



VANDERBILT UNIVERSITY
MEDICAL CENTER

Intravitreal Triple Therapy with Vancomycin, Ceftazidime, and Moxifloxacin for Bacterial Endophthalmitis

Stephen Jae Kim, MD, Kenneth Taubenslag, MD, Shriji Patel, MD

Vanderbilt University Medical Center

Vanderbilt Eye Institute



VANDERBILT UNIVERSITY
MEDICAL CENTER

Financial Disclosures

■ None



Vanderbilt Eye Institute



Summary

- Antibiotic resistance is prevalent and a major healthcare concern
- Intravitreal moxifloxacin (160 μ g) was well tolerated
- Visual acuity outcomes of eyes with endophthalmitis after cataract surgery treated with intravitreal moxifloxacin in addition to standard therapy compared favorably to those in the Endophthalmitis Vitrectomy Study treated with standard therapy alone





Acknowledgement

- Special thanks to Kenneth Taubenslag, MD for his primary role in this research



Vanderbilt Eye Institute



Background

- Increasing antibiotic resistance ¹
- Acute-onset bacterial endophthalmitis
 - vancomycin for gram-positive coverage
 - either ceftazidime or an aminoglycoside for gram-negative coverage
- Endophthalmitis Vitrectomy Study (EVS)
 - All gram-positive isolates (94.2%) were susceptible to vancomycin
 - 11% of gram-negative isolates (6.5%) were resistant to both amikacin and ceftazidime ²
 - Gram-negative infections had worse visual outcomes



1. Dave SB, Toma HS, Kim SJ. Changes in ocular flora in eyes exposed to ophthalmic antibiotics. *Ophthalmology*. 2013;120(5):937

2. Han DP, Wisniewski SR, Wilson LA, Barza M, Vine AK, Doft BH, Kelsey SF. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. *Am J Ophthalmol*. 1196;122(1):1-17.



Questions

- Is vancomycin and a 3rd or 4th generation cephalosporin (ceftazidime) enough coverage for causative organisms in 2020?
- Is single coverage for gram-negative bacteria adequate?

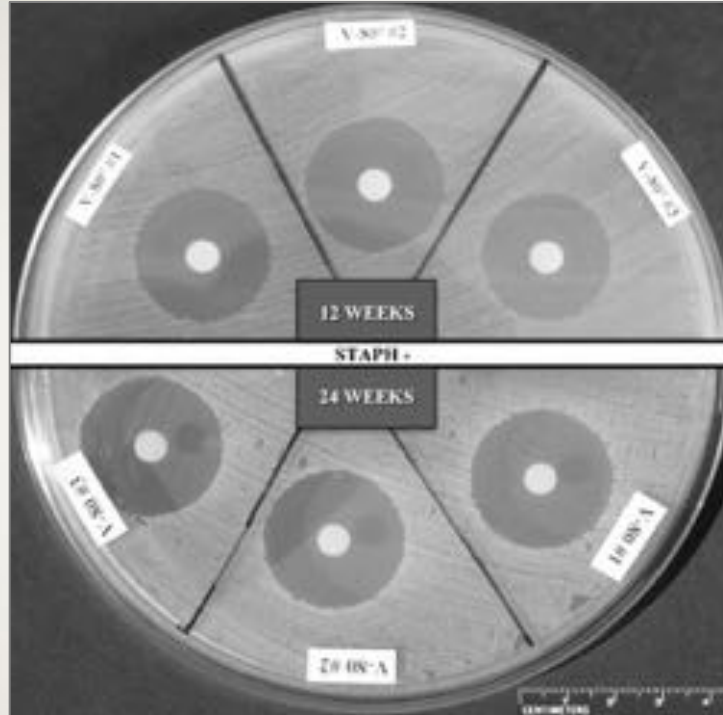


Moxifloxacin

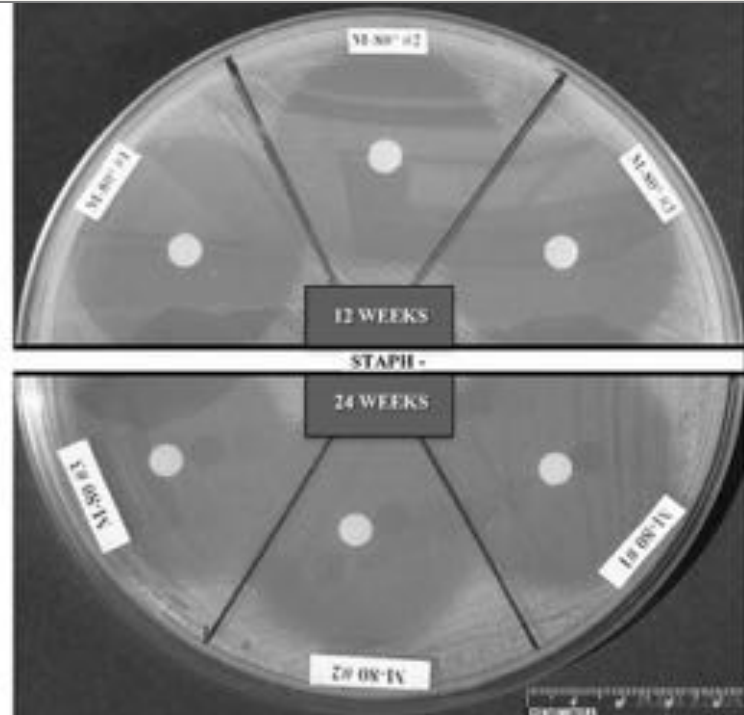
- *Broad-spectrum* 4th generation quinolone that is active against both gram-positive and gram-negative bacteria
- Inhibits DNA gyrase and topoisomerase IV, enzymes necessary to unwind bacterial DNA for replication



Vancomycin



Moxifloxacin



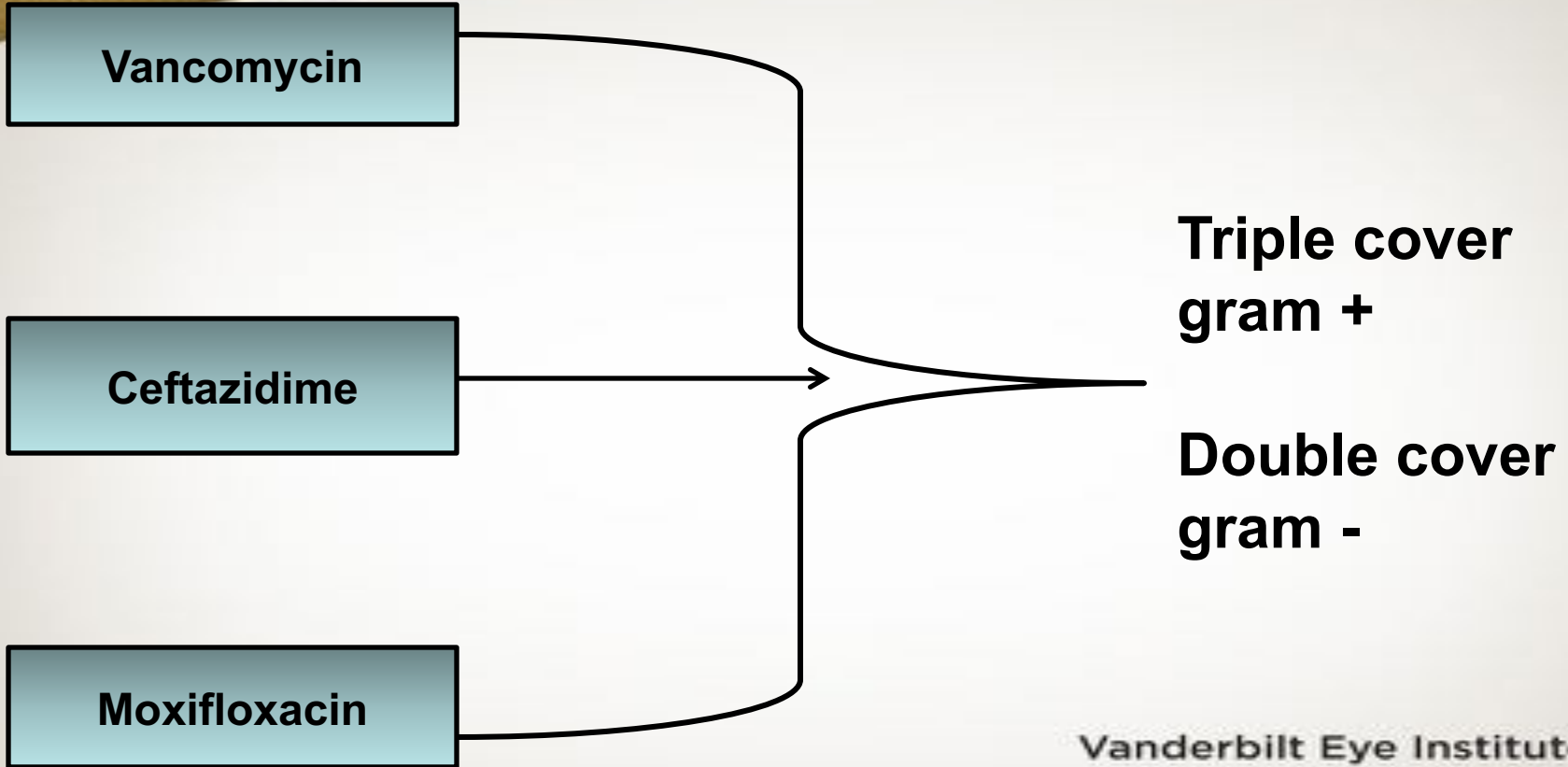


- Oral administration of 400 mg moxifloxacin results in intravitreal drug levels that exceeded the mean inhibitory concentration (MIC) 90 (1.2 $\mu\text{g/ml}$) of many bacteria implicated in endophthalmitis ¹
- Intravitreal injection of moxifloxacin at a concentration of $\leq 160 \mu\text{g}/0.1 \text{ ml}$ was nontoxic in rabbit eyes ^{2,3}

1. Lott MN, Fuller JJ, Hancock HA, Singh J, Singh H, McGwin G Jr, Marcus DM. Vitreal penetration of oral moxifloxacin in humans. *Retina*. 2008;28(3):473-6.
2. Gao H, Pennesi ME, Qiao X, Iyer MN, Wu SM, Holz ER, Mieler WF. Intravitreal moxifloxacin: retinal safety study with electroretinography and histopathology in animal models. *Invest Ophthalmol Vis Sci*. 2006;47(4):1606-11.
3. Aydin E, Kazi AA, Peyman GA, Esfahani MR. Intravitreal toxicity of moxifloxacin. *Retina*. 2006;26(2):187-90.



Added Coverage





Synergy

- “the interaction of two or more agents to produce a combined effect greater than the sum of their separate effects”
- Combination of a penicillin and aminoglycoside significantly reduces the MIC of each antibiotic

SYNERGY

$$1 + 1 = 3$$



Mechanism of Action

- Vancomycin: inhibits cell wall synthesis
 - Not effective against most gram-negative bacteria
- Ceftazidime: inhibits cell wall synthesis
 - Effective against pseudomonas aeruginosa
 - Ineffective against MRSA
- Moxifloxacin: inhibits cell replication



Purpose

- To examine visual and safety outcomes of patients with bacterial endophthalmitis treated with:
 - vancomycin 1mg
 - ceftazidime 2mg
 - moxifloxacin 160 μ g



Methods

- Single-center retrospective review of all patients treated for endophthalmitis from January 2009 to August 2019
- Inclusion criteria:
 - Bacterial endophthalmitis
 - Treatment with intravitreal vancomycin, ceftazidime, and moxifloxacin: “triple therapy”
- Patients with less than 3 months follow-up were excluded
- Patients could receive topical or systemic antibiotics and steroids at discretion of treating physician



Primary Outcomes

- Percent of eyes attaining $\geq 20/200$ Snellen visual acuity
- Percent of eyes attaining $\geq 20/50$ Snellen visual acuity
- Adverse effects



Overall Results

- 94 eyes met inclusion criteria
- 51 of 94 eyes (54%) achieved a final visual acuity of $\geq 20/200$
- 29 of 94 eyes (31%) achieved a final visual acuity of $\geq 20/50$

Table 1. Baseline Characteristics

	All patients (n=94)	Post-cataract (n=18)	Post-injection (n=18)	Bleb-associated (n=10)
Age, y Median (range)	64 (15-95)	67 (43-80)	72 (54-95)	66 (53-88)
Right eye	43 (46%)	8 (44%)	6 (33%)	8 (80%)
Female	47 (50%)	11 (61%)	11 (61%)	5 (50%)
Black	13 (14%)	1 (6%)	2 (11%)	6 (60%)
History of Diabetes	22 (23%)	2 (11%)	6 (33%)	1 (10%)
History of Glaucoma	23 (24%)	2 (11%)	4 (22%)	10 (100%)
History of AMD	14 (15%)	1 (6%)	11 (61%)	0
Days from procedure median (range)	—	5 (1-80)	3 (2-7)	—
Visual acuity				
≤LP	32 (34%)	2 (11%)	2 (11%)	4 (40%)
HM	32 (34%)	8 (44%)	7 (39%)	3 (30%)
CF (<5/200)	17 (18%)	4 (22%)	5 (22%)	1 (10%)
≥5/200	13 (14%)	4 (22%)	4 (28%)	2 (20%)
Intraocular pressure				
0-5	1 (1%)	1 (6%)	0	0
6-25	71 (76%)	16 (88%)	12 (66%)	6 (60%)
>25	22 (23%)	1 (6%)	4 (22%)	4 (40%)

ute



Subgroup Analysis

- Visual acuity survival curves were superior for patients with post-cataract endophthalmitis compared to post-injection ($P < 0.005$) or bleb-associated ($P < 0.005$)

Figure 1

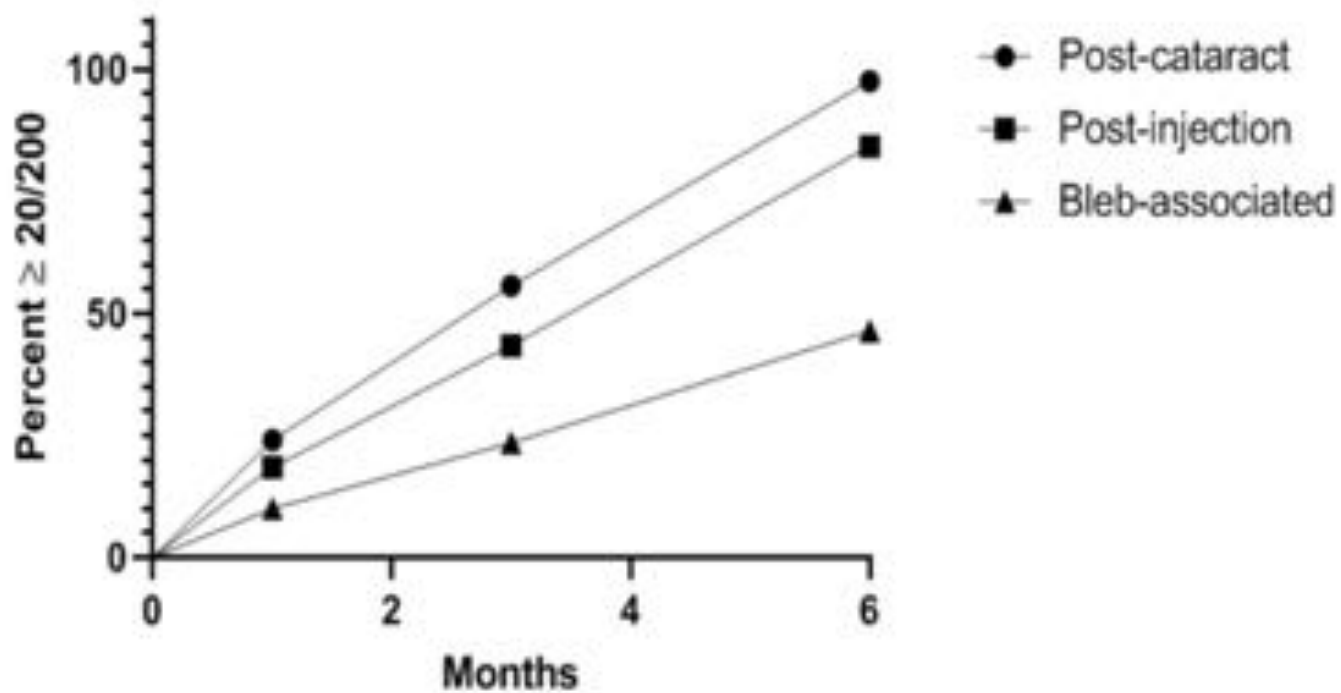
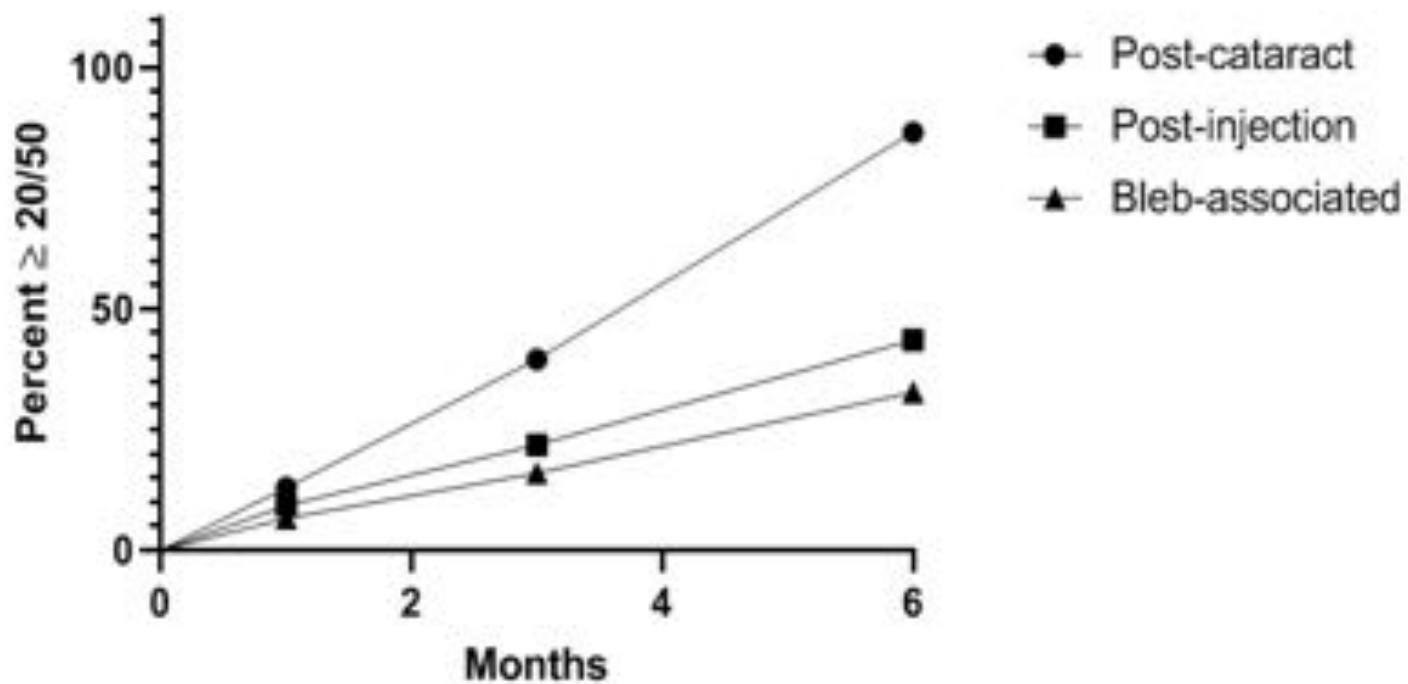


Figure 2





Post-cataract

- 17 of 18 (94%) eyes with post-cataract endophthalmitis obtained $\geq 20/200$ visual acuity (78% of patients achieved $\geq 20/200$ in EVS)¹
- 14 of 18 (77%) obtained $\geq 20/50$ visual acuity (59% of patients achieved $\geq 20/50$ in EVS)¹

1. Results of the Endophthalmitis Vitrectomy Study: A Randomized Trial of Immediate Vitrectomy and of Intravenous Antibiotics for the Treatment of Postoperative Bacterial Endophthalmitis. *Arch Ophthalmol.* 1995;113(12):1479–1496.



Safety of Moxifloxacin

- No cases of macular infarction
- No higher rates of retinal detachment
- No cases of excessive inflammation



Conclusions

- Intravitreal moxifloxacin (160 μ g) appeared to be well tolerated
- Visual acuity outcomes of post-cataract endophthalmitis group treated with triple therapy compared favorably to EVS
- Addition of moxifloxacin to standard treatment with vancomycin and ceftazidime for acute bacterial endophthalmitis may be advantageous

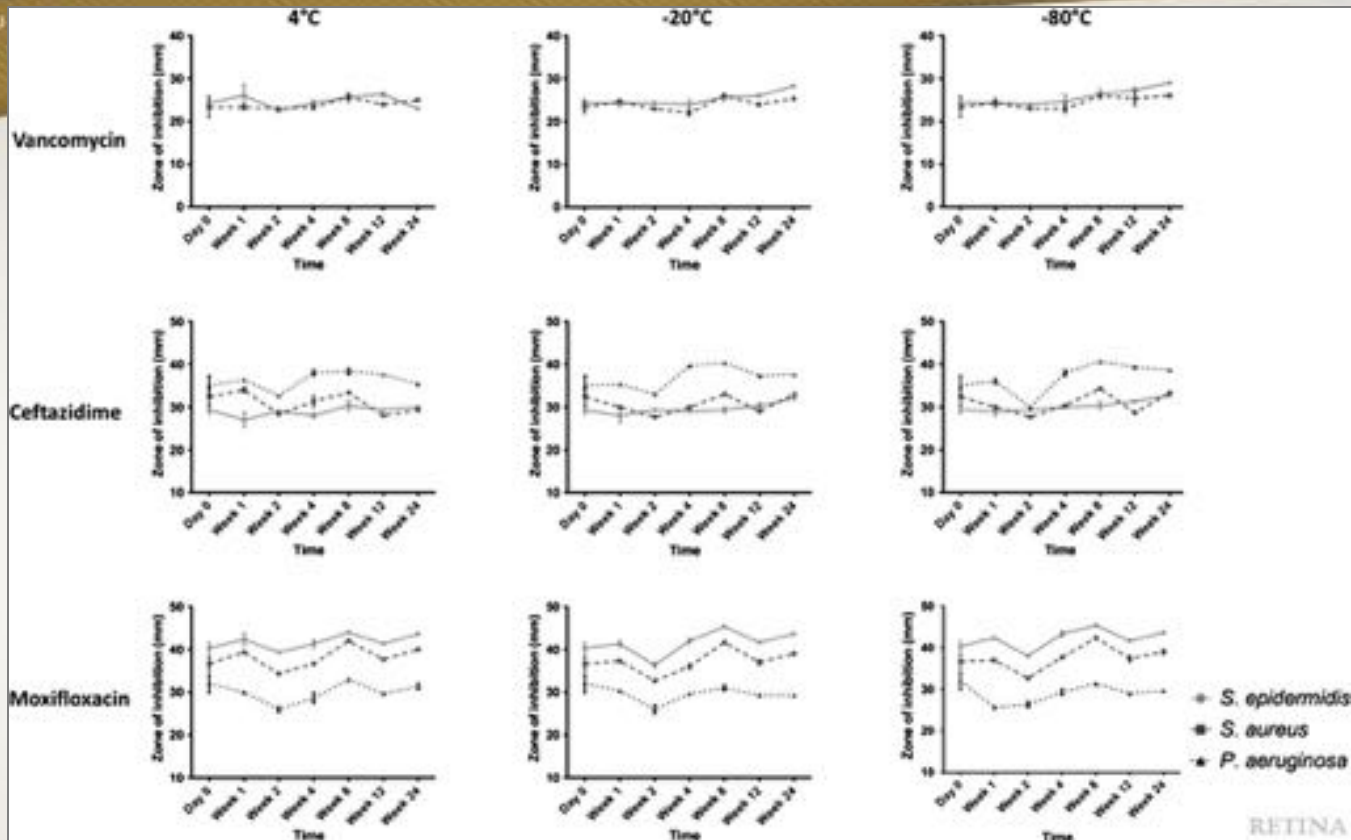


VANDERBILT UNIVERSITY
MEDICAL CENTER

Thanks for your Attention !



Vanderbilt Eye Institute



RETINA

Long-term potency, sterility, and stability of vancomycin, ceftazidime, and moxifloxacin for treatment of bacterial endophthalmitis. Mehta S, Armstrong BK, Kim SJ, Toma H, West JN, Yin H, Lu P, Wayman LL, Recchia FM, Sternberg P Jr. Retina. 2011;31(7):1316-22.

Table 4. Cumulative Final Visual Acuity by Treatment Type*

Snellen Equivalent	Visual Acuity Score (No. of Letters)	No. (%) of Patients		P	No. (%) of Patients		P
		Vitrectomy (n=201)	Tap/Biopsy (n=193)		IV Antibiotics (n=193)	No IV Antibiotics (n=201)	
20/25 or better	≥80	60 (29.9)	67 (34.7)		62 (32.1)	65 (32.3)	
20/40 or better	≥70	108 (53.7)	101 (52.3)	.78	99 (51.3)	110 (54.7)	.50
20/50 or better	≥65	127 (63.2)	114 (59.1)		114 (59.1)	127 (63.2)	
20/100 or better	≥50	154 (76.6)	139 (72.0)	.30	140 (72.5)	153 (76.1)	.42
20/200 or better	≥35	165 (82.1)	150 (77.7)		154 (79.8)	161 (80.1)	
10/200 or better	≥20	175 (87.1)	159 (83.4)		163 (84.5)	171 (85.1)	
5/200 or better	≥5	185 (92.0)	164 (85.0)	.03	168 (87.1)	181 (90.1)	.35
LP or better	≥LP	193 (96.0)	183 (94.8)		182 (94.3)	194 (96.5)	

*IV indicates intravenous; LP, light perception.

Results of the Endophthalmitis Vitrectomy Study: A Randomized Trial of Immediate Vitrectomy and of Intravenous Antibiotics for the Treatment of Postoperative Bacterial Endophthalmitis. *Arch Ophthalmol.* 1995;113(12):1479–1496.