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Time to First Culture Positivity Among Critically Ill Adults With Methicillin-Resistant *Staphylococcus aureus* Growth in Respiratory or Blood Cultures

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Abstract

Background: For critically ill adults receiving empirical vancomycin, the duration of negative cultures after which vancomycin may be discontinued without risking subsequent growth of methicillin-resistant *Staphylococcus aureus* (MRSA) remains unknown. **Objective:** We hypothesized that if sputum cultures did not grow MRSA or blood cultures did not grow Gram-positive cocci on Gram stain by 48 hours, those cultures would not subsequently demonstrate MRSA. **Methods:** We conducted an ancillary analysis from patients enrolled in the Isotonic Solutions and Major Adverse Renal Events Trial (SMART). In this cohort of patients, we collected data on the time of either MRSA identification in culture or Gram-positive cocci identification on Gram stain and rate of vancomycin discontinuation. **Results:** Of the 15 802 patient admissions in the SMART study, 6553 (41.5%) received empirical intravenous vancomycin. Respiratory sputum cultures demonstrated MRSA during 178 patient admissions. Among respiratory cultures that would ultimately grow MRSA, 85% were positive within 48 hours, and 97% were positive within 72 hours. Cultures demonstrated MRSA bacteremia during 85 patient admissions. In 83 cases (97.6%) of MRSA bacteremia, Gram-positive cocci were identified within 48 hours after the culture was obtained. **Conclusion and Relevance:** This analysis of a large cohort of critically ill adults receiving empirical vancomycin found that *Staphylococcus aureus* was present in all but 15% of cases of MRSA-positive respiratory cultures after 48 hours, whereas Gram-positive cocci were identified within 48 hours during nearly all episodes of MRSA bacteremia. These findings may inform the timing of discontinuation of empirical vancomycin among critically ill adults.

Keywords

infectious disease, critical care, antibiotics, vancomycin, sepsis, pneumonia

Background

Expanding antimicrobial resistance patterns, adverse drug reactions, and the time, money, and resources associated with monitoring highlight the importance of antimicrobial stewardship, specifically the de-escalation of antibiotics.[1] Vancomycin is often prescribed empirically for coverage of suspected or possible *StaphylococcuStaphylococcus aureus* infections because it has activity against both methicillin-resistant and methicillin-susceptible strains.[2] Current guidelines recommend empirically covering for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia for patients with certain risk factors, including a known history of MRSA colonization or infection, recent antibiotic exposure, recent hospitalizations, pulmonary infiltrates with cavitary features, and/or complicated skin and soft-tissue infections.[3]

Limited evidence informs the optimal timing of discontinuation of empirical vancomycin in clinical practice.[4-6] There is little data to guide de-escalation based on the time to positivity of respiratory cultures. Of the studies focusing on blood cultures, many focus on using time to positivity as a marker of disease severity rather than for stewardship purposes.[7,8] One observational study evaluated antibiotic streamlining practices but did not evaluate

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the rate of de-escalation at 48 hours or if the patients grew an organism that was resistant to the narrowed regimen.[4] Two studies evaluated the time to blood culture positivity to quantify the prevalence of bacterial bloodstream infection detection and determined that a bacterial bloodstream infection should be identified within 48 to 72 hours, if present.[5,6] These studies were relatively small and did not evaluate sites of infection other than bacteremia or antibiotic de-escalation practices. Additionally, although rapid diagnostic testing is now utilized in many institutions, these tests are often only performed once a culture is positive. Thus, they do not inform clinical decision making during the time a blood culture remains negative. Rapid diagnostic testing is also limited to blood cultures at many institutions because of the lack of quantification of bacteria and inability to differentiate between colonization versus active infection.[9]

We designed an ancillary study of a large pragmatic trial to examine the time from cultures being collected to *Staphylococcus aureus* growth on sputum cultures and preliminary identification of Gram-positive cocci on Gram stain of blood cultures among adult intensive care unit (ICU) patients being treated with empirical vancomycin for MRSA. We hypothesized that 48 hours of negative respiratory and blood cultures would represent a time point beyond which MRSA would not grow on sputum cultures and Gram-positive cocci that would ultimately be speciated as MRSA would not grow in blood cultures, and thus, vancomycin could safely be discontinued.

Methods

Study Design and Oversight

We conducted a prospective cohort ancillary study to the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) study to evaluate the point in microbiological workup at which results of respiratory secretion and blood cultures could be interpreted as excluding MRSA and, thus, no longer warranting the empirical vancomycin therapy.[10] SMART was a cluster-randomized, cluster-crossover trial comparing balanced crystalloids with saline for intravenous fluid therapy among adult patients from 5 ICUs at Vanderbilt University Medical Center (VUMC) in Nashville, TN, from June 2015 to April 2017. All adult patients who were admitted to the ICU during the study period were enrolled into SMART at the time of ICU admission. Results of SMART have been reported previously.[10] The current observational ancillary study was approved as exempt by the Institutional Review Board at Vanderbilt University Medical Center.

Patient Population

All adults enrolled in SMART who met the following criteria were included in this ancillary study: (1) had sputum or blood cultures collected, (2) were receiving intravenous vancomycin, and (3) were being empirically treated for MRSA pneumonia or bacteremia.

Sputum and Blood Cultures

Respiratory cultures are collected in a sealed screw cap container and sent to the lab for culture. On arrival into the microbiology laboratory, the sputum is inoculated onto agar-based media and spread on a glass slide for Gram stain. Negative sputum cultures are finalized at 48 hours as either "No growth" or a quantitated "Upper respiratory bacteria." For sputum cultures containing predominant pathogens, the patient report is updated at each stage of the workup process until the identification and antimicrobial susceptibility testing are complete.

Blood cultures at the study hospital are recommended to be performed in duplicate from 2 separate sites, although patients in whom only one set of blood cultures could be obtained were still included in this analysis. Blood is collected in 2 BACTEC bottles, an aerobic and anaerobic bottle, for each site collected. BACTEC bottles are incubated in the BD BACTEC FX instrument in the microbiology lab, where they are automatically monitored every 10 minutes. When positive, the BD BACTEC FX instrument alarms visually and audibly to alert the microbiologist to perform additional testing. First, a Gram stain is performed, and the result is reported to the team. Positive blood cultures are inoculated to the appropriate agar-based media according to the Gram stain findings. Once an organism or organisms are isolated on the media, further testing is performed on the BD Phoenix for identification and antimicrobial susceptibility testing. Negative blood cultures are automatically finalized as "No growth in 5 days" after the fifth day of incubation, and bottles are discarded.

Data Collection

All culture data were electronically extracted from the institutional microbiology laboratory database. At VUMC, all patients routinely have 2 blood cultures collected when infection is suspected, although patients with only a single culture growing MRSA were also included in this analysis. All patients who had sputum cultures collected through production and endotracheal tube aspirate, and all bronchoscopic cultures that grew MRSA were included as respiratory cultures. First, the time at which the initial respiratory culture was collected was documented. Second, the time at which preliminary *Staphylococcus aureus*, which was ultimately determined to be MRSA, was identified was collected. Next, the time at which the sputum culture was considered to be finalized was collected.

All patients with any blood culture that grew MRSA were reviewed. If patients were persistently culture positive

for MRSA, only the first set of blood cultures was collected. First, the time at which the initial blood cultures were collected was documented. Second, the time at which initial identification of Gram-positive cocci occurred was collected. Next, the time at which preliminary *Staphylococcus aureus*, which was ultimately determined to be MRSA, was identified was collected. Finally, the time at which the blood cultures were considered to be finalized was collected.

End Points

The primary outcomes were the time from cultures being collected to *Staphylococcus aureus* growth on sputum cultures and preliminary identification of Gram-positive cocci on Gram stain of blood cultures. Secondary outcomes included the time to growth of *Staphylococcus aureus* on blood cultures and the prevalence of inappropriate vancomycin discontinuation.

Statistical Analysis

As an ancillary analysis of data from a clinical trial with a fixed size, a prospective power calculation was not performed. Categorical data are reported as frequencies and percentages. Continuous data are reported as medians and interquartile ranges (IQRs). To determine which baseline covariates were independently associated with growth of MRSA in culture more than 48 hours after cultures were collected, multivariable logistic regression modeling was performed. Given that the indication for initiation of vancomycin is not standardized across the institution, variables were chosen a priori and included age, gender, discharge unit, mechanical ventilation, and predicted risk of in-hospital mortality. Statistical analyses were performed with IBM SPSS Statistics, version 25 (Vienna, Austria).

Results

Among 15 802 patient admissions in the SMART dataset, 9249 (58.5%) did not receive intravenous vancomycin and were excluded from the current study. The remaining 6553 patient admissions received intravenous vancomycin and were included in the current study. Of these, 178 had culture data consistent with MRSA pneumonia, and 85 had culture data consistent with MRSA bacteremia (Figure 1). Baseline characteristics of those 263 patients are presented in Table 1. The median age was 55 years, and 65.7% of patients received mechanical ventilation. The most common ICU admitting diagnosis was sepsis (39.5%), followed by respiratory failure (15.6%), and trauma or orthopedic injury (15.2%).

The median time to preliminary identification of *Staphylococcus aureus* in respiratory cultures was 33.3 (IQR = 24.6-44.1) hours. Among respiratory cultures that ultimately grew MRSA, 42 (23%) were positive by 24 hours, 153 (85%) by 48 hours, and 173 (97%) by 72 hours. The longest time for a respiratory culture to grow MRSA was 104 hours (Figure 2).

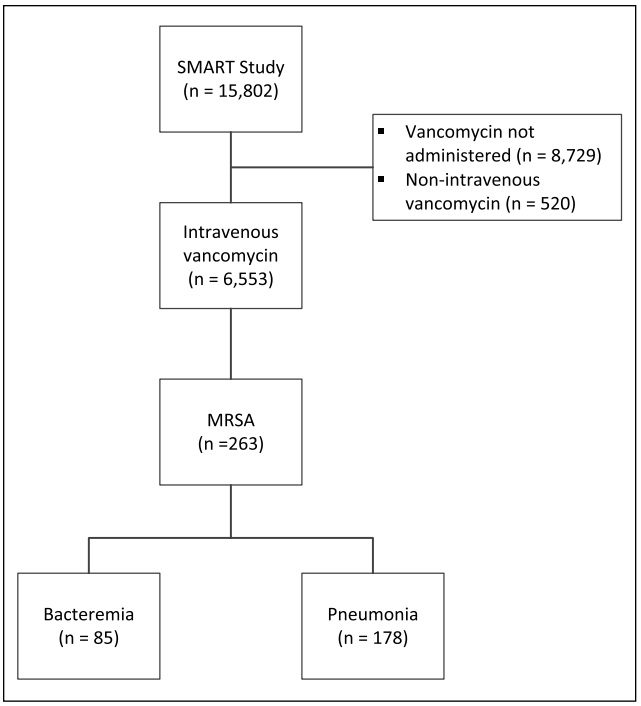

Figure 1. Flow diagram of patient inclusion.
Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Gram-positive cocci were identified on Gram stain of blood cultures at a median time of 21.3 hours (IQR = 17-24.8). All cultures that ultimately grew MRSA in the blood were correctly identified as Gram-positive cocci on the initial assessment by the microbiology lab. Of the 85 cases of MRSA bacteremia, identification of Gram-positive cocci in blood cultures occurred within 48 hours in 83 (97.6%), and at 50 and 95 hours in the remaining 2 cases (Figure 3A). The median time to specific MRSA species identification was 45.5 [41.9-50.8] hours for bacteremia. Despite identification of Gram-positive cocci on culture in 62 patients within 24 hours, no blood cultures identified MRSA by 24 hours. Of the 85 blood cultures that ultimately grew MRSA, 52 (61%) did so by 48 hours and 83 (98%) did so by 72 hours. The longest time for a blood culture to show growth of Gram-positive cocci that ultimately were identified as MRSA was 113 hours (Figure 3B). All vancomycin was de-escalated based on Gram stain or preliminary result. Vancomycin was appropriately continued in all MRSA culture-positive patients and was not prematurely discontinued. Of the 5 cases that grew MRSA in a respiratory culture after 72 hours and the 2 cases that grew MRSA in a blood culture after 48 hours, all had another indication for continuing vancomycin.

In multivariable logistic regression analysis, patients' predicted risk of mortality was the only independent risk factor for identification of MRSA in respiratory or blood cultures greater than 48 hours following cultures being collected (Table 2). A sensitivity analysis was conducted to evaluate the indication for vancomycin in the analysis for variables associated with MRSA growth greater than 48 hours after culture collection and was not related to the outcome.

Discussion

This ancillary study of a large randomized trial among a broad population of critically ill adults receiving empirical vancomycin found that among respiratory cultures that ultimately grew MRSA, only 85% were positive within 48 hours, whereas 97% were positive within 72 hours. However, Gram-positive cocci were identified within 48 hours in 97.6% of cases of that would ultimately be identified as MRSA bacteremia. These findings may suggest that, among critically ill adults, discontinuation of empirical vancomycin after 48 hours of negative blood cultures may be unlikely to miss cases of blood cultures that ultimately grow MRSA but might miss some respiratory cultures that are ultimately positive for MRSA.

Antimicrobial de-escalation varies considerably in clinical practice, with studies showing it occurring in 35% to 45% of patients receiving antibiotics in ICUs.[11-13] De-escalation ensures targeted therapy, limits antimicrobial resistance, and reduces cost. Vancomycin is frequently used empirically, with no current guidance on when empirical vancomycin should be discontinued in the absence of MRSA. Our data suggest that empirical vancomycin to cover MRSA can be safely discontinued after 72 hours of negative respiratory cultures and 48 hours of negative blood. This practice would, however, result in premature discontinuation in 3% of patients with positive sputum cultures for MRSA and 2.4% of patients with bacteremia that would ultimately grow MRSA. The ramifications of this are not clear, particularly in the outlier patients where time to culture positive was longer because vancomycin would likely be out of the patients' systems by 113 and 95 hours, respectively.

Similar to our data, Moustos et al[5] evaluated the time to positive blood cultures for major pathogens at a large tertiary academic hospital and determined that 98.5% of all Gram-positive bacteremias were detected within 3 days of blood culture. Three isolates of 202 positive bottles required 4 or more days of incubation to flag positive, all of which were *Staphylococcus aureus*.[5] A retrospective study at a large academic medical center found that the median time to detection of Gram-positive cocci in clusters was 15.2 hours.[6] The results of our current study are similar, although Pardo et al[6] reported a shorter time to positivity on Gram stain and identification of MRSA. The time to positivity of MRSA bacteremia in 52 cultures in our study was 85% by 24 hours and 98% by both 48 and 72 hours. Many factors might explain this, including differences in timing of blood cultures with respect to initiation of antibiotics; population demographics, including immunosuppression and indwelling catheters; and microbiological detection methods.

Table 1. Baseline Characteristics.[a]

Characteristic	n = 263
Age (years)	55 [43-66]
Sex, male	155 (59%)
Race	
White	212 (81%)
Black or African American	31 (11.8%)
Asian	3 (2.7%)
Unknown	16 (6.6%)
Declined	1 (0.9%)
ICU	
Medical	96 (37%)
Nonmedical	165 (63%)
ICU LOS (days)	5.4 [2.6-13.6]
Primary diagnosis at ICU admission	
Sepsis or septic shock	104 (39.5%)
Respiratory failure	30 (15.6%)
Trauma or orthopedic injury	27 (15.2%)
Pneumonia	16 (10.7%)
Other	16 (9.8%)
Congestive heart failure	10 (6.4%)
Intracranial hemorrhage	9 (6.3%)
Malignancy	10 (5%)
Stroke	7 (4.6%)
Cardiovalvular disease	5 (3.2%)
Seizure	4 (2.9%)
Cirrhosis or hepatic failure	3 (2.2%)
N/A	3 (2.2%)
Altered mental status	3 (2.1%)
Aortic aneurysm or dissection	3 (2.1%)
Gastrointestinal bleeding	3 (1.8%)
Complication of diabetic mellitus	2 (1.3%)
Acute or chronic kidney injury	2 (1.2%)
Ingestion or envenomation	2 (1.1%)
Acute coronary syndrome	2 (1%)
Burn	1 (0.7%)
Arrhythmia	1 (0.7%)
Predicted risk of in-hospital mortality (%)	10.9 [2.9-27.6]
Mechanical ventilation	165 (62.7%)
60-Day mortality	70 (26.6%)

Abbreviations: ICU, intensive care unit; LOS, length of stay; N/A, not available.

[a]Data are given as number (%) or median [interquartile range]. Predicted risk of in-hospital mortality is an estimated probability of death before hospital discharge generated through the Vizient database (formerly University Health System Consortium; details at http://www.vizientinc.com).

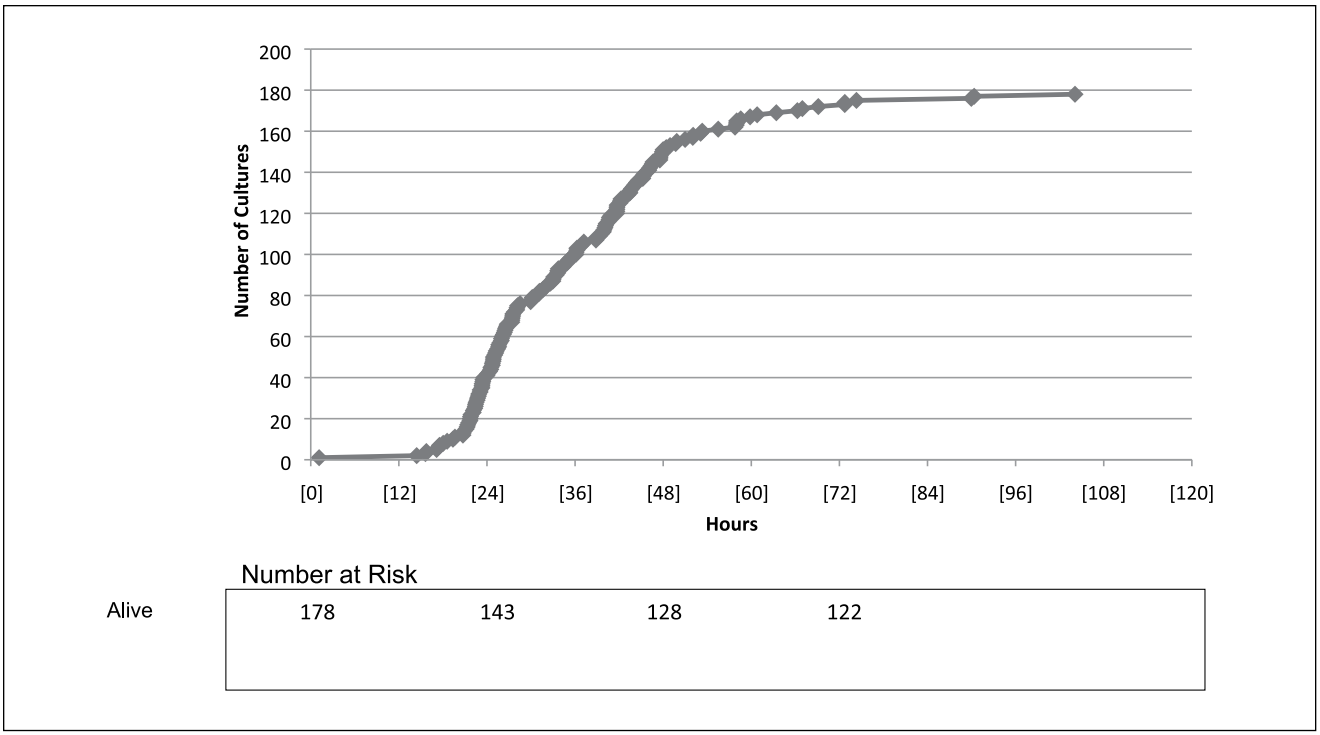

Figure 2. Time to positivity of *Staphylococcus aureus* respiratory cultures.

Few prior studies have evaluated the application of time to culture positive to antibiotic de-escalation in clinical practice. Liu et al[4] evaluated the frequency of antibiotic de-escalation of a commonly used empirical regimen, vancomycin and piperacillin-tazobactam. The authors found that antibiotic regimens were de-escalated in 151 (63%) and 175 (73%) patients by 72 and 96 hours, respectively.[4] However, this study did not evaluate when an infectious organism was identified or if the patients grew an organism beyond 72 hours that was resistant to the narrowed regimen. The present study sought to evaluate the time to positivity of MRSA specifically and apply that knowledge to its effects in clinical practice regarding de-escalation of vancomycin.

The strengths of this study include the large patient cohort and evaluation of the incidence and time to positive cultures for both MRSA respiratory cultures and bacteremia; no prior study has evaluated respiratory cultures. Recent literature has focused on utilizing MRSA nasal screening to streamline empirical therapy for pneumonia, but this is the first study to specifically look at vancomycin and de-escalation timing relative to culture results.[14,15]

Limitations include the single-center analysis because the microbiology-laboratory results reflect only one institution's practice. Increasing availability of rapid molecular identification diagnostics capable of detecting MRSA by identifying the penicillin-binding protein 2a or the *mecA* gene, respectively,[16] may decrease the importance of understanding the time to culture positivity in MRSA bacteremia and pneumonia. Our study was undertaken prior to the initiation of these newer detection technologies at our institution. However, although rapid diagnostic testing is now utilized in many institutions, many of these tests, with the exception of the T2, are only performed once a culture is positive, thus not informing clinical decision making regarding antibiotic de-escalation in the setting of a negative culture.[17] Rapid diagnostic testing is also only utilized in blood cultures, not sputum cultures, at this time in many institutions because of the lack of quantification of bacteria and inability to differentiate between colonization versus active infection. Our results are limited to specifically MRSA respiratory infections or bacteremia and do not include other sources of MRSA or infections from other species. Systems other than BACTEC may have longer time to positivity for blood cultures. Although BACTEC is a commonly used system, these results may not apply to institutions that use other laboratory systems. This study only included critically ill patients and might not apply to non–critically ill patients and would not apply to patients with sources of infection other than a pneumonia or bacteremia. Additionally, microbiological data are not the only factor that should be considered when discontinuing antibiotics; a patient's clinical presentation must also be examined. For example, for patients with more severe illness, specific risk factors for MRSA such as indwelling access or hemodialysis, recent hospitalizations, pulmonary infiltrates with cavitary features, and/or complicated skin and

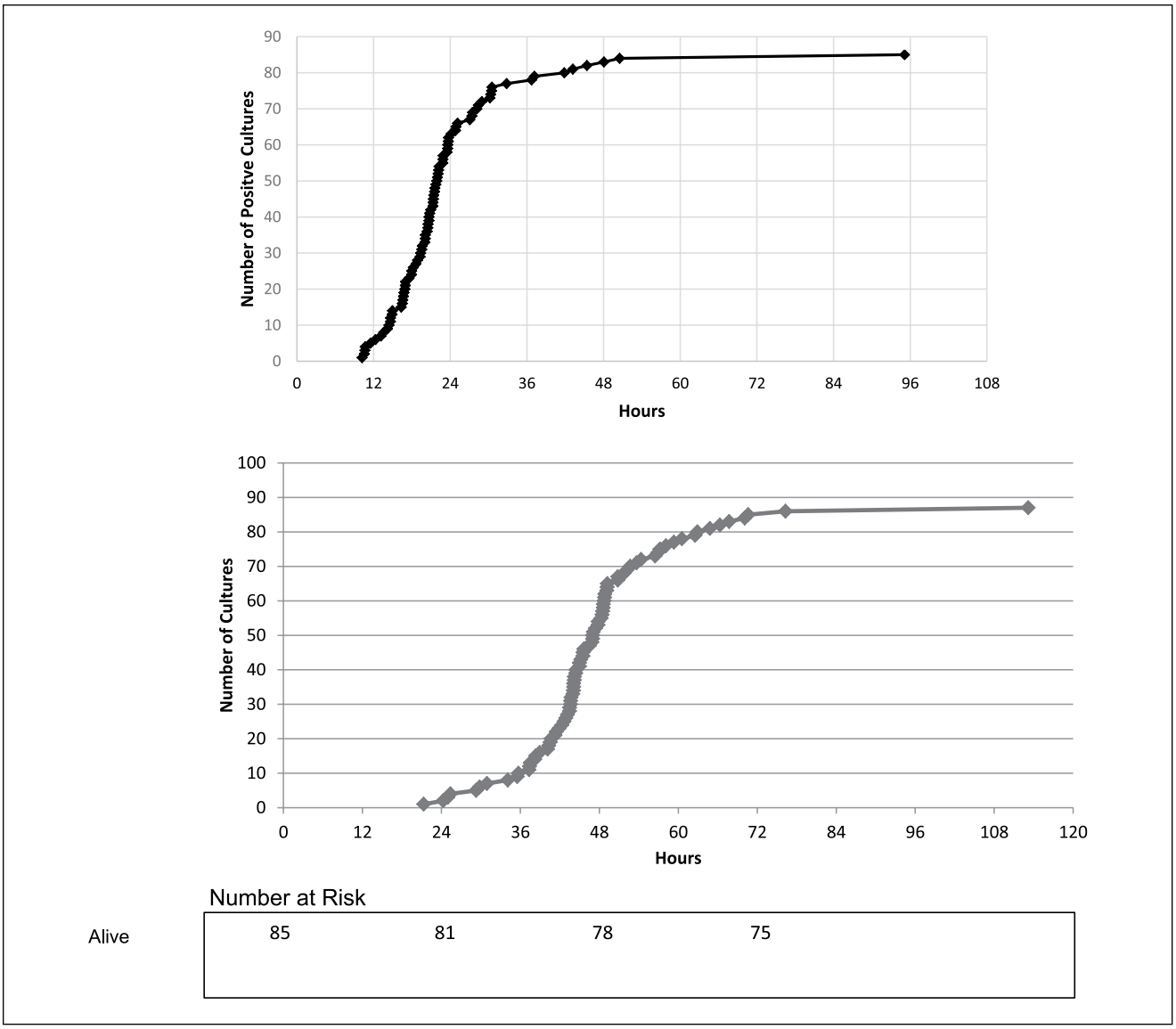

Figure 3. A. Time to positivity of Gram-positive cocci bacteremias. B. Time to positivity of *Staphlycoccus aureus* bacteremias.

Table 2. Logistic Regression Analysis for Variables Associated With MRSA Growth Greater Than 48 Hours After Cultures Were Drawn.[a]

Variable	Odds Ratio	95% CI	*P* Value
Age	0.994	0.976-1.012	0.493
Gender	0.865	0.462-1.617	0.649
Discharge unit	0.827	0.682-1.002	0.053
Ventilator	0.865	0.456-1.641	0.657
Predicted risk of in-hospital mortality	0.09	0.013-0.596	0.013

[a]Predicted risk of in-hospital mortality is an estimated probability of death before hospital discharge generated through the Vizient database (formerly University Health System Consortium; details at http://www.vizientinc.com).

soft-tissue infections, empirical continuation of vancomycin may be clinically reasonable even in the absence of negative culture. Future studies should evaluate other Gram-positive, Gram-negative, and fungal organisms to assess time to culture positivity and antimicrobial de-escalation practices.

Conclusion

In this analysis of a large cohort of critically ill adults receiving empirical vancomycin, 85% of sputum cultures were positive by 48 hours, whereas 97% were positive by 72 hours that ultimately grew MRSA. Gram-positive cocci were identified within 48 hours in 97.6% of cases of MRSA

bacteremia. These findings may inform the safety of discontinuing empirical MRSA therapy after 48 to 72 hours of negative respiratory and blood cultures among critically ill adults. Additionally, this study fills an important void in medical literature by providing some guidance on de-escalation based on time to positivity of respiratory cultures.

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Declaration of Conflicting Interests

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