Standardized Treatment and Assessment Pathway Improves Mortality in Adults with Methicillin-resistant *Staphylococcus aureus* Bacteremia: STAPH-Study

Sara ALOSAIMY\textsuperscript{1}, Abdalhamid M. LAGNF\textsuperscript{1}, Taylor MORRISETTE\textsuperscript{1}, Sarah CJ JORGENSEN\textsuperscript{1,2}, Trang D. TRINH\textsuperscript{1,3}, Evan J ZASOWSKI\textsuperscript{1,4}, Marco R SCIPIONE\textsuperscript{5}, Jing J ZHAO\textsuperscript{6}, Ryan MYNATT\textsuperscript{7,8}, Shelby HERBIN\textsuperscript{5}, Sorabh DHAR\textsuperscript{8,9}, Teena CHOPRA\textsuperscript{8,10}, James JANISSE\textsuperscript{11}, Nicholas REBOLD\textsuperscript{1}, Jason M POGUE\textsuperscript{8,12}, Michael J. RYBAK\textsuperscript{1,5,11}

\textsuperscript{1} Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

\textsuperscript{2} Department of Pharmacy, Mount Sinai Hospital, Toronto, ON, Canada

\textsuperscript{3} Department of Clinical Pharmacy, University of California San Francisco School of Pharmacy San Francisco School of Pharmacy, California, USA

\textsuperscript{4} Department of Clinical Sciences, Touro University California College of Pharmacy, Vallejo, California, USA

\textsuperscript{5} Department of Pharmacy, Detroit Receiving Hospital, Detroit Medical Center, Detroit, MI, USA

\textsuperscript{6} Harper University Hospital, Detroit, MI

\textsuperscript{7} University of Kentucky, Lexington, KY, USA

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, MI, USA.

Division of Infectious Diseases, John D. Dingell, Veterans Administration Medical Center, Detroit, MI, USA.

Detroit Medical Center, Detroit, MI, USA.

Department of Family Medicine and Public Health Sciences, School of Medicine, Wayne State University, Detroit, MI, USA.

Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, USA

*Indicates current affiliation

**Corresponding Author**

Michael J. Rybak

Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

259 Mack Ave., Detroit, MI, USA, 48201

Phone: 313-577-4376

Fax: 313-577-9310

Email: m.rybak@wayne.edu
Abstract:

Background

Methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections (BSI) management remains challenging for clinicians. Numerous *in vitro* studies report synergy when vancomycin (VAN)/daptomycin (DAP) were combined with beta-lactams (BL), which has led to clinical implementation of these combinations. While shorter durations of bacteremia have often been reported, there has been no significant impact on mortality.

Methods

The Detroit Medical Center (DMC) developed and implemented a clinical pathway algorithm for MRSA BSI treatment in 2016 that included the early use of BL combination therapy with standard-of-care (VAN or DAP) and a mandatory infectious diseases consultation. This was a retrospective, quasi-experimental study at the DMC between 2013-2020. Multivariable logistic regression was used to assess the independent association between pathway implementation and 30-day mortality while adjusting for confounding variables.

Results

Overall, 813 adult patients treated for MRSA BSI were evaluated. Compared to pre-pathway (PRE) patients (n=379), those treated post-pathway (POST) (n=434) had a significant reduction in 30-day and 90-day mortality; 9.7% in POST vs. 15.6% in PRE (p=0.011) and 12.2% in POST vs. 19.0% in PRE (p=0.007), respectively.

The incidence of acute kidney injury (AKI) was higher in the PRE compared to POST; 9.6% vs. 7.2% (p=0.282), respectively. After adjusting for confounding variables including infectious diseases consult, POST was independently associated with a reduction in 30-day mortality (adjusted odds ratio [aOR], 0.608; 95% confidence interval [CI], 0.375-0.986).
Conclusions

Implementation of a MRSA BSI treatment pathway with early use of BL reduced mortality with no increased in AKI. Further prospective evaluation of this pathway approach is warranted.

Keywords: Beta-lactams, MRSA, bloodstream infections, Gram-positive infections, combination therapy
Background:

Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI) are associated with significant mortality, morbidity and increased healthcare expenditures (1, 2). Several strategies had been previously investigated by our group to improve patient outcomes in MRSA BSI (3-5). Combination therapy (CT) with a beta-lactam (BL) in MRSA BSI has been proposed as a treatment strategy due to multiple reports demonstrating *in vitro* synergy between vancomycin (VAN)/ daptomycin (DAP) and BLs(6-10). To date, studies evaluating combination VAN or DAP with BLs have shown shorter days of bacteremia, lower hospital stays and reduction in infection recurrence but not evidence of mortality benefit (11-16). In most of these evaluations, the BL was typically an “add-on” as an escalation of therapy in refractory infections or as part of an empiric therapy where the BL was used as empiric therapy for Gram-negative infections and not purposely for the treatment of MRSA. The only prospective trials that have evaluated BL CT were the Combination Antibiotics for Methicillin Resistant *Staphylococcus aureus* CAMERA-1, CAMERA-2 studies and the pilot study of DAP plus ceftaroline versus VAN (17-19). Both studies found shorter days of bacteremia, but no difference in mortality. The CAMERA-2 study was prematurely stopped due to high rates of acute kidney injury (AKI) in patients receiving VAN and flucloxacillin or cloxacillin (18). While cefazolin was one of the BL options, there were too few patients receiving these antibiotics to draw any reliable conclusions (18, 20). The DAP plus ceftaroline study, albeit limited with a small sample size found a significant survival benefit among patients receiving the combination versus those receiving VAN alone, which led to early termination of the trial(19).

Based on the potential for improved outcomes with the use of BL CT, infectious diseases (ID) consultation, as well as microbiological assessment a clinical pathway was developed at the Detroit Medical Center (DMC) with early use of BL CT as initial therapy for the treatment of MRSA bacteremia until at least 48 hours after blood culture sterilization.
The primary BL was cefazolin, however; cefepime and other BL agents were allowed per patient specifics. Notably, treatment modifications may occur on days 3-5 of therapy and if necessary, followed by assessment of these modifications on days 7-10. These were aimed to improve success rates with VAN or DAP, prevent the emergence of resistance, and reduce escalation to alternative, more costly and broad-spectrum agents. The objective of this study was to evaluate the baseline characteristics and clinical outcomes of patients prior to and after the implementation of the MRSA BSI pathway at the DMC.

Methods:

Study design and population

We conducted a retrospective, quasi-experimental study at the DMC between December, 2013 and June, 2020. The DMC is a single large healthcare-system that includes eight hospitals within the greater Detroit area of Michigan. The DMC operates eight hospitals and institutes, including the Children’s Hospital of Michigan, Detroit Receiving Hospital, Harper University Hospital, Huron Valley-Sinai Hospital, Hutzel Women’s Hospital, Rehabilitation Institute of Michigan, Sinai-Grace Hospital, and DMC Cardiovascular Institute. Patients were screened and included if they were: 1) age ≥ 18 years and 2) ≥ 1 MRSA-positive blood culture meeting the Centers for Disease Control and Prevention Criteria for BSI. Exclusion criteria are illustrated in (Figure 2). Patients were classified in the pre-pathway (PRE) group if they were admitted prior to pathway implementation date (i.e. on or after September first, 2016) or in the post-pathway (POST) group if admitted after pathway implementation date. Only patients first encounter was collected and repeat encounters were excluded. This study was reviewed and approved by the WSU IRB and the DMC Research Review Committee.
**Patient consent statement**

Patient consent statement was not required for this retrospective analysis.

**Data collection and study definitions**

Patients’ data were derived from the electronic medical record and entered into REDcap (Research Electronic Data Capture, Vanderbilt University). All blood cultures were processed at the DMC central microbiology laboratory according to standard procedures. MicroScan (Siemens Healthcare Diagnostics), Phoenix (BD) and Verigene (Luminex), Etest (biomerieux) were utilized for antimicrobial susceptibility testing and/or bacterial identification depending on the time period. Variables associated with BSI were determined based on clinical notes and microbiological/diagnostic reports. Pathway was defined in details in (Figure 1) as well as our institution’s portal (21). The severity of illness and patient comorbidity were assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Charlson Comorbidity Index (CCI), respectively. Both were assessed at time of index blood culture. Prolonged bacteremia was defined as lasting >120 hours (24). Patients who died before clearing their bacteremia were excluded from the prolonged BSI analysis. In order to account for antibiotic adjustments during therapy, we described several anti-MRSA/BL regimen scenarios in (Table 2). Thirty-day and 90-day mortality were defined as death from any cause at 30 and 90 days, respectively. Sixty-day recurrence was defined as >1 MRSA positive blood culture following clearance within 60 days of index blood culture collection. Safety outcomes are defined in (Table 1) and (Table 3). Sources of bacteremia, occurrence of side effects, and other clinical variables were collected based on laboratory assessment and/or medical notes by the treating physician.
**Outcome**

The primary outcome was 30-day mortality. Secondary endpoints included 90-day mortality, 60-day recurrence, prolonged bacteremia, duration of bacteremia, hospital length of stay, ID consult and AKI. All clinical outcome time points were measured from index blood culture collection.

**Statistical analysis**

Descriptive statistics were used to evaluate patients’ demographics. Nominal data were reported as counts and percentages, and continuous data were reported as medians and interquartile ranges (IQR). Categorical variables were compared by the chi-squared and continuous variables were compared by Mann-Whitney U test, as appropriate. Multivariable logistic regression was used to assess the independent association between POST and 30-day mortality while adjusting for confounding variables. POST, along with all variables associated with 30-day mortality in the bivariate analysis at a P-value <0.2 were entered into the model simultaneously and removed using a backward stepwise approach. Covariates were retained in the model if the P-value for the likelihood ratio test for their removal was <0.1. The variance inflation factor was used to assess the multicollinearity of covariates in the model with values in the range of 1-5 considered acceptable. When certain variables were collinear, the variable with the highest number of patients was retained. The Hosmer-Lemeshow goodness of fit test was used to assess the model’s fit. All tests were two tailed with P-values < 0.05 considered statistically significant. If a patient died due to coronavirus disease 2019 (COVID-19) in POST, that patient was excluded from the regression analysis.

To account for inherent changes over the study time period such as in medical practices, strain epidemiology, and patient mix that may have influenced clinical outcomes, we performed an interrupted time series analysis. We examined changes over time as well
as differential changes over time in the PRE and POST periods. Also, within POST group, classification and regression tree (CART) analysis was performed to determine the time to start BL most predictive of 30-day mortality. To assess the independent association between time to BL dichotomized at the CART derived cut-point and 30-day mortality, a multivariable logistic regression model was performed. Additionally, we also repeated the multivariable logistic regression analysis using 90-day mortality as an outcome. IBM SPSS software, version 26.0 (SPSS, Inc., Chicago, IL) was used for all calculations.

Results:

Overall, 1,155 BSI patients were evaluated and 342 were excluded. A total of 813 adult patients treated for MRSA BSI were evaluated (PRE, n=379 and POST, n=434) (Figure 2). The entire cohort was predominately male (75.4%) with median (IQR) age of 50.5 (39.6-61.2) years. The median (IQR) APACHE II and CCI were 17 (11 – 23) and 3 (1-5), respectively. A comparison of baseline characteristics between PRE and POST are provided in (Table 1). Some notable differences were observed between the two groups. Diabetes was more prominent in the PRE compared to POST; 44.6% vs. 36.2% (P=0.015), as well as heart failure; 26.6% vs. 19.6% (P=0.017) and previous hospitalization; 40.9% vs. 29.0% (P<0.0001). Conversely, lack of comorbid conditions was less common in PRE compared to POST; 3.7% vs. 9.2%, respectively (P=0.002). Vancomycin susceptibilities over the two study periods are displayed in (Table 1). Criteria of anti-MRSA agents or BL regimens in the PRE and POST groups are illustrated in (Table 2). The most common first anti-MRSA agent is VAN in both PRE and POST; 90.0% and 95.9%, respectively (P=0.001). Lack of BL CT (i.e. monotherapy (MT)) was most common in PRE 48.5%, while the most common first BL agent was cefepime in POST 46.8%. The most common anti-MRSA agent at 48-hours was VAN in both PRE and POST; 70.2% and 85.7%, respectively (P<0.001). Lack of BL combination was common in PRE 63.3%, while the most common BL agent at 48-hours was cefazolin 44.5% in POST. The most common primary anti-MRSA agent is VAN in both PRE
and POST; 53.0% and 71.2%, respectively (P<0.001). Among patients who had a BL, the most common primary BL agent was cefepime in PRE 16.5% and cefazolin 55.7% in POST.

Thirty-day and 90-day mortality were higher in PRE compared to POST, 15.6% vs. 9.7% (p = 0.011) and 19.0% vs. 12.2% (p=0.007), respectively (Figure 3). Sixty-day recurrence was comparable between PRE and POST; 5.8% and 4.3%, respectively (P = 0.978). In PRE, 24.5% of patients experienced prolonged bacteremia, compared to 21.8% in POST group (P = 0.362). Regarding bacteremia duration, the mean (SD) was 4.2 (4.2) vs. 3.6 (2.6) days in the PRE and POST, respectively (P < 0.001). The vast majority of patients had an ID consult 92.7%, which was more common in POST compared to PRE; 94.5% and 90.8%, respectively (P=0.042). The median (IQR) hospital length of stay was similar in POST group compared to the PRE 11 (8-19) and 12 (8-19) days, respectively (P = 0.486). The incidence of AKI in the entire cohort was 8.3% and was higher in the PRE compared to POST; 9.6% and 7.2% respectively but not statistically significant (P=0.282). With CART analysis for the time to start a BL, none of the cut-off points identified by CART were predictive of the primary endpoint in the entire cohort.

A bivariate comparison of baseline criteria between patients with and without 30-day mortality (Table 3). Notable differences between the two groups at the prespecified P-value were included in the multivariable logistic regression model (Supplemental material Table 1). Based on the final variables retained in the model, the pathway was independently associated with a reduction in 30-day mortality (adjusted odds ratio [aOR], 0.608; 95% confidence interval [CI], 0.375-0.986). Other variables independently associated with 30-day mortality are listed in (Table 4.). In the interrupted time series analysis when differential changes over time in the PRE and POST periods were examined for 30-day mortality as well as overall changes overtime, the effect of time was not statistically significant (P=0.710; P=0.404, respectively) (Figure 4). This indicates that 30-day mortality was not changing as a function of time and that the improvement in survival was due to POST intervention (Supplemental material Figure 1). Additionally, when ID consult was excluded as a study
variable and was considered as a component of POST in the logistic regression model, the primary analysis results remained consistent. Moreover, when the model was performed using 90-day mortality as the outcome with the same variables for the primary analysis, treatment within pathway was also independently associated with reduced odds of 90-day mortality of the outcome (adjusted odds ratio [aOR], 0.634; 95% CI, 0.412-0.977). Hosmer and Lemeshow Test demonstrated an acceptable P-value (P=0.788).

Discussion:

As opposed to previous evaluations of BL CT, we initiated a formalized clinical pathway for the treatment of MRSA BSI. The pathway required early BL CT as a key component in addition to a mandatory ID consult, microbiological evaluation and prespecified timely therapy assessments. Our study demonstrated a significant difference in both 30-day and 90-day mortality even after adjusting for confounding variables, including ID consultation. There are important differences worth highlighting from previous evaluations of BL combination. First the BL was initiated early in the treatment course as a function of the clinical pathway. Because early use of BL (i.e. within 48 hours) was established in most patients (370, 88.9%), we were unable to determine a specific time to start BL that was most predictive of outcomes. This may have contributed to the improved mortality observed in our study. This was in contrast to CAMERA-2, where the average time to randomization was 48 hours(18). This ultimately caused the majority of the MT arm to receive therapy within 72 hours of randomization, thus potentially misclassifying the MT arm towards the null. In addition, many of the CT patients did not receive any BL until 72 hours into their BSI culture, exceeding the window of which benefit is highly projected. Additionally, while ID consult is a known contributor to improved outcomes in MRSA BSI patients, we controlled for this factor to demonstrate it was not the primary driver of the mortality benefit (25, 26).

Of interest, while we demonstrated that less patients experienced persistent bacteremia in POST compared to the PRE; this was not statistically significant. However,
there was a statistically significant decrease in bacteremia duration; 4.2 v. 3.6 days in the PRE compared to POST respectively. Although not all reports have not been able to demonstrate such an improvement, most studies demonstrated a statistically significant decrease in bacteremia by 1-2 days (11, 13-15, 17-19). It is important to note that persistent bacteremia has been correlated with but not validated as a marker for mortality (27, 28).

Although there were a few differences in underlying comorbid conditions between the PRE and POST, these factors did not play an impactful role on mortality as observed in our regression model. In addition, the clinical microbiology laboratory has used both Microscan (primarily PRE) and Phoenix (primarily POST) automated susceptibility platforms over the course of nine years. MicroScan has been shown to more likely overcall an MIC value of 2 mg/L, whereas Phoenix tends to under call an MIC of 2mg/L (29, 30). Therefore, it was not surprising to find more MIC values of 2 mg/L reported in PRE compared to POST, as Microscan was utilized in this time period. In addition, some isolates were also tested by Etest which also by virtue of differences in inoculum tends to read higher than automated testing or Clinical & Laboratory Standards Institute (CLSI) microdilution method. Of interest, our laboratory at Wayne State University frequently performs vancomycin MICs for various research purposes using the “gold standard” broth microdilution technique on MRSA bloodstream isolates from the Detroit Medical Center. We went back and were able to match 414 BSI isolates that were from patients in the pre (110/379) and post 314/434) time periods. In the pre-period, 90% of the VAN MICs were 1 or less and in the post-period 95% are 1 mg/L or less. Therefore, there does not seem to be any major difference in vancomycin susceptibility between the two time periods. Overall, because of the inability to correctly identify VAN MIC of 1 mg/L and 2 mg/L in the entire cohort of patients, the exact impact of the VAN MIC on clinical outcome is unclear in this analysis.

AKI was relatively low in our cohort, even when BL were combined with VAN. First, it is important to note that CAMERA-1 and CAMERA-2 used flucloxacillin, a semi-synthetic penicillin associated with significant nephrotoxicity risks for the majority of the patients (17,
In a secondary nephrotoxicity analysis of the CAMERA-2, AKI was independently more common in the flucloxacillin/VAN group but not for the cefazolin/VAN group (31). In our clinical pathway, cefepime (n=282, 34.6%) and cefazolin (n=149, 34.6%) were the most common BL used in POST, suggesting that cephalosporin-based regimens appear to be safer when combined with VAN than penicillin-based. A recent meta-analysis of CT studies also suggest that there is no difference in AKI between CT and MT where notably most of the included studies had a cephalosporin-based BL (16). Second, VAN AUC-guided dosing which is associated with lower AKI was implemented at the DMC in 2015 and is consequently more prevalent in POST compared to PRE (32, 33). Third, our institution had switched from piperacillin/tazobactam to cefepime as the primary empiric Gram-negative agent of choice in 2015. As evident from the results, piperacillin/tazobactam was more prominent in PRE compared to POST (P<0.001). Lastly, there is a lower proportion of patients on nephrotoxins in POST compared to the PRE (P<0.0001)(34). Collectively, it is possible that the combination of these factors have contributed to the lower incidence of AKI in POST which we have previously demonstrated in studies conducted at our healthcare center (32, 35, 36).

Less patients were on DAP or ceftaroline as the primary anti-MRSA agent in POST compared to PRE; (24.7%) vs. (34.6%) and (3.5%) vs.(11.9%), respectively. This demonstrates that we were able to improve success rates with VAN and decrease the use of more costly and broad-spectrum agents.

Our study differs from previous evaluations of CT for the treatment of MRSA BSI since it is a real-world extensive evaluation of how a comprehensive pathway that incorporates diagnostics, timely ID consult and systematic early utilization of CT can improve patient outcomes. While cefazolin is the mainstay of BL choice in the pathway, other BL were also acceptable to pair with the anti-MRSA agent. We previously demonstrated that cefepime can positively impact patients’ outcomes in MRSA BSI (13). In order to account for a possible selection bias in patients with concomitant MRSA and Gram-negative infections...
who have a higher anticipated mortality risk, we excluded those with polymicrobial bacteremia. Therefore, the impact of empiric cefepime as opposed to targeted BL agents is minimal. Additionally, because the study had a large sample size, particularly for a real-world analysis, we were able to detect and thus adjust for various confounding variables that may have contributed to positive clinical outcomes. To ensure that the results were not biased by pre and post variable imbalances, we repeated the logistic regression analysis with selected high risk groups. In addition, we performed an inverse probability of treatment weighting (IPTW) analysis. The results of both of these analyses remained consistent with the primary findings and statistically significant (supplemental material Table 2).

This study is not without limitations. First, this was a retrospective study and is challenged by inherent limitations of the design. Second, despite this being a multi-center study, it was limited to hospitals within a single healthcare system and the results may not be generalizable to other patient populations. Additionally, because the time frame of the study was over nine years, it may be possible that improvements in medical practices have contributed to patient outcomes as well as changes in strain epidemiology and virulence. However, we attempted to control for this by performing additional analyses using time in study period as a variable and the results remained consistent. Notably, we did find an increase in excess mortality during the last 4 months of our study period (i.e. March to June of 2020) which may be related to the peak of the COVID-19 pandemic at the state of Michigan (37, 38). Additionally, although we have observed an improvement in 90-day mortality; this is likely impacted by improvement in 30-day mortality. Lastly, although our clinical pathway was reliant on CT with BL, the impact of pathway as an entire process might have been the driver of mortality rather than BL CT alone; and thus, might explain the mortality benefit observed in our study but not in previous studies.
In conclusion, we have shown that a comprehensive clinical pathway to manage MRSA BSI can have a positive impact on patient outcomes, particularly improved survival. We demonstrated that the selection of the BL, such as cefazolin or cefepime, for CT is important as our results show that CT was safe and not associated with increased incidence of AKI. Lastly, while multiple anti-MRSA agents and BL were included in the clinical pathway, the predominant regimens were VAN/cefazolin and VAN/cefepime. Therefore, it would be of interest if future studies including prospective evaluations would be directed on evaluating anti-MRSA agents other than VAN in CT with these BLs.
Acknowledgements:

A proportion of patients in this analysis had been presented, in part, at American Society for Microbiology (ASM); October 3-7, 2018 San Francisco, CA (abstract 2379) and the Infectious Diseases Society of America (IDSA) Meeting; October 2-6 2019 Washington, DC (abstract 2250) and the following publications Alosaimy et al, Jorgensen et al, and Zasowski et al (11-13).

Funding

No funding or sponsorship was received for this study or publication of this article.

Conflict of interest

SA, AMF, EZ, TM, SH, JJZ, JJ, RM, JMP, SD, MRS, TT, TC and NR have nothing to disclose, SCJJ: has received speaker’s honorarium from Melinta and Sunovion, MJR: Research support, consultant or speaker for Allergan, Contrafect, Melinta, Merck, Motif, Paratek, Tetraphase, Shionogi, Spero and is partially supported by NIAID AI121400 and AI1300056-04.
Table 1: Bivariate Comparison of Baseline Demographics and Clinical Criteria Between Patients in Pre-pathway and Post-pathway

| Criteria                          | Pre-pathway (n=379) | Post-pathway (n=434) | P-value |
|----------------------------------|---------------------|----------------------|---------|
| **Demographics**                 |                     |                      |         |
| Age, years                       | 60 (50-71)          | 59 (47 – 68)         | 0.123   |
| Age => 65                        | 146 (38.5)          | 149 (34.3)           | 0.215   |
| Race                             |                     |                      | 0.013   |
| African American                 | 293 (77.3)          | 320 (74.8)           |         |
| Caucasian                        | 75 (19.8)           | 81 (18.9)            |         |
| Others                           | 11 (2.9)            | 33 (7.6)             |         |
| Weight, kg                       | 77.7 (64.3 – 96.0)  | 76.8 (62.5 – 95.2)   | 0.395   |
| BMI=> 30                         | 136 (35.9)          | 137 (31.7)           | 0.210   |
| **Comorbid conditions**          |                     |                      |         |
| AKI                              | 105 (27.7)          | 111 (25.6)           | 0.493   |
| Cerebrovascular disease<sup>1</sup> | 62 (16.4)          | 63 (14.5)            | 0.467   |
| Chronic pulmonary disease<sup>2</sup>  | 110 (29.0)         | 102 (23.5)           | 0.074   |
| Moderate to severe or on chronic dialysis | 133 (35.1) | 129 (29.7)           | 0.102   |
| Chronic dialysis<sup>3</sup>     | 87 (23)             | 101 (23.3)           | 0.915   |
| Connective tissue disease<sup>4</sup> | 44 (11.6)          | 31 (7.1)             | 0.028   |
| Dementia                         | 38 (10.0)           | 35 (8.1)             | 0.329   |
| Diabetes, any                    | 169 (44.6)          | 157(36.2)            | 0.015   |
| Without end organ damage         | 55 (14.5)           | 32 (7.4)             | 0.001   |
| Condition                                | Onset With End Organ Damage | Onset Without End Organ Damage | Significant Difference |
|------------------------------------------|----------------------------|--------------------------------|-------------------------|
| With end organ damage                    | 115 (30.3)                 | 125 (28.8)                     | 0.631                   |
| Heart failure                            | 101 (26.6)                 | 85 (19.6)                      | 0.017                   |
| Hemiplegia                               | 9 (2.4)                    | 7 (1.6)                        | 0.435                   |
| Immunodeficiency, any                    | 28 (7.4)                   | 18 (4.1)                       | 0.046                   |
| AIDS (CD4 < 200)                         | 8 (2.1)                    | 10 (2.3)                       | 0.852                   |
| HIV                                      | 18 (4.7)                   | 15 (3.5)                       | 0.351                   |
| Leukemia                                 | 2 (0.5)                    | 0 (0.0)                        | 0.130                   |
| Lymphoma                                 | 3 (0.8)                    | 6 (1.4)                        | 0.422                   |
| Tumor with metastasis                    | 15 (4.0)                   | 12 (2.8)                       | 0.344                   |
| Tumor without metastasis                 | 11 (2.9)                   | 3 (0.7)                        | 0.016                   |
| Liver disease, any                       | 56 (14.8)                  | 38 (8.8)                       | 0.007                   |
| **Mild**                                 | **45 (11.9)**              | **29 (6.7)**                   | **0.010**               |
| **Moderate or severe**                   | **11 (2.9)**               | **9 (2.1)**                    | **0.447**               |
| Myocardial infarction                    | 32 (8.4)                   | 30 (6.9)                       | 0.412                   |
| No conditions                            | 14 (3.7)                   | 40 (9.2)                       | 0.002                   |
| Peptic ulcer disease                     | 4 (1.1)                    | 3 (0.7)                        | 0.572                   |
| Peripheral vascular disease              | 56 (14.8)                  | 79 (18.2)                      | 0.190                   |
| Prior hospitalization for ≥48 hours      | 155 (40.9)                 | 126 (29.0)                     | <0.0001                 |
| in 90 days prior to index culture        |                            |                                |                         |
| Prior MRSA in 365 days preceding         | 46 (12.1)                  | 39 (9.0)                       | 0.143                   |
| index culture                            |                            |                                |                         |
| Prior MSSA in 365 days preceding         | 2 (0.5)                    | 3 (0.7)                        | 0.766                   |
| index culture                            |                            |                                |                         |
| Prior surgery in 30 days preceding       | 22 (5.8)                   | 10 (2.3)                       | 0.010                   |
| index culture                            |                            |                                |                         |
| PWID               | 56 (14.8) | 55 (12.7) | 0.384 |
|-------------------|-----------|-----------|-------|
| Sources of bacteremia<sup>a</sup> |           |           |       |
| Bone and joint    | 59 (15.6) | 57 (13.1) | 0.322 |
| Endovascular      | 4 (1.1)   | 0 (0.0)   | 0.032 |
| Central nervous system abscess | 6 (1.6)   | 2 (0.5)   | 0.106 |
| Infective endocarditis | 59 (15.6) | 46 (10.6) | 0.035 |
| Intraabdominal    | 6 (1.6)   | 7 (1.6)   | 0.973 |
| Intravenous catheter | 56 (14.8) | 78 (18.0) | 0.220 |
| Invasive prosthetic device | 16 (4.2) | 12 (2.8) | 0.256 |
| Other             | 34 (9.0)  | 47 (10.8) | 0.377 |
| Pneumonia         | 95 (25.1) | 74 (17.1) | 0.005 |
| Skin and soft tissue | 99 (26.1) | 102 (23.5) | 0.388 |
| Urinary           | 10 (2.6)  | 16 (3.6)  | 0.397 |
| Unknown           | 31 (8.2)  | 36 (8.3)  | 0.952 |
| Vertebral abscess | 3 (0.8)   | 6 (1.4)   | 0.422 |
| Others Factors    |           |           |       |
| APACHE II         |           |           |       |
| APACHE => 30      | 17 (11-23) | 17 (11 – 22) | 0.415 |
| CCI               |           |           |       |
| CCI=>5            | 50 (13.2) | 41 (9.6)  | 0.103 |
| Intensive Care Setting<sup>g</sup> | 3 (1 – 5) | 3 (1 – 4) | 0.005 |
| Infectious Diseases Consult | 116 (30.6) | 110 (25.3) | 0.095 |
| Time to consult ID, hours | 73 (19.3) | 70 (16.3) | 0.266 |
| Source Control pursued<sup>10</sup> | 344 (90.8) | 410 (94.5) | 0.042 |
|                   | 21.8 (4.4-39.2) | 13.3 (1.5-33.1) | 0.015 |
|                   | 371 (39.4) | 179 (43.7) | 0.223 |
| Automated VAN MIC Testing | 370 (97.6) | 417 (96.1) | 0.212 |
|---------------------------|------------|------------|-------|
| Performed                 |            |            |       |
| 0.5                       | 7 (1.9)    | 40 (9.6)   | <0.001|
| 1                         | 175 (47.3) | 368 (88.2) | <0.001|
| 2                         | 188 (50.8) | 9 (2.2)    | <0.001|
| VAN Etest Performed       | 100 (26.4) | 337 (77.6) | <0.001|
| 1                         | 23 (23.0)  | 76 (22.6)  | 0.925 |
| 2                         | 77 (77.0)  | 261 (60.1) | 0.925 |
| AKI 11                    |            |            |       |
| VAN TDM by AUC 12         | 65 (24.2)  | 151 (47.2) | <0.0001|
| VAN AUC                   | 474.0 (401.3) – 461.2 (370.0) – 0.197 | 550.8 – 543.0 |
| On at least one nephrotoxic agent 13 | 70 (24.0) | 25 (7.5) | <0.0001 |
| On VAN                    | 64 (21.9)  | 24 (7.2)   | <0.0001|
| Not on VAN                | 44 (15.1)  | 6 (1.8)    | <0.0001|
| Other Safety Outcome      |            |            |       |
| CPK increase 74           | 9 (2.4)    | 1 (0.2)    | 0.006 |
| Clostridium difficile     | 16 (4.2)   | 9 (2.1)    | 0.077 |

Data presented as median (IQR) and/or n (percentages) as appropriate

AKI: acute kidney injury; AIDS: Acquired immunodeficiency syndrome, APACHE II: Acute Physiology and Chronic Health Evaluation, BMI: body mass index, CCI: Carlson comorbidity index, CD4: cluster of differentiation 4, COPD: chronic obstructive pulmonary disease, DVT: deep venous thrombosis, HIV: human immunodeficiency virus, TDM: therapeutic drug monitoring, MRSA: methicillin resistant Staphylococcus aureus, MSSA: methicillin sensitive Staphylococcus aureus, TIA: transient ischemic attack, OA: osteoarthritis, PWID: Person who inject drugs, VAN: vancomycin
1 stroke or TIA
2 asthma or COPD
3 hemodialysis or peritoneal dialysis
4 OA or rheumatic arthritis
5 chronic hepatitis without cirrhosis
6 portal hypertension or cirrhosis
7 DVT, chronic venous disease
8 Some patients may have had more than one source of infection
9 When obtaining index culture

10 In PRE, intravenous catheter removal (n=3), valvular replacement (n=1), cardiac device removal (n=2), incision and drainage (n=5), debridement (n=3). In POST, intravenous catheter removal (n=45), valvular replacement (n=3), cardiac device removal (n=5), incision and drainage (n=32), debridement (n=20), amputation (n=3), other (n=16).

11 Among patients who did not have hemodialysis or peritoneal dialysis (pre, n=292 and post, n=333). AKI was defined as an increase in serum creatinine (Scr) of ≥ 0.5 mg/dl or ≥ 50% increase of Scr from baseline, whichever is greater, on 2 consecutive measurements from initial VAN dose until 72 hours after the last dose (13, 35).

12 Among entire population of patients managed with vancomycin for ≥48 hours (pre, n=269 and post, n=320)

13 Those include vancomycin. Most commonly while on VAN in PRE is diuretics (n=27), followed by Nonsteroidal anti-inflammatory drugs (n=25), while in POST is diuretic (n=9), followed by vasopressor (n=6). While not on VAN in PRE is diuretics (n=15), followed by Nonsteroidal anti-inflammatory drugs (n=21), while in POST is diuretic (n=2), followed by Angiotensin II Receptor Blockers or angiotensin receptor blocker (n=2).

14 Increased creatinine phosphokinase (CPK) was defined as increase of CPK to > 600 U/L (if baseline < 200 U/L) or > 1000 U/L (if baseline > 200 U/L) from the initiation of drug to 72 hours after discontinuation of drug.
Table 2: Treatment Characteristics of Patients Pre-pathway and Post-pathway

| First Pathway Agent | Pre-pathway (n=379) | Post-pathway (n=434) | P-Value |
|---------------------|---------------------|----------------------|---------|
| **First MRSA-agent** |                     |                      |         |
| Vancomycin          | 341 (90.0)          | 416 (95.9)           | 0.001   |
| Daptomycin          | 27 (7.1)            | 12 (2.8)             | 0.004   |
| Ceftaroline         | 9 (2.4)             | 4 (0.9)              | 0.099   |
| **First BL-regimen** |                     |                      |         |
| None                | 184 (48.5)          | 18 (4.1)             | <0.001  |
| Cefepime            | 79 (20.8)           | 203 (46.8)           | <0.001  |
| Cefazolin           | 22 (5.8)            | 127 (29.3)           | <0.001  |
| Ceftaroline         | 0 (0.0)             | 10 (2.3)             | 0.008   |
| Ceftriaxone         | 29 (7.7)            | 49 (11.3)            | 0.098   |
| Piperacillin / Tazobactam | 37 (9.8) | 13 (3.0)             | <0.001  |
| Others              | 28 (7.3)            | 14 (3.2)             | 0.551   |
| **Time to start BL, h** |                   |                      |         |
| Cefepime            | 1.9 [0.4 - 9.4]     | 1.6 [0.3 – 17.5]     | 0.873   |
| Cefazolin           | 39.1 [27.4 – 64.2]  | 39.4 [27.7 – 54.9]   | 0.748   |
| **Duration of BL, days** |                   |                      |         |
| Cefepime            | 1.2 [0.2 - 7.8]     | 1.3 [0.5-3.0]        | 0.932   |
| Cefazolin           | 3.0 [3 – 6]         | 4.3 [1.5-5.6]        | 0.925   |
### Anti-MRSA agent at 48-hours

|                | Group 1 (n=412) | Group 2 (n=513) | p-value |
|----------------|-----------------|-----------------|---------|
| Vancomycin     | 266 (70.2)      | 372 (85.7)      | <0.001  |
| Daptomycin     | 74 (19.5)       | 43 (9.9)        | <0.001  |
| Ceftaroline    | 20 (5.3)        | 6 (1.4)         | 0.002   |

### BL-regimen at 48-hours

|                | Group 1 (n=412) | Group 2 (n=513) | p-value |
|----------------|-----------------|-----------------|---------|
| None           | 240 (63.3)      | 24 (8.5)        | <0.001  |
| Cefepime       | 44 (11.6)       | 88 (20.3)       | <0.001  |
| Cefazolin      | 21 (5.5)        | 193 (44.5)      | <0.001  |
| Ceftaroline    | 0 (0)           | 14 (3.2)        | <0.001  |
| Ceftriaxone    | 24 (6.3)        | 50 (11.5)       | 0.010   |
| Piperacillin / Tazobactam | 24 (6.9) | 15 (3.5) | 0.027 |
| Others         | 24 (6.3)        | 5 (1.2)         | <0.001  |

### Primary Pathway agent

|                | Group 1 (n=412) | Group 2 (n=513) | p-value |
|----------------|-----------------|-----------------|---------|
| Vancomycin     | 201 (53.0)      | 309 (71.2)      | <0.001  |
| Daptomycin     | 131 (34.6)      | 107 (24.7)      | 0.002   |
| Ceftaroline    | 45 (11.9)       | 15 (3.5)        | <0.001  |

### Primary BL-regimen

|                | Group 1 (n=412) | Group 2 (n=513) | p-value |
|----------------|-----------------|-----------------|---------|
| Cefepime       | 62 (16.5)       | 88 (20.3)       | 0.551   |
| Cefazolin      | 21 (5.5)        | 242 (55.7)      | <0.001  |
| Ceftaroline    | 1 (0.26)        | 1 (0.23)        | 0.565   |
|                | Median (IQR) |     |     |
|----------------|--------------|-----|-----|
| Ceftriaxone    | 22 (5.8)     | 27 (6.2) | 0.031 |
| Piperacillin / |              |     |     |
| Tazobactam     | 15 (3.9)     | 6 (1.4)  | <0.001 |
| Others         | 17 (8.7)     | 27 (6.3) | 0.269 |

BL: Beta-lactam, hrs: hours, MRSA: methicillin resistant *Staphylococcus aureus*

Values in median (IQR) or n (percentages)

1. First anti-MRSA agent or BL regimen was defined as the agent the patient received first during encounter

2. Indicates from start of MRSA culture

3. If regimen started before MRSA, time is considered 0

4. Anti-MRSA agent or BL regimen at 48-hours was defined as the agent/regimen received at 48-hours starting from the first anti-MRSA and/or BL.

5. None implies that after applying the 48-hour rule, no other beta lactams were given (i.e. beta lactam duration was less than 48 hours)

6. Primary anti-MRSA agent or BL regimen was defined as the agent/regimen with the longest duration of treatment during the same encounter, only among those with a BL combination
Table 3: Bivariate Comparison of Baseline Demographics and Clinical Criteria Between Patients with 30-day mortality and Patients with No 30-day mortality

| Criteria                                    | 30-day Mortality (n=101) | No 30-day Mortality (n=712) | P-Value |
|---------------------------------------------|--------------------------|-----------------------------|---------|
| Demographics                                |                          |                             |         |
| Age, years                                  | 71 (62 - 80)             | 59 (46 – 68)                | 0.006   |
| Age => 65                                    | 71 (70.3)                | 224 (31.5)                  | <0.001  |
| Race                                        |                          |                             | 0.365   |
| African American                            | 78 (78.0)                | 535 (75.7)                  | 0.610   |
| Caucasian                                   | 19 (19.0)                | 137 (19.4)                  | 0.929   |
| Others                                      | 4 (3.9)                  | 40 (5.6)                    |         |
| BMI=> 30                                    | 30 (30.0)                | 243 (34.2)                  | 0.408   |
| Comorbid conditions                         |                          |                             |         |
| AKI                                         | 41 (40.6)                | 175 (24.6)                  | 0.001   |
| Cerebrovascular disease<sup>1</sup>         | 18 (17.8)                | 107 (15.0)                  | 0.466   |
| Chronic pulmonary disease<sup>2</sup>       | 36 (35.6)                | 176 (24.7)                  | 0.019   |
| Chronic kidney disease                      |                          |                             |         |
| Moderate to severe chronic kidney disease or on chronic dialysis | | | |
| Chronic dialysis<sup>3</sup>               | 18 (17.8)                | 170 (23.9)                  | 0.177   |
| Connective tissue disease<sup>4</sup>       | 14 (13.9)                | 61 (8.6)                    | 0.085   |
| Dementia                                    | 18 (17.8)                | 55 (7.7)                    | 0.001   |
| Diabetes disease, any                       | 35 (34.7)                | 291 (40.9)                  | 0.233   |
| Condition                                      | Without end organ damage | With end organ damage | p-value |
|-----------------------------------------------|--------------------------|-----------------------|---------|
| Heart failure                                 | 5 (5.0)                  | 82 (11.5)             | 0.046   |
| Hemiplegia                                    | 30 (29.7)                | 210 (29.5)            | 0.966   |
| Immunodeficiency, any                         | 35 (34.7)                | 151 (21.2)            | 0.003   |
| AIDS (CD4 < 200)                              | 9 (8.9)                  | 37 (5.2)              | 0.131   |
| HIV                                           | 2 (2.0)                  | 16 (2.2)              | 0.864   |
| Leukemia                                      | 2 (2.0)                  | 31 (4.4)              | 0.258   |
| Lymphoma                                      | 0 (0)                    | 2 (0.3)               | 0.594   |
| Tumor, any                                    | 13 (12.9)                | 28 (3.9)              | <0.001  |
| without metastasis                            | 4 (4.0)                  | 10 (1.4)              | 0.065   |
| with metastasis                               | 9 (8.9)                  | 18 (2.5)              | 0.001   |
| Liver disease, any                            | 10 (9.9)                 | 84 (11.8)             | 0.577   |
| Mild                                          | 7 (6.9)                  | 67 (9.4)              | 0.418   |
| Moderate or severe                            | 3 (3.0)                  | 17 (2.4)              | 0.724   |
| Myocardial infarction                         | 16 (15.8)                | 46 (6.5)              | 0.001   |
| No conditions                                 | 3 (3.0)                  | 51 (7.2)              | 0.113   |
| Peptic ulcer disease                          | 2 (2.0)                  | 5 (0.7)               | 0.193   |
| Peripheral vascular disease                   | 19 (18.8)                | 116 (16.3)            | 0.524   |
| Prior hospitalization in 48 hours in 90 days prior to index culture | 43 (42.6) | 238 (33.4) | 0.070 |
| Prior MRSA in 365 days                        | 9 (8.9)                  | 76 (10.7)             | 0.588   |
| preceding index culture | | |
|-------------------------|-----------------|---------------|
| Prior MSSA in 365 days  | 0 (0)           | 5 (0.7)       | 0.398 |
| Prior surgery in 30 days| 3 (3.0)         | 29 (4.1)      | 0.594 |
| PWID                    | 4 (4.0)         | 107 (15.0)    | 0.002 |

| Sources of bacteremia^a | | |

|                      | | |
|-----------------------|-----------------|---------------|
| Bone and joint        | 1 (1.0)         | 115 (16.2)    | <0.001 |
| Endovascular          | 1 (1.0)         | 3 (0.4)       | 0.445  |
| Central nervous system| 0 (0.0)         | 8 (1.1)       | 0.284  |
|                      | | |
| Infective endocarditis| 11 (10.9)      | 94 (13.2)     | 0.517  |
| Intraabdominal        | 1 (1.0)         | 12 (1.7)      | 0.602  |
| Intravenous catheter  | 9 (8.9)         | 125 (17.6)    | 0.028  |
| Invasive prosthetic device | 3 (3.0)   | 25 (3.5)      | 0.780  |
| Other                 | 6 (5.9)         | 75 (10.5)     | 0.149  |
| Pneumonia             | 41 (40.6)       | 128 (18.0)    | <0.001 |
| Skin and soft tissue  | 12 (11.9)       | 189 (26.5)    | <0.001 |
| Urinary               | 5 (5.0)         | 21 (2.9)      | 0.285  |
| Unknown               | 15 (14.9)       | 52 (7.3)      | 0.010  |
| Vertebral abscess     | 1 (1.0)         | 8 (1.1)       | 0.904  |

| Others Factors | | |
|----------------|-----------------|---------------|
| APACHE II      | 24 (18 – 31)    | 16 (10 - 22)  | <0.001 |
| APACHE => 30   | 33 (33.0)       | 58 (8.2)      | <0.001 |
|                          | CCI     | CCI=>5   | <0.001 |
|-------------------------|---------|----------|--------|
|                         | 4 (2 - 6 | 3 (1 - 5 ) |        |
| Intensive Care Setting  | 32 (32.3) | 111 (15.7) | <0.001 |
| Infectious Diseases    | 87 (86.1) | 667 (93.7) | 0.006  |
| Consult                 |         |          |        |
| Source Control          | 19 (19.6) | 306 (44.7) | <0.001 |
| Automated VAN MIC Testing | 98 (97.0) | 689 (96.8) | 0.889  |
| Performed               |         |          |        |
| 0.5                     | 8 (8.2)  | 39 (5.7)  | 0.328  |
| 1                       | 62 (63.3)| 481 (69.8)| 0.190  |
| 2                       | 28 (28.6)| 169 (24.5)| 0.387  |
| VAN Etest Performed     | 49 (48.5)| 388 (54.5)| 0.613  |
| 1                       | 86 (22.2)| 13 (26.5 )| 0.492  |
| 2                       | 36 (73.5)| 302 (77.8)| 0.492  |
| AKI 11                  |         |          |        |
| VAN TDM by AUC 12       | 14 (17.7)| 202 (39.6)| <0.001 |
| VAN AUC                 | 517.5 (358.5 – 555.4) | 463.0 (380.0 – 543.4) | 0.642 |
| On at least one         |         |          |        |
| nephrotoxic agent 13    |         |          |        |
| On VAN                  | 18 (21.7)| 77 (14.2) | 0.077  |
| Not on VAN              | 5 (6.0)  | 45 (8.3)  | 0.476  |
| Other Safety Outcome    |         |          |        |
| CPK increase 14         | 1 (1.0)  | 9 (1.3)   | 0.815  |
| *Clostridium difficile* | 7 (6.9)  | 18 (2.5)  | 0.016  |
Data presented as median (IQR) and/or n (percentages)

AKI: acute kidney injury; AIDS: Acquired immunodeficiency syndrome, APACHE II: Acute Physiology and Chronic Health Evaluation, BMI: body mass index, CCI: Carlson comorbidity index, CD4: cluster of differentiation 4, COPD: chronic obstructive pulmonary disease, DVT: deep venous thrombosis, HIV: human immunodeficiency virus, MRSA: methicillin resistant Staphylococcus aureus, MSSA: methicillin sensitive Staphylococcus aureus, TIA: transient ischemic attack, OA: osteoarthritis, PWID: Person who inject drugs

1 stroke or TIA
2 asthma or COPD
3 hemodialysis or peritoneal dialysis
4 OA or rheumatic arthritis
5 chronic hepatitis without cirrhosis
6 portal hypertension or cirrhosis
7 DVT, chronic venous disease
8 Some patients may have had more than one source of infection
9 When obtaining index culture
10 In 30-day mortality, intravenous catheter removal (n=3), incision and drainage (n=1), debridement (n=2). In patients with no 30-day mortality, intravenous catheter removal (n=45), valvular replacement (n=4), cardiac device removal (n=7), incision and drainage (n=36), debridement (n=21), amputation (n=3), other (n=16)
11 Among patients who did not have hemodialysis or peritoneal dialysis (30-day mortality, n=83 and no 30-day mortality, n=542). AKI was defined as an increase in serum creatinine (Scr) of ≥ 0.5 mg/dl or ≥ 50% increase of Scr from baseline, whichever is greater, on 2 consecutive measurements from initial VAN dose until 72 hours after the last dose (13, 35).
12 Among entire population of patients managed with vancomycin managed with vancomycin for =>48 hours (30-day mortality, n=79 and no 30-day mortality, n=510)
13 Most commonly while on VAN in 30-day mortality is diuretics (n=11), followed by piperacillin-tazobactam and contrast media (n=5) and in patients with no 30-day mortality is diuretic (n=25), followed by piperacillin-tazobactam and contrast media (n=5). While not on VAN in 30-day mortality is diuretics (n=11), followed by
followed by Angiotensin II Receptor Blockers or angiotensin receptor blocker (n=3). In patients who are not on VAN and have experienced 30-day mortality, the most common agent was Nonsteroidal anti-inflammatory drugs, diuretics and Angiotensin II Receptor Blockers or angiotensin receptor blocker (n=2).

Increased creatinine phosphokinase (CPK) was defined as increase of CPK to > 600 U/L (if baseline < 200 U/L) or > 1000 U/L (if baseline > 200 U/L) from the initiation of drug to 72 hours after discontinuation of drug.
Table 4: Multivariable Logistic Regression for Factors Independently Associated With 30-day Mortality

| Variable                                      | OR      | P-value | 95% CI   | aOR    | P-value | 95% CI   |
|-----------------------------------------------|---------|---------|----------|--------|---------|----------|
| POST                                          | 0.681   | 0.140   | 0.409-1.134 | 0.608  | 0.044   | 0.375-0.986 |
| Age => 65 years                                | 3.156   | <0.001  | 1.827-5.454 | 3.314  | <0.001  | 2.003-5.483 |
| APACHE II score                               | 1.075   | <0.001  | 1.041-1.111 | 1.084  | <0.001  | 1.053-1.115 |
| Diabetes with no end organ damage              | 0.280   | 0.017   | 0.98-0.798 | 0.257  | 0.009   | 0.092-0.714 |
| PWID                                          | 0.419   | 0.138   | 0.133-0.385 | 0.092  | 0.017   | 0.009-0.774 |
| Myocardial infarction                         | 2.257   | 0.036   | 1.053-4.837 | 2.214  | 0.030   | 1.080-4.535 |
| Source of Bacteremia, other                   | 0.408   | 0.082   | 0.148-0.428 | 0.073  | 0.169   | 0.274-1.082 |
| Source of Bacteremia, intravenous catheter    | 0.244   | 0.004   | 0.093-0.248 | <0.001 | 0.115   | 0.010-0.536 |
| Source of Bacteremia, skin and soft tissue    | 0.118   | 0.527   | 0.235-0.552 | 0.096  | 0.274   | 0.010-1.111 |
| Source of bacteremia, bone and joint          | 0.071   | 0.012   | 0.009-0.077 | 0.013  | 0.010   | 0.009-0.581 |

Abbreviation: aOR: adjusted odds ratio, APACHE II: Acute Physiology and Chronic Health Evaluation, CCI: Carlson comorbidity index, CI, confidence interval, OR: odds ratio, PWID: Person who inject drugs, POST: post-pathway
Variables included in the model include: 1) Acute kidney injury, 2) age=> 65 years, 3) any immune-deficiency condition, 4) APACHE II, 5) CCI, 6) chronic pulmonary disease, 7) infectious diseases consult, 8) intensive care admission upon index culture, 9) dementia, 10) diabetes without end organ damage, 11) heart failure, 12) moderate to severe chronic kidney disease or on chronic dialysis, 13) myocardial infarction, 14) no comorbid medical conditions, 15) peptic ulcer disease, 16) prior hospitalization in 48 hours in 90 days prior to index culture, 17) post-pathway, 18) source control, 19) source is bone and joint, 20) source is intravenous catheter, 21) source is other site, 22) source is pneumonia, 23) source is skin and soft tissue infection, 24) source is unknown.

Hosmer-Lemeshow goodness-of-fit test P = .192; variance inflation factor 1–5 for all variables included at model entry.

One patient was excluded from the analysis due to the coronavirus disease 2019 (n=1).
References:

1. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012;25(2):362-86.
2. Wang FD, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. Am J Infect Control. 2008;36(2):118-22.
3. Murray KP, Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, et al. Early use of daptomycin versus vancomycin for methicillin-resistant Staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis. 2013;56(11):1562-9.
4. Claeys KC, Zasowski EJ, Casapao AM, Lagnf AM, Nagel JL, Nguyen CT, et al. Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of Methicillin-Resistant Staphylococcus aureus Bloodstream Infections. Antimicrob Agents Chemother. 2016;60(10):5841-8.
5. Kullar R, Davis SL, Kaye KS, Levine DP, Pogue JM, Rybak MJ. Implementation of an antimicrobial stewardship pathway with daptomycin for optimal treatment of methicillin-resistant Staphylococcus aureus bacteremia. Pharmacotherapy. 2013;33(1):3-10.
6. Climo MW, Patron RL, Archer GL. Combinations of vancomycin and beta-lactams are synergistic against staphylococci with reduced susceptibilities to vancomycin. Antimicrob Agents Chemother. 1999;43(7):1747-53.
7. Leonard SN. Synergy between vancomycin and nafcillin against Staphylococcus aureus in an in vitro pharmacokinetic/pharmacodynamic model. PLoS One. 2012;7(7):e42103.
8. Hagihara M, Wiskirchen DE, Kuti JL, Nicolau DP. In vitro pharmacodynamics of vancomycin and cefazolin alone and in combination against methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2012;56(1):202-7.
9. Tran KN, Rybak MJ. β-Lactam Combinations with Vancomycin Show Synergistic Activity against Vancomycin-Susceptible Staphylococcus aureus, Vancomycin-Intermediate S. aureus (VISA), and Heterogeneous VISA. Antimicrob Agents Chemother. 2018;62(6).
10. Dilworth TJ, Leonard SN, Vilay AM, Mercier RC. Vancomycin and piperacillin-tazobactam against methicillin-resistant Staphylococcus aureus and vancomycin-intermediate Staphylococcus aureus in an in vitro pharmacokinetic/pharmacodynamic model. Clin Ther. 2014;36(10):1334-44.
11. Alosaimy S, Sabagha NL, Lagnf AM, Zasowski EJ, Morissette T, Jorgensen SCJ, et al. Monotherapy with Vancomycin or Daptomycin versus Combination Therapy with β-Lactams in the Treatment of Methicillin-Resistant Staphylococcus Aureus Bloodstream Infections: A Retrospective Cohort Analysis. Infect Dis Ther. 2020;9(2):325-39.
12. Jorgensen SCJ, Zasowski EJ, Trinh TD, Lagnf AM, Bhatia S, Sabagha N, et al. Daptomycin Plus β-Lactam Combination Therapy for Methicillin-resistant Staphylococcus aureus Bloodstream Infections: A Retrospective, Comparative Cohort Study. Clin Infect Dis. 2020;71(1):1-10.
13. Zasowski EJ, Trinh TD, Atwan SM, Merzyakova M, Langf AM, Bhatia S, et al. The Impact of Concomitant Empiric Cefepime on Patient Outcomes of Methicillin-Resistant Staphylococcus aureus Bloodstream Infections Treated With Vancomycin. Open Forum Infect Dis. 2019;6(4):ofz079.
14. Casapao AM, Jacobs DM, Bowers DR, Beyda ND, Dilworth TJ. Early Administration of Adjuvant β-Lactam Therapy in Combination with Vancomycin among Patients with
Methicillin-Resistant Staphylococcus aureus Bloodstream Infection: A Retrospective, Multicenter Analysis. Pharmacotherapy. 2017;37(11):1347-56.

15. McCreary EK, Kullar R, Geriak M, Zasowski EJ, Rizvi K, Schulz LT, et al. Multicenter Cohort of Patients With Methicillin-Resistant Staphylococcus aureus Bacteremia Receiving Daptomycin Plus Ceftaroline Compared With Other MRSA Treatments. Open Forum Infect Dis. 2020;7(1):ofz538.

16. Kale-Pradhan PB, Giuliano C, Jongekrijg A, Rybak MJ. Combination of Vancomycin or Daptomycin and Beta-lactam Antibiotics: A Meta-analysis. Pharmacotherapy. 2020;40(7):64-88.

17. Davis JS, Sud A, O’Sullivan MVN, Robinson JO, Ferguson PE, Foo H, et al. Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial. Clin Infect Dis. 2016;62(2):173-80.

18. Tong SYC, Lye DC, Yahav D, Sud A, Robinson JO, Nelson J, et al. Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia: A Randomized Clinical Trial. Jama. 2020;323(6):527-37.

19. Geriak M, Haddad F, Rizvi K, Rose W, Kullar R, LaPlante K, et al. Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia. Antimicrob Agents Chemother. 2019;63(5).

20. Gandhi TN, Malani PN. Combination Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: Not Ready for Prime Time. Jama. 2020;323(6):515-6.

21. Guidelines for the treatment of staphylococcus aureus bacteremia. Detroit Medical Center. Updated September AA, 2021. 
https://www.dropbox.com/s/djhp7amff4gc2uk/S%20aureus%20bacteremia%20pathway.pdf?dl=0.

22. Hornak JP, Anjum S, Reynoso D. Adjunctive ceftaroline in combination with daptomycin or vancomycin for complicated methicillin-resistant Staphylococcus aureus bacteremia after monotherapy failure. Ther Adv Infect Dis. 2019;6:204936119886504.

23. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32.

24. Zacharioudakis IM, Zervou FN. Defining the Breakpoint Duration of Staphylococcus aureus Bacteremia Predictive of Poor Outcomes. Clin Infect Dis. 2020.

25. Paulsen J, Solligård E, Damås JK, DeWan A, Åsvold BO, Bracken MB. The Impact of Infectious Disease Specialist Consultation for Staphylococcus aureus Bloodstream Infections: A Systematic Review. Open Forum Infect Dis. 2016;3(2):ofw048.

26. Chesdachai S, Kline S, Helmin D, Rajasingham R. The Effect of Infectious Diseases Consultation on Mortality in Hospitalized Patients With Methicillin-Resistant Staphylococcus aureus, Candida, and Pseudomonas Bloodstream Infections. Open Forum Infect Dis. 2020;7(1):ofaa010.

27. Rose WE, Eickhoff JC, Shukla SK, Pantrangi M, Rooijakkers S, Cosgrove SE, et al. Elevated serum interleukin-10 at time of hospital admission is predictive of mortality in patients with Staphylococcus aureus bacteremia. J Infect Dis. 2012;206(10):1604-11.
28. Hawkins C, Huang J, Jin N, Noskin GA, Zembower TR, Bolon M. Persistent Staphylococcus aureus bacteremia: an analysis of risk factors and outcomes. Arch Intern Med. 2007;167(17):1861-7.
29. Rybak MJ, Vidaillac C, Sader HS, Rhomberg PR, Salimnia H, Briski LE, et al. Evaluation of vancomycin susceptibility testing for methicillin-resistant Staphylococcus aureus: comparison of Etest and three automated testing methods. J Clin Microbiol. 2013;51(7):2077-81.
30. Revolinski SL, Doern CD. Point-Counterpoint: Should Clinical Microbiology Laboratories Report Vancomycin Minimum Inhibitory Concentrations? J Clin Microbiol. 2021.
31. Liu J, Tong SYC, Davis JS, Rhodes NJ, Scheetz MH, Group tCS. Vancomycin exposure and acute kidney injury outcome: a snapshot from the CAMERA2 study. Open Forum Infectious Diseases. 2020.
32. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835-64.
33. Lodise TP, Drusano G. Vancomycin Area Under the Curve-Guided Dosing and Monitoring for Adult and Pediatric Patients With Suspected or Documented Serious Methicillin-Resistant Staphylococcus aureus Infections: Putting the Safety of Our Patients First. Clin Infect Dis. 2021.
34. Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician. 2008;78(6):743-50.
35. Finch NA, Zasowski EJ, Murray KP, Mynatt RP, Zhao JJ, Yost R, et al. A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity. Antimicrob Agents Chemother. 2017;61(12).
36. Navalkele B, Pogue JM, Karino S, Nishan B, Salim M, Solanki S, et al. Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin-Tazobactam Compared to Those on Vancomycin and Cefepime. Clin Infect Dis. 2017;64(2):116-23.
37. Woolf SH, Chapman DA, Sabo RT, Weinberger DM, Hill L, Taylor DDH. Excess Deaths From COVID-19 and Other Causes, March-July 2020. Jama. 2020;324(15):1562-4.
38. Centers for Disease Control and Prevention. Weekly counts of deaths by state and select causes -AD, 2020. https://data.cdc.gov/NCHS/Weekly-Counts-of-Deaths-by-State-and-Select-Causes/muzy-jte6.
Figure 2

BSI MRSA Patients from (12/2013 - 05/2020) (n=1155)

- Age less than 18 years old (n=10)
- Polymicrobial (n=150)
- Prisoner and/or pregnant women (n=13)

Anti-MRSA therapy duration <48 hours (n=162)

- Admission was from external cancer institute (n=7)

Eligible patients (n=813)

BSI: Blood stream infection, MRSA: Methicillin resistant Staphylococcus aureus
Figure 3

- 30-day Mortality: Pre-pathway 15.60%, Post-pathway 9.70%
P = 0.011
- 90-day Mortality: Pre-pathway 12.0%, Post-pathway 12.20%
P = 0.007
- Bacteremia duration > 120 Hours: Pre-pathway 24.50%, Post-pathway 21.80%
P = 0.362
- Nephrotoxicity: Pre-pathway 9.60%, Post-pathway 7.20%
P = 0.282
Figure 4

Patient who died from COVID-19 had been excluded from primary analysis (n=1)