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Effect of Infectious Disease Consultation on 30-Day Readmission Among Patients with *Staphylococcus aureus* Bacteremia

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By

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B.A., Colorado College, 2010

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An abstract of
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Abstract

Effect of Infectious Disease Consultation on 30-Day Readmission
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Staphylococcus aureus bacteremia (SAB), defined as the isolation of *S. aureus* from at least one blood culture from a symptomatic patient, is the second most common cause of hospital bloodstream infections and one of the leading causes of infective endocarditis. Infectious disease consultation (IDC) has been associated with improved SAB management and reduced mortality among patients with SAB, but few studies have examined the association with 30-day readmissions in this population. This study explored the association between IDC and 30-day all-cause hospital readmission in 939 index admissions with SAB admitted to two 500-bed academic medical centers between 2010 and 2014. In multivariate regression, IDC had a protective, but non-significant, effect against 30-day all-cause readmissions (adjusted odds ratio [aOR]: 0.9, 95% confidence interval [CI]: 0.7, 1.2). Delayed time to IDC (> 7 days) from positive culture result also had a deleterious, though non-significant, effect on readmissions compared to IDC within two days of positive culture (aOR: 1.5, 95% CI: 0.6, 4.1). In this study, a Charlson score of 3 or greater (aOR: 1.5, 95% CI: 1.1, 2.0), lymphoma (aOR: 3.1, 95% CI: 1.1, 8.3), low albumin (aOR: 1.5, 95% CI: 1.1, 2.1), and MRSA bacteremia (aOR: 1.5, 95% CI: 1.1, 2.0) were associated with readmission, while end-stage renal disease (ESRD), other types of cancer, liver disease, and community onset bacteremia were not. These data suggest that IDC may be protective for hospital readmission, but the observed relationship may be confounded by variables not measured in this population. Further studies should focus on improved measures of acuity to better assess the relationship of IDC to readmission.

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Chapter I: Background and Literature Review

Staphylococcus aureus bacteremia (SAB)

Staphylococcus aureus bacteremia, defined as the isolation of *S. aureus* from at least one blood culture from a symptomatic patient, is the second most common cause of hospital-onset bloodstream infections and the leading cause of infective endocarditis (IE).[1,2] The incidence of SAB is estimated to be between 15 and 40 cases per 100,000 population per year, and mortality rates for SAB range from 10-50%.[3-6] SAB can cause serious complications including infective endocarditis, valvular vegetation, osteomyelitis, septic arthritis, and death. The optimal, guideline-based management of SAB includes echocardiography, appropriate antibiotic therapy, repeat blood culture, and removal of infectious foci (where possible).[4] Because of the complexity of caring for patients with a seemingly simple infection (a positive blood culture with a common pathogen), expert care may provide additional benefit.

Infectious Disease Consultation (IDC)

Infectious disease physicians are trained in the diagnosis, treatment, and management of infections, including SAB. Infectious disease consult (IDC) has been shown to improve outcomes and enhance patient satisfaction in a variety of patients.[7] However, IDC rates among admissions with SAB are heterogeneous by time period and setting, ranging from 33% to over 90%.[3-6,8-19] The optimal timing of IDC also varies, as there is no accepted standard. One study found that among patients with an ID evaluation, 68% of consults were one within two days after a bacteremia diagnosis.[4] The timing of IDC relative to the positive culture may affect the current understanding of the effect of IDC on outcome.

IDC and SAB management

The literature shows a generally positive association between IDC and improved intermediate (process) outcomes, which include follow-up blood cultures, echocardiography, appropriate antimicrobial therapy, and removal of infectious foci. [4,20]

Follow-up blood cultures are used to document clearance of *S. aureus*. Twelve published studies found significant associations between IDC and follow-up blood cultures, with cultures occurring more frequently among admissions with consult.[4,8-10,13-16,18,19,21]

The Infectious Diseases Society of America (IDSA) guideline for methicillin-resistant *S. aureus* (MRSA), which is often extrapolated to methicillin-sensitive *S. aureus* (MSSA), recommends echocardiography for all patients with bacteremia.[20] Two types of echocardiography are used: transthoracic (TTE) and transesophageal (TEE). TEE is more sensitive for identifying endocarditis, but is more invasive and may not be appropriate for low-risk patients.[2] Eleven studies examined the prevalence of echocardiography in SAB patients, ten of these found significant differences between SAB cases with and without IDC.[3-5,8-10,15,16,18,19,21]

Studies examining the relationship between IDC and antimicrobial therapy, a cornerstone of SAB management, have demonstrated that consult is associated with appropriate antibiotic selection and duration. A meta-analysis of published literature found that appropriate antistaphylococcal agents were prescribed in 80.4% of cases with IDC, compared with 70.5% of those without IDC (risk ratio [RR]: 1.1, 95% CI: 1.1-1.2).[6] Of 12 studies that examined antibiotic duration, 10 found significant associations between IDC and appropriate duration of antibiotic treatment.[3-5,8-10,13-16,18,19,21-23]

Failure to remove infectious foci has the strongest association with mortality and relapse in SAB patients among management strategies.[22,24] The prevalence of removal of infectious foci and its association with IDC varied widely in the published literature, but the majority found that removal of infectious foci was higher among patients with ID evaluation than those without.[5,8,9,14-16,18,19,23]

Four studies examined the impact of IDC on adherence to SAB care bundles or complete IDSA guideline adherence. In addition to being more likely to receive individual care elements, all four studies found significant differences in care standard completion between patients with IDC and those without. Patients with ID consultation were more likely to receive the full bundle of care for SAB – between 74% and 89% - compared with those without ID consultation – between 40% and 64%.[11,13,15,19]

IDC and outcomes among patients with SAB

Existing studies of IDC for SAB show null to positive associations with patient outcomes. Most studies of IDC have assessed associations with mortality and/or recurrence, but few have examined readmission. Age, health, and organism factors have also been associated with outcomes among patients with SAB and may confound findings related to IDC.

Overall, studies have found protective effects of IDC against mortality among patients with SAB at short, mid-range, and long-term endpoints (Appendix Table 1). All seven studies examining IDC and in-hospital mortality have found protective effects, and the majority of those (five studies) found these effects to be significant.[3,4,8,13-15,18,25] Studies of one-week post-discharge mortality found similar protective effects.[8,10,17] Of nine studies examining IDC and 1-month mortality, six found a significant reduction in mortality among the IDC group compared to the non-IDC group.[5,8-10,17-19,23,26] Fewer data support the association between IDC and lower longer-

term mortality. Three studies found a significant protective association between 90-day mortality and ID consult while four others also showed protective, but non-significant, associations.[3,9,17,22,23,27]

Among seven studies investigating relapse or reinfection, only one showed a significant difference in relapse between IDC and non-IDC groups.[3,9,11,15,17,22,23] A meta-analysis of all seven studies found that the risk of relapse among patients with IDC was lower than that among patients without IDC (RR: 0.6, 95% CI: 0.4-1.0).[6]

Previously published associations between IDC and other outcomes (length of stay [LOS] and endocarditis) are varied. In six studies examining the association between LOS and IDC, only one found a significant difference in LOS between IDC and non-IDC groups.[4,9,10,14,19,23] Overall, rates of infective endocarditis were higher among patients with IDC than patients without consult, in part, because ID is usually called for more complicated, high-risk patients who are more likely to develop endocarditis. Three studies found a significant difference between the two groups while one study found a directionally similar, but non-significant difference.[10,14,15,22]

Many characteristics have been examined for their association with outcomes among patients with SAB, including demographic characteristics, underlying health indicators and conditions, and organism factors. Overall, studies indicate an association between older age and mortality and in SAB patients.[3,9,11,26,28] Studies of IDC and SAB patient outcomes have also found a correlation between underlying health, as indicated by aggregate scores (including Charlson Comorbidity Index), and patient outcomes.[9,11,18,26] The individual conditions examined by studies and their associations with SAB outcomes have been heterogeneous. Diabetes[26], cirrhosis[5,29], malignancy[5], peripheral vascular disease[5], immunosuppression[30], chronic renal failure[30], and steroid therapy[17,18] were all associated with mortality among SAB patients. The available

literature on organism attributes and their association with SAB patient outcomes is varied. Several studies found that methicillin resistance was not associated with relapse or mortality.[11,21,31] However, several other studies found a positive association between resistance and mortality.[3,9,32,33] The association between hospital-onset SAB and mortality is unclear with some studies finding a protective effect and others finding a null effect.[9,28,30,33]

Readmissions

Starting in 2012, the Centers for Medicare and Medicaid Services (CMS) implemented penalties via reduced reimbursement for hospitals with higher than expected 30-day readmission rates for certain conditions. Academic medical centers offering care for high acuity patients with limited insurance, such as the Emory hospitals, frequently suffer these financial penalties.[34] Because readmissions tax hospital resources and result in reductions in reimbursement, researchers have investigated ways to prevent readmissions. Leppin et al. identified 18 discharge-related interventions aimed at reducing readmissions.[35] Many researchers have developed models to attempt to predict readmissions, but most have "poor predictive ability."[36]

Despite the importance of hospital readmissions to both patient outcomes and hospital reimbursement, few studies have investigated the association between SAB-related IDC and readmission (Appendix Table 1). In part, this may be due to the length of time between completion of antibiotic therapy and relapse (median 36 days; range 10-190 d) and reinfection (median 99 days; range 45-194 d)[29] being beyond the 30-day readmission window considered by CMS. Nguyen et al. found that 30-day readmission rate decreased from 11.0% to 1.1% (p=0.008) when an IDC intervention was implemented for SAB patients.[19] Keller et al. found a protective but non-significant effect of IDC against 60-day, 30-day and 7-day all-cause readmissions.[37] Martin et al. found a null association between IDC and 30-day readmissions.[13]

Chapter II: Manuscript

Title: Effect of Infectious Disease Consultation on 30-Day Readmission Among Patients with *Staphylococcus aureus* Bacteremia

Authors: Laura M. King; Jesse T. Jacob, MD, MSc; Chad Robichaux, MPH

Abstract: *Staphylococcus aureus* bacteremia (SAB), defined as the isolation of *S. aureus* from at least one blood culture from a symptomatic patient, is the second most common cause of hospital bloodstream infections and one of the leading causes of infective endocarditis. Infectious disease consultation (IDC) has been associated with improved SAB management and reduced mortality among patients with SAB, but few studies have examined the association with 30-day readmissions in this population. This study explored the association between IDC and 30-day all-cause hospital readmission in 939 index admissions with SAB admitted to two 500-bed academic medical centers between 2010 and 2014. In multivariate regression, IDC had a protective, but non-significant, effect against 30-day all-cause readmissions (adjusted odds ratio [aOR]: 0.9, 95% confidence interval [CI]: 0.7, 1.2). Delayed time to IDC (> 7 days) from positive culture result also had a deleterious, though non-significant, effect on readmissions compared to IDC within two days of positive culture (aOR: 1.5, 95% CI: 0.6, 4.1). In this study, a Charlson score of 3 or greater (aOR: 1.5, 95% CI: 1.1, 2.0), lymphoma (aOR: 3.1, 95% CI: 1.1, 8.3), low albumin (aOR: 1.5, 95% CI: 1.1, 2.1), and MRSA bacteremia (aOR: 1.5, 95% CI: 1.1, 2.0) were associated with readmission, while end-stage renal disease (ESRD), other types of cancer, liver disease, and community onset bacteremia were not. These data suggest that IDC may be protective for hospital readmission, but the observed relationship may be confounded by variables not measured in this population. Further studies should focus on improved measures of acuity to better assess the relationship of IDC to readmission.

Introduction

Staphylococcus aureus bacteremia (SAB), defined as the isolation of *S. aureus* from at least one blood culture from a symptomatic patient, is the second most common cause of hospital-onset bloodstream infections and the leading cause of infective endocarditis (IE) in most parts of the world.[1,2] The management of SAB includes echocardiography, appropriate antibiotic therapy, repeat blood culture, and removal of infectious foci (where possible).[4]

Infectious disease consultation (IDC) has been shown to improve outcomes and enhance patient satisfaction in a variety of patients.[7] However, IDC rates are heterogeneous by time period and setting, ranging from 33% to over 90% of admissions with SAB.[3-6,8-19] Because of the complexity of caring for patients with a seemingly simple infection (a positive blood culture with a common pathogen), expert care may provide additional benefit in improving patient outcomes. IDC has been shown to have a protective effect against mortality in SAB patients, although its effect upon recurrence is less clear (Appendix Table 1).

Starting in 2012, the Centers for Medicare and Medicaid Services (CMS) implemented penalties via reduced reimbursement for hospitals with 30-day readmission rates over expected levels. As a result, hospitals have placed greater emphasis on understanding and preventing readmissions in recent years. Although several studies have examined the relationship between infectious disease consultation and mortality, few have examined the relationship between IDC and readmission. This study, conducted at Emory University Hospital (EUH) and EUH Midtown (EUHM), seeks to investigate the association between IDC and 30-day all-cause readmission among patients with positive SAB cultures during index admission between 2010 and 2014.

Methods

Study design

This study is a cohort study of adult inpatient admissions with at least one positive blood culture for *Staphylococcus aureus* between January 1, 2010 and December 31, 2014 at two 500-bed academic medical centers in Atlanta, GA. For patients with multiple admissions with positive *S. aureus* blood cultures, only the first such admission during the study period was considered the index admission. Data on patient demographics, clinical measures, infectious disease consult, and readmission were extracted from Emory Healthcare's Clinical Data Warehouse.

An admission was eligible for inclusion in the study if the patient was at least 18 years old at time of admission, was known to have survived past 30 days after discharge, had a length of stay greater than two days, and did not leave against medical advice (Figure 1). Survival through the 30-day post-discharge window was considered to have occurred if the patient had a visit at an Emory Healthcare facility 30 days or more after the index admission discharge date.

Definitions

Exposure

IDC, the exposure variable, was considered to have occurred during index admission if the admission record contained a note from any infectious disease provider (attending physician, advance practice provider, or fellow).

Primary outcome Thirty-day all-cause readmission was defined as an inpatient admission to one of the Emory hospitals within 30 days of index admission discharge. Emergency department visits not resulting in hospital admission were excluded.

Covariates

Race was categorized as Black, non-Black, or missing due to the sparsity of non-Black and non-White participants. Age at time of index admission was calculated using patient date of birth and index admission admit date. Age was dichotomized at 65 years.

Comorbidities were extracted from the medical electronic record using standard ICD-9 codes. When a comorbidity is a progression of another included in this study, only the most severe progression was considered to be present (e.g., mild liver disease and severe liver disease) for calculation of Charlson scores and logistic modeling. For modeling purposes, diabetes with and without complications were combined, however, for Charlson score calculations, they were kept separate.

Laboratory values (with the exception of hemoglobin) were categorized into high or low values reflecting extreme health conditions. Albumin values of 3.0 or below at admission was defined as low albumin. Low white blood cell count (WBC) was considered present if WBC was less than or equal to 4.2 x $10^3/\mu L$ and high WBC was considered present if WBC was greater than or equal to x $10^3/\mu L$. Hemoglobin was treated as a continuous variable.

Community-onset SAB was defined as a positive culture collected within 3 days of the admit date (including if positive culture was collected prior to admission), while hospital-onset was defined as SAB occurring after day 3 of admission.

Statistical analyses

Categorical variables were compared between exposure groups using the Pearson χ^2 test and continuous variables were compared using the Mann-Whitney Test. Bivariate logistic regression was conducted to estimate the association between all potential confounders and IDC and all

potential confounders and readmission. Potential confounders that were associated with both IDC and readmission in bivariate analyses were included in multivariate logistic regression models. Variables were also included in the model if previous studies and/or clinical experience suggested they were associated with the exposure and outcome.

Four different multivariate logistic models were fit to assess the best model for the study data (Appendix Table 2). Models varied by continuous versus categorical age and individual comorbidities versus Charlson score. Each model was fit for the entire study population and then again stratified by hospital to evaluate if estimates varied by facility since the patient populations at the two hospitals were potentially different. Collinearity was assessed with condition indices over 30 and Variance Decomposition Proportions over 0.5 as thresholds. Variables that exceeded these thresholds were evaluated for removal in order to improve the stability and reliability of the model. Likelihood ratio "chunk tests" and backwards elimination were used to test for significant interaction in each model. Confounding was then assessed using a backwards change in estimate approach. The Hosmer-Lemeshow and c-statistic (area under the ROC curve) were used to identify goodness of fit. Variables were retained in the models if dropping them resulted in a greater than 10% change in estimate from the "gold standard" model or if their inclusion improved model fit. Statistical analyses were conducted at the alpha=0.05 level. All analyses were performed using SAS 9.4 (Cary, NC).

Results

Study population

There were 1621 admissions with a positive *Staphylococcus aureus* bacteremia culture, 939 of which met the inclusion criteria of this study (Figure 1). Fifty-five percent of eligible admissions had an infectious disease consult during admission (Table 1, Figure 2). The median age at time of

index admission was 56.8 years and 31% of the study population was over 65 (Table 1). The majority of the study population, 63%, was black; among those with IDC, 55% were black compared with 74% among those who did not receive IDC. Over the study period, the total number of admissions with SAB decreased while the number of SAB admissions with IDC increased (Figure 1).

Overall, the most common comorbidity was diabetes (38%) followed by end stage renal disease (ESRD, 34%) and congestive heart failure (CHF, 31%) (Table 1). The proportion of patients with diabetes was similar between the IDC and non-IDC groups, however the proportions of patients with ESRD (24% vs. 45%, respectively) and CHF (35% vs. 27%) varied. Over half of all patients (58%) had a Charlson score of three or above. Less than 10% of patients had no comorbidities. At admission, 55% of patients had low albumin values (<3.0 g/dL) and 62% had high ($\geq$ 9.1 x $10^3/\mu L$) white blood cell counts. Almost half (47%) of admissions had SAB resistant to oxacillin. This proportion was similar in both groups. During the study period, the number of MSSA bacteremia cases decreased, while the number of MRSA cases increased (Appendix Figure 1). The majority of cases (82%) of SAB were community onset (Table 1).

The median length of stay was 11 days (IQR: 7-19 d). The proportion of admissions with an ICU stay was higher among those with IDC (45%) than among those without IDC (36%). Overall, 20% of admissions had endocarditis; this proportion was higher among those with IDC (25%) compared with those without IDC (15%). Ventilator and vasopressor use was also higher in the IDC group. The majority of patients (67%) were discharged home. Among those with IDC, 23% were discharged to a nursing home compared to 17% among those without IDC. Almost all (97%) of the patients with ID consult underwent echocardiography, compared with 76% among those without IDC. Transesophageal echocardiography was also more frequent in the IDC group. Every patient had at least one follow-up blood culture. Eighty-seven percent of the patients with

IDC had at least one negative follow-up culture compared to 74% of patients without IDC, a significant difference.

Age, race, health indicators, community-onset SAB, and IDC distribution differed significantly between EUH and EUHM (Appendix Table 3). Overall the population at EUHM was younger than at EUH (median age 55.1 vs. 58.4) and more patients were black (80% vs. 46%) at EUHM. Over 64% of patients at EUHM had a Charlson score of three or more compared with 52% at EUH. ESRD, diabetes, and hemiplegia were significantly more frequent at EUHM, while all forms of cancer and severe liver disease were significantly more prevalent among SAB patients at EUH. IDC was provided significantly less frequently at EUHM (52%) compared with EUH (59%, p=0.03).

Association of IDC, readmission, and covariates

In both bivariate and multivariate analyses, IDC was not significantly protective against 30-day all-cause readmission (Table 2). Among those with IDC during index admission, the odds of experiencing a readmission within 30 days were 0.90 times those among patients without IDC during index admission (aOR: 0.9, 95% CI: 0.7, 1.2). In bivariate analyses, Charlson score ≥ 3, ESRD, leukemia, lymphoma, tumor, low albumin, and MRSA were significantly associated with readmission. Only lymphoma (aOR: 3.1, 95% CI: 1.1, 8.3), low albumin (aOR: 1.5, 95% CI: 1.1, 2.1), and MRSA (aOR: 1.5, 95% CI: 1.1, 2.0) showed significant associations with readmission in the multivariate model with individual comorbidities and Charlson score ≥ 3 was associated with readmission in the multivariate model with Charlson score and no individual comorbidities (aOR: 1.5, 95% CI: 1.1, 2.0).

Several intermediary outcomes were associated with IDC (Table 3). The odds of IDC among those with endocarditis was almost twice the odds among those without endocarditis (OR: 1.9,

95% CI: 1.3, 2.6). Patients with at least one overnight stay in the ICU had odds of IDC 1.5 times those without an ICU stay (OR: 1.4, 95% CI: 1.1, 1.9). The odds of any form of echocardiograph was 9.9 times higher among those with IDC than among those without IDC (OR: 9.9, 95% CI: 5.7, 17.1). However, the associations of all intermediary outcomes and readmission were not statistically significant.

Among those with IDC, most patients (54%) were seen prior to positive culture results for SAB (Table 4). In general, IDC and positive culture results occurred within a short time period (Figure 3); 31% of patients with IDC had the consult within 2 days of positive culture, 10% between 3-7 days after positive culture, and 5% more than 7 days after positive culture. The longest time between positive culture and subsequent IDC was 35 days (Table 4). The overall distribution of time between positive culture result and IDC was similar between EUH and EUHM (Appendix Figure 2), with most consults occurring around the same time as culture results.

Readmissions were highest for all admissions during the first three days following discharge (Figures 4 and 5). In this period, the proportion of patients with readmission was higher among those with IDC during index admission than among those without IDC (Figure 4). Overall, the "survival" probability for time to readmission was similar for both individuals with IDC and those without IDC (p-value for Log-Rank test: 0.44, Figure 5).

Discussion

In our study of 939 admissions with SAB, we found that IDC was associated with lower odds of 30-day all-cause readmission. Likewise, delayed time to IDC had a deleterious, though non-significant, effect on readmissions, though neither of these associations achieved statistical significance. Previous studies have found rates of 30-day readmission among SAB patients

ranging from 11%[19,31] to 41%[37]. Almost 30% of our study population experienced a readmission event. The high rate of readmissions in our population may have been due to the high frequency of comorbidities in our population, with over 90% having at least one comorbid condition. Few individual health conditions were significantly associated with readmission in bivariate and multivariate regression. Rather than a single condition contributing to readmission, multiple comorbidities together may increase the risk of readmission in this study. A Charlson score of three or above, indicating at least two comorbid conditions, was significantly associated with readmission in both bivariate and multivariate analyses. Previous studies by Choi et al. and Saunderson et al. found similar associations between Charlson scores over three and adverse outcomes (mortality or relapse) in SAB patients.

Among those who had an IDC, longer time to consult after positive culture result verification was associated with higher odds of readmission. Although this association is non-significant, the step-wise increase in bivariate risk seems to indicate at least a directional association between how quickly an IDC intervention occurs and patient outcomes. The adjusted estimates indicate that early intervention prior to culture verification has a protective effect against readmission. Interestingly, there seems to be little difference between IDC within the first 2 days after culture result and within 3-7 days after culture result. However, after 7 days the odds of readmission increase with delayed treatment. In our study, IDC was strongly associated with echocardiographs and other studies have found an association between IDC and appropriate antibiotic use.[3-5,9,15,17,18,21] Early use of appropriate treatments and interventions in the IDC group may decrease the risk of readmission.

Previous studies have demonstrated that IDC is associated with adherence to SAB management strategies.[11,13,15,19] In this study, the only management strategies we were able to observe via administrative data were echocardiographs (TTE and TEE) and follow-up culture. We observed

an almost ten-fold increase in the odds of echocardiograph among patients with IDC compared to patients without IDC. Both the odds of TEE and TEE were higher among those with IDC, with a greater increase in TTE. Previous studies have similarly found significant differences between IDC and non-IDC groups in echocardiography.[3-5,8-10,15,16,18,19,21] There was a significant association between endocarditis and IDC, which may be partially attributable both to ID being called for complex cases with endocarditis and the higher use of echocardiography among patients with IDC and resultant ability to diagnose endocarditis. However, the association between endocarditis and readmission was null and the association between echocardiography and readmission was also non-significant. Negative follow-up culture was associated with IDC (OR: 1.3; 95% CI: 0.9, 1.9). More frequent documented clearance of *S. aureus* from the bloodstream among those with ID evaluation may be related to enhanced adherence to other management strategies in IDC group, but that relationship could not be evaluated in this study.

Low albumin was also associated with readmission (aOR: 1.5, 95% CI: 1.1, 2.1). Low albumin can be caused by many acute and chronic conditions including liver disease, kidney disease, cancer, and diabetes, and so may also serve to some extent as an aggregate measure of underling health. Lymphoma was the only individual comorbidity that was significantly associated with 30-day readmission (aOR: 3.1, 95% CI: 1.1, 8.3). This may be related both to the natural history of the disease and to planned readmissions for lymphoma patients.

In this study, ESRD appeared protective against readmission in both bivariate and multivariate analyses. This was unexpected given the high-risk nature of these patients who frequently have multiple comorbidities and often have central venous catheters, a risk factor for *S. aureus* bloodstream infections and relapse. Typically, readmission rates are higher among ESRD patients compared to non-ESRD patients;[38] a 2007 study by Troidle et al. found that 24% of hemodialysis patients with SAB experience readmission.[39] The protective effect of ESRD against readmissions

in our study may be due to treatment protocols for ESRD patients. Vancomycin is often used as a first-line treatment for SAB among patients with ESRD.[40] Given the high prevalence of MRSA in our study population, this tendency to treat ESRD patients with fever using empiric vancomycin (which is effective against MRSA) may provide this group with improved outcomes compared to others in the population who may not receive the appropriate antistaphylococcal agent as quickly. The apparent protective nature of ESRD against readmission among SAB patients may also be the result of index event bias. Index event bias occurs when a disease, in this case SAB, is used as the index event that defines a target population for study of another outcome. Risk factors for the selection disease may then show "reverse" associations with the end outcome due to stratifying on a collider by selecting the population with disease.[41,42]

Even though the populations at EUH and EUHM were demographically dissimilar, readmissions were similar across hospitals. This suggests that factors other than demographics may be more important in patient outcomes. In previous studies, both age and sex have been associated with unfavorable outcomes in SAB patients.[3,9,11,26,28] In multivariate analysis in this study, older age had a protective but non-significant effect, which may also be related to index event bias as discussed previously.

Almost half of the SAB cases were due to MRSA. This may contribute to the higher than expected readmission rate observed in this study population as MRSA was significantly associated with 30-day readmission (aOR: 1.5, 95% CI: 1.1, 2.0). Previous studies on mortality and relapse in SAB patients have found that MRSA is significantly associated with unfavorable patient outcomes.[3,9,32,33] Our findings indicate that this association extends to hospital readmissions.

This study had several important limitations. These limitations could result in potential misclassification bias, unmeasured confounding, and errors in the estimation of readmissions. One of the largest limitations was the use of administrative data in order to estimate clinical effect.[43] IDC and dichotomous covariates were noted as present if they were listed within the admission record. If physician notes (in the case of IDC) or ICD-9 codes (in the case of covariates) were not present, we had to assume that the elements that they represent were absent from the admission. This may lead to misclassification bias related to both the exposure and confounding variables and underestimation of IDC and comorbidities. In addition, although all providers use ICD-9 codes to document clinical conditions as part of billing, the specificity of coding practices may vary. As a result, comorbidities may be misclassified, particularly conditions that lie on a spectrum (e.g., renal disease and end-stage renal disease).

The method of ascertaining readmissions was also a limitation that could lead to misclassification bias of the outcome. Readmission was considered to have occurred if a patient was readmitted to a hospital in the healthcare system, but would not capture patients re-admitted outside the healthcare system. This may be especially important since individuals may come to Emory if they are in need of advanced or specialized care during their index admission but then may return to a different hospital for a less serious readmission. This could lead us to underestimate the number of readmissions. However, given the high rate of readmissions observed in this study, this is not likely to be a major factor. Additionally, all-cause 30-day readmission was assessed because it was not feasible to account for planned admissions (chemotherapy, planned surgical procedure etc.). In our data, we are unable to distinguish between planned readmissions/observation stays and unplanned readmissions. This may lead us to overestimate the number of unplanned readmissions.

The study was limited to patients with a visit to any Emory facility (including physicians, outpatient clinics, hospitals, and dialysis centers) 30 days or more after index admission discharge. We limited the study in this way to exclude patients who died during the 30-day discharge window and so were not at risk for the full period. This selection criterion has the potential to exclude healthier individuals who do not have another healthcare encounter at an Emory facility. This could bias our estimates of readmission upwards as we exclude healthy individuals with no readmissions and could also bias our population towards those with more comorbidities who would utilize Emory healthcare services, such as dialysis clinics, chemotherapy infusion clinics, and specialty physicians. We know that some automatically generated lab reports were counted as an Emory encounter for the purposes of including patients in the study. If a patient actually expired during the 30-day discharge period but an automatically generated report tied to their Emory patient ID was generated, they would have been erroneously included in our study.

There is also likely unmeasured confounding from additional sources. Using administrative data, we were unable to identify the severity of bacteremia or acuity of illness, which could be an important confounder. In addition, other health conditions, such as use of steroids and immune-suppression, associated with adverse outcomes in SAB patients in previous studies, were not considered here.

Because readmissions will continue to be a focus for years to come, an understanding the factors that contribute to readmissions among SAB patients, a vulnerable population, is necessary. This study is one of the largest studies of IDC among patients with SAB, examines readmissions, an understudied outcome, and includes a sample of demographically diverse patients from two hospitals. Our study shows that IDC is protective against readmission, but not significantly so. Early IDC intervention appeared protective while delayed consult appeared to increase the odds

of readmission. Further studies should focus on improved measures of acuity to better assess the relationship of IDC to readmission.

References

1. Buitron de la Vega P, Tandon P, Qureshi W, et al. Simplified risk stratification criteria for identification of patients with MRSA bacteremia at low risk of infective endocarditis: implications for avoiding routine transesophageal echocardiography in MRSA bacteremia. *Eur J Clin Microbiol Infect Dis.* 2016;35(2):261-268.
2. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, et al. Clinical management of Staphylococcus aureus bacteraemia. *Lancet Infect Dis.* 2011;11(3):208-222.
3. Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation--a study of 521 patients in Germany. *J Infect.* 2009;59(4):232-239.
4. 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(10):1451-1461.
5. Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK. The value of infectious diseases consultation in Staphylococcus aureus bacteremia. *Am J Med.* 2010;123(7):631-637.
6. Vogel M, Schmitz RP, Hagel S, et al. Infectious disease consultation for Staphylococcus aureus bacteremia - A systematic review and meta-analysis. *J Infect.* 2016;72(1):19-28.
7. Petrak RM, Sexton DJ, Butera ML, et al. The value of an infectious diseases specialist. *Clin Infect Dis.* 2003;36(8):1013-1017.
8. Tissot F, Calandra T, Prod'hom G, et al. Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality. *J Infect.* 2014;69(3):226-234.
9. Saunderson RB, Gouliouris T, Nickerson EK, et al. Impact of routine bedside infectious disease consultation on clinical management and outcome of Staphylococcus aureus bacteraemia in adults. *Clin Microbiol Infect.* 2015;21(8):779-785.
10. Robinson JO, Pozzi-Langhi S, Phillips M, et al. Formal infectious diseases consultation is associated with decreased mortality in Staphylococcus aureus bacteraemia. *Eur J Clin Microbiol Infect Dis.* 2012;31(9):2421-2428.
11. Pragman AA, Kuskowski MA, Abraham JM, Filice GA. Infectious Disease Consultation for Staphylococcus aureus Bacteremia Improves Patient Management and Outcomes. *Infect Dis Clin Pract (Baltim Md).* 2012;20(4):261-267.
12. Nguyen OK, Makam AN, Clark C, et al. Predicting all-cause readmissions using electronic health record data from the entire hospitalization: Model development and comparison. *J Hosp Med.* 2016;11(7):473-480.
13. Martin L, Harris MT, Brooks A, Main C, Mertz D. Management and outcomes in patients with Staphylococcus aureus bacteremia after implementation of mandatory infectious diseases consult: a before/after study. *BMC Infect Dis.* 2015;15:568.
14. Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from Staphylococcus aureus bacteremia. *Medicine (Baltimore).* 2009;88(5):263-267.
15. 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(7):1000-1008.
16. Fries BL, Licitra C, Crespo A, et al. Infectious diseases consultation and the management of Staphylococcus aureus bacteremia. *Clin Infect Dis.* 2014;58(4):598-599.
17. Forsblom E, Ruotsalainen E, Ollgren J, Jarvinen A. Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus Bacteremia. *Clin Infect Dis.* 2013;56(4):527-535.

18. Choi SH, Cho SY, Park JH, Chung JW. Impact of infectious-disease specialist consultations on outcomes of Staphylococcus aureus bacteremia in a hospital with a low volume of patients with S. aureus bacteremia. *J Infect.* 2011;62(2):181-185.
19. Nguyen CT, Gandhi T, Chenoweth C, et al. Impact of an antimicrobial stewardship-led intervention for Staphylococcus aureus bacteraemia: a quasi-experimental study. *J Antimicrob Chemother.* 2015;70(12):3390-3396.
20. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin Infect Dis.* 2011;52(3):285-292.
21. Nagao M, Iinuma Y, Saito T, et al. Close cooperation between infectious disease physicians and attending physicians can result in better management and outcome for patients with Staphylococcus aureus bacteraemia. *Clin Microbiol Infect.* 2010;16(12):1783-1788.
22. Fowler VG, Jr., Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis.* 1998;27(3):478-486.
23. Saunderson RB, Gouliouris T, Cartwright EJ, et al. Impact of infectious diseases consultation on the management of Staphylococcus aureus bacteraemia in children. *BMJ Open.* 2014;4(7):e004659.
24. Jensen AG, Wachmann CH, Espersen F, Scheibel J, Skinhoj P, Frimodt-Moller N. Treatment and outcome of Staphylococcus aureus bacteremia: a prospective study of 278 cases. *Arch Intern Med.* 2002;162(1):25-32.
25. Paulsen J, Solligard E, Damas JK, DeWan A, Asvold 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. Mylotte JM, Tayara A. Staphylococcus aureus bacteremia: predictors of 30-day mortality in a large cohort. *Clin Infect Dis.* 2000;31(5):1170-1174.
27. Pastagia M, Kleinman LC, Lacerda de la Cruz EG, Jenkins SG. Predicting risk for death from MRSA bacteremia. *Emerg Infect Dis.* 2012;18(7):1072-1080.
28. Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. Staphylococcus aureus bacteraemia--Nationwide assessment of treatment adequacy and outcome. *J Infect.* 2011;62(5):339-346.
29. Chang FY, Peacock JE, Jr., Musher DM, et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore).* 2003;82(5):333-339.
30. Kaech C, Elzi L, Sendi P, et al. Course and outcome of Staphylococcus aureus bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. *Clin Microbiol Infect.* 2006;12(4):345-352.
31. Baxi SM, Clemenzi-Allen A, Gahbauer A, et al. Vancomycin MIC Does Not Predict 90-Day Mortality, Readmission, or Recurrence in a Prospective Cohort of Adults with Staphylococcus aureus Bacteremia. *Antimicrob Agents Chemother.* 2016;60(9):5276-5284.
32. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. *Lancet Infect Dis.* 2014;14(10):967-975.
33. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in Staphylococcus aureus bacteremia. *Infect Control Hosp Epidemiol.* 1998;19(1):32-37.
34. Joynt KE, Jha AK. Characteristics of hospitals receiving penalties under the Hospital Readmissions Reduction Program. *Jama.* 2013;309(4):342-343.

35. Leppin AL, Gionfriddo MR, Kessler M, et al. Preventing 30-day hospital readmissions: a systematic review and meta-analysis of randomized trials. *JAMA Intern Med.* 2014;174(7):1095-1107.
36. Kansagara D, Englander H, Salanitro A, et al. Risk prediction models for hospital readmission: a systematic review. *Jama.* 2011;306(15):1688-1698.
37. Keller SC, Ciuffetelli D, Bilker W, et al. The Impact of an Infectious Diseases Transition Service on the Care of Outpatients on Parenteral Antimicrobial Therapy. *J Pharm Technol.* 2013;29(5):205-214.
38. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med.* 2009;360(14):1418-1428.
39. Troidle L, Eisen T, Pacelli L, Finkelstein F. Complications associated with the development of bacteremia with Staphylococcus aureus. *Hemodial Int.* 2007;11(1):72-75.
40. Chan KE, Warren HS, Thadhani RI, et al. Prevalence and Outcomes of Antimicrobial Treatment for Staphylococcus aureus Bacteremia in Outpatients with ESRD. *J Am Soc Nephrol.* 2012;23(9):1551-1559.
41. Dahabreh IJ, Kent DM. Index event bias: an explanation for the paradoxes of recurrence risk research. *Jama.* 2011;305(8):822-823.
42. Flanders WD, Eldridge RC, McClellan W. A nearly unavoidable mechanism for collider bias with index-event studies. *Epidemiology.* 2014;25(5):762-764.
43. Iezzoni LI. Using administrative diagnostic data to assess the quality of hospital care. Pitfalls and potential of ICD-9-CM. *International journal of technology assessment in health care.* 1990;6(2):272-281.

Tables

Table 1. Characteristics of index admissions with *S. aureus* bacteremia (SAB), 2010-2014

Characteristic	*No. (%) or median (IQR)*			*p*
	IDC N = 518	**Non-IDC N = 421**	**Total N = 939**	
Demographics				
Age, years	57.4 (46.5 - 68.0)	56.6 (44.7 - 67.1)	56.8 (45.3 - 67.5)	0.58
Age > 65 years	160 (30.9%)	131 (31.1%)	291 (31.0%)	0.94
Female	216 (41.7%)	198 (47.0%)	414 (44.1%)	0.10
Race				<0.001
White	218 (43.9%)	103 (25.4%)	321 (35.6%)	
Black	271 (54.5%)	298 (73.6%)	569 (63.1%)	
Other	8 (1.6%)	4 (1.0%)	12 (1.3%)	
Hospital				0.03
EUHM	240 (46.3%)	226 (53.7%)	466 (49.6%)	
EUH	278 (53.7%)	195 (46.3%)	473 (50.4%)	
Comorbidities and laboratory findings				
Charlson score	3 (2 - 5)	3 (2 - 5)	3 (2 - 5)	0.20
Charlson score ≥ 3	287 (55.4%)	259 (61.5%)	546 (58.2%)	0.06
End-Stage Renal Disease	125 (24.1%)	190 (45.1%)	315 (33.6%)	<0.001
Renal Disease	45 (8.7%)	11 (2.6%)	56 (6.0%)	<0.001
Any diabetes	197 (38.0%)	158 (37.5%)	355 (37.8%)	0.88
Diabetes w/ comp.	79 (15.3%)	72 (17.1%)	151 (16.1%)	0.44
Diabetes w/o comp.	118 (22.8%)	86 (20.4%)	204 (21.7%)	0.39
Leukemia	8 (1.5%)	19 (4.5%)	27 (2.9%)	0.01
Lymphoma	10 (1.9%)	11 (2.6%)	21 (2.2%)	0.48
Metastatic Solid Tumor	29 (5.6%)	28 (6.7%)	57 (6.1%)	0.50
Tumor	84 (16.2%)	73 (17.3%)	157 (16.7%)	0.65
Myocardial Infarction	42 (8.1%)	29 (6.9%)	71 (7.6%)	0.48
Congestive heart failure	179 (34.6%)	112 (26.6%)	291 (31.0%)	0.01
Cerebrovascular disease	66 (12.7%)	58 (13.8%)	124 (13.2%)	0.64
Peripheral disease	46 (8.9%)	38 (9.0%)	84 (9.0%)	0.94
Chronic pulmonary disease	100 (19.3%)	58 (13.8%)	158 (16.8%)	0.02
Severe liver disease	18 (3.5%)	6 (1.4%)	24 (2.6%)	0.048
Mild liver disease	16 (3.1%)	12 (2.9%)	28 (3.0%)	0.83
Dementia	15 (2.9%)	14 (3.3%)	29 (3.1%)	0.71
Peptic Ulcer Disease	13 (2.5%)	9 (2.1%)	22 (2.3%)	0.14
Connective tissue disorder	36 (7.0%)	24 (5.7%)	60 (6.4%)	0.44
Hemiplegia	15 (2.9%)	8 (1.9%)	23 (2.5%)	0.33
HIV	47 (9.1%)	18 (4.3%)	65 (6.9%)	0.004
Transplant	71 (13.7%)	55 (13.1%)	126 (13.4%)	0.77
White blood cell count				
Low (<4.2)*	31 (6.0%)	31 (7.4%)	62 (6.6%)	0.40
High (>9.1)**	327 (63.1%)	256 (60.8%)	583 (62.1%)	0.47
Low albumin (<3) †	296 (57.9%)	212 (51.6%)	508 (55.1%)	0.05
Hemoglobin	6.0 (5.3-7.4)	5.9 (5.3-6.8)	6.0 (5.3-7.2)	0.58
Methicillin-resistance‡	254 (49.1%)	187 (44.7%)	441 (47.2%)	0.18
Community onset §	431 (83.2%)	337 (80.0%)	768 (81.8%)	0.21

Characteristic	*No. (%) or median (IQR)*			*p*
	IDC N = 518	**Non-IDC N = 421**	**Total N = 939**	
Clinical indicators				
Length of stay	13 (8-21)	10 (7-17)	11 (7-19)	0.19
ICU stay	232 (44.8%)	150 (35.6%)	382 (40.7%)	0.004
Endocarditis	127 (24.5%)	62 (14.7%)	189 (20.1%)	<0.001
Ventilator use	92 (17.8%)	35 (8.3%)	127 (13.5%)	<0.001
Vasopressor given	167 (32.2%)	96 (22.8%)	263 (28.0%)	0.001
Discharge disposition				0.004
Home	339 (65.4%)	294 (69.8%)	633 (67.4%)	
Nursing home	121 (23.4%)	70 (16.6%)	191 (20.3%)	
Hospice	22 (4.3%)	31 (7.4%)	53 (5.6%)	
Rehab	28 (5.4%)	13 (3.1%)	41 (4.4%)	
Other hospital	8 (1.5%)	13 (3.1%)	21 (2.2%)	
SAB management				
Echocardiography	502 (96.9%)	320 (76.0%)	822 (87.5%)	<0.001
Transthoracic	442 (85.3%)	283 (67.2%)	725 (77.2%)	<0.001
Transesophageal	298 (57.5%)	142 (33.7%)	440 (46.9%)	<0.001
Any follow-up culture	518 (100.0%)	421 (100.0%)	939 (100.0%)	-
Negative follow-up culture	449 (86.7%)	312 (74.1%)	761 (81.0%)	<0.001

* White blood cell count $\leq 4.2 \times 10^3/\mu L$ at admission

** White blood cell count ($\geq 9.1 \times 10^3/\mu L$ at admission

† Albumin value < 3.0 g/dL at admission

‡ Methicillin resistant ≥ 1 susceptibility reading resistant to oxacillin

§ Positive blood culture collected within 3 days of admission

Table 2. Bivariate and multivariate associations of exposure and covariates and 30-day all-cause readmission following index admission with *S. aureus* bacteremia (SAB), 2010-2014

	Odds Ratio (95% CI)	
Variable	**Bivariate**	**Multivariate**
Infectious Disease Consult	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[A]
Age over 65 years old	0.8 (0.5, 1.0)	0.7 (0.5, 1.0) [A]
Female	1.2 (0.9, 1.7)	1.3 (0.9, 1.7) [A]
Black Race	0.9 (0.7, 1.2)	1.0 (0.7, 1.5) [A]
Hospital	0.8 (0.6, 1.0)	1.0 (0.7, 1.3) [A]
Charlson score ≥ 3	1.4 (1.1, 1.9)	1.5 (1.1, 2.0) [B]
Dialysis	1.0 (0.8, 1.2)	-
End-Stage Renal Disease	0.7 (0.5, 0.9)	0.8 (0.5, 1.1) [A]
Renal Disease	1.3 (0.7, 2.3)	-
Any diabetes	0.9 (0.6, 1.1)	-
Diabetes w/ comp.	0.9 (0.6, 1.3)	-
Diabetes w/o comp.	0.9 (0.6, 1.2)	-
Leukemia	2.7 (1.3, 5.9)	1.6 (0.6, 4.0) [A]
Lymphoma	5.1 (2.0, 12.8)	3.1 (1.1, 8.3) [A]
Metastatic Solid Tumor	1.7 (1.0, 3.0)	-
Tumor	1.9 (1.3, 2.7)	1.3 (0.9, 2.1) [A]
Myocardial infarction	0.8 (0.4, 1.3)	-
Congestive Heart Failure	0.9 (0.7, 1.2)	-
Cerebrovascular disease	1.4 (0.9, 2.1)	-
Peripheral disease	1.0 (0.6, 1.6)	-
Chronic pulmonary disease	1.4 (1.0, 2.0)	-
Severe liver disease	1.2 (0.5, 2.9)	1.1 (0.4, 2.8) [A]
Mild liver disease	1.4 (0.6, 3.0)	-
Dementia	0.9 (0.4, 2.1)	-
Peptic Ulcer Disease	1.4 (0.6, 3.4)	-
Connective tissue disorder	1.1 (0.6, 2.0)	-
Hemiplegia	1.6 (0.7, 3.7)	-
HIV	1.3 (0.7, 2.2)	-
Transplant	1.2 (0.8, 1.7)	-
Low WBC*	1.5 (0.9, 2.5)	-
High WBC**	0.9 (0.7, 1.2)	-
Low albumin†	1.6 (1.2, 2.1)	1.5 (1.1, 2.1) [A]
Hemoglobin	1.0 (0.9, 1.1)	-
MRSA‡	1.4 (1.1, 1.9)	1.5 (1.1, 2.0) [A]
Community onset SAB§	0.7 (0.5, 1.0)	0.9 (0.6, 1.3) [A]

* White blood cell count ≤ 4.2 x 10^3/μL at admission

** White blood cell count (≥ 9.1 x 10^3/μL at admission

† Albumin value less than 3.0 g/dL at admission

‡ Methicillin Resistant ≥ 1 susceptibility reading resistant to oxacillin

§ Positive culture collected within 3 days of admission

[A] In a model with IDC, age over 65, black race, sex, MRSA, Community onset SAB, hospital, severe liver disease, ESRD, leukemia, lymphoma, tumor, and low albumin

[B] In a model with IDC, age over 65, black race, sex, hospital, Charlson score ≥3 MRSA, Community onset SAB

Table 3. Bivariate association of secondary/intermediary outcomes with infectious disease consultation (IDC) and 30-day readmission following index admission with *S. aureus* bacteremia, 2010-2014

	Odds Ratio (95% CI)	
Variable	**IDC**	**30-day Readmission**
Ventilator	2.4 (1.6, 3.6)	0.9 (0.6, 1.3)
Endocarditis	1.9 (1.3, 2.6)	1.0 (0.7, 1.4)
Vasopressor use	1.6 (1.2, 2.2)	1.1 (0.8, 1.5)
Intensive care unit stay	1.5 (1.1, 1.9)	1.3 (1.0, 1.7)
Echocardiography	9.9 (5.7, 17.1)	1.2 (0.8, 1.9)
Transthoracic	2.8 (2.1, 3.9)	1.2 (0.8, 1.7)
Transesophageal	2.7 (2.0, 3.5)	1.1 (0.8, 1.4)
Negative follow-up culture	1.3 (0.9, 1.9)	2.3 (1.6, 3.2)

Table 4. Association of time from positive culture to infectious disease consult (IDC) and 30-day all-cause readmission following index admission with *S. aureus* bacteremia evaluated by an infectious disease (ID) physician, 2010-2014

Days from positive culture to IDC	**N (%)**	**OR (95% CI)**	**aOR (95% CI)[A]**
Prior to culture results	282 (54.4%)	1.0 (0.7, 1.6)	0.8 (0.5, 1.3)
Within 2 days	158 (30.5%)	Ref.	Ref.
3-7 days	54 (10.4%)	1.2 (0.6, 2.4)	1.0 (0.5, 2.0)
>7 days	24 (4.6%)	1.3 (0.5, 3.4)	1.5 (0.6, 4.1)

[A] In a model with age over 65, black race, sex, MRSA, community acquired SAB, hospital, severe liver disease, ESRD, leukemia, lymphoma, tumor, and low albumin

Table 5. Association of infectious disease (ID) physician affiliation and 30-day all-cause readmission following index admission with *S. aureus* bacteremia evaluated by an ID physician at Emory University Hospital Midtown (EUHM), 2010-2014

ID Physician Affiliation	**N (%)**	**OR (95% CI)**	**aOR (95% CI)[A]**
Emory	212 (88.3%)	1.5 (0.6, 3.7)	1.1 (0.4, 3.1)
Non-Emory	28 (11.7%)	Ref.	Ref.

[A] In a model with age over 65, black race, sex, MRSA, community acquired SAB, hospital, severe liver disease, ESRD, leukemia, lymphoma, tumor, and low albumin

Figures

Figure 1. Selection criteria for study in patients with *S. aureus* bacteremia (SAB)

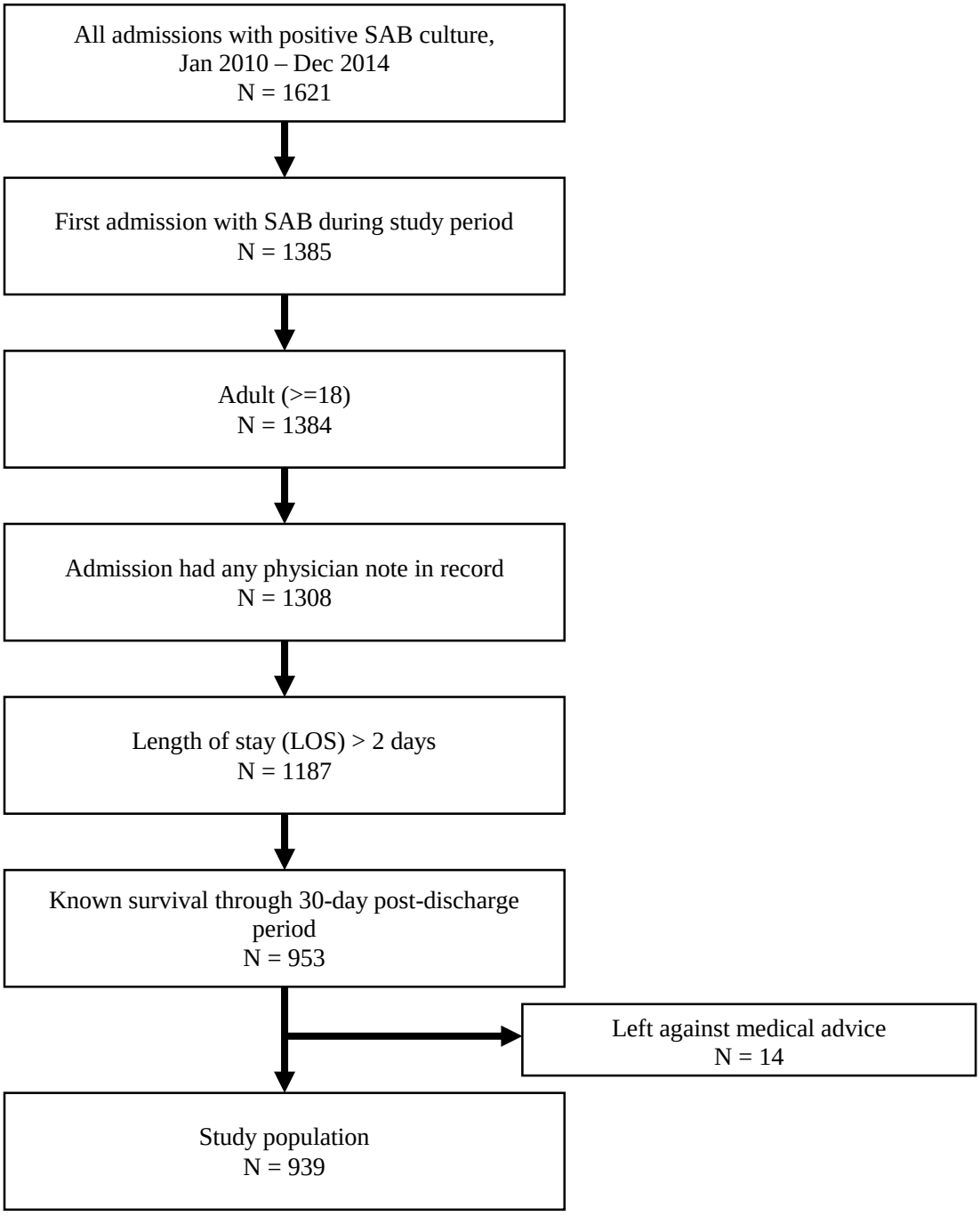


Figure 2. Total admissions with positive *S. aureus* bacteremia (SAB) culture and SAB admissions with infectious disease consult (IDC), 2010-2014

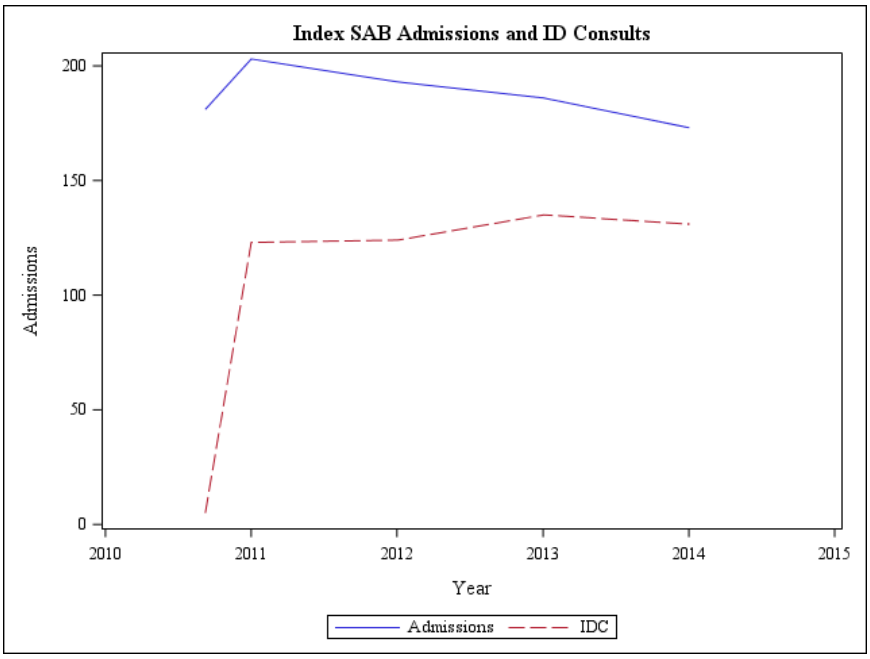


Figure 3. Time from positive culture result to first infectious disease consult (IDC) among patients with *S. aureus* bacteremia (SAB), 2010-2014

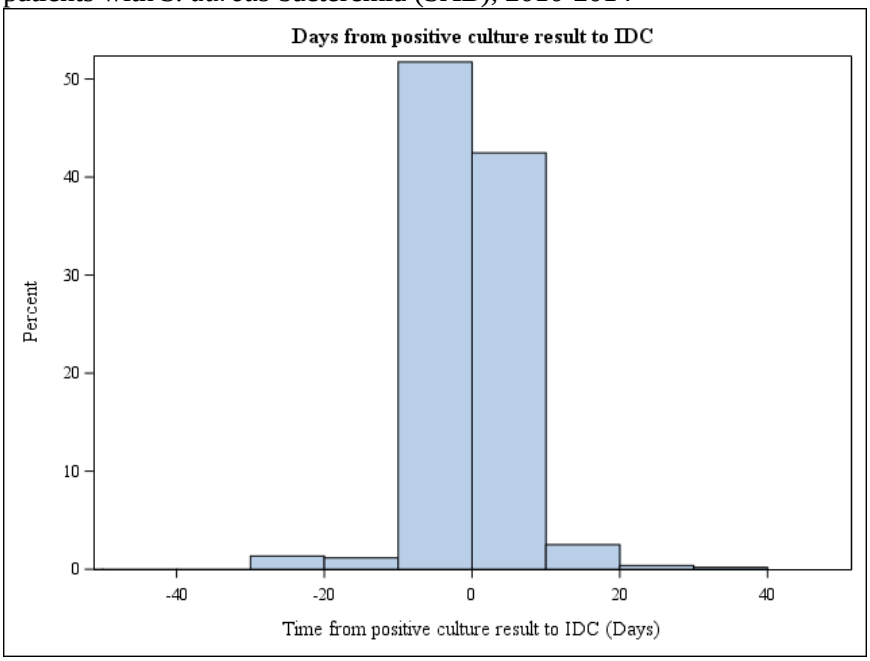


Figure 4. Time to readmission by infectious disease consult (IDC) occurrence during index admission among patients with *S. aureus bacteremia* (SAB), 2010-2014

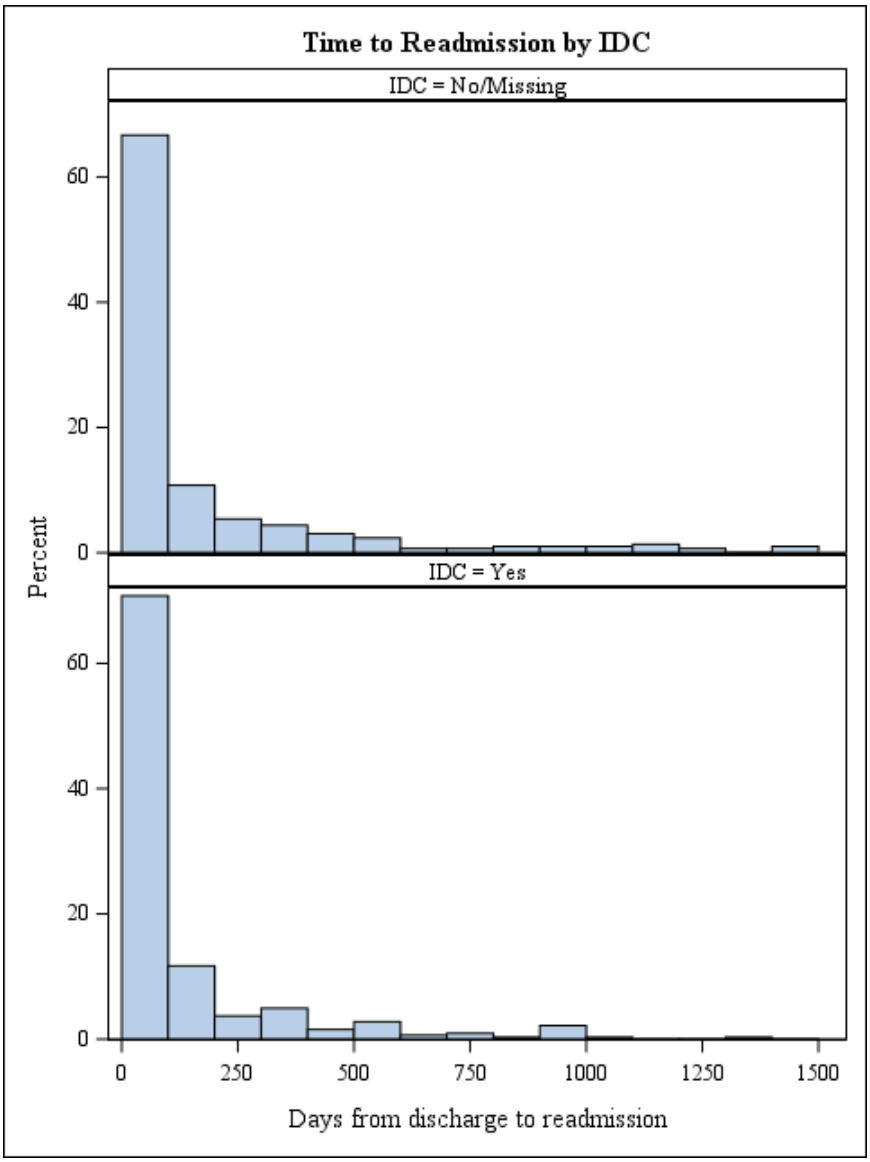
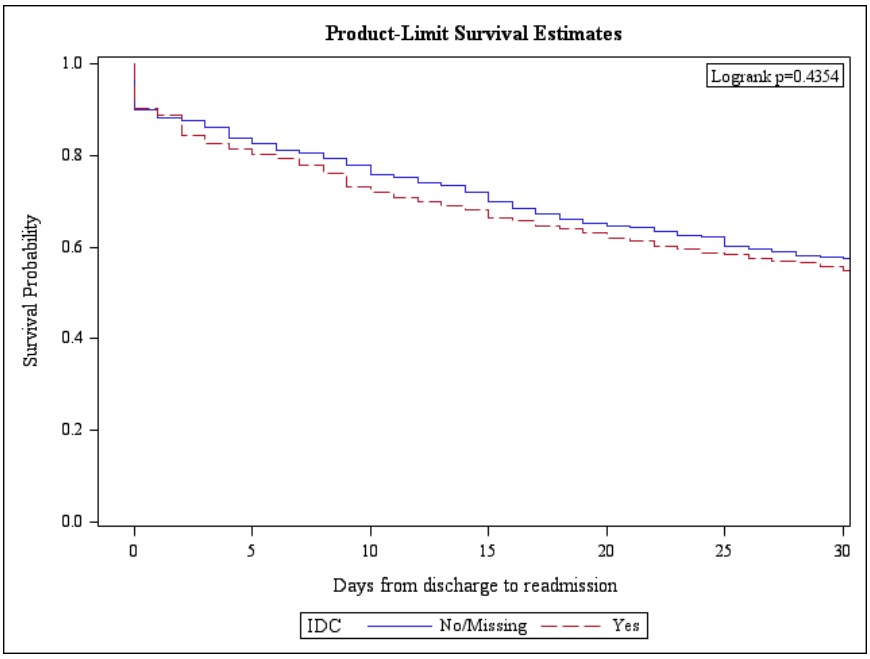


Figure 5. Survival curves for time to readmission by infectious disease consult (IDC) occurrence during index admission among patients with *S. aureus bacteremia* (SAB), 2010-2014



Chapter III: Summary, Public Health Implications, Future directions

In this study of over 900 admissions with SAB, we found that IDC provided a protective, but non-significant, benefit against 30-day all-cause readmissions. Early intervention by an ID professional relative to positive culture result showed a protective, but also non-significant, effect against 30-day readmission. Underlying patient health was important in 30-day readmissions, although in our study population few individual health conditions were found to be associated with readmission when IDC and organism characteristics were taken into account. MRSA was associated with increased odds of readmission, both controlling for other factors and in bivariate analysis. IDC was associated with greater adherence to observed SAB management strategies, which has potential implications for not only readmissions, but also other patient outcomes.

Our findings suggest that IDC is protective against readmissions and should be considered in all cases of SAB as it improves process measures, such as use of echocardiography. Early intervention by an ID professional, even before confirmation of infection via culture results, decreases the likelihood of readmission within 30 days of discharge, an important metric for both hospitals and patients. This study, taken in concert with previously published studies on IDC and mortality and readmission, suggests that IDC among patients with known and suspected SAB should be prioritized. This is especially true among patients with MRSA bacteremia, which increases the likelihood of readmission.

Future research should focus on improving the validity of this study by including measures of acuity of illness and other types of hospitals, assessing the accuracy of using administrative data to address readmission factors in SAB patients, and exploring the effect of IDC on other major pathogens of bacteremia where there are evidence-based guidelines, such as *Candida* spp.

This study could be further improved by using chart review in addition to administrative data to identify confounding conditions and infectious disease consult. This would help mitigate the misclassification bias in this study. In addition, linking to death records to identify and exclude patients who die during the 30-day post-discharge period may introduce less bias than the method of selection used here. Utilizing these methods in a study would not only improve the validity of future studies, but would also enable a comparison of administrative data against clinical data. The sensitivity and specificity of administrative data in capturing comorbidities and IDC among SAB patients is not known. Since administrative data is readily available in most health systems and can provide valuable information, being able to quantify its validity in capturing clinical data could help inform how it is used and improve study quality in the field.

Additional studies looking at additional readmission outcomes may provide further insight into the relationship between IDC and readmission. In addition to 30-day readmission, 90-day and 1-year readmission should be examined. Although the 30 day mark has significance due to CMS regulations on readmissions, 90 days may be more clinically meaningful for SAB patients; the length of time between completion of antibiotic therapy and reinfection or relapse ranges from 10-194 days.[29] This study adds to the body of literature suggesting the importance of IDC in improving outcomes among patients with *S. aureus* bacteremia by adding prevention of readmissions to the previously studied outcomes including survival.

Appendix

Appendix Table 1. Studies on the association of infectious disease consult (IDC) and adverse outcomes in *S. aureus* bacteremia (SAB) cases by type of outcome

Study	N	Observation period	Type of estimate	Estimate (95% CI/p-value) or percent in IDC vs. percent in non-IDC, p-value
In-hospital mortality				
Rieg et al., 2009[3]	521	Admission	OR	0.6 (0.4-1.0)
Martin et al., 2015[13]	252	Admission	OR	1.0 (0.5-1.7)
Jenkins et al., 2008[15]	234	Admission	Fisher's Exact	6% vs. 9%, p=0.40
Choi et al., 2011[18]	100	Admission	Not stated	35.7% vs. 56.9%, p=0.04
Lahey et al., 2009[14]	240	Admission	HR	0.4 (p = 0.01)
Bai et al., 2015[4]	847	Admission	HR	0.7 (0.5-1.0)
Short term mortality				
Tissot et al., 2014[8]	176	30 days	OR	0.4, (0.2-0.9)
Robinson et al., 2012[10]	599	30 days	Pearson's χ^2	8.0% vs. 27.0%, p<0.001
Mylotte et al., 2012[26]	293	30 days	OR	1.4 (0.7-3.0)*
Honda et al., 2010[5]	341	28 days	HR	0.4 (0.2-0.9)
Saunderson et al., 2015[9]	271	30 days	HR	0.6 (0.4-1.0)
Forsblom et al., 2013[17]	342	28 days	OR	0.1 (0.0-0.3)
Nguyen et al., 2015[19]	170	30 days	Pearson's χ^2	11.4% vs. 19.5%, p=0.20
Nagao et al., 2010[21]	346	30 days	Fisher's Exact	25.8% vs. 16.4%, p=0.04
Choi et al., 2011[18]	100	30 days	Not stated	28.6% vs. 46.6%, p = 0.07
Long term mortality				
Rieg et al., 2009[3]	521	90 days	OR	0.5 (0.3-0.9)
Fowler et al., 1998[22]	244	12 weeks	Fisher's Exact	SAB-related: 8.0 vs. 6.8%, NS; non-SAB-related: 6.3% vs. 10.6%, NS
Pragman et al., 2012[11]	197	12 weeks	OR	1.5 (0.3-7.3)*
Saunderson et al., 2015[9]	271	90 days	HR	0.9 (0.6-1.3)
Forsblom et al., 2013[17]	342	90 days	OR	0.1 (0.1-0.3)
Pastagia et al., 2012[27]	603	90 days	RR	0.7 (0.6-0.9)
Robinson et al., 2012[10]	599	1 year	HR	0.6 (0.4-0.8)
Honda et al., 2010[5]	341	1 year	HR	1.00 (0.6-1.4)

Study	N	Observation period	Type of estimate	Estimate (95% CI/p-value) or percent in IDC vs. percent in non-IDC, p-value
Recurrence (reinfection and relapse)				
Fowler et al., 1998[22]	244	12 weeks	Fisher's Exact	6.3% vs. 18.2%, p<0.01
Pragman et al., 2012[11]	197	12 weeks	OR	3.0, (1.0-9.1)
Forsblom et al., 2013[17]	342	90 days	OR	0.2 (0.0-1.3)
Chang et al., 2003[29]	505	6 months	Percent	9.4%
Rieg et al., 2009[3]	521	90 days	Pearson's χ^2	7% vs. 5%, NS
Jenkins et al., 2008[15]	234	12 weeks	Fisher's Exact	4% vs. 7%, p=0.27
Saunderson et al., 2015[9]	571	30 days	Fisher's Exact	0% vs. 1.4%, p=0.3
Saunderson et al., 2015[9]	571	90 days	Fisher's Exact	2.2% vs. 4.1%, p=0.3
Readmission				
Nguyen et al., 2015[19]	170	30-days	Pearson's χ^2	Readmission with recurrence: 1.1% vs. 11%, p=0.01; Readmission with metastatic disease secondary to SAB: 1.1% vs. 6.1%, p=0.11
Keller et al. 2013[37]	488	60 days	OR	0.5 (0.1-1.3)
Keller et al. 2013[7]	488	30 days	OR	0.4 (0.2-1.5)
Keller et al. 2013[7]	488	7 days	OR	0.4 (0.0-4.4)
Martin et al. 2015[13]	252	30 days	OR	1.0 (0.6-16.7)

OR = odds ratio; HR = hazard ratio; RR = Risk Ratio

*IDC as referent

Appendix Table 2. Models fit to data, post-collinearity and interaction assessment, pre-confounding assessment

Model Covariates	Hospital Stratification	aOR (95% CI)	p-value for HL	C-statistic
Age (continuous), race*, sex, hospital, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	None	0.9 (0.7,1.2)	0.6	0.6
Age (continuous), race*, sex, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	EUHM only	0.9 (0.5,1.5)	0.2	0.7
Age (continuous), race*, sex, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	EUH only	0.8 (0.5,1.3)	0.7	0.6
Age category**, race*, sex, hospital, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	None	0.9 (0.7,1.2)	0.5	0.6
Age category**, race*, sex, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	EUHM only	0.9 (0.5,1.4)	0.9	0.7
Age category**, race*, sex, ESRD, leukemia, lymphoma, renal disease, tumor, severe liver disease, low albumin, MRSA, community onset SAB	EUH only	0.8 (0.5,1.3)	0.7	0.6
Age (continuous), race*, sex, hospital, high/low Charlson score***, MRSA, community onset SAB	None	0.9 (0.7, 1.3)	0.9	0.6
Age (continuous), race*, sex, high Charlson score***, MRSA, community onset SAB	EUHM only	1.1 (0.7,1.7)	0.1	0.6
Age (continuous), race*, sex, high Charlson score***, MRSA, community onset SAB	EUH only	0.8 (0.5,1.2)	0.9	0.6
Age category**, race*, sex, high Charlson score***, MRSA, community onset SAB	None	0.9 (0.7,1.3)	0.4	0.6
Age category**, race*, sex, high Charlson score***, MRSA, community onset SAB	EUHM only	1.1 (0.7,1.7)	0.6	0.6
Age category**, race*, sex, high Charlson score***, MRSA, community onset SAB	EUH only	0.8 (0.5,1.2)	1.0	0.6

* Black vs. non-Black race
** Age dichotomized at 65
*** High = Charlson score ≥ 3

Appendix Table 3. Characteristics of index admissions with *S. aureus* bacteremia (SAB), 2010-2014, by hospital

	No. (%) or median (IQR)			
Characteristic	**EUHM N = 466**	**EUH N = 473**	**Total N = 939**	***p***
Demographics				
Age, years	55.1 (44.5 - 66.3)	58.4 (46.7 - 68.4)	56.8 (45.3 - 67.5)	0.007
Over 65 years old	125 (26.8%)	166 (35.1%)	291 (31.0%)	0.006
Female	211 (45.3%)	203 (42.9%)	414 (44.1%)	0.47
Race				<0.001
White	86 (19.0%)	235 (52.3%)	321 (35.6%)	
Black	363 (80.1%)	206 (45.9%)	569 (63.1%)	
Other	4 (0.9%)	8 (1.8%)	12 (1.3%)	
Comorbidities and health indicators				
Charlson score	3 (2 - 5)	3 (1 - 5)	3 (2 - 5)	0.001
Charlson score ≥ 3	301 (64.6%)	245 (51.8%)	546 (58.2%)	<0.001
ESRD	218 (46.8%)	97 (20.5%)	315 (33.6%)	<0.001
Renal Disease	27 (5.8%)	29 (6.1%)	56 (6.0%)	0.83
Any diabetes	192 (41.2%)	163 (34.5%)	355 (37.8%)	0.03
Diabetes w/ comp.	93 (20.0%)	58 (12.3%)	151 (16.1%)	0.001
Diabetes w/o comp.	99 (21.2%)	105 (22.2%)	204 (21.7%)	0.72
Leukemia	1 (0.2%)	26 (5.5%)	27 (2.9%)	<0.001
Lymphoma	2 (0.4%)	19 (4.0%)	21 (2.2%)	<0.001
Metastatic Solid Tumor	20 (4.3%)	37 (7.8%)	57 (6.07%)	0.02
Tumor	52 (11.2%)	105 (22.2%)	157 (16.7%)	<0.001
Myocardial Infarction	38 (8.2%)	33 (7.0%)	71 (7.6%)	0.50
Congestive Heart Failure	158 (33.9%)	133 (28.1%)	291 (31.0%)	0.06
Cerebrovascular disease	52 (11.2%)	72 (15.2%)	124 (13.2%)	0.07
Peripheral disease	42 (9.0%)	42 (8.9%)	84 (9.0%)	0.94
Chronic pulmonary disease	85 (18.2%)	73 (15.4%)	158 (16.8%)	0.25
Severe liver disease	7 (1.5%)	17 (3.6%)	24 (2.6%)	0.04
Mild liver disease	12 (2.6%)	16 (3.4%)	28 (3.0%)	0.47
Dementia	14 (3.0%)	15 (3.2%)	29 (3.1%)	0.88
Peptic Ulcer Disease	11 (2.4%)	11 (2.3%)	22 (2.3%)	0.97
Connective tissue disorder	33 (7.1%)	27 (5.7%)	60 (6.4%)	0.39
Hemiplegia	16 (3.4%)	7 (1.5%)	23 (2.5%)	0.05
HIV	49 (10.5%)	16 (3.4%)	65 (6.9%)	<0.001
Transplant	30 (6.4%)	96 (20.3%)	126 (13.4%)	<0.001
White blood cell count				
Low (<4.2)*	21 (4.5%)	41 (8.7%)	62 (6.6%)	0.01
High (>9.1)**	305 (65.5%)	278 (58.8%)	583 (62.1%)	0.04
Low albumin†	219 (48.2%)	289 (61.8%)	508 (55.1%)	<0.001
Hemoglobin	6.0 (5.3-7.4)	5.9 (5.2-6.9)	6.0 (5.3-7.2)	0.49
Organism factors				
MRSA‡	210 (45.3%)	231 (49.0%)	441 (47.2%)	0.25
Community onset SAB§	414 (88.8%)	354 (74.8%)	768 (81.8%)	<0.001
Clinical indicators				
Length of stay	11 (8-18)	12 (7-20)	11 (7-19)	0.001
ICU use	182 (39.1%)	200 (42.3%)	382 (40.7%)	0.31
ICU days	4 (2-9)	5 (2-11)	4 (2-10)	0.28
Endocarditis	50 (10.7%)	139 (29.4%)	189 (20.1%)	<0.001
Ventilator use	59 (12.7%)	68 (14.4%)	127 (13.5%)	0.44
Vasopressor given	111 (23.8%)	152 (32.1%)	263 (28.0%)	0.005

	No. (%) or median (IQR)			
Characteristic	**EUHM N = 466**	**EUH N = 473**	**Total N = 939**	***p***
Discharge disposition				0.004
Home	332 (71.2%)	301 (63.6%)	633 (67.4%)	
Nursing home	96 (20.6%)	95 (20.1%)	191 (20.3%)	
Hospice	15 (3.2%)	38 (8.0%)	53 (5.6%)	
Rehab	15 (3.2%)	26 (5.5%)	41 (4.4%)	
Other hospital	8 (1.7%)	13 (2.8%)	21 (2.2%)	
SAB management				
IDC	240 (51.5%)	278 (58.8%)	518 (55.2%)	0.03
Echo	414 (88.8%)	408 (86.3%)	822 (87.5%)	0.23
TTE	353 (75.8%)	372 (78.7%)	725 (77.2%)	0.29
TEE	220 (47.2%)	220 (46.5%)	440 (46.9%)	0.83
Follow-up culture	466 (100.0%)	473 (100.0%)	939 (100.0%)	-
Negative follow-up culture	387 (83.1%)	374 (79.1%)	761 (81.0%)	0.12

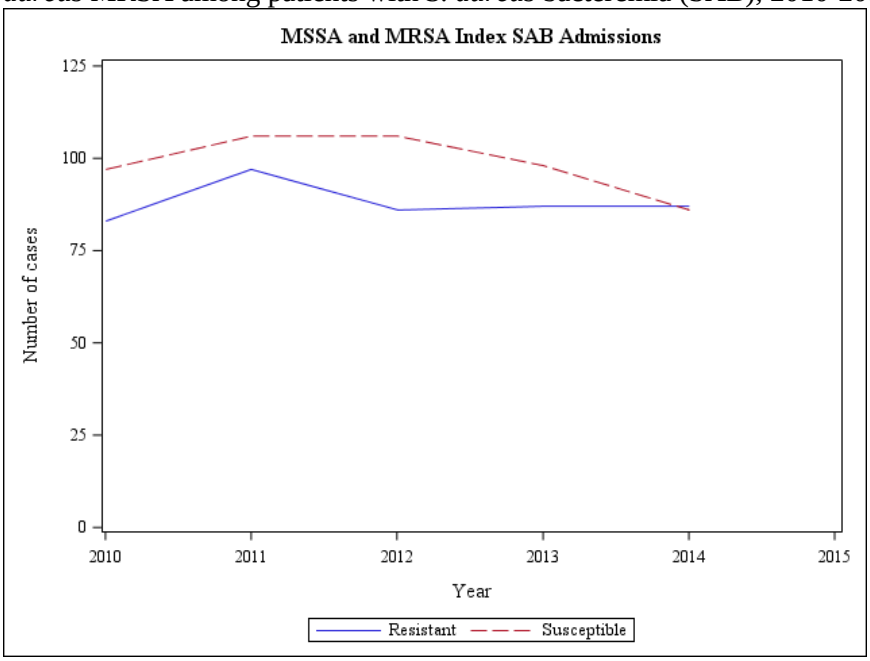
* White blood cell count $\leq 4.2 \times 10^3/\mu L$ at admission

** White blood cell count ($\geq 9.1 \times 10^3/\mu L$ at admission

† Albumin value < 3.0 g/dL at admission

§ Positive blood culture collected within 3 days of admission

Appendix Figure 1. Methicillin-susceptible *S. aureus* **(**MSSA) versus methicillin-resistant *S. aureus* MRSA among patients with *S. aureus* bacteremia (SAB), 2010-2014



Appendix Figure 2. Time from positive culture result to first infectious disease consult (IDC) among patients with *S. aureus* bacteremia (SAB) by hospital, 2010-2014