Effectiveness of Daptomycin for MRSA Bloodstream Infections with Vancomycin MIC 1.5-2.0 mg/L: A Multi-center Evaluation of Clinical and Microbiological Outcomes

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AMENDED ABSTRACT

BACKGROUND: Despite mounting evidence that vancomycin (V) efficacy declines for treatment of MRSA bloodstream infections (BSI) with V MIC > 1, clinical studies examining optimal antimicrobial therapy for these patients are limited. Few multicenter investigations have been performed to establish the efficacy of daptomycin (D) for this indication.

METHODS: Multicenter, retrospective study, examining clinical & microbiological outcomes of D, when used as initial or early therapy (≤5 d prior V) in MRSA BSI with V MIC 1.5-2.0. Overall failure included: 60-d all-cause mortality, 7-d persistence, discontinue for failure or adverse event, 30-d relapse.

RESULTS: 93 D-treated cases from 11 US institutions were enrolled (2007-2012). Median (IQR) age was 61 (50-77); APACHE II was 14 (10-18); 90% had ID consult; 77% had echocardiogram. Clinical features: ICU stay (30%), dialysis (23%), immunocompromised (19%), cancer (16%). V MICs were 1.5 & 2.0 for 32% & 68%, respectively. 54% received ≤2 d prior V; 17% received no prior V. Most common BSI focus: bone/joint (30%), endocarditis (IE) (23%), skin (20%), unknown source (15%). Median D dose: 6 mg/kg (range, 6-10). The majority (79%) cleared bacteremia by d 4: 58% of IE, 67% of mycotic aneurysm/ septic thrombophlebitis, 69% of unknown source, 80% of catheter, 88% bone/joint, 94% skin & 100% abdominal/urinary. Overall composite failure was 30% (28/93): 18% due to 60-d all cause mortality, 10% for lack of MRSA clearance by d 7, 4% switched to alternative due to clinical/microfailure. No recurrence was noted. Some had >1 failure reason. 30- & 60-d all cause mortality was 10% (9/93) & 18% (17/93), respectively. 60-d mortality, attributable to MRSA, occurred in 3% (3/93). Logistic regression identified 60-d all-cause mortality to be associated with ICU stay (OR, 4.43 [95% CI, 1.39-14.2]; p=0.012) & increased age (OR, 1.04 [95% CI, 1.00-1.07]; p=0.038). No relationship was noted between time to bacteremia clearance (by 4 & 7 d, respectively) & 60-d mortality (p=0.204 & p=0.468, respectively).

CONCLUSION: MRSA bacteremia is a heterogeneous disease with different rates of response to antimicrobial therapy based on the primary focus of infection. Patient mortality was related to severity of illness (ICU stay) & advanced age. In this multicenter study, D therapy appears to be an option in MRSA BSI with V MIC 1.5-2.

INTRODUCTION

- Single center studies suggest a potential clinical advantage of daptomycin over vancomycin for MRSA bloodstream infection (BSI) when vancomycin MICs are >1 µg/ml [1-2]
- Few multicenter investigations have been performed to establish the efficacy of daptomycin for this scenario [3]

OBJECTIVE

- To examine clinical and microbiological outcomes of daptomycin, when used as initial or early therapy (≤5 days of prior vancomycin) in MRSA BSI with vancomycin MICs of 1.5-2.0 µg/ml
- To define matching criteria for comparison of daptomycin and vancomycin for MRSA BSI with vancomycin MICs of 1.5-2.0 µg/ml

METHODS

- Multicenter, retrospective investigation of MRSA-BSI with vancomycin MIC values of 1.5-2.0 µg/ml
- Electronic case report forms were used by independent, trained study investigators at each site to collect demographic, clinical and microbiological information
- Data monitoring was conducted by an independent third-party
- Institutional review board approved the investigation at each site

Patient Selection

- Hospitalized adults (>18 years of age) who received daptomycin (>6 mg/kg) for at least 3 days as treatment of MRSA bacteremia were eligible
  - Inclusion criteria:
    - Blood culture(s) positive for MRSA with a vancomycin MIC of 1.5 or 2.0 µg/ml
    - Receipt of initial anti-MRSA therapy within 72 hours of index blood culture collection
  - Exclusion criteria:
    - Known prior MRSA-BSI in the proceeding 30 days
    - Prosthetic valve endocarditis, infected cardiac device, MRSA pneumonia, or polymicrobial bacteremia
    - Tunneled catheter related bacteremia as the only site of infection without complications
    - Concomitant use of daptomycin and vancomycin for > 24 hours
    - Receipt of >5 days of vancomycin prior to the initiation of daptomycin
- Consecutive daptomycin-treated subjects meeting enrollment criteria were selected retrospectively (consecutive with the most recent daptomycin case first from study initiation in 2012), and enrolled patients with the shortest course of prior vancomycin preferentially (<3 days prior vancomycin followed by 4-5 days of prior vancomycin)

Microbiologic Data Collected

- All blood culture results and dates for all positive and negative blood cultures were obtained
- Susceptibility data for vancomycin and daptomycin was collected for the first positive and last positive blood culture

Clinical Data Collected

- Age, gender, institution, comorbid conditions, APACHE II score, and if an ID consult was obtained
- Daptomycin initial and final dose, dosing interval, length of therapy
- Prior, concomitant and follow-up antibiotic therapy details, including dose, length of therapy, and discontinuation and switch reason
- Bacteremia Source Hierarchy – Although each patient in this analysis had positive blood cultures for MRSA, in order to place each patient with more than one reported infection type into only one category, they were assigned to a single category by the following hierarchy: endovascular > extravascular > non-tunneled central catheter only
- Hospitalization details from initiation of therapy through 60-days after end of therapy

Outcomes and Definitions

- Outcomes investigated included:
  - Composite failure was a composite endpoint that included:
    - 60-day all-cause mortality
    - 7-day clinical or microbiological failure
    - 30-day BSI relapse
    - Failure at end of therapy (discontinue or change study drug therapy for failure or adverse event)
  - Bacteremia clearance at day 4 and day 7
- Identification of predictors of the above outcomes were used to identify match criteria for vancomycin-treated patients, for comparison of daptomycin and vancomycin in a subsequent comparative matched study

Data Analysis

- Statistical comparisons of interest were performed using univariate and multivariate analyses
- Dichotomous variables were compared by means of χ^2 analysis or Fisher's exact test, when appropriate
- Continuous and ordinal variables were compared using Kruskal-Wallis analysis of variance and Mann-Whitney U tests
- Multivariate analysis to detect potential relationships among clinical factors and daptomycin treatment response was performed using logistic regression
- Statistical significance was defined as P<0.05
- All statistics were performed in duplicate by two individuals (TC [see Acknowledgements] and author PM), and were performed using SAS, Systat 11, GraphPad and/or EpiInfo Analysis

RESULTS

Patient Demographics and Characteristics

- 93 Daptomycin-treated cases from 11 US institutions were enrolled (2007-2012)
  - Of these patients, the median (IQR) age was 61 (50-77); median (IQR) APACHE II was 14 (10-18); 90% had ID consult; and 77% had an echocardiogram
- Clinical features included: ICU stay (30%), dialysis (23%), immunocompromised (19%), cancer (16%)
- 54% received ≤2 days of vancomycin prior to daptomycin therapy; 17% received no prior vancomycin

Daptomycin Dosage Regimen

- The median daptomycin dose was 6 mg/kg (range, 6 - 10 g/kg)
  - Daptomycin was dosed >8 mg/kg in 24% (22/93)
- The median duration of daptomycin was 16 days (range, 3 – 142 days)

Infection Characteristics

- Most common BSI focus: bone/joint (30%), endocarditis (23%), skin (20%), unknown source (15%)
- Vancomycin MICs were 1.5 & 2.0 µg/ml for 32% & 68%, respectively

Clinical Outcomes

- Overall composite failure was 30% (28/93) (Table 1)
  - 18% due to 60-d all cause mortality, 10% for lack of MRSA clearance by day 7, 4% switched to alternative for daptomycin failure. No recurrence was noted. Some had >1 failure reason
    - 60-d mortality, attributable to MRSA, occurred in 3% (3/93)
- An ICU stay and increased age were more common in patients with overall failure (Table 2)
- The majority of patients (79%) cleared their bacteremia by day 4 (Table 3):
  - 58% of endocarditis
  - 67% of mycotic aneurysm/ septic thrombophlebitis
  - 69% of unknown source
  - 80% of catheter
  - 88% bone/joint
  - 94% skin
  - 100% abdominal/urinary
- Logistic regression identified infection type to be associated with bacteremia clearance by day 4
  - MRSA BSI where skin was primary bacteremia type were over 8 fold likely to clear by day 4 vs those due to other sources
    - OR, 8.50 (95% CI, 1.02-70.6), p=0.0475
- Logistic regression identified 60-d all-cause mortality to be associated with ICU stay and increased age (Table 4)
- No relationship was noted between time to bacteremia clearance (by 4 & 7 days, respectively) and 60-day all-cause mortality (p=0.204 & p=0.468, respectively)

Table 1. Primary Outcome Details (Composite Failure) for the 93 Daptomycin-Treated Study Patients

Reason for Treatment Failure	Daptomycin (n=93)
Overall Failure	28 (30%)
60-day all cause mortality	17 (18%)
30-day all cause mortality	9 (10%)
60-d Mortality attributable to MRSA Bacteremia[a]	3 (3%)
Clinical or Microbiological Failure at day 7	12 (13%)
Documented Bacteremia for ≥ 7 Days despite DAP therapy[b]	8/81 (10%)
Failure at End of Study Drug Therapy	9 (10%)
Switched to alternative due to clinical/micro failure	4 (4%)
Death during therapy	4 (4%)
Care withdrawn	1 (1%)
Discontinued DAP due to an adverse event	0
Relapse within 30-days of EOT	0

[a] The 3 attributable deaths occurred on days 5, 8 & 13; all with endocarditis (2 left, 1 right); none received surgical intervention/not candidates; Daptomycin dose: 7.5, 6 & 6 mg/kg, 1 had follow-up culture with VISA (daptomycin MIC 3; vancomycin MIC 3)

[b] An assessment of bacteremia clearance at 7 days was unable to be made in 12 cases

Table 2. Patient Characteristics and Outcomes

Characteristic	All Daptomycin Treated (n=93)	Daptomycin Failure Group (n=28)	Daptomycin Non-Failure Group (n=65)	*P* Failure vs. Non-Failure
Age in yrs; mean ± SD (median)	61±18 (61)	66±18 (69)	59±18 (58)	0.059
Male sex, n (%)	50 (54%)	15 (54%)	35 (54%)	0.981
Weight in kg; mean ± SD (median)	81±26 (77)	84±37 (73)	81±20 (79)	0.558
CrCl in ml/min; mean ± SD (median)	103±71 (100)	85±64 (81)	111±73 (106)	0.155
Infectious Disease consult, n (%)	84 (90%)	26 (93%)	58 (89%)	0.587
ICU anytime during therapy	28 (30%)	14 (50%)	14 (22%)	0.006
Select Condition, n (%)				
IVDU	9 (10%)	3 (11%)	6 (9%)	0.824
Malignancy	15 (16%)	3 (11%)	12 (18%)	0.351
Dialysis	21 (23%)	8 (29%)	13 (20%)	0.364
Trauma	10 (11%)	4 (14%)	6 (9%)	0.470
Immunocompromised	18 (19%)	5 (18%)	13 (20%)	0.810
Steroids	11 (12%)	4 (14%)	7 (11%)	0.630
Shock	19 (20%)	6 (21%)	13 (20%)	0.875

Table 3. Bloodstream Infection Types and Clearance by Day 4 and Day 7

Infection Characteristic	Cleared Bacteremia by Day 4	Cleared Bacteremia by Day 7
Any Infection	67/85 (79%)	73/81 (90%)
By Hierarchy Bloodstream Infection Type		
Endovascular	22/35 (63%)	26/32 (81%)
Endocarditis	11/19 (58%)	13/17 (77%)
Mycotic aneurysm / Septic thrombophlebitis	2/3 (67%)	2/3 (67%)
Unknown	9/13 (69%)	11/12 (92%)
Extravascular	41/45 (91%)	43/44 (98%)
Bone & Joint	22/25 (88%)	24/25 (96%)
Skin & Skin Structure	17/18 (94%)	17/17 (100%)
Urinary Tract / Intra-abdominal	2/2 (100%)	2/2 (100%)
Central Venous Line Associated only	4/5 (80%)	4/5 (80%)

*Patients who did not have sufficient serial blood culture data available to be evaluated at these time points were not included in the above analysis.

Table 4. Multivariate Analysis of Factors Associated with 60-day All-Cause Mortality

Factor	OR (95% CI)	*P*
Age	1.04 (1.00 – 1.07)	0.038
ICU stay	4.43 (1.38 – 14.2)	0.012

CONCLUSIONS

- MRSA bacteremia is a heterogeneous disease with different rates of response to antimicrobial therapy based on the primary focus of infection
- Patient mortality was related to severity of illness (ICU stay) and advanced age
- Bacteremia clearance by day 4 was related to BSI type
- Our findings support matching criteria by infection type, severity of illness (e.g., ICU stay) and age, consistent with single center investigations of MRSA bloodstream infections with vancomycin MICs >1 µg/ml [1-2]
- In this multicenter study, daptomycin therapy appears to be an option in MRSA bloodstream infections with vancomycin MICs of 1.5-2 µg/ml

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REFERENCES

1. Moore CL et al. *Clin Infect Dis* 2011; 51: 1074-80
2. Murray KP et al. *Clin Infect Dis* 2013; 56: 1562-9.
3. Crompton JA et al. *J Antimicrob Chemother* 2010; 65: 1784-91.