Epidemiology and Clinical Outcomes of non-HACEK Gram-negative Infective Endocarditis

Sunish Shah, PharmD; Lloyd G Clarke, B.Sc Hons; Ryan K. Shields, PharmD, MS
University of Pittsburgh Medical Center, Pittsburgh, PA

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Contact Information:
Sunish Shah
E-mail:shahs7@UPMC.edu

INTRODUCTION

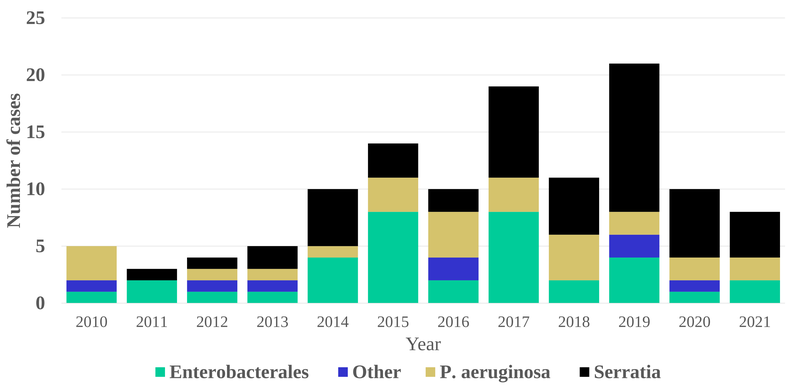
- Infective endocarditis (IE) due to non-HACEK Gram-negative (GN) pathogens is rare; optimal treatment has not yet been defined
- The objective of this study was to report the epidemiology, clinical characteristics, and outcomes of GNIE across our health system

METHODS

- Adult patients with GNIE were identified through using Boolean search terms "Endocarditis" and "*Serratia*", "*Pseudomonas*", "*Burkholderia*", "*Stenotrophomonas*", "*Acinetobacter*", "*Klebsiella*", "*Escherichia*", "*Enterobacter*", "*Citrobacter*" or "*Proteus*" across 13 hospitals in Pennsylvania between April 2010 and December 2021
- Patients were included if they met DUKE criteria for definitive endocarditis
- Patients with persistently positive blood cultures for Gram-positive pathogens or yeast were excluded if valve cultures did not grow GN bacteria
- Combination therapy was defined as receipt of two or more antimicrobial agents with documented in vitro activity against the primary pathogen for >72 hours
- Clinical failure was defined as a composite of all-cause mortality or microbiologic failure at day 42
- Microbiologic failure was defined as an escalation of antimicrobial therapy after emergence of resistance, increased vegetation size, or failure to clear blood cultures by day 14

RESULTS

Epidemiology of GNIE cases over time



Footnote: 8 (6.5%) of cases were polymicrobic with at least one other GN pathogen: *K. pneumonia* (n=3): *E. cloacae complex*; *S. maltophillia* and *E. aerogenes*; *P. mirabilis, S. marcescens* (n=2): *P. aeruginosa*; *Acinetobacter* spp. *S. maltophillia* (n=1): *A. junii, P. mirabilis* (n=1): *P. penneri E. coli* (n=1): *P. mirabilis*

RESULTS

Overview

- A total of 1,324 patients were identified by search criteria and 123 were included in the study **(Figure)**
- *Serratia* spp. were the most common cause of GNIE (43%; 53/123) followed by *P. aeruginosa* (21%; 26/123) and Klebsiella spp. (14%; 17/123)
- Patients with GNIE secondary to other Enterobacterales were more likely to have underlying cirrhosis compared to all other GNIE patients (14% vs 1%, P=0.008)
- Prosthetic valve endocarditis was identified in 17% (21/123) of patients with GNIE and was most common in GNIE secondary to P. aeruginosa (30.8%; 8/26)
- Microbiologic failure rates were higher for *P. aeruginosa* (23%; 6/26) than other pathogens (6%; 6/97, P=0.004)

Risk factors associated with GNIE clinical failure

Factors associated with clinical failure	42 day Cure (n=97)	42 Day Failure (n=26)	P-value
Age, median (IQR)	45 (32-65)	60 (49-71)	0.013
Male gender, n (%)	56 (58)	21 (81)	0.031
White ethnicity, n (%)	86 (89)	23 (89)	> 0.999
Pitt Bacteremia Score, median (IQR)	1 (0-3)	3 (1-6)	0.005
CCI, median (IQR)	1 (0-3)	2 (1-3)	0.463
Left sided/ multiple valves involved, n (%)	60 (62)	24 (92)	0.004
Prosthetic valve endocarditis, n (%)	17 (18)	4 (15)	> 0.999
Prior endocarditis, n (%)	26 (27)	2 (8)	0.063
Pathogen recovered from valve, n (%)	N=34 19 (56)	N=7 5 (71)	0.679
Confirmed vegetation > 1cm, n (%)	55 (57)	19 (73)	0.129
CNS Septic emboli, n (%)	22 (23)	13 (50)	0.006
Combination therapy, n (%)	43 (44)	10 (39)	0.592
Initial (> 1 week) of beta-lactam backbone or monotherapy, n (%)	92 (95)	25 (96)	0.783
Index isolate MDR, n (%)	17 (18)	9 (35)	0.0581
Days of therapy, median (IQR)	48 (43-54)	17 (12-27)	< 0.001
Days of double coverage, (%)	n=55 16 (5-44)	n=12 9 (5-17)	0.148
Managed surgically, n (%)	42 (43)	7 (27)	0.129
Positive repeat blood cultures, n (%)	40 (41)	14 (54)	0.249
Days of blood culture positivity among those with positive repeat blood cultures, median (IQR)	N=40 4 (2-7)	N=14 10 (3-18)	0.05
Days to surgery, median (IQR)	N=42 11 (7-15)	N=7 17 (10-32)	0.071
Total hospital LOS, median (IQR)	22 (14-41)	21 (11-30)	0.328

CCI: Charleson Comorbidity Index; MDR: Multiple drug resistance; LOS: Length of Stay; CNS: Central Nervous System

Multivariate model for clinical failure	OR	95% CI	P-value
Age (per year)	1.03	1.01-1.05	0.035
Pitt Bacteremia Score (per point)	1.29	1.1-1.53	0.002
Left sided or multiple valves involved	5.79	1.2-28	0.029
Multivariate model for 90-day mortality			
Age (per year)	1.05	1.02-1.08	0.006
Receipt of surgical management	0.25	0.06-0.95	0.042

- Among the cohort of 89 patients with GNIE due to *Serratia spp*. and other Enterobacterales, rates of clinical failure were numerically lower among those who received combination (n=31) versus monotherapy (n=58) (9.7% vs 25.9%, P=0.09)
- Among the 26 patients with GNIE due to *P. aeruginosa*, rates of clinical failure were numerically higher among those who received combination (n=19) versus monotherapy (n=7) (37% vs. 0%; P=0.134)

Patients who inject drugs

Factors associated with PWID	PWID (n=64)	Other (n=59)	P-value
Age, median (IQR)	34 (30-41)	67 (61-75)	< **0.001**
Septic emboli, n (%)	57 (89)	24 (41)	< **0.001**
CCI, median (IQR)	0 (0-1)	3 (2-5)	< **0.001**
***Serratia spp*.**	45 (70)	8 (14)	< **0.001**
Confirmed vegetation > 1cm, n (%)	49 (77)	25 (42)	< **0.001**
Managed surgically, n (%)	31 (48)	18 (31)	**0.042**
Total hospital LOS, median (IQR)	27 (18-43)	15 (11-27)	**0.002**
30-day readmission[1], n (%)	N=56 10 (18)	N=50 19 (38)	**0.02**
90-day mortality, n (%)	8 (13)	17 (29)	**0.025**
9-month relapse among 90-day survivors, n (%)	N=56 12 (21)	N=42 3 (7)	0.087

PWID: Persons Who Inject Drugs; CCI: Charleson Comorbidity Index.; LOS: Length of Stay
1. Percentages were calculated among those who survived to hospital discharge

CONCLUSIONS

- *Serratia* spp. was identified as the most common etiology of GNIE, particularly among PWID
- Age was also associated with an increased risk of death within 90 days, while surgical management was found to protect against death within 90 days
- Across all patients, we did not identify a clinical benefit to combination therapy; however, among patients with GNIE due to Enterobacterales, specifically, rates of clinical failure and death were numerically lower among those who received combination versus monotherapy