Comparison of Ceftaroline in Combination with Either Vancomycin or Daptomycin for the Treatment of Methicillin-resistant *Staphylococcus aureus* Bacteremia

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Background

- The current standard of care for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is vancomycin (VAN) or daptomycin (DAP) monotherapy
- Recent studies have suggested that combination therapy with a beta-lactam, such as ceftaroline (CPT), may be preferred to monotherapy for select patients with MRSA bacteremia (MRSA-B)[1-4]
- Direct comparison between combination regimens is lacking
- At Atrium Health, providers utilize both VAN+CPT and DAP+CPT, typically in the setting of persistent MRSA-B

Objective

To compare clinical outcomes in patients who received combination therapy with VAN+CPT or DAP+CPT for the treatment of MRSA-B

Methods

- Multicenter, retrospective, IRB-approved cohort study admitted one of 10 Atrium Health facilities from 4/2017 – 6/2019
- Inclusion criteria:
  - ≥ 18 years old
  - Received VAN+CPT or DAP+CPT for ≥ 48 hours for treatment of initial MRSA-B episode
- Exclusion criteria:
  - Primary respiratory or central nervous system infection
  - Polymicrobial infection requiring treatment with additional antibiotic(s) prior to blood culture clearance
  - Left against medical advice
  - Deceased/transitioned to comfort care within 48 hours of index culture collection
  - Transferred from non-Atrium facility
  - Transferred to outside hospital prior to definitive treatment course prescribed
- Primary outcome: Clinical success defined as survival at 90 days, sterilization of blood cultures within 96 hours of combination therapy initiation (microbiological response), no perceived clinical failure requiring a change in MRSA-active therapy, and absence of 90-day recurrence
- Secondary outcomes:
  - Time to culture clearance from combination therapy initiation
  - 30 day and in-hospital mortality
  - Adverse events prompting antibiotic discontinuation
  - Hospital and intensive care unit (ICU) lengths of stay (LOS)
- Statistical analysis:
  - Continuous variables: two-sided t-tests and non-parametric Kruskal-Wallis tests
  - Categorical variables: Pearson's chi-square and Fischer's exact tests
  - A subgroup analysis was performed using Pearson's chi-square test to evaluate timing of combination therapy among clinical successes
  - Sample size of 108 patients estimated to achieve 80% power (70 patients VAN+CPT, 38 patients DAP+CPT)

Results

Figure 1. Patient selection

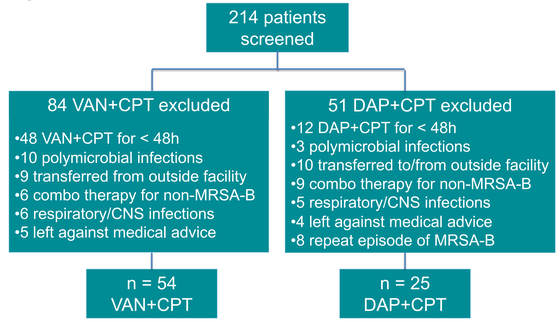
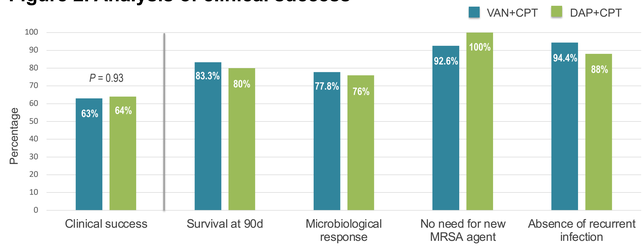


Figure 2. Analysis of clinical success



- Rates of clinical success were not significantly different in those initiated on combination therapy within 5 days of culture collection compared to those with delayed combination therapy.

Table 1. Baseline characteristics

	VAN+CPT (n=54)	DAP+CPT (n=25)	P-value
Male sex, n (%)	29 (53.7)	14 (56.0)	0.85
Age, years, median [IQR]	48.4 [33.1-58.8]	61.0 [47.0-72.1]	**0.014**
History of IV drug use, n (%)	25 (46.3)	7 (28.0)	0.12
Presence of central line, n (%)	7 (13.0)	1 (4.0)	0.22
Presence of hardware, n (%)			
Prosthetic joint/TKA[a]	2 (3.7)	4 (16.0)	0.076
Prosthetic cardiac valve	1 (1.9)	1 (4.0)	0.54
Pacemaker/ICD[b]	4 (7.4)	2 (8.0)	0.99
Other	10 (18.5)	7 (28.0)	0.34
Pitt Bacteremia Score, median [IQR]	2.5 [1.0-4.0]	2.0 [1.0-3.0]	0.15
Foci of infection, n (%)			0.058
Central line	6 (11.1)	1 (4.0)	
Skin/soft tissue	9 (16.7)	3 (12.0)	
Bone/joint	9 (16.7)	11 (44.0)	
Urinary tract	0	1 (4.0)	
Other	1 (1.9)	0	
Unknown	4 (7.4)	3 (12.0)	
Endovascular	25 (46.3)	6 (24.0)	
Endocarditis	22 (40.7)	4 (16.0)	**0.030**
Pacemaker/ICD[b]	3 (5.6)	0	0.55
Hemodialysis graft	1 (1.9)	1 (4.0)	0.54
Septic thrombophlebitis	0	1 (4.0)	0.32
Source control attempted, n (%)	36 (66.7)	15 (60.0)	0.76
≥ 24h of empiric beta-lactam[c], n (%)	43 (79.6)	21 (84.0)	0.65

[a]Total knee arthroplasty, [b]Implantable cardioverter defibrillator, [c]during first 72h of VAN/DAP

Table 2. Outcomes

	VAN+CPT (n=54)	DAP+CPT (n=25)	P-value
Time to combination therapy[a] (d), median [IQR]	4.4 [2.9-5.8]	5.8 [3.3-6.4]	0.31
Duration of combination therapy (d), median [IQR]	8.9 [5.7-14.3]	7.9 [4.5-10.8]	0.62
Time from combination therapy to culture clearance (d), median [IQR]	2.1 [0.7-3.9]	2.0 [0.9-3.0]	0.83
In-hospital mortality, n (%)	4 (7.4)	3 (12.0)	0.67
30-d mortality, n (%)	3 (5.6)	3 (12.0)	0.37
Hospital LOS (d), median [IQR]	41.3 [18.9-50.3]	28.2 [15.7-42.4]	0.13
ICU LOS (d), median [IQR]	9.1 [3.1-15.0]	9.4 [4.1-17.3]	0.59

[a]from index blood culture collection

Table 3. Adverse events requiring therapy discontinuation

	VAN+CPT (n=54)	DAP+CPT (n=25)	P-value
Nephrotoxicity[a], n (%)	8/48 (16.7)	0	**0.042**
AKIN Stage 1 AKI[b]	1/8 (12.5)	-	
AKIN Stage 2 AKI[c]	7/8 (87.5)	-	
Need for new renal replacement therapy	3/8 (37.5)	-	
Rash, n (%)	4 (7.4)	0	0.30
Elevated creatine phosphokinase, n (%)	0	2 (8.0)	0.097
Thrombocytopenia, n (%)	2 (3.7)	0	0.99

[a]assessed in those without baseline renal replacement therapy
[b]increase in SCr ≥ 2x baseline
[c]increase in SCr ≥ 4 mg/dL or ≥ 3x baseline, or need for new renal replacement therapy

Discussion/Conclusions

- Rates of clinical success were similar between patients receiving VAN+CPT and DAP+CPT
- Combination regimens were primarily used for salvage therapy at our practice sites
- Rates of clinical success were similar in those with early and delayed initiation of combination therapy; however, many patients with delayed combination therapy did receive ≥ 24 hours of an empiric beta-lactam during their initial VAN/DAP monotherapy course
- Patients in the VAN+CPT group experienced significantly higher rates of nephrotoxicity, despite their generally younger age
- VAN was dosed per pharmacy protocol via trough-based therapeutic drug monitoring
  - Further data are needed to assess impact of area under the curve (AUC)-based VAN monitoring and rates of nephrotoxicity in this patient population
- DAP/CPT may be preferred in patients with baseline renal impairment or risk for renal toxicity
- Limitations of our study include the retrospective design, differences in baseline age and infection source, and small sample size
- Although underpowered to detect small differences, these results can be used to generate hypotheses and develop larger comparative studies in the future

References

1. Davis JS, et al. *Clin Infect Dis*. 2016;62(2):173-80.
2. Geriak M, et al. *Antimicrob Agents Chemother*. 2019;63(5):e02483-18.
3. McCreary EK, et al. *Open Forum Infect Dis*. 2019;7(1):ofz538.
4. Tong SYC, et al. *JAMA*. 2020;323(6):527-37.

Disclosures

The authors have no potential conflicts of interest to disclose.

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