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Clinical Outcomes of Ceftriaxone versus Penicillin G for Complicated Viridans Group Streptococci Bacteremia

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BACKGROUND

- Viridans group streptococci (VGS) are an infrequent cause of bloodstream infections, accounting for approximately 2% of positive blood cultures in immunocompetent adults in the United States
- In immunocompetent patients with intact host defenses, VGS is considered to have low virulence. However, VGS can be a leading cause of bacteremia in febrile neutropenic patients, leading to shock, respiratory compromise, and mortality in up to 20% of patients. Concomitant infections in VGS bacteremia such as endocarditis can occur, requiring prolonged antibiotic therapy, and are associated with mortality rates of 4 to 16%
- Optimal treatment strategies for VGS bacteremia have not been well-defined. Both penicillin G (PCN G) and ceftriaxone (CTX) are frequently used for definitive treatment in clinical practice, and the American Health Association (AHA) lists both agents as first line treatment options for VGS infective endocarditis (IE)
- Previous observational studies have described the use of different treatment options for VGS bacteremia and IE, but comparative assessment of clinical outcomes between different agents is limited. We hypothesize that CTX is associated with more adverse effects than PCN G when used for complicated VGS bacteremia, and these risks may outweigh the benefit of its once daily dosing

OBJECTIVE

To evaluate clinical outcomes between CTX and PCN G for the prolonged treatment of complicated VGS bacteremia

METHODS

Study Design

- A single-center retrospective study was performed between January 2013 and June 2019 at New York University Langone Health (NYULH), an 800-bed, urban, tertiary care, academic medical center.
- Patients with 1 or more blood cultures positive for a VGS isolate and who received at least 1 dose of either CTX, PCN G, or ampicillin (AMP) were identified and screened for inclusion.

Inclusion Criteria	Exclusion Criteria
≥18 years of age Received ≥4 weeks of treatment for a presumed complicated VGS bacteremia episode	Did not receive study drug therapy for at least 50% of a ≥ 4 week course Had polymicrobial blood culture with non-VGS isolates that were not considered contaminants Had a blood culture with VGS that was considered to be a contaminant Transitioned to hospice care during their treatment course Died during treatment before receiving 50% of the total course Had first VGS bacteremia episode before the study period Received therapy at an outside hospital

Outcomes

Primary	Composite of safety endpoints, including hospital readmission due to VGS bacteremia or an adverse event from antibiotic therapy, *C. difficile* infection (CDI), treatment modification or discontinuation due to an antibiotic-related adverse event, and development of extended spectrum beta-lactamase (ESBL) resistance
Secondary	Individual safety endpoints, VGS bacteremia recurrence, hospital readmission, and all-cause mortality

All outcomes were assessed for the 6-month period following initial positive blood culture

Definitions

- Complicated bacteremia - requiring at least 4 weeks of therapy to treat infection source
- VGS bacteremia recurrence - development of a subsequent case of VGS bacteremia with the same species after completion of the initial treatment course

RESULTS

Table 1. Baseline Characteristics

Variables	CTX (n = 64)	PCN G/AMP (n = 30)	P value
Age, median years (IQR)	69 (58, 81)	64 (52, 80)	0.422
Male	42 (65.6)	22 (73)	0.455
Ethnicity			
White	50 (78.1)	21 (70)	0.393
African American	7 (10.9)	2 (7)	0.714
Hispanic	5 (7.8)	2 (7)	1.000
Asian	2 (3.1)	4 (13)	0.080
Other/not specified	0 (0)	1 (3)	0.319
Past Medical History			
Congestive heart failure	17 (26.6)	6 (20)	0.490
Coronary artery disease	12 (18.8)	6 (20)	0.886
Diabetes mellitus	9 (14.1)	7 (23)	0.265
End organ damage	2/9 (22.2)	2/7 (29)	0.603
Chronic kidney disease (moderate or severe)	7 (10.9)	2 (7)	0.714
Chronic obstructive pulmonary disease	4 (6.3)	2 (7)	1.000
Liver disease	3 (4.7)	0	0.549
Solid tumor	2 (3.1)	2 (7)	0.590
Leukemia	2 (3.1)	0 (0)	1.000
Lymphoma	1 (1.6)	1 (3)	0.539
Charlson comorbidity index (CCI), median (IQR)	4 (2, 5)	3 (2, 5)	0.386
Pitt bacteremia score (PBS), median (IQR)	0 (0, 2)	1 (0, 2)	0.764
Prior episode of *C. difficile* infection	0 (0)	0 (0)	n/a
Concomitant proton pump inhibitor or H2 receptor antagonist administration	20 (32.3)	10 (33)	0.918

Table 2. VGS Bacteremia Treatment Details

VGS Bacteremia Treatment	CTX (n = 64)	PCN G/AMP (n = 30)	P value
Hospital length of stay, median days (IQR)	8 (5, 11)	10 (6, 13)	0.159
Admission to Intensive Care Unit (ICU)	8 (12.5)	7 (23)	0.229
Duration of ICU stay, median days (IQR)	4.5 (1, 9)	6 (3, 7)	0.779
Beta-lactam allergy	14 (21.9)	0	0.004
Penicillin	13/14 (93)		
Cephalosporin	1/14 (7)		
Source removal	16/62 (25)	12/25 (48)	**0.045**
Time to source removal, median days (IQR)	1 (0, 9)	5 (2.3, 8.5)	0.277
Susceptibility, susceptible + intermediate			
Penicillin	62 (96.9)	30 (100)	1.000
Intermediate	16/62 (25)	4/30 (13.3)	0.709
Ampicillin	61 (95.3)	30 (100)	0.549
Intermediate	9/61 (14.1)	4/30 (13)	1.000
Ceftriaxone	62 (96.9)	24 (80)	0.027
Intermediate	1/62 (1.6)	1/24 (4.2)	0.590
Empiric therapy			
Vancomycin	57 (89.1)	25 (83)	0.512
Ceftriaxone	4 (6.3)	0 (0)	0.303
Other	3 (4.7)	5 (17)	0.105
Definitive therapy			
Ceftriaxone	56 (87.5)	0 (0)	-
Penicillin G	6 (9.4)	26 (87)	-
Ampicillin	1 (1.6)	4 (13)	-
Cefazolin	1 (1.6)	0 (0)	-
Infectious Diseases consult	63 (98.4)	30 (100)	1.000
Combination therapy with gentamicin	12 (18.8)	13 (43)	**0.012**
Duration, median days (IQR)	3 (1.5, 13.5)	14 (5.5, 27.5)	**0.034**
Time to documented clearance of blood culture, median days (IQR)	2 (1, 3)	1.5 (1, 2)	**0.079**
Duration of total therapy, median days (IQR)	41.5 (30, 44)	42.5 (31.8, 47.3)	0.334
Duration of definitive therapy, median days (IQR)	36.5 (25.3, 42)	39.5 (28, 41.3)	0.354
Duration of treatment arm, median days (IQR)	38 (27, 43)	39.5 (28, 41.3)	0.961
Outpatient line access	62 (97.9)	30 (100)	1.000
Peripherally inserted central catheter (PICC)	59 (95.2)	30 (100)	0.548
Midline	3/62 (4.8)	0 (0)	0.548

All data in tables expressed as n (%) unless otherwise noted.

Figure 1. VGS Species (%)

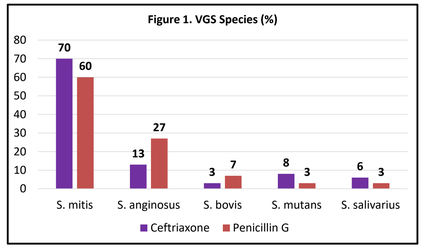
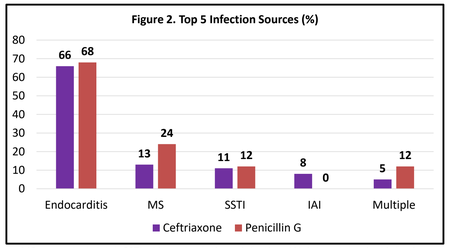


Figure 2. Top 5 Infection Sources (%)



MS: musculoskeletal; SSTI: skin and soft tissue infection; IAI: intra-abdominal infection

Table 3. Outcomes

	CTX (n = 64)	PCN G/AMP (n = 30)	P value
Primary Endpoint			
Composite safety endpoint	9 (14.1)	8 (26.7)	0.139
Secondary Endpoints			
Composite safety endpoint components			
At least 1 readmission due to VGS or therapy	7 (10.9)	6 (20)	0.336
Microbiological evidence of ESBL	1 (1.6)	1 (3)	0.539
C. difficile infection	1 (1.6)	1 (3)	0.539
Therapy modification or discontinuation due to adverse drug event	0 (0)	0 (0)	0.549
Infection recurrence	0 (0)	0 (0)	n/a
Hospital readmission			
At least 1 readmission in 6-months	24 (37.5)	16 (53)	0.148
Number of readmissions, median days (IQR)	0 (0,1)	1 (0,1.25)	0.341
Time to first readmission, median days (IQR)	31 (15,60)	53 (29,91)	0.135
All cause mortality	0 (0)	2 (7)	0.100

Table 4. Univariate and Multivariate Analyses

	Primary Composite Outcome Met (n = 17)	Primary Composite Outcome Not Met (n = 77)	Univariate OR (CI)	P-value	Multivariate OR (CI)	P value
CTX	9 (52.9)	53 (71.4)	0.45 (0.154-1.316)	0.139	0.53 (0.144-1.957)	0.342
Duration of treatment arm ≥4 weeks	14 (82.4)	52 (67.5)	2.24 (0.590-8.526)	0.227	1.84 (0.433-7.776)	0.410
Source removal	**2 (11.8)**	**26 (33.8)**	**0.26 (0.056-1.231)**	**0.073**	**0.13 (0.021-0.822)**	**0.030**
Coronary artery disease	1 (5.9)	18 (24)	0.2 (0.025-1.598)	0.181	0.10 (0.010-1.126)	0.063
Gentamicin ≥ 2 weeks duration	4 (23.5)	6 (7.8)	3.64 (0.901-14.713)	0.078	6.55 (0.893-48.106)	0.065
Congestive heart failure	3 (17.6)	20 (26.7)	0.59 (0.153-2.268)	0.547	-	-
Endocarditis	10 (52)	48 (62)	0.86 (0.296-2.517)	0.787	-	-
CCI	4 (3,4.5)	4 (2,5)	-	0.784	-	-
PBS	1 (0,2)	0 (0,2)	-	0.781	-	-
Age ≥65 years	8 (47.1)	46 (59.7)	0.60 (0.208-1.722)	0.338	-	-
S. mitis	6 (37.5)	23 (29.9)	1.41 (0.458-4.333)	0.563	-	-
Infection source identified	15 (88.2)	72 (93.5)	0.54 (0.095-3.028)	0.606	-	-
Moderate or severe CKD	2 (11.8)	7 (9.1)	1.33 (0.252-7.065)	0.664	-	-

CTX: ceftriaxone; CCI: Charlson comorbidity index; PBS: Pitt bacteremia score; CKD: chronic kidney disease

CONCLUSION

- Compared to PCN G and AMP, CTX was not associated with an increased risk of ESBL resistance, CDI, hospital readmission due to VGS or therapy complications, or therapy modification due to an adverse drug event
- Overall rate of patients who met the primary outcome highlights importance of identifying relevant risk factors
- Further exploration in a larger prospective trial is warranted