pharmacies using the US Pharmacopeia (USP) 797 guidelines in the USA.[5] As reported in the Endophthalmitis Vitrectomy Study (EVS)[6] in 1994 and the Antibiotic Resistance Monitoring in Ocular micRoganisms (ARMOR) 2009 surveillance study,[7] 100% of the Gram-positive organisms from culture positive cases were found to be susceptible to vancomycin. Endophthalmitis may also be caused by organisms which are resistant or have reduced susceptibility to standard antimicrobial regimens. Specifically, there have been recent reports of reduced vancomycin susceptible or vancomycin resistant organisms (*Streptococcus*, *Enterococcus*, *Staphylococcus*, and *Leuconostoc* species) causing endophthalmitis.[8–25]

The current study evaluates the published reports of endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance, and summarises the treatment outcomes in these patients.

METHODS

All endophthalmitis cases caused by Gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance, reported on PubMed from the years 1990 to 2015, were reviewed. The data were analysed with respect to clinical presentation, microbiological profile, management, and clinical outcomes.

RESULTS

Using these 18 reports, there were 27 endophthalmitis cases caused by Gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance.[8–25]

Detailed information of all the cases is summarised in tables 1 and 2. The ages of patients ranged from newborn to 88 years. Fourteen out of 23 patients were males (information not available for remaining four cases). The aetiologies of endophthalmitis were exogenous in 19/27 (11 post-cataract surgery, 2 post-penetrating keratoplasty, 1 post-glaucoma surgery, 4 post-open globe injury, 1 post-intravitreal ranibizumab injection), and endogenous in 4/27; no details were available about the four remaining patients.

The causative organisms included *Enterococcus* species (7/27, 6 exogenous and 1 endogenous), coagulase-negative staphylococci (4/27, 3 exogenous and 1 endogenous), *Staphylococcus aureus* (4/27, 2 exogenous and 2 endogenous), *Bacillus* species (4/27, all exogenous), *Streptococcus* species (3/27 cases), *Leuconostoc* species (3/27, both exogenous), and *Staphylococcus hominis* (1/27, exogenous). Microbiological methods used to determine antibiotic susceptibility in these reported cases included broth microdilution, disk diffusion, and culture analysis (table 3).

In the current series of the reports of endophthalmitis caused by Gram-positive organisms with reduced susceptibility and/or resistance to vancomycin, antibiotic susceptibility patterns were reported for 14 patients and nine were found to be multidrug resistant. These organisms were resistant to other drugs including fluoroquinolones (5 patients), penicillins (5 patients), cephalosporins (3 patients), and aminoglycosides (2 patients). Systemic treatment was administered in 19/27 patients. These included fluoroquinolones (11/19 cases), linezolid (5/19 cases), daptomycin (1/19 cases), and others (including rifampicin, penicillins, and cefpodoxime (tables 1 and 2)). Intravitreal antibiotics were administered in all cases. In addition, five patients (all exogenous endophthalmitis) received systemic linezolid and had favourable outcomes in 4/5 cases (complete resolution of infection and visual acuity improvement of at least two lines, except in patients whose vision was limited by coexisting pathology such as central retinal vein occlusion, age-related macular degeneration, optic atrophy, etc). Intravitreal quinupristin/dalfopristin (0.4 mg/0.1 mL) was administered in 3/27 patients, with a favourable outcome.

Visual acuity of 20/400 or better at the final follow-up was recorded in 10/26 patients (38.5%, data were not available for one patient). Six patients had enucleation or no light perception and another six patients had only light perception at the last follow-up examination.

DISCUSSION

Among all Gram-positive organisms with reduced vancomycin susceptibility, *Staphylococcus* was the most frequently isolated organism in the current study. As reported in the EVS,[2] coagulase-negative staphylococci and *Staphylococcus aureus* were the most frequently isolated organism. The first case of vancomycin resistant *Staphylococcus aureus* was reported from Japan in 1997.[26] Among *Staphylococcus aureus* isolates, the incidence of methicillin resistance has gradually increased in a more recent series.[27] In a large case series reported in 2010, 41% of *Staphylococcus aureus* endophthalmitis isolates were found to be methicillin resistant.[27] Exposure to fluoroquinolones has been identified as a risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection in hospitalised patients by

Weber *et al*[28] due to changes in adhesion and favoured colonisation. All of these cases were sensitive to vancomycin, which is used as first line intravitreal antimicrobial therapy in endophthalmitis cases.

Enterococcus species with decreased sensitivity to vancomycin (minimum inhibitory concentration (MIC) >4) was reported as early as 1957.[2930] In 1988, the first cases of vancomycin resistant *Enterococcus faecalis* and *Enterococcus faecium* (MICs ≥32 mg/mL) were reported from England,[31] 32 France,[33] Germany,[34] and the USA.[3536] In 1993, almost 14% of enterococci isolated from intensive care units (ICU) in the USA were resistant to vancomycin.[37] In 1999, a review of respiratory infections reported that 26% of the enterococcal infections seen in ICUs were vancomycin resistant.[38] Including severe sepsis and septic shock, mortality rates as high as 60–70% have been reported in patients with vancomycin resistant enterococcal (VRE) infections.[39] Among ocular infections the first case of endogenous endophthalmitis reported to be a VRE infection occurred in a 70-year-old immunosuppressed female patient (with acute myelogenous leukaemia) who was managed with multiple drugs but eventually underwent enucleation.[23] Postoperative endophthalmitis caused by *Enterococcus* species is uncommon (reported in 2–4% of the positive isolates) but all isolates were reported to be sensitive to vancomycin as per studies published in 1996 and 2005.[640]

Endophthalmitis caused by *Bacillus* species is a common isolate in open globe injury infections. In an endophthalmitis case series (1990–2007) from the USA,[41] all 22 *Bacillus* isolates were susceptible to vancomycin. Similarly in a long term (14 year, 2006–2013) study of post-traumatic endophthalmitis cases from India,[42] 95.1% (98/103) of cases were reported to be susceptible to vancomycin. However, in the current review, 4/27 cases of endophthalmitis with reported reduced vancomycin susceptibility were caused by *Bacillus* species. *Leuconostoc* species, well-known to be opportunistic infectious agents with intrinsic resistance to vancomycin,[10] 11 22 were reported in three of 27 cases in the current review. *Leuconostoc* species are microaerophilic, catalase-negative, Gram-positive cocci with high intrinsic resistance to vancomycin, and are often mistaken for *Streptococcus* species because of similar biochemical characteristics. *Leuconostoc* is a rare opportunistic infectious agent, and more often infects immunocompromised people. The current series also included cases caused by *Streptococcus* species (3/27) with reduced vancomycin susceptibility, and these three patients underwent enucleation/evisceration.[8]

In order to reduce the risk of postoperative endophthalmitis, antibiotics have been used in irrigating fluid perioperatively[4344] or injecting intracamerally[45] during cataract surgery. In the Centers for Disease Control and Prevention (CDC) guidelines for appropriate use of vancomycin[46] and the report by the Rockefeller University Workshop[47] published in 1994, the prophylactic use of vancomycin was discouraged in view of the risk of increasing the prevalence of VRE and MRSA. Because of the short duration of drug exposure, prophylactic use of vancomycin in irrigating solution was found to be ineffective against the organisms causing endophthalmitis.[48] In 2007, two postoperative endophthalmitis cases were reported[1820] with vancomycin resistant *Enterococcus* species. In 2011, endophthalmitis caused by vancomycin resistant *Staphylococcus* species was reported for the first time.[1314]

Intravitreal moxifloxacin has been utilised for the management of endophthalmitis with multidrug resistant bacteria.[49] The possible overuse of antibiotics in medical practice, the emergence of resistant organisms and of newer infections, and the promotion of antibiotics by the pharmaceutical industry may play an important role in the emergence of drug resistant strains. By the selective advantage of resistant strains in this environment, these resistant bacteria may propagate and become a significant medical liability.

The microbiology laboratory plays an important role in the diagnosis of reduced vancomycin susceptibility. Susceptibility tests with maximum accuracy should be used. Agar dilution, disk diffusion, E-test, agar screen plate, Vitek GPS-TA and GPS-101, and Microscan overnight and rapid panels are performed to test for vancomycin susceptibility in enterococci. However, the most reliable and easy screening test for detection of VanA, VanB and VanC is the agar screening method. Agar dilution, broth MIC, E-test MIC, and a few commercial tests (Microscan and Vitek 2) are performed to test for vancomycin susceptibility in *Staphylococcus aureus*. The agar dilution and broth MIC methods are CLSI (Clinical and Laboratory Standards Institute) approved.[50–52]

Systemic treatment is not universally recommended in the treatment of all endophthalmitis categories. In post-cataract surgery endophthalmitis, systemic antibiotics are not generally utilised in most cases. However, in the presence of post-traumatic or endogenous endophthalmitis, systemic antibiotics are often utilised. Vancomycin is often recommended in life threatening or organ threatening infections caused by susceptible organisms. When vancomycin resistant organisms are present, alternative antibiotics may include systemic or intravitreal linezolid, quinupristin/dalfopristin, daptomycin, tigecycline or other antibiotics to which the organism is susceptible on sensitivity testing.

Based on microbiology susceptibility tests, other treatment options include linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline (table 4) in such cases.[50–68] Multidrug resistance is an important consideration in the management of these infections. Table 5 highlights the mechanism of resistance in these organisms.[506970] Organisms labelled as vancomycin resistant should be evaluated by the tests and interpretive criteria mentioned above. For management of severe life threatening infections caused by vancomycin resistant organisms, linezolid and quinupristin/dalfopristin were the only two drugs approved by the FDA in 1999.[71]

As reported by the CDC in 2013,[72] every year two million people in the USA become infected with bacteria that are antibiotic resistant. Every year antibiotic resistance adds $20 billion (£13 billion, €18.5 billion) in excess direct healthcare costs, with additional costs to society for lost productivity as high as $35 billion (£23 billion, €32 billion) a year. To combat and halt resistance, the CDC recommends various measures for the prevention of infection and spread of resistance. These measures include immunisation, infection control actions in healthcare settings, safe food preparation and handling, general hand washing, tracking clinical data on antibiotic-resistant infections, causes of infections, root cause analysis, and antibiotic stewardship programmes.[73]

CONCLUSIONS

Vancomycin is an important first line antibiotic for the management of Gram-positive organisms causing endophthalmitis. In the current review of the literature, *Enterococcus*, *Staphylococcus* and *Streptococcus* species were the most common isolates with reduced susceptibility and/or vancomycin resistance. A significant limitation of the current review is that the various laboratory test methods used to detect drug resistance in different reports were not uniform. The cost and access to testing can be a barrier to the detection of reduced vancomycin susceptibility. In endophthalmitis patients with reduced vancomycin susceptibility and/or vancomycin resistance, visual acuity outcomes were generally poor.

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References

1. Olson JC, Flynn HW Jr, Forster RK, et al. Results in the treatment of postoperative endophthalmitis. Ophthalmology. 1983; 90:692–9. [PubMed: 6604248]
2. Levine DP. Vancomycin: a history. Clin Infect Dis. 2006; 42(Suppl 1):S5–12. [PubMed: 16323120]
3. Homer P, Peyman GA, Koziol J, et al. Intravitreal injection of vancomycin in experimental staphylococcal endophthalmitis. Acta Ophthalmol (Copenh). 1975; 53:311–20. [PubMed: 1101624]
4. Davis JL, Koidou-Tsiligianni A, Pflugfelder SC, et al. Coagulase-negative staphylococcal endophthalmitis. Increase in antimicrobial resistance. Ophthalmology. 1988; 95:1404–10. [PubMed: 3265776]
5. Shienbaum G, Flynn HW Jr. Compounding bevacizumab for intravitreal injection: does USP <797> always apply? Retina (Philadelphia, Pa). 2013; 33:1733–4.
6. Han DP, Wisniewski SR, Wilson LA, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1996; 122:1–17. [PubMed: 8659579]
7. Haas W, Pillar CM, Torres M, et al. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. Am J Ophthalmol. 2011; 152:567–74.e3. [PubMed: 21652021]
8. Kuriyan AE, Weiss KD, Flynn HW Jr, et al. Endophthalmitis caused by streptococcal species: clinical settings, microbiology, management, and outcomes. Am J Ophthalmol. 2014; 157:774–80.e1. [PubMed: 24418264]
9. Rishi E, Rishi P, Nandi K, et al. Endophthalmitis caused by Enterococcus faecalis: a case series. Retina. 2009; 29:214–17. [PubMed: 19050669]
10. Kumudhan D, Mars S. Leuconostoc mesenteroids as a cause of post-operative endophthalmitis–a case report. Eye (Lond). 2004; 18:1023–4. [PubMed: 15060561]
11. Durkin SR, Badenoch PR, Lake S, et al. Chronic postoperative endophthalmitis with isolation of Leuconostoc and Olsenella uli in an Indigenous man. Clin Experiment Ophthalmol. 2008; 36:801–2. [PubMed: 19128392]
12. Sharma S, Desai RU, Pass AB, et al. Vancomycin-resistant enterococcal endophthalmitis. Arch Ophthalmol. 2010; 128:794–5. [PubMed: 20547961]
13. Das MK, Pathengay A, Shah GY, et al. Vancomycin-resistant coagulase negative Staphylococcus endophthalmitis following cataract surgery. J Cataract Refract Surg. 2011; 37:1908–9. [PubMed: 21852070]

14. Hernandez-Da Mota SE. Quinupristin/dalfopristin in Staphylococcus aureus endophthalmitis: a case report. J Med Case Rep. 2011; 5:130. [PubMed: 21453475]
15. Stroh EM. Quinupristin/dalfopristin in vancomycin-resistant Staphylococcus aureus endophthalmitis. Arch Ophthalmol. 2012; 130:1323–4. [PubMed: 23044949]
16. Khera M, Pathengay A, Jindal A, et al. Vancomycin-resistant Gram-positive bacterial endophthalmitis: epidemiology, treatment options, and outcomes. J Ophthalmic Inflamm Infect. 2013; 3:46. [PubMed: 23607574]
17. Won JY, Kim M. Vancomycin-resistant Staphylococcus hominis endophthalmitis following cataract surgery. Clin Ophthalmol. 2013; 7:1193–5. [PubMed: 23818754]
18. Bains HS, Weinberg DV, Feder RS, et al. Postoperative vancomycin-resistant Enterococcus faecium endophthalmitis. Arch Ophthalmol. 2007; 125:1292–3. [PubMed: 17846378]
19. Hernandez-Camarena JC, Bautista-de Lucio VM, Navas A, et al. Delayed-onset post-keratoplasty endophthalmitis caused by vancomycin-resistant Enterococcus faecium. Case Rep Ophthalmol. 2012; 3:370–4. [PubMed: 23185179]
20. Tang CW, Cheng CK, Lee TS. Community-acquired bleb-related endophthalmitis caused by vancomycin-resistant enterococci. Can J Ophthalmol. 2007; 42:477–8. [PubMed: 17508051]
21. Hillier RJ, Arjmand P, Rebick G, et al. Post-traumatic vancomycin-resistant enterococcal endophthalmitis. J Ophthalmic Inflamm Infect. 2013; 3:42. [PubMed: 23514354]
22. Damasceno NP, Horowitz SA, Damasceno EF. Leuconostoc as a cause of endophthalmitis post-intravitreal injection of ranibizumab. Ocul Immunol Inflamm. 2015; 21:1–2.
23. Esmaeli B, Holz ER, Ahmadi MA, et al. Endogenous endophthalmitis secondary to vancomycin-resistant enterococci infection. Retina. 2003; 23:118–19. [PubMed: 12652247]
24. Dedania VS, Hale BP, Bhatnagar P. Endogenous endophthalmitis due to clinically vancomycin-resistant Staphylococcus aureus. Retin Cases Brief Rep. 2015; 9:59–60. [PubMed: 25383838]
25. Relhan N, Albini T, Pathengay A, et al. Bilateral endogenous endophthalmitis caused by vancomycin-resistant Staphylococcus epidermidis in a neonate. J Ophthalmic Inflamm Infect. 2015; 5:11. [PubMed: 25883685]
26. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. Lancet. 1997; 350:1670–3. [PubMed: 9400512]
27. Major JC Jr, Engelbert M, Flynn HW Jr, et al. Staphylococcus aureus endophthalmitis: antibiotic susceptibilities, methicillin resistance, and clinical outcomes. Am J Ophthalmol. 2010; 149:278–83.e1. [PubMed: 19926069]
28. Weber SG, Gold HS, Hooper DC, et al. Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis. 2003; 9:1415–22. [PubMed: 14718085]
29. Barry AL, Thornsberry C, Jones RN. Evaluation of teicoplanin and vancomycin disk susceptibility tests. J Clin Microbiol. 1986; 23:100–3. [PubMed: 2939101]
30. Chandrasekar PH, Price S, Levine DP. In-vitro evaluation of cefpirome (HR 810), teicoplanin and four other antimicrobials against enterococci. J Antimicrob Chemother. 1985; 16:179–82. [PubMed: 2933380]
31. Johnson AP, Uttley AH, Woodford N, et al. Resistance to vancomycin and teicoplanin: an emerging clinical problem. Clin Microbiol Rev. 1990; 3:280–91. [PubMed: 2143434]
32. Uttley AH, Collins CH, Naidoo J, et al. Vancomycin-resistant enterococci. Lancet. 1988; 1:57–8.
33. Leclercq R, Derlot E, Duval J, et al. Plasmid-mediated resistance to vancomycin and teicoplanin in Enterococcus faecium. N Engl J Med. 1988; 319:157–61. [PubMed: 2968517]
34. Lutticken R, Kunstmann G. Vancomycin-resistant Streptococcaceae from clinical material. Zentralbl Bakteriol Mikrobiol Hyg A. 1988; 267:379–82. [PubMed: 3376618]
35. Sahm DF, Kissinger J, Gilmore MS, et al. In vitro susceptibility studies of vancomycin-resistant Enterococcus faecalis. Antimicrob Agents Chemother. 1989; 33:1588–91. [PubMed: 2554802]
36. Vincent S, Knight RG, Green M, et al. Vancomycin susceptibility and identification of motile enterococci. J Clin Microbiol. 1991; 29:2335–7. [PubMed: 1939593]

37. Centers for Disease Control and Prevention (CDC). Nosocomial enterococci resistant to vancomycin—United States, 1989–1993. MMWR Morb Mortal Wkly Rep. 1993; 42:597–9. [PubMed: 8336690]
38. McGeer AJ, Low DE. Vancomycin-resistant enterococci. Semin Respir Infect. 2000; 15:314–26. [PubMed: 11220414]
39. Edmond MB, Ober JF, Dawson JD, et al. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. Clin Infect Dis. 1996; 23:1234–9. [PubMed: 8953064]
40. Recchia FM, Busbee BG, Pearlman RB, et al. Changing trends in the microbiologic aspects of postcataract endophthalmitis. Arch Ophthalmol. 2005; 123:341–6. [PubMed: 15767476]
41. Miller JJ, Scott IU, Flynn HW Jr, et al. Endophthalmitis caused by Bacillus species. Am J Ophthalmol. 2008; 145:883–8. [PubMed: 18295182]
42. Jindal A, Pathengay A, Mithal K, et al. Endophthalmitis after open globe injuries: changes in microbiological spectrum and isolate susceptibility patterns over 14 years. J Ophthalmic Inflamm Infect. 2014; 4:5. [PubMed: 24548669]
43. Gills JP. Filters and antibiotics in irrigating solution for cataract surgery. J Cataract Refract Surg. 1991; 17:385.
44. Sobaci G, Tuncer K, Tas A, et al. The effect of intraoperative antibiotics in irrigating solutions on aqueous humor contamination and endophthalmitis after phacoemulsification surgery. Eur J Ophthalmol. 2003; 13:773–8. [PubMed: 14700098]
45. Anijeet DR, Palimar P, Peckar CO. Intracameral vancomycin following cataract surgery: an eleven-year study. Clin Ophthalmol. 2010; 4:321–6. [PubMed: 20463800]
46. Preventing the spread of vancomycin resistance—a report from the Hospital Infection Control Practices Advisory Committee prepared by the Subcommittee on Prevention and Control of Antimicrobial-Resistant Microorganisms in Hospitals; comment period and public meeting—CDC. Notice. Fed Regist. 1994; 59:25758–63. [No authors listed]. [PubMed: 10136017]
47. Tomasz A. Multiple-antibiotic-resistant pathogenic bacteria. A report on the Rockefeller University Workshop. N Engl J Med. 1994; 330:1247–51. [PubMed: 8139650]
48. Gritz DC, Cevallos AV, Smolin G, et al. Antibiotic supplementation of intraocular irrigating solutions. An in vitro model of antibacterial action. Ophthalmology. 1996; 103:1204–8. discussion 08–9. [PubMed: 8764788]
49. Jacobs DJ, Grube TJ, Flynn HW Jr, et al. Intravitreal moxifloxacin in the management of Ochrobactrum intermedium endophthalmitis due to metallic intraocular foreign body. Clin Ophthalmol. 2013; 7:1727–30. [PubMed: 24039392]
50. Howden BP, Davies JK, Johnson PD, et al. Reduced vancomycin susceptibility in Staphylococcus aureus, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clin Microbiol Rev. 2010; 23:99–139. [PubMed: 20065327]
51. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 16th informational supplement. Vol. 26. Clinical and Laboratory Standards Institute; 2006.
52. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Vol. 26. Clinical and Laboratory Standard Institute; 2009.
53. Nailor MD, Sobel JD. Antibiotics for gram-positive bacterial infections: vancomycin, teicoplanin, quinupristin/dalfopristin, oxazolidinones, daptomycin, dalbavancin, and telavancin. Infect Dis Clin North Am. 2009; 23:965–82, ix. [PubMed: 19909893]
54. Fiscella RG, Lai WW, Buerk B, et al. Aqueous and vitreous penetration of linezolid (Zyvox) after oral administration. Ophthalmology. 2004; 111:1191–5. [PubMed: 15177970]
55. Duke SL, Kump LI, Yuan Y, et al. The safety of intraocular linezolid in rabbits. Invest Ophthalmol Vis Sci. 2010; 51:3115–19. [PubMed: 20042664]
56. Saleh M, Jehl F, Dory A, et al. Ocular penetration of topically applied linezolid in a rabbit model. J Cataract Refract Surg. 2010; 36:488–92. [PubMed: 20202550]
57. Sueke H, Kaye S, Neal T, et al. Minimum inhibitory concentrations of standard and novel antimicrobials for isolates from bacterial keratitis. Invest Ophthalmol Vis Sci. 2010; 51:2519–24. [PubMed: 20019362]

58. Finch RG. Antibacterial activity of quinupristin dalfopristin—rationale for clinical use. Drugs. 1996; 51:31–7. [PubMed: 8724814]
59. Williamson JC, Glazier SS, Peacock JE Jr. Successful treatment of ventriculostomy-related meningitis caused by vancomycin-resistant Enterococcus with intravenous and intraventricular quinupristin/dalfopristin. Clin Neurol Neurosurg. 2002; 104:54–6. [PubMed: 11792478]
60. Auckenthaler R, Courvalin P, Féger C, et al. International Study Working G. In vitro activity of quinupristin/dalfopristin in comparison with five antibiotics against worldwide clinical isolates of staphylococci. Clin Microbiol Infect. 2000; 6:608–12. [PubMed: 11168064]
61. Lorian V, Fernandes F. Synergic activity of vancomycin-quinupristin/dalfopristin combination against Enterococcus faecium. J Antimicrob Chemother. 1997; 39A:63–6.
62. Gupta M, Durand ML, Sobrin L. Vancomycin resistance in ocular infections. Int Ophthalmol Clin. 2011; 51:167–81. [PubMed: 21897149]
63. Coskun E, Okumus S, Gurler B, et al. Comparison of intravitreal vancomycin and daptomycin application in experimental methicillin-resistant Staphylococcus aureus (MRSA) endophthalmitis in rabbits. Cutan Ocul Toxicol. 2013; 32:222–7. [PubMed: 23368969]
64. Buzzacco DM, Carroll CP. Intravitreal daptomycin in a case of bilateral endogenous endophthalmitis. Arch Ophthalmol. 2012; 130:940–1. [PubMed: 22776941]
65. Sakarya R, Sakarya Y, Ozcimen M, et al. Ocular penetration of topically applied 1% daptomycin in a rabbit model. J Ocul Pharmacol Ther. 2013; 29:75–8. [PubMed: 23020811]
66. Ozcimen M, Sakarya Y, Ozcimen S, et al. Pharmacokinetics of intravenously administered tigecycline in eye compartments: an experimental study. Graefes Arch Clin Exp Ophthalmol. 2014; 252:1993–7. [PubMed: 25150050]
67. Horozoglu F, Metan G, Sever O, et al. Intravitreal tigecycline treatment in experimental Acinetobacter baumannii endophthalmitis. J Chemother. 2012; 24:101–6. [PubMed: 22546766]
68. Goktas S, Kurtoglu MG, Sakarya Y, et al. New therapy option for treatment of methicillin-resistant Staphylococcus aureus keratitis: tigecycline. J Ocul Pharmacol Ther. 2015; 31:122–7. [PubMed: 25330310]
69. Arthur M, Courvalin P. Genetics and mechanisms of glycopeptide resistance in enterococci. Antimicrob Agents Chemother. 1993; 37:1563–71. [PubMed: 8215264]
70. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev. 2000; 13:686–707. [PubMed: 11023964]
71. Jones DB. Emerging vancomycin resistance: what are we waiting for? Arch Ophthalmol. 2010; 128:789–91. [PubMed: 20547959]
72. Health UDo, Services H. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: Centers for Disease Control and Prevention; 2013. http://www.cdc.gov/drugresistance/threat-report
73. Holzmann-Pazgal G, Khan AM, Northrup TF, et al. Decreasing vancomycin utilization in a neonatal intensive care unit. Am J Infect Control. 2015; 43:1255–7. [PubMed: 26277573]

Table 1

Reported cases of reduced vancomycin susceptible organisms causing exogenous endophthalmitis: clinical features, microbiology and treatment outcomes[8–25]

Category (Author/year)	Age/sex	VA (initial)	VA (final)	Treatment	Topical antibiotics	Systemic antibiotics	Isolates	Comment (outcome/ coexisting pathology)
After cataract surgery								
Kumudhan *et al*, 2004	76/M	LP	HM	VB+IOAB (V+A)	CFC, G	CFC	*Leuconostoc mesenteroides*	(U)
Durkin *et al*, 2008	43/M	CF	20/40	VB+IOAB (V+C), PPV+IOAB (V+C)	NA	None	*Leuconostoc* species	(F)
Sharma *et al*, 2010	73/F	CFCF	20/200	PPV+IOAB (V+C)	Ch, G	Linezolid	*Enterococci* species	(F) ARMD
Das *et al*, 2011	57/M	HM	20/60	VB+IOAB (V+A)	MFC	None	CNS	(F) RD
Hernandez-Da Mota *et al*, 2011	55/M	HM	20/40	VB+IOAB (Q/D+C+D)	NA	None	CNS	(F)
Stroh *et al*, 2012	83/M	HM	20/50	PPV+ACW+RW+IOAB (Q/D+C) IOAB−Q/D+A	V,C	Linezolid+minocycline—21 days, and R+M—3 months	*Staphylococcus aureus*	(F)
	78/M	LP	CF	PPV+ACW+RW+IOAB (V+C) IOAB (V+C) IOAB (Q/D+A)	V,C	Linezolid + minocycline—21 days, and R+M—3 months	*Staphylococcus aureus*	(F) CRVO
Khera *et al*, 2013	70/F	LP	LP	PPV+IOAB+IOL explants	V+A	Gatifloxacin	*Staphylococcus epidermidis*	(U)
	70/M	LP	20/20	PPV+IOAB	V+A	CFC	*Bacillus* species	(F)
	60/M	LP	LP	PPV+IOAB	V+C	CFC	*Enterococcus faecalis*	(U)
Won *et al*, 2013	80/M	CF	20/400	VB+IOAB (V+C) PPV+SOI +IOL explant	Tp+V	–	*Staphylococcus hominis*	(F)
After PK								
Bains *et al*, 2007	73/F	LP	20/80	PPV+IOAB (V+A)	V+G	Linezolid+ampicillin	*Enterococcus faecium*	(F) Pale disc
Hernandez *et al*, 2012	51/F	LP	LP	PPV+IOAB (V+C+D)	MFC, Cef	Linezolid for 1 week (iv)	*Enterococcus* species	(U)
After glaucoma surgery								
Tang *et al*, 2007	79/F	HM	HM (30 cm)	PPV+PPL+IOAB (V+A) IOAB – ampicillin	NA	Penicillin G	*Enterococcus faecalis*	(U)
After open globe								
Hillier *et al*, 2013	88/M	HM	20/200	PPV+PPL+IOFB−R+IOAB (V+C+D) IOAB – ampicillin +Amikacin	G	Ampicillin+clindamycin followed by MFC	*Enterococcus gallinarum*	(F) RD
Khera *et al*, 2013	20/M	LP	CF 1 m	CTR+PPV+IOAB (V+C) and PPV+membranectomy+IOAB (C+T)	CFC	CFC	*Bacillus macerrans*	(U)
	5/M	LP	LP	CTR+PPL+PPV+IOAB (V+C+A)	CFC	CFC	*Bacillus cereus*	(U)
	4/F	HM	LP	CTR+PPL+PPV+IOAB (V+C)	CFC	CFC	*Bacillus* species	(U)
After intravitreal injection								
Damasceno *et al*, 2015	89/M	LP	NLP	VB+IOAB (V+A), IOAB (A) twice	MFC	Gatifloxacin	*Leuconostoc* species	(U)

This table excludes the four cases reported in references 5 and 6 as complete details were not available.

(F), favourable outcome; (U), unfavourable outcome; A, amikacin; ACW, anterior chamber wash; ARMD, age related macular degeneration; C, ceftazidime; Cef, ceftriaxone; CF 1 m, counting fingers at 1 m; CFC, ciprofloxacin; CFCF, counting fingers close to face; CF, counting fingers; Ch, chloramphenicol; CNS, coagulase-negative staphylococci; CRVO, central retinal vein occlusion; CTR, corneal tear repair; d, days; D, dexamethasone; F, female; G, gentamicin; HM, hand motions; IOAB, intravitreal antibiotics; IOFB-R, intraocular foreign body removal; iv, intravenous; LP, light perception; M, male; MFC, moxifloxacin; M, minocycline; NA, information not available; NLP, no light perception; PK, penetrating keratoplasty; PPL, pars plana lensectomy; PPV, pars plana vitrectomy; Q/D, quinupristin/dalfopristin; RD, retinal detachment; R, rifampin; RW, resuturing of wound; SOI, silicone oil injection; Tp, teicoplanin; T, triamcinolone; V, vancomycin; VA, visual acuity; VB, vitreous biopsy.

Table 2

Reported cases of reduced vancomycin susceptible organisms causing endogenous endophthalmitis: clinical features, microbiology and treatment outcomes[1623–25]

Category (author/year)	Age/ sex	VA (initial)	VA (final)	Treatment	Topical antibiotics	Systemic antibiotics	Isolates	Comments (outcome)
Esmaeli *et al*, 2003	70/F	LP	Enuc	IOAB (V+C)	NA	Rifampin+cefepime +trovafloxacin+alatrofloxacin	Enterococci	(U) Enucleation
Khera *et al*, 2013	16/F	LP	Enuc	PPV+IOAB	CFC	CFC	*Staphylococcus aureus*	(U) Enucleation
Dedania *et al*, 2014	48/F	HM	LP	IOAB (V+C) IOAB (clinda+amika)	NA	Vancomycin, daptomycin	*Staphylococcus aureus*	(U)
Relhan *et al*, 2015	18d/M	–	FL	VB+IOAB (V+C+D), IOAB (P/T)	CFC	Cefpodoxime	Coagulase-negative staphylococci	Good

(F), favourable; (U), unfavourable; Amika, amikacin; C, ceftazidime; CFC, ciprofloxacin; D, dexamethasone; Enuc, enucleation; F, female; FL, follows light; HM, hand motions; IOAB, intravitreal antibiotics; LP, light perception; M, male; NA, information not available; P/T, piperacillin-ticarcillin; PPV, pars plana vitrectomy; V, vancomycin; VA, visual acuity; VB, vitreous biopsy.

Table 3

Sensitivities of reduced vancomycin susceptible isolates reported in literature[12–212325]

Report (Author/year)	Isolates	Sample used	Susceptibility method used	Alternative sensitive antibiotics	Resistance in addition to vancomycin
Sharma *et al*, 2010	*Enterococcus* species	Vitreous culture	Vitek-2	Ch, linezolid, Q/D	Ampicillin, LFC, erythromycin, penicillin, streptomycin, tetracycline, CFC
Das *et al*, 2011	CNS	Vitreous culture	Disk diffusion	–	GFC, OFC, CFC, MFC (I), piperacillin-tazobactam (I)
Hernandez-Da Mota *et al*, 2011	CNS	Vitreous culture	In vitro tests not performed. Clinically responsive to Q/D	NA	–
Stroh *et al*, 2012	*Staphylococcus aureus*	Aqueous & Vitreous culture	Vitek-2	Ch, linezolid, Q/D	MFC, clindamycin, imipenem, methicillin,
Bains *et al*, 2007	*Enterococcus faecium*	Aqueous, Vitreous & donor corneal rim culture	MIC—broth microdilution (MIC 64 mg/mL)	NA	–
Tang *et al*, 2007	*Enterococcus faecalis*	Vitreous culture	Information not available	Ampicillin, penicillin	All common antibiotics (not mentioned in paper)
Hillier *et al*, 2013	*Enterococcus gallinarum*	Vitreous culture	Information not available	Ampicillin, clindamycin	–
Esmaeli *et al*, 2003	*Enterococcus* species	Vitreous culture	Information not available	NA	–
Khera *et al*, 2013	*Bacillus*, *Staphylococcus*, *Enterococcus* species	Vitreous culture	Disk diffusion	CFC, G, amikacin CFC, GFC –	Cefazolin, chloramphenicol Ofloxacin, A, Ch, G Cefazolin, CFC, OFC, A, G Ch, ceftazidime
Hernandez-Camarena *et al*, 2012	*Enterococcus faecium*	Vitreous culture	MIC—broth microdilution (MIC 32 mg/mL)	Linezolid, tetracycline	–
Won *et al*, 2013	*Staphylococcus hominis*	Vitreous culture	MIC—broth microdilution (MIC 8–16 mg/mL)	TMP/SMZ, teicoplanin	LFC, MFC, CFC, cefazolin
Relhan *et al*, 2014	CNS	Vitreous culture	Disk diffusion	G, piperacillin-tazobactam	Ampicillin, erythromycin

(I), intermediate sensitivity; A, amikacin; CFC, ciprofloxacin; Ch, chloramphenicol; CNS, coagulase-negative staphylococci; GFC, gatifloxacin; G, gentamicin; LFC, levofloxacin; MFC, moxifloxacin; MIC, minimum inhibitory concentration; NA, data not available; OFC, ofloxacin; Q/D, quinupristine-dalfopristine; TMP/SMZ, trimethoprim-sulfamethoxazole.

Table 4

Treatment options for infections caused by reduced vancomycin susceptibility—listed by generic (and commercial) names

	Linezolid (Zyvox)[50–54]	Quinupristine/dalfopristine (Synercid)[55–57]	Daptomycin (Cubicin)[58–62]	Tigecycline (Tygacil)[63–68]
Class	Oxazolidinone (fermentation byproduct of *Streptomyces roseosporus*)	Streptogramin (isolated from *Streptomyces pristinaespiralis*)	Cyclic lipopeptide	Glycylcycline (a derivative of minocycline)
Mechanism of action	Inhibits initiation of protein synthesis by binding 23S rRNA of the 50S subunit of bacterial ribosome	Inhibits bacterial protein synthesis by interfering with function of 23S RNA (quinidine: dalfopristine=3:7)	Terminates bacterial DNA, RNA and protein synthesis and cell death by forming transmembrane channels in cell membrane and depolarisation of membrane potential	Inhibits bacterial protein synthesis by irreversibly binding to 30 S ribosomal unit
Route and dose	*Oral*—600 mg twice daily *Intravenous*—600 mg twice daily *Intravitreal*—300 mg/0.1 mL (rabbits) *Topical*—2 mg/mL (rabbits)	*Intravenous*—7.5 mg/kg 8 hourly *Intravitreal*—0.4 mg/0.1 mL *In vitro*—MIC_{90} 0.5–2 mg/L	*Intravenous*—4–6 mg/kg per day *Intravitreal*—200 mg/0.05 mL (rabbits) Topical—1% (rabbits)	*Intravenous*—100 mg/100 ml over 30–60 min followed by 50 mg twice daily *Intravitreal*—0.5–1 mg/0.1 mL (rabbits) *Topical*—10–50 mg/mL (rabbits)
Side effects with systemic dose	Reversible myelosuppression, irreversible peripheral neuropathy, optic neuropathy (when used for >14 days)	Arthralgia, myalgia, pain and Periphlebitis at injection site	Not significant Minor gastrointestinal disturbances	Hypersensitivity-like reaction
Spectrum of activity	GPO, MRSA, VRSA, VISA, VRE, CNS, GNO, mycobacteria	MRSA, VISA, VRSA, *Streptococcus* species, CNS	VRSA, VRE, *Staphylococcus*, *Streptococcus*, *Enterococcus* species	MSSA, MRSA, VISA, VRE, *Escherichia coli* and *Klebsiella pneumonia*
Others	First pharmacologically active oxazolidinone (fermentation byproduct of *Streptomyces roseosporus*). Good intraocular availability after intravenous and oral administration	First intravitreal (0.4 mg/0.1 mL) use of quinupristin/dalfopristin acute postoperative endophthalmitis in 2011	Pharmacokinetics are linear at dose of 4–12 mg/kg/day. Available only in intravenous formulation	Minimum inhibitory concentration 90 (MIC90) of MDR bacteria range from 0.12–4 μg/mL

CNS, coagulase-negative staphylococci; FDA, US Food and Drug Administration; GNO, Gram-negative organism; GPO, Gram-positive organisms; MDR, multidrug resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; VISA, vancomycin intermediate sensitive *Staphylococcus aureus*; VRE, vancomycin resistant *Enterococcus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

Table 5

Mechanisms of reduced vancomycin susceptibility or vancomycin resistance among various strains of *Enterococcus* and *Staphylococcus* species

Organisms	Mechanism of reduced vancomycin susceptibility
Enterococci	By acquisition of following genotypes: VanA/VanB/VanC/VanD/VanE
Staphylococci Fully resistant strains Strains with reduced vancomycin susceptibility ►Vancomycin intermediate *Staphylococcus aureus* ►Heterogeneous VISA (hVISA)	By acquisition of VanA gene from vancomycin resistant enterococci (VRE) By having mutations in either graRS/vraSR/walKR operon leading ultimately to cell wall thickening, decreased autolysis, reduced protein A production, increased capsule expression, increased D-alanylation of teichoic acid, and reduced accessory gene regulator (agr) activity. These are the vancomycin susceptible *Staphylococcus aureus* strains which upon subculture produce subcolonies with vancomycin resistance