

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



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# 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 nonsynergistic (> 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

adult patients with gram-negative infections. BMC Infect Dis. 2019;19:718

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

# RFSIII TS

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) Arr  Possible Infective Endocarditis 17 (53.1) 9 (52.9)  Caucasian, n (%) 31 (96.9) 14 (82.4) 0.0777  Charlson Comorbidity Index, median (interquartile [IQR])  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-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  Tricuspid 9(28.1) 3 (17.6) 0.116  Pulmonary 0 (0) 2 (11.8) 0.116  Pulmonary 0 (0) 2 (11.8) 0.116  AKI at baseline, n (%)  Infectious Disease 31 (96.9) 14 (82.4) 0.077  Cardiothoracic Surgery 15 (46.9) 4 (23.5) 0.110			K	:SULI	<b>&gt;</b>		
Without GEN (n=32)   With GEN (n=17)   Value	Table 1. Patient Demographic Characteristics						
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   Endotrice   11 (64.9)   10 (64.7)   0.949   Endotrice   11 (64.9)   12 (65.6)   11 (64.7)   0.949   Endotrice   13 (65.9)   14 (82.4)   0.077   14 (82.4)   0.077   15 (65.9)   14 (82.4)   0.077   15 (65.9)   14 (82.4)   0.077   15 (65.9)   14 (82.4)   0.077   15 (65.9)				Р			
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Possible Infective Endocarditis	Modified Duke Criteria Category, n (%)						
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Caucasian, n (%) Charlson Comorbidity Index, median (interquartile [IQR]) Pitt Bacteremia Score, median (IQR) ICU at Time of Index Culture, n (%)  **Methicillin-susceptible** *Methicillin-resistant** Sites of infection, n (%)  **Pulmonary** *Musculoskeletal** *Other infection site**  Prosthetic Valve, n (%)  *Aortic** *Aorti	Possible Infective Endocarditis	17 (53.1)	9 (52.9)				
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ICU at Time of Index Culture, n (%)		4.0 (5.2)	4.0 (4.0)	0.619	Na		
Staphylococcus aureus, n (%)         * Methicillin-susceptible         22 (68.8)         12 (70.6)         * Methicillin-susceptible	Pitt Bacteremia Score, median (IQR)	2.0 (4.0)	1.0 (2.0)	0.096	G		
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<ul> <li>Methicillin-resistant</li> <li>Sites of infection, n (%)</li> <li>Pulmonary</li> <li>Skin/soft Tissue</li> <li>Musculoskeletal</li> <li>Other infection site</li> <li>Prosthetic Valve, n (%)</li> <li>Aortic</li> <li>Aortic</li> <li>Tricuspid</li> <li>Tricuspid</li> <li>Pulmonary</li> <li>Al (43.8)</li> <li>(47.1)</li> <li>Prosthetic Valve, n (%)</li> <li>Aortic</li> <li>Aortic</li> <li>Pollmonary</li> <li>Mitral</li> <li>Tricuspid</li> <li>Pulmonary</li> <li>O(0)</li> <li>(11.8)</li> <li>(17.6)</li> <li>(18.8)</li> <li>(17.6)</li> <li>(18.8)</li> <li>(18.8)<td>Staphylococcus aureus, n (%)</td><td></td><td></td><td></td><td></td></li></ul>	Staphylococcus aureus, n (%)						
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 (%)  Left-sided Endocarditis, n (%)  Aortic  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  Pulmonary  0 (0) 2 (11.8) 0.116  AKI at baseline, n (%)  Infectious Disease  31 (96.9) 14 (82.4) 0.077  Cardiology  Cardiothoracic Surgery  15 (46.9) 4 (23.5) 0.110	<ul> <li>Methicillin-susceptible</li> </ul>	22 (68.8)	12 (70.6)		•		
<ul> <li>Pulmonary</li> <li>Skin/soft Tissue</li> <li>Skin/soft Tissue</li> <li>4 (12.5)</li> <li>11 (34.4)</li> <li>4 (23.5)</li> <li>0.433</li> <li>Skin/soft Tissue</li> <li>8 (25.0)</li> <li>3 (17.6)</li> <li>0.557</li> <li>Musculoskeletal</li> <li>4 (12.5)</li> <li>5 (15.6)</li> <li>0.940</li> <li>Other infection site</li> <li>11 (34.4)</li> <li>8 (47.1)</li> </ul> Prosthetic Valve, n (%) <ul> <li>28 (87.5)</li> <li>16 (94.1)</li> <li>0.466</li> </ul> Valve Type Involved, n (%) <ul> <li>Aortic</li> <li>26 (81.2)</li> <li>10 (58.8)</li> <li>0.091</li> <li>Mitral</li> <li>7 (21.9)</li> <li>9 (52.9)</li> <li>0.027</li> <li>Tricuspid</li> <li>9(28.1)</li> <li>3 (17.6)</li> <li>0.116</li> <li>Pulmonary</li> <li>0 (0)</li> <li>2 (11.8)</li> <li>0.116</li> <li>Pulmonary</li> <li>0 (0)</li> <li>2 (11.8)</li> <li>0.116</li> </ul> Per AKI at baseline, n (%) <ul> <li>14 (43.8)</li> <li>8 (47.1)</li> <li>0.825</li> </ul> Specialist Consult, n (%) <ul> <li>Infectious Disease</li> <li>31 (96.9)</li> <li>14 (82.4)</li> <li>0.077</li> <li>Cardiology</li> <li>21 (65.6)</li> <li>14 (82.4)</li> <li>0.217</li> <li>Cardiothoracic Surgery</li> <li>15 (46.9)</li> <li>4 (23.5)</li> <li>0.110</li> </ul>	<ul> <li>Methicillin-resistant</li> </ul>	10 (31.2)	5 (29.4)				
• Skin/soft Tissue • Skin/soft Tissue • Musculoskeletal • Other infection site  Prosthetic Valve, n (%)  Left-sided Endocarditis, n (%) • Aortic • Aortic • Mitral • Pulmonary • Tricuspid • Pulmonary • MKI at baseline, n (%) • Infectious Disease • Skin/soft Tissue  8 (25.0)  3 (17.6) 0.557  Re  8 (27.1)  9 (15.6) 0.940  11 (34.4) 8 (47.1)  12 (100) 17 (100) 1.00 1.00 1.00 1.00 1.00 1.00 1.00	Sites of infection, n (%)				•		
<ul> <li>Musculoskeletal</li> <li>Other infection site</li> <li>11 (34.4) 8 (47.1)</li> <li>Prosthetic Valve, n (%)</li> <li>Left-sided Endocarditis, n (%)</li> <li>Aortic</li> <li>Aortic</li> <li>Mitral</li> <li>Tricuspid</li> <li>Pulmonary</li> <li>AKI at baseline, n (%)</li> <li>Infectious Disease</li> <li>Cardiology</li> <li>Cardiothoracic Surgery</li> <li>Other infection 0.940</li> <li>A (12.5) 5 (15.6) 0.940</li> <li>A (100) 1.00</li> <li>A (94.1) 0.466</li> <li>A (94.1) 0</li></ul>	<ul> <li>Pulmonary</li> </ul>	11 (34.4)	4 (23.5)	0.433			
• Other infection site  Prosthetic Valve, n (%)  Left-sided Endocarditis, n (%)  • Aortic  • Aortic  • Mitral  • Tricuspid  • Pulmonary  • Tricuspid  • Pulmonary  • MKI at baseline, n (%)  • Infectious Disease  • Cardiology  • Cardiothoracic Surgery  • Cardiothoracic Surgery  11 (34.4)  8 (47.1)  8 (47.1)  10 (58.8)  10 (58.8)  0.091  7 (21.9)  9 (52.9)  0.027  7 (21.9)  9 (52.9)  0.027  10 (58.8)  10 (58.8)  0.091  11 (43.8)  12 (43.8)  13 (17.6)  14 (43.8)  14 (43.8)  15 (46.9)  16 (46.9)  17 (100)  1.00  1.0	• Skin/soft Tissue	8 (25.0)	3 (17.6)	0.557			
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 (%)         26 (81.2)         10 (58.8)         0.091           • 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 (%)         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	<ul> <li>Musculoskeletal</li> </ul>	4 (12.5)	5 (15.6)	0.940	Re		
Left-sided Endocarditis, n (%)       28 (87.5)       16 (94.1)       0.466         Valve Type Involved, n (%)       26 (81.2)       10 (58.8)       0.091         • 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 (%)       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	<ul> <li>Other infection site</li> </ul>	11 (34.4)	8 (47.1)				
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 (%)       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	Prosthetic Valve, n (%)	32 (100)	17 (100)	1.00			
• Aortic • Aortic • Mitral • Mitral • Tricuspid • Pulmonary • Do (0) • Mitral • Pulmonary • Do (0) • Linfectious Disease • Cardiothoracic Surgery • Cardiothoracic Surgery • Aortic • 26 (81.2) • 10 (58.8) • 0.091 • 7 (21.9) • 9 (52.9) • 0.027 • 7 (21.9) • 9 (52.9) • 0.027 • 0.116 • Pel Mitral • 0 (0) • 2 (11.8) • 0.116 • Pel Mitral • 14 (43.8) • (47.1) • 0.825 • 15 (46.9) • 14 (82.4) • 0.217 • 15 (46.9) • 18 (43.5) • 19 (10 (58.8) • 0.091 • 0.0027 • 10 (10 (58.8) • 0.0027 • 11 (82.4) • 0.016 • 0.0027 • 12 (65.6) • 14 (82.4) • 0.217 • 15 (46.9) • 15 (46.9) • 10 (58.8) • 0.091 • 10 (58.8) • 0.091 • 10 (58.8) • 0.091 • 10 (58.8) • 0.0027 • 10 (10 (58.8) • 0.0027 • 10 (10 (58.8) • 0.0027 • 10 (10 (58.8) • 0.0027 • 10 (58.8) • 0.0027 • 10 (58.8) • 0.0027 • 11 (82.4) • 0.0027 • 12 (65.6) • 14 (82.4) • 0.016 • 13 (10 (58.8) • 0.0027 • 14 (82.4) • 0.0027 • 15 (46.9) • 16 (81.2) • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 17 (10 (58.8) • 0.0027 • 18 (10 (58.8) • 0.0027 • 0.002	Left-sided Endocarditis, n (%)	28 (87.5)	16 (94.1)	0.466			
<ul> <li>Mitral</li> <li>Tricuspid</li> <li>Pulmonary</li> <li>Mitral</li> <li>Pulmonary</li> <li>Mitral</li> <li>Pulmonary</li> <li>MKI at baseline, n (%)</li> <li>Specialist Consult, n (%)</li> <li>Infectious Disease</li> <li>Cardiology</li> <li>Cardiothoracic Surgery</li> <li>Mitral</li> <li>7 (21.9)</li> <li>9 (52.9)</li> <li>0.027</li> <li>14 (1.8)</li> <li>14 (1.8)</li> <li>14 (1.8)</li> <li>14 (1.8)</li> <li>15 (1.8)</li> <li>16 (1.8)</li> <li>17 (1.9)</li> <li>18 (1.8)</li> <li>18 (1.8)</li> <li>19 (1.8)</li> <li>10 (1.8)</li> <li>10 (1.8)</li> <li>11 (1.8)</li> <li>12 (1.8)</li> <li>13 (17.6)</li> <li>14 (1.8)</li> <li>14 (1.8)</li> <li>15 (1.8)</li> <li>16 (1.8)</li> <li>17 (1.8)</li> <li>18 (1.8)</li> <li>18 (1.8)</li> <li>19 (1.8)</li> <li>10 (1.8)</li> <li>10 (1.8)</li> <li>11 (1.8)</li> <li>12 (1.8)</li> <li>13 (17.6)</li> <li>14 (1.8)</li> <li>14 (1.8)</li> <li>15 (1.8)</li> <li>16 (1.8)</li> <li>17 (1.8)</li> <li>18 (1.8)</li> <li>1</li></ul>	Valve Type Involved, n (%)						
<ul> <li>Tricuspid</li> <li>Pulmonary</li> <li>O (0)</li> <li>2 (11.8)</li> <li>O.116</li> <li>Pulmonary</li> <li>AKI at baseline, n (%)</li> <li>Specialist Consult, n (%)</li> <li>Infectious Disease</li> <li>Cardiology</li> <li>Cardiothoracic Surgery</li> <li>O (0)</li> <li>2 (11.8)</li> <li>O.116</li> <li>Peters</li> <li>AKI at baseline, n (%)</li> <li>14 (43.8)</li> <li>B (47.1)</li> <li>O.825</li> <li>O.825</li> <li>Infectious Disease</li> <li>O (0)</li> <li>14 (82.4)</li> <li>O (0)</li> <li>O (11.8)</li> <li>O (11.8)</li></ul>	• Aortic	26 (81.2)	10 (58.8)	0.091			
<ul> <li>Tricuspid</li> <li>Pulmonary</li> <li>AKI at baseline, n (%)</li> <li>Infectious Disease</li> <li>Cardiology</li> <li>Cardiothoracic Surgery</li> <li>19(28.1)</li> <li>3 (17.6)</li> <li>0.116</li> <li>14 (43.8)</li> <li>4 (47.1)</li> <li>0.825</li> <li>14 (82.4)</li> <li>14 (82.4)</li> <li>15 (46.9)</li> <li>4 (23.5)</li> <li>10.110</li> </ul>	• Mitral	7 (21.9)	9 (52.9)	0.027	Tr		
AKI at baseline, n (%)       14 (43.8)       8 (47.1)       0.825         Specialist Consult, n (%)       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	<ul> <li>Tricuspid</li> </ul>	9(28.1)	3 (17.6)	0.116			
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	<ul> <li>Pulmonary</li> </ul>	0 (0)	2 (11.8)	0.116	Pe		
• 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	AKI at baseline, n (%)	14 (43.8)	8 (47.1)	0.825			
• Cardiology • Cardiothoracic Surgery  21 (65.6) 14 (82.4) 0.217  15 (46.9) 4 (23.5) 0.110	Specialist Consult, n (%)						
• Cardiotogy  • Cardiotogy  • Cardiotogy  15 (46.9) 4 (23.5) 0.217	• Infectious Disease	31 (96.9)	14 (82.4)	0.077			
	<ul> <li>Cardiology</li> </ul>	21 (65.6)	14 (82.4)	0.217	90		
Valve Surgery, n (%) 7 (21.9) 3 (17.6) 0.727	Cardiothoracic Surgery	15 (46.9)	4 (23.5)	0.110	MI		
	Valve Surgery, n (%)	7 (21.9)	3 (17.6)	0.727	146		

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)			
<ul> <li>Intermittent Dosing:</li> <li>1-1.5 mg/kg q8-12h, n (%)</li> </ul>	0 (0)	11 (64.7)			
• Time to GEN, mean $\pm$ SD	N/A	2.0 ± 3.0			
• Days of GEN Therapy, mean $\pm$ 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

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# 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.