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Case report

Endophthalmitis caused by gram-positive bacteria resistant to vancomycin: Clinical settings, causative organisms, antimicrobial susceptibilities, and treatment outcomes

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ABSTRACT

Purpose: To report the clinical settings, causative organisms, antimicrobial susceptibilities, and treatment outcomes of patients with endophthalmitis caused by gram-positive bacteria resistant to vancomycin.

Methods: Retrospective case series of all patients with culture-proven endophthalmitis caused by gram-positive bacteria resistant to vancomycin between January 2010 and December 2016 in LV Prasad Eye Institute, Visakhapatnam, India.

Results: The current study included 14 patients. The clinical settings were post-cataract surgery in 8/14 (57.1%) and open globe injury in 6/14 (42.8%). Primary intervention for all patients included tap and intravitreal antibiotic injection. During subsequent follow-up, pars plana vitrectomy was performed in 6 patients and one patient underwent penetrating keratoplasty. Mean number of intravitreal antibiotic injections performed were 3.4 per patient. The most common organisms isolated were coagulase-negative *Staphylococci* in 6/14 (42.8%), *Staphylococcus aureus* in 5/14 (35.7%), *Streptococcus* sp in 2/14 (14.2%) and *Bacillus* sp in 1/14 (7.14%). In addition to vancomycin, resistance to multiple drugs (three or more groups of antibiotics) was found in all 14 cases. Antimicrobial susceptibility results showed susceptibility to amikacin in 7/14 (50.0%), gatifloxacin in 6/14 (42.8%), moxifloxacin in 3/13 (23.0%), cefazoline in 5/14 (35.7%), cefuroxime in 3/14 (21.4%), ciprofloxacin in 2/14 (14.2%) and linezolid in 5/5 (100%). The mean duration of follow-up was 30.7 weeks (6 weeks–90 weeks). At last follow-up, visual acuity (VA) of 20/200 or better was recorded in 7/14 (50%) and VA < 5/200 occurred in 7/14 (50%).

Conclusion and importance: Antimicrobial susceptibility testing may help in selection of suitable antimicrobial agents for repeat intravitreal injection. Inspite of retreatment with intravitreal antibiotics, these patients generally had poor VA outcomes.

1. Introduction

Endophthalmitis is sight threating condition which is most commonly caused by gram-positive bacteria. Multidrug resistance though rare is an emerging concern in the management of endophthalmitis.[1] Antibiotic resistance among ocular pathogens is increasing as is worldwide systemic antibiotic resistance. Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a more common cause of ocular infection.[2,3] Previous studies have noted the changing trends in the antibiotic susceptibility of the causative organisms in endophthalmitis.[4–7] Vancomycin, a glycopeptide antibiotic, is considered for empirical coverage of most gram-positive organisms (Streptococcus, Staphylococcus, and Bacillus spp.) causing endophthalmitis.

There are only few reports of vancomycin resistance noted to occur in Enterococcus, Staphylococcus and Bacillus spp. associated with endophthalmitis.[8,9] The purpose of this study is to evaluate clinical settings, antimicrobial susceptibility and treatment outcomes in endophthalmitis caused by vancomycin resistant gram-positive bacteria.

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2. Methodology

The current study is a retrospective case series of patients with culture-proven endophthalmitis caused by gram-positive bacteria resistant to vancomycin between January 2010 and December 2016 managed in LV Prasad Eye Institute, Visakhapatnam. The institutional review board approved the study (IRB protocol no: LEC-09-16-018), and adhered to the guidelines of the declaration of Helsinki. Individual treating physician decided the treatment without a predefined study protocol. The undiluted vitreous biopsy samples were subjected to microbiology analysis with Gram stain and KOH for microscopy, and inoculated for culture growth directly onto 5% sheep blood agar, chocolate agar, thioglycollate, and brain-heart infusion broth and Sabouraud dextrose agar. When same organism was noted growing on two or more media, or confluent growth was noted at the site of inoculation on at least one solid medium, or if the growth on medium was consistent with microscopy findings, the culture was considered positive. Kirby Bauer disk diffusion technique was utilized to test for antibiotic susceptibility testing. Favorable outcome was defined as best corrected visual acuity (BCVA) of 20/200 or better at last follow-up.

3. Results

Among 126 culture-positive bacterial endophthalmitis, there were 14/126 (11.11%) patients with endophthalmitis caused by gram-positive bacteria resistant to vancomycin cases. In addition to vancomycin, resistance to multiple drugs (three or more groups of antibiotics), was reported in all 14 (100%) patients. Mean age at the time of treatment was 43.7 years (range 3–70 years). There was no gender predisposition (M: F = 7:7). The clinical setting was post-cataract surgery in 8/14 (57.1%) patients and open globe injury in 6/14 (42.8%) patients. Visual acuity at presentation was poor in all 14 patients (counting fingers – 3 patients, hand motions – 5 patients, light perception 6 patients). The organisms isolated were coagulase-negative *Staphylococci* in 6/14 (42.8%) patients, *Staphylococcus aureus* in 5/14 (35.7%) patients, *Streptococcus* spp. in 2/14 (14.2%) patients and *Bacillus* spp. in 1/14 (7.1%) patient.

Primary intervention for all patients included tap and intravitreal antibiotic injection (Table 1). During subsequent follow-up, pars plana vitrectomy was performed in 6 patients and one patient underwent penetrating keratoplasty. Mean number of intravitreal antibiotic injections performed were 3.4 per patient. Antimicrobial susceptibility results showed susceptibility to amikacin in 7/14 (50.0%), gatifloxacin in 6/14 (42.8%), cefazoline in 5/14 (35.7%), moxifloxacin in 3/13 (23.0%), cefuroxime in 3/14 (21.4%), ciprofloxacin in 2/14 (14.2%) and linezolid in 5/5 (100%) isolates. Linezolid was tested in isolates of 5 patients only in which 5/5 (100%) were sensitive and in those 5 patients, second intravitreal injection with linezolid (400 μg/0.1 ml) was administered.[10] Mean duration of follow-up was 30.7 weeks (6–90 weeks). Among the 7/14 (50%) patients with visual acuity of 20/200 or better at final follow-up, the causative organisms were coagulase-negative *Staphylococcus* in 4 cases and *Staphylococcus aureus* in 3 cases. However, among the patients with visual acuity of 5/200 or worse [7/14 (50%)] at final follow-up, the causative organisms were *Streptococcus* species in 2 cases, coagulase-negative *Staphylococcus* in 2 cases, *Staphylococcus aureus* in 2 cases, and Bacillus species in 1 case. There was no definite correlation between the causative organism and visual outcome. Visual acuity outcomes are influenced by multiple factors including etiology of endophthalmitis, causative organisms, resistance/susceptibility pattern of causative organisms, associated injuries and comorbidities, delay in presentation and other ocular/systemic factors. Furthermore, in view of the small sample size, no definitive clinical or statistical significance can be confirmed.

4. Discussion

Vancomycin is commonly used antibiotic for infections caused by gram-positive bacteria, and acts by inhibiting cell wall synthesis. Vancomycin blocks the transglycosylation of late precursors to the nascent peptidoglycan chain as it has a high affinity to the d-Ala d-Ala C-terminus of the pentapeptide, and prevents subsequent cross-linking by transpeptidation.[11]

Organisms may acquire resistance to antibiotics by inherent or acquired mechanisms.[12] Vancomycin resistant bacteria are increasingly reported and is now encountered across the globe. Reduced susceptibility to vancomycin has been noted in multiple bacterial species including *Enterococcus*, *Staphylococcus* and *Streptococcus* species.[1,11,13] An isolate of methicillin-resistant *Staphylococcus aureus* (MRSA) with decreased susceptibility to vancomycin was first reported in Japan in 1997.[14] Esmaeli et al., in 2003, reported a case of endophthalmitis caused by *Enterococcus faecalis* isolate resistant to vancomycin.[15] Vancomycin was advised as an initial empirical antibiotic against gram-positive organisms even before the EVS.[4,16] In the Endophthalmitis Vitrectomy Study (EVS) in 1994 and the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study, 100% of gram-positive organisms were found to be susceptible to vancomycin. In a PubMed review of all endophthalmitis cases reported from the years 1990–2015, endophthalmitis caused by gram-positive organisms with reduced vancomycin susceptibility and/or vancomycin resistance, revealed generally poor visual outcomes.[1]

Antimicrobial Susceptibility Testing - In the current study, fluoroquinolone resistance was reported in 4/5 (80%) *Staphylococcus aureus* isolates, 6/6 (100%) of coagulase-negative *Staphylococcus* isolates with 2 isolates susceptible to only gatifloxacin, 1/2 (50%) of *Streptococcus* isolates. Emerging resistance to fluoroquinolones has been documented for ocular gram-positive organisms.[17,18] Resistance to fluoroquinolones typically arises as a result of alteration in the target enzyme (topoisomerase IV) and of changes in drug entry.[19] In current series, there was poor susceptibility to fluoroquinolones among isolates, with only 42.8% susceptible to gatifloxacin, 23.0% susceptible to moxifloxacin and 14.2% susceptible to ciprofloxacin. In a retrospective data analysis of endophthalmitis isolates reported that non-susceptibility of CoNS to all three generations of fluoroquinolones increased over the time-period of 22 years significantly.[20] Non-susceptibility to amikacin was reported in 7/14 (50%) of isolates in the current study. Antimicrobial susceptibility test for linezolid was performed for 5/14 patients and all were susceptible to linezolid. All 14 cases were noted to have multidrug resistance. Resistance to three or more other group of antibiotics is reported in literature.[21]

In the current study, mean number of intravitreal antibiotic injections performed were 3.4 per patient. The second intravitreal antibiotic injection was performed after the antimicrobial susceptibility reports became available. However, in 3 patients (patient # 5, 6 and 7 in Table 1) second antibiotic injection was performed before the susceptibility report was available as the clinical status was worsening. Intravitreal linezolid was used in the management of 5 patients based on the antimicrobial susceptibility testing and all these patients. In the current study, coagulase-negative Staphylococcus was the most common vancomycin-resistant organism, there is a possibility that this may be simply due to the fact that coagulase-negative Staphylococcus is the most common organism associated with postoperative endophthalmitis (particularly cataract surgery).

Although there is limited experience in patients, the management of endophthalmitis caused by gram-positive bacteria resistant to vancomycin may include alternative antibiotics such as quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline.[22] Experimental (*in-vivo* and *in-vitro)* studies have reported safety and efficacy of intravitreal use of these alternative antibiotics.[1] There are no published large clinical case series on the intravitreal use of these newer drugs, but the current study does provide some insight into this topic.

Table 1
Baseline characteristics, clinical setting, causative organism, management, and clinical outcomes of the patients with endophthalmitis caused by gram-positive bacteria resistant to vancomycin.

S.no	Age/sex	Clinical setting	Duration of symptoms (days)	Culture report	VA at presentation	Primary intervention	Second intervention	No. of IOAB	Follow-up duration (weeks)	Antimicrobial susceptibility Results	Final VA
1	45/M	Trauma	3	*Bacillus species*	LP	CTR + T&I (V + A)	A + D	2	12	S – C, CFC, GFC, A Int – MFC R—V, Cefa, OFC	NLP
2	70/F	Postoperative	20	*Staphylococcus aureus*	LP	PPV + T&I (V + A + D)	Cefa + D	4	16	S – Cefa, A, T Int - MFC R—V, C, CFC, OFC, GFC,	LP
3	3/M	Trauma	3	*Staphylococcus aureus*	LP	PPL + PPV + T&I (V + I + D)	Cefa + D[a]	5	24	S – C, Cefa, Int– CFC, MFC R—V, OFC, GFC, A	CF
4	54/F	Postoperative	45	Coagulase-negative Staphylococcus	CF	PPV + T&I (V + C + D)	A + D[a]	5	56	S - A R—V, C, Cefa, CFC, OFC, GFC, MFC, T	20/200
5	57/M	Postoperative	30	Coagulase-negative Staphylococcus	HM	AC Tap + T&I (V + A + D)	Cefa + D[a]	2	8	S – C, GFC Int– MFC, Cefa R—V, CFC, OFC, A	LP
6	31/M	Trauma	1	Coagulase-negative Staphylococcus	LP	CTR + BB + PPL + PPV + IOFBR, T&I (V + A + D)	Cefa + D[a]	2	90	S – C, GFC, Int – MFC,Cefa R—V, CFC, OFC, A	20/40
7	4/M	Trauma	3	Streptococcus species	LP	CTR + T&I (V + A + D)	Cefa + [a]	3	12	S – C, T Int– V, CFC R – Cefa, OFC, GFC, A, MFC	CF
8	5/F	Trauma	5	*Streptococcus pneumoniae*	LP	PPL + PPV + T&I (V + A + D)	Cefa + D[a]	4	20	S – C, Cefa, CFC, GFC, MFC, T R—V, OFC, A	LP
9	56/F	Postoperative	6	*Staphylococcus aureus*	HM	T&I (V + A + D)	L + D	2	78	S – A, L Int– C, MFC R—V, Cefa, CFC, OFC, GFC	20/40
10	36/M	Trauma	5	Coagulase-negative Staphylococcus	HM	PPL + PPV + IOFBR + T&I (V + I + D)	Cefa + D	4	36	S – C, Cefa, Int - CFC R—V, A, OFC, GFC	20/200
11	67/M	Postoperative	2	*Staphylococcus aureus*	HM	T&I (V + I + D)	L + D	5	36	S – CFC, OFC, GFC, MFC, L R—V, C, Cefa, A	20/60
12	51/F	Postoperative	3	Coagulase-negative Staphylococcus	CF	T&I (V + I + Vor + AmpB)	Cefa + D	3	24	S – C, Cefa, L Int – CFC, A, MFC R—V, OFC, GFC,	20/30
13	66/F	Postoperative	10	Coagulase-negative Staphylococcus	CF	T&I (V + I + D)	L + D	2	6	S – A, MFC, L Int – Cefa, CFC R—V, C, OFC, GFC	LP
14	68/F	Postoperative	5	*Staphylococcus aureus*	HM	T&I (V + I + D)	L + D[b]	5	12	S - L R—V, C, CFC, GFC, OFC, MFC, Cefa, A	20/125

Abbreviations: A, amikacin; AC, anterior chamber; AmpB, amphotericin-B; BB, belt buckle; C, ceftazidime; Cefa, cefazoline; CF-counting fingers; CFC, ciprofloxacin; CTR, corneal tear repair; D, dexamethasone; F, female; G, gatifloxacin; HM, hand motions; I, imipenum; IOFBR, intraocular foreign body removal; Int, intermediate; L, linezolid; LP, light perception; M, male; MFC, moxifloxacin; NLP, no light perception; OFC, ofloxacin; PPL, pars plana lensectomy; PPV, pars plana vitrectomy; T, tazobactum; T&I, tap and inject; V, vancomycin; VA, visual acuity; Vor, voriconazole.

[a] Pars Plana Vitrectomy was performed on subsequent follow-up.

[b] Penetrating keratoplaty was performed at subsequent follow-up.

Linezolid is active against most gram-positive organisms, including species of *Staphylococcus* and *Enterococcus* including those with reduced vancomycin susceptibility.[23] Linezolid, an oxazolidinone antibiotic inhibits protein synthesis and is active in vitro against vancomycin-resistant *Enterococcus*, MRSA, vancomycin-resistant *Staphylococcus aureus*, and penicillin-resistant *Streptococcus pneumoniae*. In 2007, Bains et al. reported the use of systemic linezolid in the successful treatment of endophthalmitis following penetrating keratoplasty caused by vancomycin resistant *E. faecium*.[24] Safety profile and efficacy of intraocular linezolid has been investigated in experimental studies with in rabbits.[10,25]

Antimicrobial susceptibility testing guides the management in patients not responding to the initial management. However, in patients without the availability of susceptibility testing, various alternative options can be considered. It is also important to be aware of susceptibility/resistance patterns with respect to geographical area for appropriate and timely use of alternative antimicrobials. In patients where antimicrobial susceptibility testing is not available or cannot be performed due to high cost or culture-negative vitreous specimen, these options can be considered.

Some antimicrobials (such as amikacin and cefazolin) are primarily reserved for treatment of gram-negative organisms. However, in patients with infections caused by gram-positive organisms which are susceptible only to either amikacin or cefazolin, the use of these antimicrobial agents is justified.

Overall, favorable visual outcomes were noted in 50% patients. Visual outcomes at final follow-up were better in cases with Staphylococcus infection compared to Streptococcal infection. Improvement in visual acuity from baseline was reported in 3/5 (60%) of *Staphylococcus aureus* infection, 4/6 (67%) of *Staphylococcus epidermidis* infection and 0/2 (0%) of Streptococcus infections. Final Visual acuity 20/200 or better was noted in 5/8 (62.5%) cases in post-operative endophthalmitis and 2/6 (33.3%) in post-traumatic endophthalmitis. This difference in the visual outcomes among post-operative and post-traumatic endophthalmitis cases can be due to different causative organisms, variable virulence of the causative organisms, delay in presentation, and concurrent associated injuries.

The current study is limited by its retrospective nature, the small sample size, and the antimicrobial susceptibility testing performed only by Kirby Bauer disk diffusion method. Kirby Bauer testing may not be as accurate or reliable as the microdilution method. However, Kirby Bauer method is less expensive, less time consuming, and reasonably accurate compared to the microdilution method.

5. Conclusion

In the current study of 14 endophthalmitis cases caused by gram-positive organisms with reduced susceptibility to vancomycin, the most common organism identified was coagulase-negative *Staphylococcus* in a postoperative setting. Antimicrobial susceptibility testing may help in selection of suitable antimicrobial agents for repeat intravitreal injection. With the limited published data and authors' experience, the use of alternative agents can be considered when vancomycin resistance is documented or clinically suspected. Inspite of retreatment with intravitreal antibiotics, these patients generally had poor VA outcomes.

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Conflicts of interest

None of the authors have any financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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