Multicenter Evaluation of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis with and without Gentamicin: Is it Time to Revisit?

Tho H. Pham, PharmD;[1,2] Grace Erdman, PharmD;[3] Kyle C. Molina, PharmD, BCIDP, AAHIVP;[3,4]
Matthew A. Miller, PharmD, BCIDP;[34] Vanthida Huang, PharmD, BSPHM, FCCP[1,2]

[1]Department of Pharmacy Practice, Midwestern University College of Pharmacy-Glendale Campus, Glendale, AZ; [2]HonorHealth John C. Lincoln Medical Center, Phoenix, AZ;
[3]Department of Pharmacy, University of Colorado Hospital, Aurora, CO; [4]Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO

@ThoPham27

IDWeek 2022
Poster #1986

BACKGROUND

- *Staphylococcus aureus* prosthetic valve infective endocarditis (SA-PVIE) is associated with high mortality and long-term clinical complications.
- Gentamicin (GEN) combination with anti-staphylococcal antibiotics and rifampin is the preferred treatment for SA-PVIE. The evidence is due to synergism observed *in vitro* data and small retrospective studies demonstrated early clearance in *S. aureus* bloodstream infection.
- GEN is nephrotoxic; therefore, prolonged treatment may lead to acute kidney injury (AKI) which linked to poorer prognosis.
- The clinical benefits of GEN on infection-related outcomes remain unclear.

METHODS

Study Design: Multicenter, retrospective cohort conducted at HonorHealth Network and UCHealth System.

Inclusion: Hospitalized adult (≥ 18 years) patients with definite or possible SA-PVIE by modified Duke Criteria receiving ≥ 48 hours of treatment within 48 hours of index culture between January 1, 2014 to January 1, 2022.

Exclusion: Polymicrobial bacteremia upon admission; receiving concomitant antibiotics for other infections that also cover the index pathogen; receiving GEN for non-synergistic (> 3 mg/kg/day) regimen or < 48 hours; withdrawal of care within 48 hours of diagnosis; or renal replacement therapy.

Outcomes

Primary:
- Treatment failure (requiring change of antimicrobial therapy based on detection of new cardiac vegetation, septic paravalvular complications, development of abscess, or new surgical intervention)

Secondary:
- Persistent bacteremia
- 30-day mortality
- 90-day mortality
- Nephrotoxicity during therapy

Statistical analysis: Descriptive analyses were performed using R statistics (Lucent Technologies, Murray Hill, NJ).

RESULTS

Table 1. Patient Demographic Characteristics

	Without GEN (n=32)	With GEN (n=17)	P value
Age (years), mean ± standard deviation (SD)	61.8 ± 21.8	60.0 ± 20.1	0.778
Male, n (%)	21 (65.6)	11 (64.7)	0.949
Modified Duke Criteria Category, n (%)			
Definite Infective Endocarditis	15 (46.9)	8 (47.1)	
Possible Infective Endocarditis	17 (53.1)	9 (52.9)	
Caucasian, n (%)	31 (96.9)	14 (82.4)	0.077
Charlson Comorbidity Index, median (interquartile [IQR])	4.0 (5.2)	4.0 (4.0)	0.619
Pitt Bacteremia Score, median (IQR)	2.0 (4.0)	1.0 (2.0)	0.096
ICU at Time of Index Culture, n (%)	14 (43.8)	8 (47.1)	0.825
Staphylococcus aureus, n (%)			
• Methicillin-susceptible	22 (68.8)	12 (70.6)	
• Methicillin-resistant	10 (31.2)	5 (29.4)	
Sites of infection, n (%)			
• Pulmonary	11 (34.4)	4 (23.5)	0.433
• Skin/soft Tissue	8 (25.0)	3 (17.6)	0.557
• Musculoskeletal	4 (12.5)	5 (15.6)	0.940
• Other infection site	11 (34.4)	8 (47.1)	
Prosthetic Valve, n (%)	32 (100)	17 (100)	1.00
Left-sided Endocarditis, n (%)	28 (87.5)	16 (94.1)	0.466
Valve Type Involved, n (%)			
• Aortic	26 (81.2)	10 (58.8)	0.091
• Mitral	7 (21.9)	9 (52.9)	0.027
• Tricuspid	9(28.1)	3 (17.6)	0.116
• Pulmonary	0 (0)	2 (11.8)	0.116
AKI at baseline, n (%)	14 (43.8)	8 (47.1)	0.825
Specialist Consult, n (%)			
• Infectious Disease	31 (96.9)	14 (82.4)	0.077
• Cardiology	21 (65.6)	14 (82.4)	0.217
• Cardiothoracic Surgery	15 (46.9)	4 (23.5)	0.110
Valve Surgery, n (%)	7 (21.9)	3 (17.6)	0.727

Table 2. PVIE Antimicrobial Regimens

	Without GEN (n=32)	With GEN (n=17)	P value
Days of Anti-staphylococcal Therapy, median (IQR)	41 (35)	41 (32)	0.563
Empiric Vancomycin, n (%)	31 (96.9)	16 (94.1)	0.642
Anti-MSSA Treatment, n (%)			
Cefazolin	18 (56.2)	11 (64.7)	0.566
Nafcillin	6 (18.8)	3 (17.6)	0.924
Gentamicin			
• Dose: 3 mg/kg Daily, n (%)	0 (0)	14 (82.4)	
• Intermittent Dosing: 1-1.5 mg/kg q8-12h, n (%)	0 (0)	11 (64.7)	
• Time to GEN, mean ± SD	N/A	2.0 ± 3.0	
• Days of GEN Therapy, mean ± SD	N/A	8.6 ± 5.8	
Received Rifampin, n (%)	7 (21.9)	14 (82.4)	<0.001

Table 3. Patient Outcomes

	Without GEN (n=32)	With GEN (n=17)	P value
Treatment Failure, n (%)	7 (22.6)	3 (17.6)	0.138
Persistent Bacteremia, n (%)	14 (43.8)	4 (23.5)	0.219
30-day Mortality, n (%)	8 (25)	8 (47.1)	0.117
90-day Mortality, n (%)	10 (31.2)	9 (52.9)	0.138
Nephrotoxicity During Therapy, n (%)	13 (40.6)	6 (35.3)	0.715

CONCLUSION

- Our study demonstrates that the addition of GEN to SA-PVIE therapy may not provide additional mortality benefit.
- Compared to GEN cohort, patients without GEN potentially live longer to experience adverse events associated with SA-PVIE therapy.
- Further prospective studies are warranted to investigate the temporal relationship between GEN or rifampicin and both clinical benefits and mortality in SA-PVIE patients.

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