HHS Public Access

Author manuscript

Ophthalmol Retina. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Ophthalmol Retina. 2017 ; 1(3): 206–209. doi:10.1016/j.oret.2016.11.010.

The Susceptibility of Bacterial Endophthalmitis Isolates to Vancomycin, Ceftazidime, and Amikacin: a 23 Year-Review

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Abstract

Purpose—To investigate the *in vitro* susceptibility of Gram-positive and Gram-negative endophthalmitis bacterial isolates to vancomycin, amikacin, and ceftazidime over a 23-year period.

Design—Retrospective non-comparative laboratory case series.

Subjects—Endophthalmitis patients that were culture positive for bacteria.

Methods—Laboratory records of bacteria isolated from endophthalmitis specimens collected from January 1st 1993 to December 31st 2015 were reviewed for incidence and standard susceptibility testing.

Main outcome measures—The *in vitro* susceptibilities of bacteria cultured from endophthalmitis to vancomycin (VAN), amikacin (AMK), and ceftazidime (CEF).

Results—Patients with endophthalmitis were culture positive for bacteria in 665 cases.. Coagulase negative *Staphylococci* (CoNS) were the most common bacteria (54.6%), followed by *Streptococci* (Strep) species (20.8%), *Staphylococcus aureus* (SA) (10.2%), other Gram-positive (other-GP) bacteria (7.4%) and Gram-negative (GN) bacteria (7.1%). All Gram-positive organisms were susceptible to VAN, with the exception of 2 isolates. The *in vitro* susceptibilities of bacteria to AMK were: CoNS (95.3%), SA (75.0%), Strep (8.0%), GN (95.7%), and other-GP (81.1%). The *in vitro* susceptibilities of bacteria to CEF were: CoNS (58.5%), SA (54.4%), Strep (84.1%), GN (93.6.%), and other-GP (52.8%). There was no difference between AMK (95.7%) and CEF (93.6%) for GN coverage. AMK provided better coverage than CEF for CoNS, SA, and other-GP bacteria respectively ($p<0.05$, Fisher's exact), however, CEF appeared to provide better coverage ($p<0.001$, Fisher's exact) for Strep than AMK.

Conclusions—Based on standard *in vitro* susceptibility testing, vancomycin remains an optimal antibiotic choice for the treatment of Gram-positive endophthalmitis. AMK and CEF appear to

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No conflicting relationship exists for any author.

provide equal GN coverage, but AMK appears to provide better coverage for CoNS, SA, and other-GP, but not Strep.

Introduction

Infectious endophthalmitis is a rare and typically severe intraocular infection that can occur following either intraocular surgery or traumatic injury to the eye, as well as metastatic spread from an endogenous infection. Prompt treatment is mandatory in order to minimize severe vision loss and ocular morbidity. Samples of intraocular fluid are sent for culture while broad-spectrum intravitreal antimicrobial therapy is initially started. In cases of culture positive endophthalmitis, antibiotic therapy is subsequently tailored to the cultured microbe once culture results are available.[1, 2]

Both in order to continue to optimally treat bacterial endophthalmitis and to minimize the risk of post-procedure endophthamitis with prophylactic antibiotics, an understanding of endophthalmitis microbial spectra and antibiotic susceptibility patterns are important. This information is important in either influencing a change in management or confirming that current practices are optimal.

Vancomycin is established as first-line therapy in the treatment of Gram-positive (GP) bacterial endophthalmitis, while amikacin or ceftazidime are typically used for Gram-negative (GN) coverage[2]. There are few reports of vancomycin resistant GP bacteria in endophthalmitis[3]. Given the increasing concern with the emergence of vancomycin resistance in systemic bacterial infections, using an antibiotic combination where both antibiotics are effective against GP isolates would be beneficial and may indeed become a factor in determining the choice of the 2nd antibiotic. The purpose of this study was to investigate the *in vitro* susceptibility of Gram-positive and Gram-negative endophthalmitis bacterial isolates to vancomycin, amikacin, and ceftazidime over a 23-year period.

Methods

This was a retrospective non-comparative laboratory case series. The microbiology laboratory records of bacterial cultures isolated from culture positive bacterial endophthalmitis at the Charles T. Campbell Eye Microbiology Lab, University of Pittsburgh Medical Center, a regional tertiary referral center between January 1st 1993 to December 31st 2015 were reviewed. These data are used for determining susceptibility profiles for the in-house and community ophthalmology practices as mandated by College of American Pathologist certification (CAP, Northfield, IL). These data are de-identified to protect the privacies of the patient. Clinical presentations, circumstances, and outcomes are not available in laboratory records. *In vitro* susceptibility to vancomycin (VAN), amikacin (AMK) and ceftazidime (CEF) was assessed using the Kirby Bauer disk diffusion method with serum breakpoint standard interpretations.[4] The intravitreal concentrations of the tested antibiotics are higher than can be achieved systemically, thus the serum standards may over report resistance.

Specimens were obtained from varying combinations of anterior chamber, vitreous and vitrectomy samples. Study outcome measures included bacterial species identified, as well

as *in vitro* susceptibility of these identified organisms to vancomycin, ceftazidime and amikacin.

Results

1. Endophthalmitis isolates

A total of 665 bacterial endophthalmitis isolates were cultured over the 23-year study period.

2. Spectrum of organisms

92.9% of isolates were Gram-positive and 7.1% were Gram-negative. Coagulase negative Staphylococci (CoNS) were the commonly cultured bacteria (54.6%), followed by Streptococci (20.8%) and *Staphylococcus aureus* (10.2%). Other Gram-positive bacteria accounted for 7.4% of isolates. Amongst the Gram-negative bacteria isolated, *Serratia marcescens* (1.2%), Haemophilus species (1.2%) and *Pseudomonas aeruginosa* (1.1%) were the mostly frequently cultured organisms. An overview of the isolates cultured is provided in table 1.

3. Susceptibility of Gram-positive isolates to Vancomycin

All Gram-positive bacteria, with the exception of 2 isolates (*Lactobacillus* and *Fusobacterium varium*) were susceptible to vancomycin, including all Coagulase negative Staphylococci, Streptococci and *Staphylococcus aureus* cultures (table 2).

4. Susceptibility of Gram-negative isolates to Ceftazidime and Amikacin

A total of 93.6% of Gram-negative isolates were susceptible to ceftazidime and 95.7% were susceptible to amikacin. Amongst the most commonly isolated Gram-negative organisms, all *Serratia marcescens* isolates were susceptible to ceftazidime and amikacin. 87.5% of Haemophilus cultures were susceptible to ceftazidime and 100% to amikacin. Lastly, 85.7% of *Pseudomonas aeruginosa* isolated were susceptible to ceftazidime and amikacin. Table 3 depicts the susceptibility of Gram-negative isolates to both ceftazidime and amikacin. Overall, there were a total of 3 GN isolates resistant to ceftazidime and 2 GN isolates resistant to amikacin, this included the same Pseudomonas isolate resistant to both antibiotics.

5. Susceptibility of Gram-positive isolates to Ceftazidime and Amikacin

Next, in order to determine if dual coverage of Gram-positive isolates is attainable with the use of either ceftazidime or amikacin, the susceptibility of the cultured Gram-positive isolates to both ceftazidime and amikacin was reviewed. Overall, there was no significant difference between amikacin (89.8%) and ceftazidime (91.8%) for Gram-negative coverage. However, amikacin provided better coverage than ceftazidime for Coagulase negative Staphylococci, *Staphylococcus aureus*, and other-GP bacteria ($p<0.05$, Fisher's Exact). In contrast, ceftazidime appeared to provide better coverage ($p<0.001$, Fisher's Exact) for Streptococci than amikacin.

Discussion

The prompt diagnosis and immediate initiation of treatment in infectious endophthalmitis is a critical factor in ensuring a successful outcome and minimizing ocular morbidity [5]. The appropriate empiric treatment of infectious endophthalmitis requires an understanding of the likely causative microbes, as well as their susceptibility profile. In this current study, we report the spectrum of endophthalmitis bacterial isolates cultured over a 23-year period at our institution. Notably, our sample size of 665 cultured isolates makes this study one of the largest reviews of endophthalmitis isolates reported. Our results show that Gram-positive bacteria (92.9%) account for the majority of bacterial endophthalmitis cultured isolates, with Gram-negative bacteria only accounting for 7.1% of cultures. This data is consistent to other recently published reviews of endophthalmitis isolates (table 4) [6-11], with the exception of the data reported by Reddy et. al. from Hyderabad, India [12]. The high proportion of Gram-negative isolates observed in this study may be in part due to the number of reported post-traumatic cases as well as environmental factors.

Similarly, our demonstration of coagulase negative Staphylococci being the most frequently cultured Gram-positive isolate, followed by Streptococci and *Staphylococcus aureus*, is also consistent with prior reports. Given the increasing concern at the emergence of vancomycin resistance in the treatment of systemic infections and the few reports of *in vitro* Gram-positive vancomycin resistance rates reported in Gram-positive endophthalmitis cultures [13], we sought to review the rate of vancomycin resistance in our Gram-positive isolates. Our rate of Gram-positive vancomycin resistance was extremely low. Indeed, all Gram-positive bacteria, with the exception of 2 isolates were susceptible to vancomycin. Although the majority of published reports have demonstrated a low or zero rate of vancomycin resistance, the differing incidence of vancomycin resistance may in part be explained by geographic factors. Two recent studies published in North America reported a 100% and a 99.7% susceptibility of their Gram-positive isolates to vancomycin [6, 7]. Reddy et al. in their data set from Hyderabad, India also noted a 100% susceptibility of their Gram-positive isolates to vancomycin [12]. Additionally, Moloney and co-authors in Queensland, Australia similarly published a 100% susceptibility rate of their Gram-positive isolates to Vancomycin [6]. In contrast, Khera et al. at LV Prasad Eye Institute, India reported vancomycin resistance in 7 or 1.56% of their Gram-positive endophthamitis cultures [13]. Based on our data and other recent reports, it appears that the concern for vancomycin resistance that is present in systemic infections is not applicable in this setting and that vancomycin remains a suitable first choice for empiric therapy. The high susceptibility rates of Gram-positive isolates to vancomycin consistently observed may be the result of the high vitreous concentrations of antibiotic consistently achieved following intravitreal injection[14].

Our data did not show a statistically significant difference in the susceptibility of cultured Gram-negative isolates to either amikacin or ceftazidime. Jindal et al., in their series from LV Prasad, Hyderabad, reported an 18.5% rate of resistance in their Gram-negative isolates to both amikacin and ceftazidime [15]. In contrast, our results showed a low rate of multidrug resistant Gram-negative isolates, with only 1 Pseudomonas isolate resistant to both amikacin and ceftazidime. Ongoing surveillance is necessary to ensure that multi-drug resistant endophthalmitis isolates are not emerging.

Despite the susceptibility of Gram-positive isolates to vancomycin, the Gram-positive spectrum of coverage provided by either amikacin or ceftazidime may become a factor in their selection in empiric therapy. Our data showing that overall, amikacin provides better Gram-positive coverage compared to ceftazidime, may influence its use in preference to ceftazidime. To the best of our knowledge, the susceptibility of Gram-positive endophthalmitis isolates to either amikacin or ceftazidime has not been addressed in such a comprehensive manner.

In conclusion, based on *in vitro* studies, vancomycin remains an optimal antibiotic choice for the treatment of Gram-positive endophthalmitis. Amikacin and ceftazidime appear to provide equal Gram-negative coverage, but amikacin provides better coverage for the majority of Gram-positive isolates, with the exception of Streptococci. Despite the improved complementary coverage provided by amikacin, retinal toxicity may be a concern.

Acknowledgments

Financial support: National Institutes of Health CORE Grant P30 EY008098, Eye and Ear Foundation of Pittsburgh, PA and an unrestricted grant from Research to Prevent Blindness, New York, NY.

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Table 1

Bacteria isolated from the intraocular fluid of patients diagnosed with endophthalmitis

Isolates	Number	Percentage
Coagulase negative staphylococci	363	54.6%
Streptococci	138	20.8%
Staphylococcus aureus	68	10.2%
Other Gram-positive	49	7.4%
Propionibacterium acnes	15	2.3%
Bacillus cereus	13	2.0%
Diphtheroids	12	1.8%
Remaining Gram-positive	9	1.4%
Gram-negative	47	7.1%
Haemophilus species	8	1.2%
Serratia marcescens	8	1.2%
Pseudomonas aeruginosa	7	1.1%
Moraxella species	3	0.5%
Other Gram-negative	21	3.2%
Total	**665**	

Table 2

Susceptibility of Gram-positive isolates to vancomycin

Isolates	Number	Percentage
Coagulase negative staphylococci	363	100.0%
Streptococci	138	100.0%
Staphylococcus aureus	68	100.0%
Other Gram-positive	35	94.6%
Total		**99.7%**

Table 3
Susceptibility of bacterial isolates to ceftazidime and amikacin

Isolates	Susceptible to CEF		Susceptible to AMK	
	Number	Percentage	Number	Percentage
Total Gram-positive	383	63.5%	436	72.2%
Coagulase negative staphylococci *	211	58.5%	344	95.3%
Streptococci (SA) **	116	84.1%	11	8.0%
Staphylococcus aureus *	37	54.4%	51	75.0%
Other Gram-positive *	19	52.8%	30	81.1%
Total Gram-negative	**44**	**93.6%**	**44**	**95.7%**
Serratia marcescens	8	100%	8	100%
Haemophilus species	7	87.5%	8	100%
Pseudomonas aeruginosa	6	85.7%	6	85.7%
Moraxella species	3	100.00%	2	100%
Other Gram-negative	20	95.2%	20	95.2%

* $p<0.05$

** $p<0.001$

Table 4

Review and comparison of bacterial endophthalmitis isolates

	UPMC	NYEEI	BPEI	Hyderabad, India	Queensland, Australia
Study period	1993-2015	1987-2011	2002-2011	2010-2013	1998-2013
No of Isolates	665	943	375	196	193
Gram-positive (GP)	92.9%	89.2%	87.2%	37.2%	84.5%
Susceptibility of GP isolates to vancomycin	99.7%	99.7%	100%	100%	100%
Gram-negative (GN)	7.10%	10.80%	12.8%	62.8%	15.5%
Susceptibility of GN isolates to amikacin	95.7%	92.9%	not included	87.0%	100%
Susceptibility of GN isolates to ceftazidime	93.6%	91.5%	100%	82.0%	100%

UPMC = University of Pittsburgh Medical Center; NYEEI = New York Eye and Ear Infirmary [6]; BPEI = Bascom Palmer Eye Institute [7]; Hyderabad, India [12]; Queensland, Australia [8]