



A Matched Case-Control Study of Clinical Outcomes of Patients with Daptomycin Resistant and Daptomycin Susceptible Bacteremia

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ABSTRACT

Background: Multi-drug resistant (MDR) infections are a public health threat and cause significant morbidity and mortality among hospitalized patients. There are typically limited antibiotic treatment options for MDR infections making their management more difficult. Our study assessed for markers of disease severity and treatment outcomes of patients with daptomycin non-susceptible VRE (DNSVRE) compared to those with daptomycin susceptible VRE (DSVRE) bacteremia.

Methods: This was a retrospective 2:1 age, sex, and clinical syndrome-matched cohort study of patients with DNSVRE and DSVRE bacteremia over a four year period at the Yale-New Haven Health System (January 2010 - December 2013). Non-susceptibility of VRE to daptomycin was defined as isolates with a MIC >4µg/ml per CLSI guidelines. Patient outcomes including SIRS presentation, requirement for ICU stay, pressors and ventilator support as well as mortality up to 30 days post discharge were captured. Fischer's exact and Pearson's chi-squared tests as appropriate were used to assess for differences in categorical variables.

Results: There were 10 cases of DNSVRE and 19 matched cases of DSVRE bacteremia with a median age of 60 years and comprised 70% and 74% male patients respectively. Majority (70%) of cases had gastrointestinal infections as a source of bacteremia. More DNSVRE cases had underlying malignancies (90% vs 53%, p=0.046). More patients with DNSVRE bacteremia met SIRS criteria, required ICU stay and renal replacement but those differences were not statistically significant. Mortality up to 30-days post-discharge was higher but not statistically significant for DNSVRE cases (70% vs 47%, p=0.163). We observed a "MIC creep" phenomenon where the majority of patients with DNSVRE isolates (60%) had isolates that were initially susceptible to daptomycin but became more resistant following antibiotic exposure.

Conclusion: The severity of infection and mortality of patients with DNSVRE bacteremia were worse but not statistically different from that observed among their counterparts with DSVRE. Patients with DSVRE infections who do not respond to treatment should be assessed for changes in daptomycin susceptibility.

BACKGROUND

- Multi-drug resistant (MDR) infections are a public health threat and cause significant morbidity and mortality among hospitalized patients.
- There are limited antibiotic treatments for MDR infections.
- We assessed for markers of disease severity and treatment outcomes of patients with daptomycin non-susceptible VRE (DNSVRE) compared to those with daptomycin susceptible VRE (DSVRE) bacteremia.

METHODS

- A retrospective 2:1 age, sex, and clinical syndrome-matched cohort study was performed of patients with DNSVRE and DSVRE bacteremia over a four year period at Yale-New Haven Health System.
- Non-susceptibility of VRE to daptomycin was defined as isolates with a MIC >4µg/ml per CLSI guidelines.
- Patient outcomes including SIRS, ICU stay, vasopressors, and ventilator support as well as mortality up to 30 days post discharge were captured.
- Statistical analysis with Fischer's exact and Pearson's chi-squared tests.

RESULTS

Patient Demographics

VARIABLES	DSVRE (n=19)	DNSVRE (n=10)
Age		
Mean	50.3 +/- 20.9	50.4 +/- 26.9
Median days (range)	60 (20-71)	59 (21-73)
Sex		
Male	14 (73.7%)	7 (70.0%)
Female	5 (26.3%)	3 (30.0%)
Clinical Syndrome		
Primary Bloodstream Infection	6 (31.6%)	3 (30.0%)
Gastrointestinal Infection	13 (68.4%)	7 (70.0%)
Culture Unit		
Floor	14 (73.7%)	8 (80.0%)
Intensive Care Unit	5 (26.3%)	2 (20.0%)

Table 1: Patients with DSVRE and DNSVRE bacteremia were matched by age, sex, and clinical syndrome. Most cases of VRE bacteremia occurred on the floor. Patients in the ICU did not have an increased incidence of DNSVRE isolates.

Disease Severity and Outcomes

DISEASE SEVERITY AND OUTCOMES	DSVRE (n=19)	DNSVRE (n=10)
SIRS	13 (68.4%)	10 (100%)
ICU	8 (42.1%)	6 (60.0%)
Vasopressors	6 (31.6%)	3 (30.0%)
Respiratory Support	5 (26.3%)	3 (30.0%)
Renal Replacement	2 (10.5%)	3 (30.0%)
SAPSII (Rounded)		
25th Percentile	30	37
50th Percentile	43	45
75th Percentile	55	48
All Cause Mortality During Hospitalization	9 (47.4%)	5 (50.0%)
Mortality up to 30 Days Post-Discharge	9 (47.4%)	7 (70.0%)
Hospitalization Length from First Blood Culture to Alive at Time of Discharge		
Mean days	30	45
Median days (range)	24 (14-54)	31 (11-94)

Table 3: Disease severity and outcomes of DSVRE and DNSVRE bacteremia.

Comorbidities

COMORBIDITIES	DSVRE (n=19)	DNSVRE (n=10)
HIV	1 (5.3%)	0 (0.0%)
Malignancy		
Leukemia	5 (26.3%)	5 (50.0%)
Lymphoma	5 (26.3%)	5 (50.0%)
Diabetes	6 (31.6%)	4 (40.0%)
Cirrhosis	2 (10.5%)	1 (10.0%)
Immunosuppressive Medications	11 (57.9%)	8 (80.0%)
Transplant		
Stem Cell	5 (26.3%)	5 (50.0%)
Solid Organ	2 (10.5%)	0 (0.0%)
Malnutrition	13 (68.4%)	5 (50.0%)
Charlson Comorbidity Score		
25th Percentile	4	3
50th Percentile	6	6
75th Percentile	7	7

Table 2: Similar co-morbidities were observed in DSVRE and DNSVRE bacteremia. DNSVRE bacteremia was associated with malignancy, stem cell transplant, or immunosuppressive medications.

Minimal Inhibitory Concentration (MIC) Creep Phenomenon

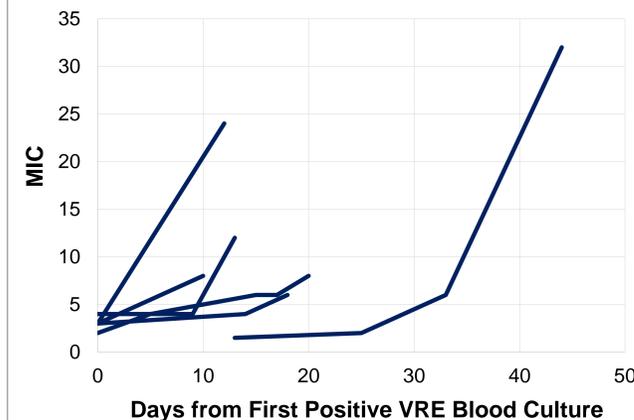


Figure 1: Six of ten patients with DNSVRE bacteremia had isolates that were initially daptomycin susceptible but became resistant with antibiotic exposure.

- 10 cases of DNSVRE and 19 matched cases of DSVRE bacteremia (**Table 1**)
 - Median age 60 years
 - 72% male
 - 70% had bacteremia from gastrointestinal infections
- DNSVRE bacteremia patients had more malignancies. (90% v 53%, p=0.046). (**Table 2**)
- More patients with DNSVRE bacteremia had SIRS, required ICU stay, and had renal replacement but there was no statistical significance. (**Table 3**)
- Higher DNSVRE mortality up to 30-days post-discharge. (70% v 47%, p=0.163)
- A "MIC creep" phenomenon was observed where 60% of patients with DNSVRE isolates had isolates that were initially susceptible to daptomycin but became resistant following antibiotic exposure. (**Figure 1**)

CONCLUSION

- Patients with DNSVRE bacteremia had increased infection severity and mortality compared to those with DSVRE bacteremia.
- Patients with DSVRE infections who do not respond to treatment should be assessed for changes in daptomycin susceptibility.

None of the authors have conflicts of interests