Methicillin-resistant/methicillin-sensitive *Staphylococcus aureus* bacteremia

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ABSTRACT

Objective: To examine the differences between the clinical presentation, management and outcome of persons bacteremic with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA), after controlling for age, sex and primary diagnosis.

Method: A review of the clinical records and laboratory data of all MRSA and MSSA bacteremic patients. Fifty matched case-control pairs were further analyzed looking for differences between the 2 populations. The study was carried out in a 500-bed adult tertiary care institution in southwestern Ontario, Canada, between 1994 and 1999.

Results: On univariate analysis a) duration of hospitalization prior to bacteremia, b) concomitant polymicrobial bacteremia, c) time to appropriate treatment, were significantly greater in the MRSA infected population. Attributable mortality was also higher, 36%-20%, but this did not achieve significance (p=0.1). On multiple logistic regression analysis, a), b) and c) remained significantly different.

Conclusions: In a 1:1 matched case-control study of *Staphylococcus aureus* bacteremia, those infected with MRSA became bacteremic later in their hospital stay, more often had a polymicrobial bacteremia and were appropriately treated later. Although mortality attributable to the MRSA bacteremia was greater, this difference did not achieve significance.

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Much has been written about the relative "virulence" of methicillin-resistant *Staphylococcus aureus* (MRSA). Although differences are described between some strains of MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA),[1-3] no virulence factors are known to be directly associated with the mec-A gene. More likely then, any difference in the outcome of infection with these organisms relates to other variables; host or therapy related. In a retrospective analysis of MRSA bacteremic patients managed at our 500-bed tertiary care institution between 1994 and 1999, we observed a crude mortality rate of 42%. This compared with 27% for those bacteremic secondary to MSSA. This difference was significant when subjected to chi 2 testing (odds ratio (OR) 2.0, confidence interval (CI) 1.0-4.1, p=0.03). Therefore, we carried out a matched case-control study to determine: a) would this difference in mortality persist? b) would other differences emerge? These observations form the basis of this report.

Methods. The inpatient records of all adults (≥18 years) with one or more positive blood culture for *Staphylococcus aureus* (*S.aureus*), identified between January 1, 1994 and 1999 were retrieved. A total of 67 MRSA and 267 MSSA cases was found. After categorizing each group by sex, age (± 5 years) and primary diagnoses, we were able to successfully match 50 pairs in a 1:1 case-control ratio. Additional information extracted included: time from admission to bacteremia as well as total hospital stay (days); maximum temperature (^{0}C) and maximum systolic pressure drop (mm Hg) at the time of bacteremia; complicating septic and non-septic events; prior

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hospitalization (<12 months); deaths, total and attributable (within 7 days of bacteremia or later if a direct sequelae of infection).[4] Also recorded was the time from bacteremia until appropriate antibiotic treatment, in 24-hour increments. Appropriateness was based upon sensitivity testing of the isolate in our microbiology laboratory using standard methodology. Other laboratory parameters examined were: numbers of positive blood cultures; remote positive cultures for the same organism; whether the bacteremia was uni- or polymicrobial and the maximum white blood cell count at that time. Statistical analysis was based on matched pairs, with each case-control pair contributing one observation to the analysis. Conditional logistic regression analysis was utilized using SAS, version 6.12. Variables with a p-value of $\leq$0.10 on univariate analysis were then subjected to multivariate analysis. Variables with a p-value of $\leq$0.05 were considered statistically significant.

Results. The clinical and laboratory results are presented in **Table 1**. Sixty-eight percent of the MRSA study group was male although males accounted for only 43% of adult admissions during this period. The group was, in general, elderly (mean age 60.6 years) and in most cases, had an underlying and ultimately fatal disease.[5] Although the MRSA group became bacteremic later in their hospital stay, the overall duration of hospitalization was not statistically different for the 2 populations (41.4, 33.9 days) but was dramatically longer than the average length of stay for all patients (6.7 days) during the time of the study. Maximum temperature and the incidence of systolic hypotension (drop $\geq$ 30 mm Hg) were the same for both groups as was endocarditis (MRSA 5, MSSA 4). The majority of patients (78%, 68%) had been in an acute care institution in the prior 12 months. Attributable deaths were higher for the MRSA group (36%, 20%), but this difference did not achieve significance (p=0.10). Interestingly, death from all causes was greater for the MSSA population (50%, 68%), but again not significantly so (p=0.13).

On univariate analysis, the MRSA group was appropriately treated later compared to those with a MSSA bacteremia. They more often had a polymicrobial bacteremia, usually with other gram-positive organisms, and were more frequently culture positive at other sites (p=0.05). This latter observation is artefactual as all MRSA patients were "screened" at non-infected sites (nose, perineum, skin); not the hospital policy for the MSSA population. Community acquired bacteremia, defined as a positive blood culture within 72 hours of admission, was the same for both groups. Those variables with a p-value <0.1 were subjected to multivariate analysis.

Length of stay prior to bacteremia, polymicrobial bacteremia, and time to appropriate therapy remained significantly different. These values are presented in **Figure 1**.

Discussion. Many authors have compared the outcome of MRSA versus MSSA sepsis, in particular looking at mortality rates. In some studies, a higher mortality has been found in the MRSA population,[6-11] others observing no differences.[4,12-17] Reasons for these differing outcomes include; definition, for example, bacteremic versus non-bacteremic populations, study design or methodology, and small sample size. For example, the difference in crude mortality we observed when all patients were compared was lost when patients were matched and attributable mortality only was considered. In our study, only bacteremic adults were compared and were controlled for age, sex and pre-morbid disease. For example, a 50-year-old diabetic male with end stage renal disease and MRSA bacteremia had to be matched with a similar male from the MSSA population. This meant we were able to successfully match only 50 of the 67 MRSA patients despite a large pool of persons bacteremic secondary to MSSA. This similarity of the matched pairs should reasonably minimize the probability of any per-existing host differences. However on multivariate analysis, differences in the 2 populations were found. These were duration of hospitalization prior to bacteremia, probability of polymicrobial bacteremia, and time from bacteremia until appropriate therapy. What do these differences mean, and how can this knowledge help one to recognize and optimally manage such patients?

Others have commented on the rarity of MRSA colonization in persons not previously hospitalized.[18] Using the classical definition of community acquired infections, that is present on admission or on-setting within 72 hours, we observed no difference in the incidence of bacteremia in 2 populations. On further examination, however, most patients had been in an acute care institution in the previous year. Expressed differently, a majority of patients with *S.aureus* bacteremia will have a history of recent hospitalization, and although MRSA bacteremias occur, on an average, later in the hospital stay, they are often present at the time of admission to hospital or soon thereafter.

Approximately 60% of patients coded MRSA positive at discharge from our institution, are screened negative (nares, axilla, perineum, wounds) on admission. Ninety-five percent of our MRSA bacteremia population were nasally colonized at the time of diagnosis. Most likely, many had become colonized during their hospital stay, subsequently, becoming bacteremic. Von Giff's study supports this assumption.[19] This could explain the overall latter onset of infection we and others have observed.[6,15] That colonization precedes infection supports our current policy of ongoing screening for MRSA in our high risk areas (critical care trauma, acute care medicine, nephrology, vascular surgery). Unfortunately, as a preventive strategy, we have enjoyed limited success with mupirocin decolonization,[20] similar to Harbath's experience and no longer practice it.[21] However, we believe colonized patients are candidates

Table 1 - Methicillin-resistant/methicillin-sensitive bacteremia: Clinical and laboratory parameters.

Clinical/Laboratory results	Details N=50	MRSA	MSSA
Clinical results	Male/Female	36/14	36/14
	Mean age (years)	60.6	60.5
	Co-morbidity[5]	7/38/5	7/38/5
	Mean maximum temperature (°C)	38.3	38.4
	Hypotension (systolic BP > 30 mm Hg)	27	25
	Treatment (appropriate/inappropriate)	42/8	47/3
	Time to treatment (24 hour increments)	17/9/12/8/4	27/13/7/1/2*
	Mean duration in hospital (total, pre-treatment)	41.4/18.2	33.9/7.4*
	Complications (septic, non-septic)	34/12	33/13
	Death (total, attributable)	25/18	34/10
	Prior hospitalization	39	34
Laboratory results	Number of positive blood cultures (1, 2, > 2)	29/13/8	29/19/2
	Positive cultures elsewhere	40	13*
	Polymicrobial	11	3*
	Mean maximum WBC (x 10^9/L)	15.3	12.4

* $p \leq 0.05$ on univariate analysis
A total of 50 matched pairs of patients were subjected to analysis. Only time to treatment, in 24-hour increments, the duration of hospitalisation prior to bacteremia, positive cultures elsewhere, and the incidence of polymicrobial bacteremia were significantly different in the 2 populations.
BP - blood pressure; WBC - white blood cell count; MRSA - methicillin-resistant *Staphylococcus aureus*; MSSA - methicillin-sensitive *Staphylococcus aureus*

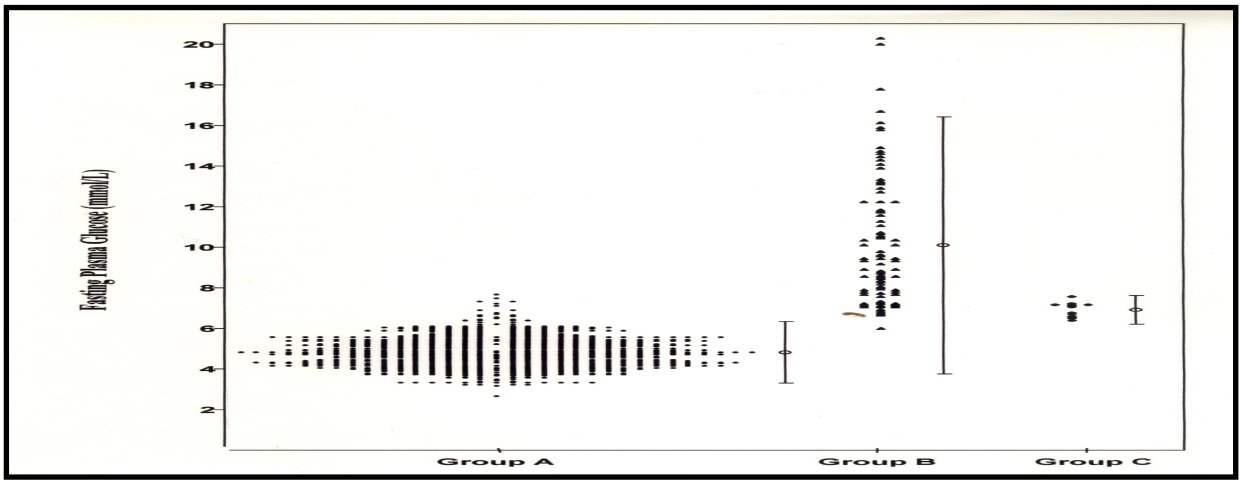

Figure 1 - Methicillin-resistant/methicillin-sensitive bacteremia: Univariate analysis. WBC - white blood cell.

for empiric vancomycin therapy if they develop clinical evidence of sepsis, given MRSA's propensity to invade the colonized, hospitalized person.[22]

Due to concerns regarding vancomycin-resistant enterococci (VRE), guidelines have been published, which do not recommend this drug's use except in specific situations.[23] Empiric administration is discouraged. This may explain the delay in treatment we observed in the MRSA group. Alternatively, as we do not restrict vancomycin usage in our hospital, this could reflect physician under awareness of the frequency with which we see MRSA sepsis. During the study, 12.5% of all *S.aureus* bacteremias were due to MRSA.

It has been demonstrated, in vitro, that the killing of *S.aureus* by vancomycin is slow compared to the βeta-lactams.[24] Studies of serious MSSA infections, such as endocarditis and bacteremic pneumonia, have reported a poor outcome for vancomycin treated patients.[24,25] For this reason, we looked at the attributable mortality in our MSSA bacteremic group treated in part, or totally, with vancomycin (14) compared to those exclusively βeta-lactam treated (36). Only one death was seen in the vancomycin population (7.1%) compared to 13 in the βeta-lactam group (36%) (OR 7.35, CI 0.8-167.6, p=0.04). This observation should not be over interpreted given the wide CI; that the minority of patients had endocarditis or pneumonia, and that some initially treated with vancomycin subsequently received a βeta-lactam. It does, however suggest that vancomycin given to the MSSA bacteremic patient, pending antibiotic sensitivity results, does not adversely effect survival.

Polymicrobial gram-positive blood stream infections are often associated with an infected intravascular catheter.[26] Although we did not document line usage, the fact that the majority of co-infecting organisms were typically skin flora supports this conclusion. It further suggests that treatment, in addition to appropriate antibiotic therapy, will often require the removal of the suspect line.

Limitations of our study were it's retrospective nature and it's size. For example, a study of 80 matched pairs, assuming the same mortality rate would have achieved statistical significance. A prospective study would be desirable, however all bacteremic patients identified over the period of study were eligible and if suitable, utilized. Our hospital places no restriction on vancomycin usage, hence the initial choice of antibiotic was the physician's prerogative. Lastly, the use of the matched case-control method should remove any intentional bias.

We conclude that MRSA as a cause of sepsis should be suspected in the elderly, long stay, male patient, particularly, if MRSA colonization has been documented previously. We believe such patients are candidates for empirical vancomycin treatment. We did not observe an adverse outcome in the MSSA infected population treated in part or totally with this agent. There was, however, a significant delay in initiating appropriate therapy in the MRSA bacteremic group and this could explain the higher attributable mortality seen in these patients. The potential impact of a short course of vancomycin therapy on the introduction and spread of multi-resistant gram-positive bacteria is an obvious concern, but must be weighed against the proven adverse effect of delaying appropriate therapy.[6]

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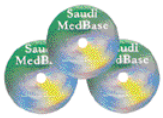

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Title: In Vitro susceptibility to fusidic acid of clinically significant *staphylococcal* isolates from ocular infections

Source: Saudi Med J 1987 Vol. 8 (2): 167-170

Abstract

A total of 163 *staphylococcus* isolates from ocular infections were tested for in vitro susceptibility to fusidic acid, using the modified bauer-kirby disc diffusion method. Susceptibility was demonstrated by 159 (98%) of the isolates and 84 (95%) of the 88 *S.Epidermidis* isolates and all (100%) of both the 70 *S.Aureus* and other *staphylococcus* species isolates. Fifty of the isolates were found to be methicillin-resistant, but of these, 48 (96%) were susceptible to fusidic acid. Forty isolates were resistant to multiple (- 5) antibiotics with 37 (93%) of these showing susceptibility to fusidic acid. No remarkable differences were seen when the susceptibility patterns of the isolates were compared by site of infection.