Usefulness of previous methicillin-resistant *Staphylococcus aureus* screening results in guiding empirical therapy for *S aureus* bacteremia

Anthony D Bai BHSc[1], Lisa Burry PharmD[2,3], Adrienne Showler MD[4,5], Marilyn Steinberg RN[2], Daniel Ricciuto MD[4,5,6,7], Tania Fernandes PharmD[8], Anna Chiu BScPhm[8], Sumit Raybardhan BScPhm MPH[9], George A Tomlinson PhD[4,10], Chaim M Bell MD PhD[2,4,10,11], Andrew M Morris MD SM[2,4,5,10]

AD Bai, L Burry, A Showler, et al. Usefulness of previous methicillin-resistant *Staphylococcus aureus* screening results in guiding empirical therapy for *S aureus* bacteremia. Can J Infect Dis Med Microbiol 2015;26(4):201-206.

BACKGROUND: *Staphylococcus aureus* bacteremia (SAB) is an important infection. Methicillin-resistant *S aureus* (MRSA) screening is performed on hospitalized patients for infection control purposes.
OBJECTIVE: To assess the usefulness of past MRSA screening for guiding empirical antibiotic therapy for SAB.
METHODS: A retrospective cohort study examined consecutive patients with confirmed SAB and previous MRSA screening swab from six academic and community hospitals between 2007 and 2010. Diagnostic test properties were calculated for MRSA screening swab for predicting methicillin resistance of SAB.
RESULTS: A total of 799 patients underwent MRSA screening swabs before SAB. Of the 799 patients, 95 (12%) had a positive and 704 (88%) had a negative previous MRSA screening swab. There were 150 (19%) patients with MRSA bacteremia. Overall, previous MRSA screening swabs had a positive likelihood ratio of 33 (95% CI 18 to 60) and a negative likelihood ratio of 0.45 (95% CI 0.37 to 0.54). Diagnostic accuracy differed depending on mode of acquisition (ie, community-acquired, nosocomial or health care-associated infection) (P<0.0001) and hospital (P=0.0002). At best, for health care-associated infection, prior MRSA screening swab had a positive likelihood ratio of 16 (95% CI 9 to 28) and a negative likelihood ratio of 0.27 (95% CI 0.17 to 0.41).
CONCLUSIONS: A negative prior MRSA screening swab cannot reliably rule out MRSA bacteremia and should not be used to guide empirical antibiotic therapy for SAB. A positive prior MRSA screening swab greatly increases likelihood of MRSA, necessitating MRSA coverage in empirical antibiotic therapy for SAB.

Key Words: *Antimicrobial stewardship; Empirical antimicrobial therapy; MRSA screening; Sensitivity; Specificity; Staphylococcus aureus bacteremia*

L'utilité d'un dépistage antérieur du *Staphylococcus aureus* résistant à la méthicilline pour orienter le traitement empirique de la bactériémie à *S. aureus*

HISTORIQUE : La bactériémie à *Staphylococcus aureus* (BSA) est une infection grave. Les patients hospitalisés subissent un dépistage du *S. aureus* résistant à la méthicilline (SARM) afin de prévenir les infections.
OBJECTIF : Évaluer l'utilité d'un dépistage antérieur du SARM pour orienter l'antibiothérapie empirique de la BSA.
MÉTHODOLOGIE : Les chercheurs ont effectué une étude de cohorte rétrospective dans six hôpitaux universitaires et hôpitaux généraux entre 2007 et 2010 auprès de patients consécutifs atteints d'une BSA confirmée ayant déjà subi un prélèvement de dépistage du SARM. Ils ont calculé les propriétés des tests diagnostiques par prélèvement pour diagnostiquer le SARM et prédire la résistance de la BSA à la méthicilline.
RÉSULTATS : Au total, 799 patients avaient déjà subi des prélèvements pour dépister le SARM avant une BSA. De ce nombre, 95 (12 %) ont présenté un résultat positif et 704 (88 %) avaient déjà subi un prélèvement pour dépister le SARM. Cent cinquante patients (19 %) avaient une bactériémie à SARM. Dans l'ensemble, les prélèvements antérieurs pour dépister le SARM avaient un ratio de probabilité positif de 33 (95 % IC 18 à 60) et négatif de 0,45 (95 % IC 0,37 à 0,54). La précision diagnostique différait en fonction du mode d'acquisition (origine non nosocomiale, origine nosocomiale ou association aux soins de santé) (P<0,0001) et de l'hôpital (P=0,0002). Dans le meilleur des cas, en présence d'une infection associée aux soins de santé, un prélèvement antérieur pour dépister un SARM s'associait à un ratio de probabilité positif de 16 (95 % IC 9 à 28) et négatif de 0,27 (95 % IC 0,17 à 0,41).
CONCLUSIONS : Un prélèvement antérieur négatif au SARM ne permet pas d'écarter une bactériémie par le SARM avec fiabilité et ne devrait pas orienter l'antibiothérapie empirique de la BSA. Un prélèvement antérieur positif au SARM accroît considérablement la probabilité de SARM, ce qui oblige à en tenir compte pour l'antibiothérapie empirique de la BSA.

Staphylococcus aureus is a leading cause of bloodstream infections and is associated with a high mortality of 10% to 30% (1-4). Methicillin-resistant *S aureus* (MRSA) is highly prevalent. In Canada, it is estimated that 27% of all S aureus bacteremia (SAB) are MRSA; however, prevalence varies greatly depending on the region (5). MRSA bacteremia results in higher mortality, longer hospital stay and increased cost compared with methicillin-susceptible *S aureus* (MSSA) (6,7).

The decision to initiate an antibiotic with activity against MRSA in empirical therapy of suspected bacteremia is complex. For MRSA bacteremia, vancomycin is the standard antimicrobial agent, because

[1]*Faculty of Medicine, University of Ottawa, Ottawa;* [2]*Mount Sinai Hospital;* [3]*Leslie Dan Faculty of Pharmacy;* [4]*Department of Medicine;* [5]*Division of Infectious Diseases, University of Toronto, Toronto;* [6]*Lakeridge Health, Oshawa;* [7]*Department of Medicine, Queen's University, Kingston;* [8]*Trillium Health Partners, Mississauga;* [9]*North York General Hospital;* [10]*University Health Network;* [11]*Institute for Clinical Evaluative Sciences, Toronto, Ontario*
Correspondence: Dr Andrew M Morris, Mount Sinai Hospital, 600 University Avenue, Suite 415, Toronto, Ontario M5G 1X5. Telephone 416-586-4800 ext 8102, fax 416-619-5535, e-mail amorris@mtsinai.on.ca

β-lactam antibiotics are ineffective (8). Early empirical antibiotic therapy with MRSA coverage in MRSA bacteremia resulted in better clinical outcomes including lower mortality (9). However, vancomycin is inferior to β-lactam antibiotics in treating MRSA bacteremia (10,11). Furthermore, use of vancomycin increases antimicrobial resistance, such as vancomycin-resistant enterococci (12). Finally, use of vancomycin in the treatment of MRSA bacteremia is associated with risk for nephrotoxicity (8). In clinical practice, empirical vancomycin for suspected bacteremia is not universally used and not added unless there is an increased risk for MRSA (13-15). Ideally, empirical vancomycin is warranted only when the probability of MRSA is sufficiently high.

MRSA screening is usually performed in hospitals for infection control purposes. However, MRSA colonization may predict infection and, therefore, MRSA status may help guide empirical therapy in SAB (16,17). We conducted a retrospective cohort study to identify the clinical utility of past MRSA screening swab in predicting methicillin resistance for patients with SAB.

METHODS

Study design

The present study used data from a larger retrospective cohort study of SAB at six acute-care academic and community hospitals in the Greater Toronto Area (Ontario) from April 1, 2007 to April 1, 2010 (18). Research ethics board approval was obtained from each institution.

Consecutive patients were included in the study if they had ≥1 positive blood culture for *S aureus* and an MRSA screening swab was performed before blood culture susceptibility results. The MRSA screening swab may have been at a current or previous admission. Only the most recent MRSA screening swab was considered. Patients <18 years of age were excluded. Patients were only included in the study once, using the first positive blood culture as the index.

Data sources

Data were obtained from patients' medical records at each site and entered into a standardized case report form. Variables collected from patient medical records included patient age, sex, hospital site, admitting service, date of MRSA screening swab collection, date and time of positive blood culture, date of admission and mode of acquisition.

MRSA screening procedure

MRSA screening criteria were similar for all sites according to Ontario provincial guidelines (19). Patients were screened if they satisfied any of the following criteria: any known history of colonization with antibiotic-resistant organism; any known history of contact with a patient known to be colonized with an antibiotic-resistant organism; admission to a health care facility in the past 12 to 24 months; or unable to provide information regarding any of the aforementioned risk factors.

For all sites, swab samples were obtained from the nares and rectum, as well as any insertion site or open wounds. Laboratory confirmation of MRSA was similar for all sites. MRSA swabs were incubated in MRSA selective media at 35°C or 37°C for approximately 24 h. Isolates were identified as *S aureus* if the rapid *S aureus* agglutination test and/or the tube coagulase test were positive. Methicillin resistance was confirmed using positive PBP2a agglutination testing and/or susceptibility testing (oxacillin screen plate or Vitek2 XL system AST-GP67 cards [Biomérieux, USA]) according to Clinical and Laboratory Standards Institute guidelines (20).

Blood culture procedure

Blood collection and culture were similar for all sites. Blood culture bottles were incubated at 35°C for a maximum of five days. Direct Gram staining was performed on all positive blood cultures, which were then subcultured onto blood agar plates. Blood agar plates were incubated at 35°C for two days. *S aureus* was identified when Gram staining showed Gram-positive cocci in clusters and tube coagulase test was positive. Methicillin resistance was determined by the same method used for MRSA screening.

Covariates

Potential covariates being considered included patient age (18 to 30, 31 to 45, 46 to 60, 61 to 75, 76 to 90 or >90 years of age), sex, hospital site, admitting service (medical, surgical or intensive care unit), time from MRSA screening swab collection to blood culture collection, time from admission to blood culture collection, MRSA screen with blood culture collection on same admission and mode of acquisition (community-acquired, nosocomial or health care-associated infection). The time from MRSA screening to blood culture collection was categorized into three groups: <2 days, two to 14 days and >14 days (21). Modes of acquisition, including community acquired, health care associated and nosocomial, were based on standard definitions (22).

Empirical antibiotic therapy

Empirical antibiotic therapy was defined as antibiotics started within three days of blood culture collection before full susceptibility results of the blood culture were known. Empirical MRSA coverage was considered to include intravenous vancomycin, quinupristin-dalfopristin or daptomycin.

Statistical analysis

Diagnostic properties of the MRSA screening swab were determined. MRSA screening was considered to be the test, and methicillin susceptibility of the first *S aureus* blood culture was considered the criterion standard. For sensitivity, specificity and predictive values, the 95% CIs were calculated using the Wilson method (23). In other analyses, when 2×2 diagnostic test tables had a cell with zero in it, 0.5 was added for calculation of diagnostic properties. For likelihood ratios, the 95% CI was also calculated (24).

Potential covariates were examined using a multivariable logistic regression model to identify variables related to differences in sensitivity and specificity, as described by Coughlin et al (25). In the logistic model, the dependent variable was the MRSA screen result and the methicillin susceptibility of the blood culture was entered as an independent variable along with other covariates. Potential covariates were as listed. Both sensitivity and specificity could be derived from the coefficients of the independent variables in the model (25). Several methods were used to confirm the significant covariates including univariate selection based on P value, full model with all covariates, as well as forward and backward stepwise regression based on the Akaike information criterion and likelihood ratio test.

To adjust for the significant covariates identified in the previous step (mode of acquisition and hospitals) from the multivariable logistic regression, the study population was stratified according to mode of acquisition. Within each subgroup, a random effects bivariate model (26) was used to calculate a summary estimate of sensitivity and specificity from the six different hospitals. The CIs for the likelihood ratios from the bivariate model were derived from a Monte Carlo simulation of 2000 samples.

Probability of post-test MRSA at different MRSA prevalence was calculated and plotted based on the pooled nonadjusted positive and negative likelihood ratios using the following formulas:

$$\text{Pre-test odds of MRSA} = \frac{\text{\% MRSA prevalence}}{100\% - \text{\% MRSA prevalence}}$$

$$\text{Post-test odds of MRSA} = \begin{array}{l}\text{pre-test odds of MRSA} \\ \text{x likelihood ratio} \\ \text{(positive or negative)}\end{array}$$

$$\text{Post-test probability of MRSA} = \frac{\text{post-test odds of MRSA}}{(\text{post-test odds of MRSA} + 1)}$$

All reported CIs were two-sided 95% intervals and all tests were two-sided with a 5% significance level. All analyses were performed using R version 3.0.1 (R Foundation for Statistical Computing, Austria). Bivariate summary estimates of diagnostic properties were performed using R package mada.

TABLE 1
Patient characteristics

Characteristic	All sites (n=799)
Age, years, median (interquartile range)	66.0 (52.0–79.0)
Male sex	501 (63)
Hospital site	
A	121 (15)
B	102 (13)
C	223 (28)
D	167 (21)
E	68 (9)
F	118 (15)
Hospital admission service	
Medical	498 (62)
Surgical	166 (21)
Intensive care unit	134 (17)
Other	1 (0.1)
Mode of acquisition	
Community acquired	190 (24)
Health care associated	296 (37)
Nosocomial	297 (37)
Unable to determine	16 (2)
Susceptibility of initial *Staphylococcus aureus* positive blood culture	
MRSA	150 (19)
Results of MRSA screening swab	
Positive	95 (12)
Negative	704 (88)
Time course of MRSA screening to blood culture, days	
MRSA screens performed before susceptibility report	799 (100)
MRSA screening to susceptibility report, median (IQR)	6.0 (3.0–18.0)
MRSA screening to culture collection, median (IQR)*	1.0 (0.0–12.0)
Culture collection to susceptibility report, median (IQR)	3.4 (2.9–5.2)

*Data presented as n (%) unless otherwise indicated. *Data available for 797 patients. MRSA Methicillin-resistant* S aureus

RESULTS

There were 799 patients who underwent a MRSA screening swab before the susceptibility results of the initial positive blood culture were known (Table 1). Of all MRSA screening swabs, 448 (56%) were performed within two days of blood culture collection; 167 (21%) within two to 14 days; 182 (23%) within >14 days; and two had missing data. The minimum time from MRSA screening swab to the susceptibility results of the initial positive blood culture was one day. Given the minimum time of one day, and the fact that processing of MRSA screening swab took 24 h, all patients in the study were assumed to have MRSA screening swab results available before or at the same time as when the methicillin susceptibility results of the initial positive blood culture were known.

Diagnostic test characteristics

These results allowed for the determination of diagnostic test characteristics for the MRSA screen in predicting methicillin resistance of the initial positive blood culture (Table 2). Diagnostic test properties are shown for each hospital site in Appendix 1.

Hospital sites and mode of acquisition (community-acquired, nosocomial or health care-associated infection) were statistically significant covariates in the final multivariable logistic regression model (Table 3). Age, sex, admitting service, time from MRSA screen to blood culture collection, time from admission to blood culture collection, and MRSA screen with blood culture collection on same admission were not significant covariates. Univariate selection based on P value and stepwise regressions all derived the same model.

TABLE 2
Diagnostic properties of methicillin-resistant *Staphylococcus aureus* (MRSA) screening in predicting methicillin susceptibility in *S aureus* blood culture

	Overall (n=799)	Community acquired (n=190)	Health care associated (n=296)	Nosocomial (n=297)
True positive*, n	84	8	44	32
True negative†, n	638	169	232	223
False positive‡, n	11	1	8	1
False negative§, n	66	12	12	41
Sensitivity	56 (48–64)	40 (22–61)	79 (66–87)	44 (33–55)
Specificity	98 (97–99)	99 (97–100)	97 (94–98)	100 (98–100)
PPV	88 (80–93)	89 (57–99)	85 (73–92)	97 (85–100)
NPV	91 (88–93)	93 (89–96)	95 (92–97)	85 (80–88)
PLR (95% CI)	33 (18–60)	68 (9–516)	24 (12–47)	98 (14–706)
NLR (95% CI)	0.45 (0.37–0.54)	0.60 (0.42–0.86)	0.22 (0.13–0.37)	0.56 (0.46–0.69)
Bivariate sensitivity¶		43 (25–64)	74 (61–84)	49 (26–72)
Bivariate specificity¶		98 (94–99)	95 (92–97)	98 (94–99)
Bivariate PLR (95% CI)¶		18 (6–51)	16 (9–28)	21 (7–57)
Bivariate NLR (95% CI)¶		0.58 (0.38–0.77)	0.27 (0.17–0.41)	0.53 (0.29–0.77)

*Data presented as % (95% CI) unless otherwise indicated. *Positive MRSA screening swab and MRSA blood culture; †Negative MRSA screening swab and MRSA blood culture ‡Positive MRSA screening swab and MRSA blood culture §Negative MRSA screening swab and MRSA blood culture ¶Bivariate summary estimate for each mode of acquisition. NLR Negative likelihood ratio; NPV Negative predictive value; PLR Positive likelihood ratio; PPV Positive predictive value*

For each mode of acquisition, a bivariate summary estimate of sensitivity, specificity and likelihood ratios were calculated from the six sites (Table 2).

The utility of MRSA screening results was modelled for different prevalences of MRSA by plotting post-test probability of MRSA, based on observed pooled and unadjusted positive and negative likelihood ratios (Figure 1).

Empirical MRSA coverage

Of 150 patients with MRSA bacteremia, 59 (39%) had empirical MRSA coverage and 91 (61%) did not. Of 91 patients with MRSA bacteremia with inappropriate empirical antibiotic therapy, 42 (46%) had a positive prior MRSA screening swab.

DISCUSSION

Our multicentre retrospective cohort study at six acute-care academic and community hospitals examined consecutive patients with SAB. From the 799 patients studied, we found that the MRSA screening swabs preceded the susceptibility results of the initial positive blood culture by a median of six days, which may have helped guide empirical antibiotic therapy.

Mode of acquisition was an important covariate for the diagnostic accuracy of the MRSA screen. The positive likelihood ratio for mode of acquisition was high, ranging from 16 to 21, regardless of how the infection was acquired. A positive likelihood ratio >10 is considered to be clinically helpful (27). Therefore, a positive MRSA screening swab may help guide treatment because the risk of methicillin resistance for SAB is increased markedly. The negative likelihood ratio ranged from 0.27 to 0.58 for different modes of acquisition. A negative likelihood ratio from 0.2 to 0.5 makes a small change to the probability of disease (27). Therefore, a negative MRSA screening swab result is not useful in ruling out MRSA bacteremia.

TABLE 3
Final logistic regression model* for probability of a positive methicillin-resistant *Staphylococcus aureus* (MRSA) screening test

Covariate	OR (95% CI)	P	P†
MRSA status on blood culture	197.47 (84.71–527.55)	<0.0001	<0.0001
Hospital site			0.0002
D	Reference		
A	0.99 (0.34–2.76)	0.9796	
B	0.57 (0.17–1.82)	0.3510	
C	0.25 (0.09–0.65)	0.0049	
E	0.06 (0.01–0.29)	0.0008	
F	0.20 (0.05–0.72)	0.0172	
Mode of acquisition			<0.0001
Community	Reference		
Health care associated	6.94 (2.38–22.55)	0.0007	
Nosocomial	1.13 (0.39–3.43)	0.8228	

**The logistic model used MRSA swab result as the dependent variable. The independent variables included methicillin susceptibility of blood culture along with the covariates listed above. CIs are likelihood ratio-based CIs. Both sensitivity and specificity can be derived from the coefficients of the model, as described by Coughlin et (26). The model used listwise deletion and included 780 patients with no missing data; †Values of the likelihood ratio test*

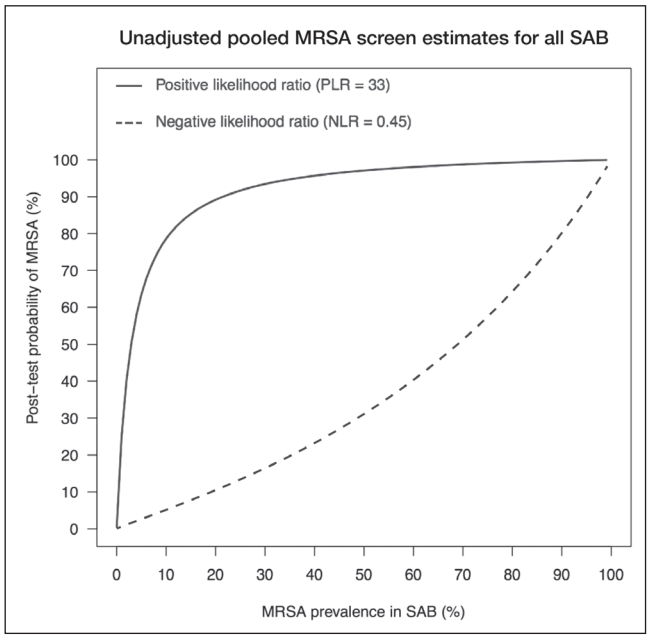

Figure 1) *Post-test probability of methicillin-resistant* Staphylococcus aureus *(MRSA) at different MRSA prevalence in* S aureus *bacteremia. NLR Negative likelihood ratio; PLR Positive likelihood ratio; SAB* S aureus *bacteremia*

There are few studies investigating the diagnostic accuracy of MRSA screening. The majority examined diagnostic accuracy of MRSA screening in the context of all clinical infections including non-*S aureus* infections (28,29). In contrast, we examined the diagnostic accuracy of MRSA swabs in SAB. One study by MacFadden et al (21) examined diagnostic accuracy of MRSA swabs in all *S aureus* infections including nonbacteremic infections. The overall specificity in our study was similar to their study, although our overall sensitivity was lower. The differences may be attributed partially to the types of clinical isolates included. Their study included isolates from both sterile and nonsterile sites that were treated with antistaphylococcal antibiotics, which could include colonization samples that were not clinical infections. In comparison, our study only included *S aureus*-positive blood cultures as clinical infections. As well, MacFadden et al (21) reported results from a single academic centre whereas the present study involved a diverse group of six academic and community hospitals. One of our study sites was also where MacFadden et al conducted their study, but there was no overlap of data between the two studies.

The present study had several strengths, including its size as the largest study, in examining the diagnostic accuracy of MRSA screening swabs in SAB. The study was conducted across many sites, both academic and community hospitals, enhancing its generalizability. In addition, methicillin susceptibility of *S aureus* determined from blood culture was an appropriate and independent standard that was uniformly performed in all patients regardless of MRSA screening swab results. Finally, the inclusion of only blood cultures growing *S aureus*, reflecting sterile site growth, ensured that all infections were true clinical infections and not colonization.

The present study had several limitations that merit discussion. First, as a retrospective chart review in which assessors of MRSA screening swab results were not blinded to the MRSA blood culture results, there could be potential information bias. However, the laboratory tests were determined and reported independent of other test results, making this unlikely. Second, there appeared to be heterogeneity in terms of diagnostic properties among MRSA hospital sites. The heterogeneity among different hospital sites might have been a result of minor differences in MRSA screening criteria, patient population at hospital sites and different rates of intrahospital MRSA transmission. However, the bivariate summary estimate accounts for this difference among hospital sites and provides a more conservative estimate of diagnostic properties. Moreover, the heterogeneity exists mainly in sites with fewer patients where corrections of adding 0.5 to all cells needed to be made. Sites with a greater number of patients had more consistent results. Finally, previous data have shown that different MRSA genotypes have a different probabilitites of causing SAB. Unfortunately, we did not collect any information on MRSA genotypes. However, MRSA genotype may not be clinically important, in that treatment of MRSA is the same regardless of MRSA genotypes in clinical practice and MRSA genotype is not considered in hospital infection control practices currently.

Our study identified the mode of acquisition as a possible significant covariate for diagnostic accuracy of MRSA screening. It may be that health care-associated infections were mostly associated with intravenous and hemodialysis therapy, and that these infections were strongly associated with pre-existent MRSA colonization. In contrast, for community-acquired and nosocomial infections, patients were more likely to be newly colonized with MRSA and, thus, were less likely to be detected by prior MRSA screening. Unlike the previous study (21), time from MRSA screening to blood culture collection was not a significant predictor. This is likely due to the fact that events such as mode of acquisition of infection and hospitalization play a more significant role in MRSA colonization and infection than the length of time. Mode of acquisition was not considered in the previous study (21).

Our study results have important clinical implications. A negative MRSA screen result does not significantly decrease the probability of MRSA bacteremia. The poor sensitivity and low negative likelihood ratio results in many false negatives. In these false-negative cases with MRSA bacteremia, withholding antibiotics with activity against MRSA based on negative MRSA screening swab may greatly increase the risk for mortality (9). Therefore, a negative MRSA screening swab is not useful and should not be considered in the decision of MRSA coverage for empirical antibiotic therapy. On the other hand, a positive prior MRSA screen rules in MRSA and empirical intravenous antibiotics with activity against MRSA should be started. In our cohort, 91 of 150 (61%) patients with MRSA bacteremia did not receive empirical MRSA coverage based on clinical judgment. In these 91 patients, the rule of a positive MRSA screen necessitating anti-MRSA empirical coverage would result in empirical MRSA coverage being added to 42 (46%) of the 91 MRSA bacteremia cases in which empirical MRSA

coverage was originally missed. Following the same rule, MRSA empirical coverage would only be added to 11 (2%) of the 649 patients with MSSA bacteremia. Thus, this rule would significantly increase the rate of correct empirical MRSA coverage in MRSA bacteremia cases while adding minimal unnecessary anti-MRSA empirical coverage in MSSA bacteremia cases.

Our findings demonstrate that screening tests for infection control purposes can provide valuable, clinically relevant information for making treatment decisions.

DISCLOSURES: The present study was largely unfunded. The Mount Sinai Hospital Antimicrobial Stewardship Program is supported by an unrestricted educational grant from Pfizer Canada, which partially supports the employment of a research coordinator (M Steinberg). A Mount Sinai Hospital Department of Medicine Summer Studentship Award funded A Bai. A Morris receives partial salary support for his antimicrobial stewardship activities from Mount Sinai Hospital and University Health Network. A Canadian Institutes of Health Research/Canadian Patient Safety Institute Chair in Patient Safety and Continuity of Care supports C Bell.

APPENDIX 1
Patient and diagnostic characteristics for each hospital site

	Hospital site					
Characteristic	**A (n=121)**	**B (n=102)**	**C (n=223)**	**D (n=167)**	**E (n=68)**	**F (n=118)**
Age, years, median (Interquartile range)	65 (46–80)	76 (63–84)	67 (55–78)	59 (49–70)	70 (56–79)	63 (53–78)
Male sex	71 (59)	52 (51)	144 (65)	119 (71)	44 (65)	71 (60)
Hospital admission service						
Medical	80 (66)	74 (73)	116 (52)	110 (66)	44 (65)	74 (63)
Surgical	22 (18)	11 (11)	52 (23)	37 (22)	12 (18)	32 (27)
Intensive care unit	19 (16)	17 (17)	54 (24)	20 (12)	12 (18)	12 (10)
Other	0 (0)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)
Mode of acquisition						
Community	32 (26)	30 (29)	42 (19)	30 (18)	20 (29)	36 (31)
Health care associated	43 (36)	42 (41)	80 (36)	80 (48)	23 (34)	28 (24)
Nosocomial	45 (37)	29 (28)	93 (42)	55 (33)	22 (32)	53 (45)
Unable to determine	1 (1)	1 (1)	8 (4)	2 (1)	3 (4)	1 (1)
MRSA on blood culture	28 (23)	19 (19)	51 (23)	24 (14)	13 (19)	15 (13)
Positive MRSA screening	22 (18)	16 (16)	25 (11)	23 (14)	3 (4)	6 (5)
Diagnostic test						
True positive, n	20	13	21	21	3	6
True negative, n	91	80	168	141	55	103
False positive, n	2	3	4	2	0	0
False negative, n	8	6	30	3	10	9
Sensitivity, % (95% CI)	71 (53–85)	68 (46–85)	41 (29–55)	88 (69–96)	25 (10–51)	41 (21–64)
Specificity, % (95% CI)	98 (93–99)	96 (90–99)	98 (94–99)	99 (95–100)	99 (92–100)	100 (96–100)
PLR (95% CI)	33 (8–134)	19 (6–60)	18 (6–49)	63 (16–250)	28 (2–511)	85 (5–1429)
NLR (95% CI)	0.29 (0.16–0.53)	0.33 (0.17–0.64)	0.60 (0.48–0.76)	0.13 (0.04–0.37)	0.76 (0.56–1.03)	0.60 (0.40–0.90)

Data presented as n (%) unless otherwise indicated. MRSA Methicillin-resistant Staphylococcus aureus; *NLR Negative likeihood ratio; PLR Positive likelihood ratio*

REFERENCES

1. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. JAMA 2012;308:50-9.
2. Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ. Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of *Staphylococcus aureus* bacteremia. Clin Infect Dis 2008;46:1000–8.
3. Wyllie DH, Crook DW, Peto TE. Mortality after *Staphylococcus aureus* bacteraemia in two hospitals in Oxfordshire, 1997-2003: Cohort study. BMJ 2006;333:281.
4. Chang FY, MacDonald BB, Peacock JE, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003;82:322-32.
5. Zhanel GG, DeCorby M, Adam H, et al. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: Results of the Canadian Ward Surveillance Study (CANWARD 2008). Antimicrob Agents Chemother 2010;54:4684-93.
6. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. Clin Infect Dis 2003;36:53-9.
7. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166-74.
8. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 2006;166:2138-44.
9. Paul M, Kariv G, Goldberg E, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2010;65:2658-65.
10. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2008;52:192-7.
11. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. BMC Infect Dis 2011;11:279.
12. Fridkin SK, Edwards JR, Courval JM, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. Ann Intern Med 2001;135:175-83.
13. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249-72.
14. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1-45.

15. Mackenzie I, Lever A. Management of sepsis. BMJ 2007;335:929-32.
16. Huang SS, Platt R. Risk of methicillin-resistant *Staphylococcus aureus* infection after previous infection or colonization. Clin Infect Dis 2003;36:281-85.
17. Davis KA, Stewart JJ, Crouch HK, Florez CE, Hospenthal DR. Methicillin-resistant *Staphylococcus aureus* (MRSA) nares colonization at hospital admission and its effect on subsequent MRSA infection. Clin Infect Dis 2004;39:776-82.
18. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality and length of stay in *Staphylococcus aureus* bacteremia: Results from a large multicenter cohort study. Clin Infect Dis 2015;60:1451-61.
19. Ontario Agency for Health Protection and Promotion, Provincial Infectious Diseases Advisory Committee (PIDAC). Annex A– Screening, testing and surveillance for antibiotic-resistant organisms (AROs) in all health care settings. Routine practices and additional precautions in all health care settings. Toronto: Queen's Printer for Ontario, Toronto, 2013.
20. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 17th edn. Wayne: Clinical and Laboratory Standards Institute, 2007.
21. Macfadden DR, Elligsen M, Robicsek A, Ricciuto DR, Daneman N. Utility of prior screening for methicillin-resistant *Staphylococcus aureus* in predicting resistance of S. aureus infections. CMAJ 2013;185:E725-E730.
22. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791-7.
23. Wilson EB. Probable inference, the law of succession, and statistical inference. J Amer Stat Assoc 1927;22:209-12.
24. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: Sample size estimation for diagnostic test studies. J Clin Epidemiol 1991;44:763-70.
25. Coughlin SS, Trock B, Criqui MH, Pickle LW, Browner D, Tefft MC. The logistic modeling of sensitivity, specificity, and predictive value of a diagnostic test. J Clin Epidemiol 1992;45:1-7.
26. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982-90.
27. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271:703-7.
28. Harris AD, Furuno JP, Roghmann MC, et al. Targeted surveillance of methicillin-resistant *Staphylococcus aureus* and its potential use to guide empiric antibiotic therapy. Antimicrob Agents Chemother 2010;54:3143-8.
29. Sarikonda KV, Micek ST, Doherty JA, Reichley RM, Warren D, Kollef MH. Methicillin-resistant *Staphylococcus aureus* nasal colonization is a poor predictor of intensive care unit-acquired methicillin-resistant Staphylococcus aureus infections requiring antibiotic treatment. Crit Care Med 2010;38:1991-5.