



# The Clinical Impact of Daptomycin Non-susceptible *Enterococcus*

## Bacteremia in Hematologic Malignancy

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### Introduction

- Enterococcus*, a gram positive bacteria typically present in gut flora, have become progressively more resistant to vancomycin.
- Vancomycin resistant *Enterococcus* (VRE) has been deemed a serious threat for antimicrobial resistance by the CDC and a high priority pathogen by the WHO.
- VRE has been associated with increased mortality in patients with blood stream infections (BSI) as compared to vancomycin sensitive *Enterococcus*
- Patients with hematologic malignancies are at high risk for VRE BSI with 30-day all-cause mortality approaching 40%.
- Daptomycin-nonsusceptible *Enterococcus* (DNSE) is on the rise, with institutional resistance rates as high as 15%.
- DNSE in our institution has been increasingly recognized
- The objective of this study was to determine risk factors associated with resistance to daptomycin among *Enterococcus* isolates and subsequently determine mortality for this patient population.

### Methods

- We performed a retrospective cohort study of hematologic malignancy patients who developed either DNSE or daptomycin-susceptible VRE bacteremia between January 1, 2008 and December 31, 2016.
- Study was limited to:
  - Hematologic malignancy
  - First episode of bacteremia
  - Patients currently admitted or admitted within 72 hours of positive culture
- Demographic information, date of infection, length of stay (LOS), and clinical outcomes were collected from the electronic medical record
- Categorical variables were analyzed with chi-square or Fisher's exact test and continuous variables were analyzed with a t-test or Wilcoxon rank sums test when appropriate. A p-value <0.05 was considered significant.

### Results

Table 1: Patient Characteristics

(n, %)	DNSE (n=34)	VRE (n=65)	p value
Age, years (median, [IQR])	49 (34-58)	51 (41-60)	0.36
Male Gender	19 (56)	41 (63)	0.52
Race/Ethnicity			
Caucasian	24 (71)	45 (69)	0.99
Black	9 (26)	18 (28)	
Hispanic	1 (3)	2 (3)	
Diagnosis			
Leukemia	23 (67)	49 (75)	0.54
Lymphoma	2 (6)	7 (11)	
Myelodysplastic syndrome	3 (9)	3 (5)	
Multiple Myeloma	2 (6)	3 (5)	
Amyloidosis	1 (3)	0 (0)	
Other	3 (9)	3 (4)	
Bone Marrow Transplantation	n = 18 (53)	n = 33 (51)	0.84
Autologous	3 (17)	2 (15)	
Allogenic, matched related	3 (17)	10 (30)	
Allogenic matched unrelated	10 (55)	12 (36)	
Other	2 (11)	6 (18)	

Table 2: Risk Factors

(n, %)	DNSE (n=34)	VRE (n=65)	p value	Odds Ratio
Charlson Comorbidity (median, [IQR])	3 (2-4)	3 (2-5)	0.90	
APACHE II (median, [IQR])	19 (16-26)	19 (15-23)	0.24	
Pitt Bacteremia (median, [IQR])	3 (0-5)	2 (0-3)	0.11	
Prior VRE colonization	n = 16 (47)	n = 24 (37)	0.44	
Prior VRE Infection	11 (32)	12 (18)	0.12	
GVHD*	n = 12 (67)	n = 11 (35)	<b>0.03</b>	3.64 [1.07-12.38]
Low Grade (0-2)	1 (8)	5 (45)		
High Grade (3-4, chronic)	11 (92)	5 (45)	<b>0.03</b>	11 [1.00-120.43]
Mucositis	8 (23)	17 (26)	0.81	
Neutropenic	25 (73)	39 (60)	0.18	
• Median days (IQR)	26 (10-49)	12.5 (7-19.75)	<b>0.03</b>	
• Neutropenia >20 days	13	9	<b>0.01</b>	4.19 [1.38-12.75]
Appropriate therapy	N = 28 (82)	N = 58 (89)	<b>0.02</b>	1.34 [1.02-1.77]
• Median days (IQR)	3.5 (2-4)	2.0 (1-3)		
LOS before bacteremia, median (IQR)	20 (7.75-40)	21 (12.5-30.5)	0.08	
• LOS >45 days prior to bacteremia	8	6	<b>0.05</b>	3.03 [0.95-9.6]

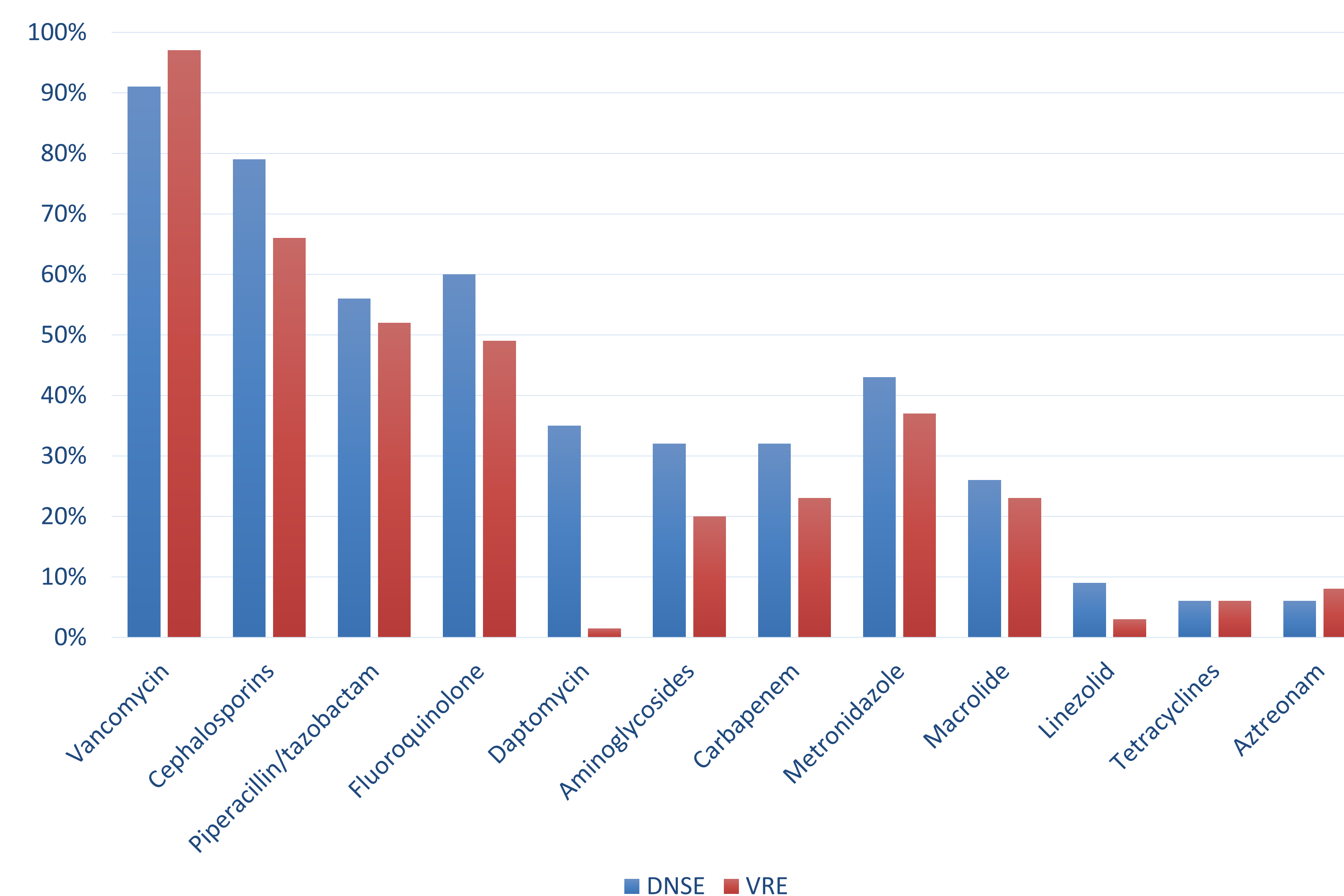
\*Data reflects patients who underwent bone marrow transplantation.

Similar cohorts in terms of gender, race, diagnosis, comorbidities, and transplant status.

Table 3: Outcomes

(n, %)	DNSE (n=34)	VRE (n=65)	p value	Odds Ratio
Resolution of bacteremia	25 (73)	54 (83)	0.26	
Total days bacteremia (median)	2 (1.5-4.5)	3.0 (2-4)	0.37	
Death	25 (73.5%)	49 (75.3%)		
• 7 day mortality	8 (24%)	11 (17%)	0.43	1.51 [0.54-4.2]
• 30 day mortality	17 (50%)	25 (38%)	0.21	1.71 [0.74-3.96]
Total LOS, median (IQR)	35(42)	36 (22)	0.12	
Total LOS greater than 50 days	12 (35)	11 (17)	<b>0.040</b>	2.68 [1.03-6.97]
• LOS prior bacteremia, median (IQR)	20(32)	21 (18)	0.08	
• LOS after bacteremia, median (IQR)	12 (24)	15 (13)	0.67	

Figure 1: Percentage of Patients With Antibiotic Exposure Within 90 Days Prior to Bacteremia



- Both cohorts were exposed to large amounts of antibiotics prior to bacteremia, but 38% vs 1.5% of DNSE cohort was exposed to daptomycin (p <0.001, OR 39.6 [4.9-321.2]).

### Discussion

- Patients with DNSE were more likely to have GVHD (particularly high grade), longer episodes of neutropenia prior to bacteremia, and trended to higher LOS before bacteremia
- Median LOS were similarly high in both groups, however, DNSE patients were more likely to have a total LOS over 50 days as compared to VRE
- 30-day mortality was similarly high in both DNSE and VRE bacteremia, 50% vs 38%. However, relative risk of death in patients with GVHD was higher for DNSE group as compared to VRE (VRE OR 1.89 [0.49-7.37] vs DNSE OR 7.87 [1.35-45.8]) **p = 0.02**
- Daptomycin exposure does not fully explain emergence of daptomycin resistance in our institution, given only 38% of patients were previously exposed and warrants further investigation.
- Infection prevention interventions targeting this particular multi-drug resistant organism are needed in this vulnerable population.

### References

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