

Contribution and Associated Outcomes of Community MRSA Strains in Bloodstream Infections

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Abstract (Revised)

Background: Community MRSA strains account for an increasing proportion of invasive MRSA infections in the U.S. We determined the epidemiology, virulence, and vancomycin (VAN) susceptibility of MRSA strains causing BSIs and associated outcomes.

Methods: Patients hospitalized during 7/05 to 12/08 with MRSA BSI per CDC definition were evaluated if they received \geq 48h of anti-MRSA therapy and had MRSA isolates available for microbiologic analysis. A nucleic acid hybridization assay (Evigene-Rainbow, AdvanDx, MA) with a 3h turnaround time for results was performed to detect presence of Pantone-Valentine leukocidin (PVL)-encoding genes and SCCmec types. We determined VAN MIC by Etest and glycopeptide-resistance detection (GRD) strips to screen for hGISA phenotype. Medical charts of patients were reviewed to obtain demographic, laboratory, and clinical information.

Results: SCCmec IV, V strains caused 52% (55/105) of BSIs; 71% (39/55) were PVL(+). Patients infected with SCCmec IV, V strains were younger (64 vs 70y), less likely to reside in nursing home (38% vs 62%, p=0.019) but equally likely to have diabetes and/or renal disease (58%). Abscess/wound was the most frequent source of infection (30%) in the SCCmec IV, V group; 8 developed endocarditis. High VAN MIC (\geq 1.5 mcg/ml) was observed in 60% (33/55) vs 70% and positive hGISA phenotype in 18% (9/50) vs 14% (7/49) SCCmec II, III compared to SCCmec I, III strains. Most (89%) received empiric VAN therapy (tough \geq 15 mcg/ml). Clinical failure and infection-related mortality were not affected by PVL status of infecting strain but were higher for patients infected with high MIC strains (45% vs 27%, p=0.09; 16% vs 5%, p=0.13) regardless of SCCmec types.

Conclusion: MRSA BSIs among hospitalized patients affect predominantly those with diabetes and/or renal disease, with 54% caused by SCCmec IV, V strains. VAN MIC determination by Etest is important to guide treatment choice for MRSA BSI whether suspected of community or nosocomial origin.

Introduction(1-3)

1. According to a large population-based surveillance conducted by CDC, bloodstream infections account for 75% of invasive MRSA infections with an increasing proportion caused by community strains.
2. Community-associated (CA) MRSA strains are characterized by SCCmec IV or V type, with many harboring the lukF/S gene that encodes the putative virulence factor, PVL toxin.
3. The burden of disease and associated outcomes amongst hospitalized patients with bloodstream infections caused by CA-MRSA strains are uncertain.

Study Objectives

1. To determine contribution of community MRSA strains in bloodstream infections among hospitalized adults.
2. To evaluate epidemiology, virulence, vancomycin susceptibility of community strains and associated outcome of BSIs caused by community MRSA strains.

Methods

Site: Huntington Hospital, 565-bed community teaching hospital

Study Population: Patients admitted from July 2005 to December 2008 with MRSA BSI who met the following inclusion criteria:

- 1) Age \geq 18 years, 2) Evidence of BSI as defined by the CDC criteria, 3) MRSA isolate saved and available for microbiologic analysis, 4) Receipt of \geq 48 hours of anti-MRSA therapy, and 5) Medical chart available for review.

Data Collection: Medical and laboratory records were retrospectively reviewed and recorded into a relational database (Microsoft Access). Relevant demographic, laboratory, microbiology data, clinical progress, and antimicrobial regimen were recorded.

DEFINITIONS

- **Clinical stability:** Return of abnormal vital signs to normal baseline values [HR \leq 100 beats/min, SBP \geq 90mm Hg, RR \leq 24 breaths/min, O₂ saturation \geq 90%, and temperature \leq 37.2°C (99°F)]
- **Clinical response:** Resolution or improvement of fever, leukocytosis, and local signs of infection evaluated at 72 hrs and end of therapy (EOT)*
- **Failure:** Absence of resolution or worsening of clinical signs and symptoms of infection
- **Relapse:** Recurrence of infection with same organism in \leq 3 month after discontinuation of therapy

* For those discharged home with antibiotic therapy, EOT clinical response was assessed on last day of hospitalization

BACTERIAL STRAINS

105 MRSA isolates causing bloodstream infections were collected from eligible patients. Control strains from NARS: NRS 22 (SCCmec II, PVL (-) control), NRS 384 (SCCmec IV, USA 300, PVL (+) control)

Testing for methicillin resistance: Confirmed using VITEK and oxacillin agar screen test (MHA containing 2% added NaCl with 6 mg/L OXA)

Vancomycin MIC via Etest (AB Biodisk, Solna, Sweden):

Strains were grown overnight on blood agar plates. Mueller-Hinton plates were inoculated with a 0.5 McFarland standard of suspension, and streaked out evenly with a swab and plate rotator. Etest strips were placed on each and incubated for 24 hours at 37°C. MIC was read as the intersect where the ellipse of growth inhibition intersects the strip; where colonies occurred within the inhibition ellipse, the higher value was taken as the MIC.

Detection of hGISA by GRD (Glycopeptide-resistance Detection) E-test:

A bacterial suspension corresponding to a 0.5 McFarland standard was plated on Mueller-Hinton agar+5% blood (MHB) and on Muller-Hinton agar plate (MHA). A GRD strip consisting of a double-sided gradient with VAN and teicoplanin was then applied to the MHB plate and a standard VAN Etest is applied to the MHA plate. The standard VAN Etest was read and recorded after 18-24 h of incubation. The zone of the Etest GRD strip was also read, at complete inhibition of growth and at 48 hours. The test isolate was considered positive for hVISA if the Etest GRD strip is \geq 8 μ g/ml for either vancomycin or teicoplanin and the standard VAN Etest MIC is \leq 4 μ g/ml.

PVL toxin and SCCmec type:

Detection of PVL-toxin encoding genes (lukS-lukF/PV) and SCCmec type was determined with the EVIGENE™ Rainbow kit (AdvanDx, Woburn, MA) qualitative nucleic acid hybridization assay according to manufacturer's instructions. In short a 10ul loopful of bacteria are lysed with lysis buffer solution for 30 minutes at 100°C. Detector probes are added to the ELISA plate with 100ul of lysed cell solution and incubated for 60 minutes to allow hybridization. Next buffer solutions are added for signal amplification and allowed to incubate for 60 minutes. Stop solution is added and results are read at 490 nm, OD readings greater than 0.500 are considered positive.

Data Analysis

Subjects were grouped according to SCCmec type and compared by demographics, microbiology (VAN MIC, virulence determined by PVL toxin), treatment received and clinical outcome.

Statistical analysis: Chi-square, Fisher's exact, and the Mann-Whitney U tests were used as appropriate. All analysis were conducted via GraphPad Prism (version 5.0). P<0.05 denotes statistical significance.

Results

Clinical and Molecular Epidemiology

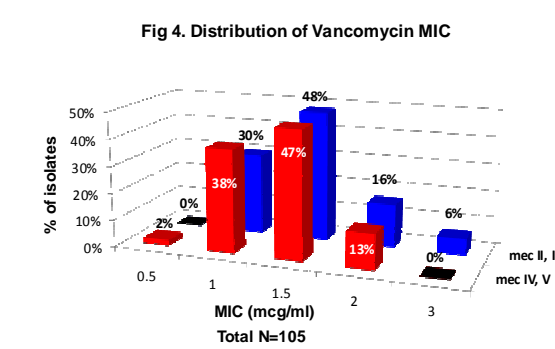
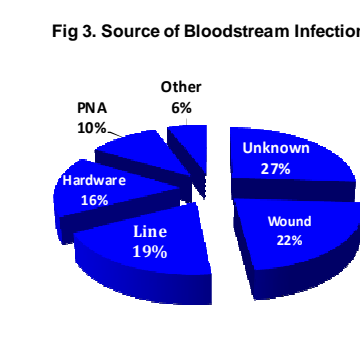
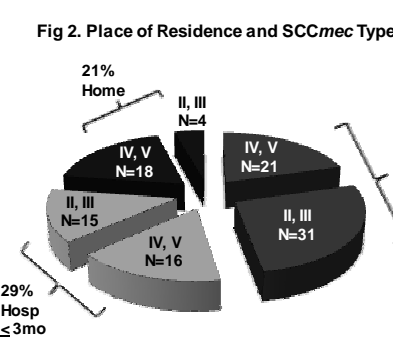
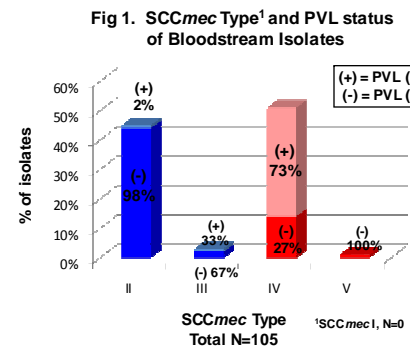


Table 1. Patient Demographics

	SCCmec IV, V (N=55)	SCCmec II, III (N=50)
Age, yrs (mean \pm SD)	64.4 \pm 18.4	70 \pm 14.4
Male/Female	18/37 (33%/67%)	21/29 (42%/58%)
Weight, kg (mean \pm SD)*	82 \pm 22	72 \pm 17
Place of residence:		
SNF**	21 (38%)	31 (62%)
Hospitalization \leq 3mo	16 (29%)	15 (30%)
Home**	18 (33%)	4 (8%)
APACHE II ^a (mean \pm SD)	16 \pm 7.5	17.6 \pm 5.8
ICU Admission	19 (35%)	15 (30%)
History of MRSA	23 (42%)	17 (34%)
Recent VAN therapy ^b	18 (33%)	13 (26%)
Co-morbid conditions:		
CVA	8 (15%)	12 (24%)
COPD	8 (15%)	11 (22%)

a. Calculated based on admission values. b. Vancomycin therapy within the last 6 months
P value: * = 0.018, ** = 0.019

Summary

1. Community MRSA strains (SCCmec IV, V) comprised of 52% of all MRSA BSIs evaluated.
2. High prevalence of SCCmec IV, V among strains causing BSIs in patients residing in nursing homes or with recent healthcare exposure (45%, 37/83) was observed.
3. Patients infected with community strains were similar to those infected with SCCmec II, III strains in terms of comorbid conditions but weighed more; CVD, diabetes, and renal disease were frequently present.
4. Wound (25%, 14/55) was the most frequent source of infection for BSIs caused by SCCmec IV, V strains; 71% of SCCmec IV, V strains were PVL(+).

(Table 1. cont)

	SCCmec IV, V (N=55)	SCCmec II, III (N=50)
Co-morbid conditions cont:		
CVD ^a	38 (69%)	38 (76%)
DM	24 (44%)	21 (42%)
Hyperlipidemia	18 (33%)	20 (40%)
Renal disease	21 (38%)	23 (46%)
Hemodialysis	13 (24%)	17 (34%)
Liver disease	3 (5%)	3 (6%)
Steroid/Immunosuppressant	6 (11%)	8 (16%)
Malignancy	9 (16%)	9 (18%)
Antibiotic Therapy		
VAN empiric therapy ^b	49 (89%)	44 (88%)
VAN containing regimen ^b	26 (47%)	26 (52%)
Non-VAN containing regimen ^c	29 (53%)	24 (48%)
Anti-MRSA tx within 24 hrs ^d	45 (82%)	46 (92%)
Anti-MRSA tx within 48 hrs ^d	52 (95%)	50 (100%)

a. CVD= HTN, Afib, CHF; b. VAN alone or in combination; c. Non-vanco agents = linezolid, daptomycin, tigecycline; d. Initiation within 24 or 48 hrs of positive blood culture

5. Overall, 65% of the isolates tested had high MIC (\geq 1.5 mcg/ml) to vancomycin. Community strains were equally likely to have high MICs and hGISA phenotype compared to SCCmec II, III strains.
6. Clinical failure rates were high in both groups with similar rates of infectious complications (endocarditis) and mortality.

References

1. Klevens et al. JAMA 2007;298:1763-71.
2. Boucher HW et al. Clin Infect Dis 2008;46:S344-9.
3. Otto M. Expert Rev Anti Infect Ther 2009;7(2):141-143.

Table 2. Clinical Outcomes

	SCCmec IV, V (N=55)	SCCmec II, III (N=50)
Hospital LOS, d ^a (median, IQR)	17 (10-30)	15 (8-25)
ICU LOS, d (median, IQR)	8 (1-15)	5 (2-8)
Time to achieve clinical stability, d (median, IQR)	4 (3-7)	3 (1-5)
72hr Response	35 (64%)	32 (64%)
End of treatment Outcome:		
Clinical Response ^b	32 (58%)	32 (64%)
Failure	23 (42%)	18 (36%)
Endocarditis	8 (15%)	7 (14%)
Mortality, overall	7 (13%)	6 (12%)
hGISA	9 (18%) ^c	7 (14%) ^d

a. d=days; b. Including complete and partial response to therapy; c. total tested isolates n=50
d. total isolates tested n=49

Conclusions

1. MRSA BSIs among hospitalized patients affect predominantly those with diabetes and/or renal disease with 52% caused by SCCmec IV, V strains.
2. VAN MIC determination by Etest is important to guide treatment choice for MRSA BSIs whether suspected of community or nosocomial origin.

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