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Penicillin Use and Duration of Bacteremia, Length of Stay, and 30-day Readmission in Hospitalized Patients with Penicillin-Susceptible Staphylococcus aureus

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Penicillin Use and Duration of Bacteremia, Length of Stay, and 30-day Readmission in Hospitalized Patients with Penicillin-Susceptible *Staphylococcus aureus*

A Thesis Presented

By

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"With all its sham, drudgery, and broken dreams, it is still a beautiful world. Be Careful. Strive to be happy."

- Max Ehrmann

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ABSTRACT

PENICILLIN USE AND DURATION OF BACTEREMIA, LENGTH OF STAY, AND 30-DAY READMISSION IN HOSPITALIZED PATIENTS WITH PENICILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS*

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Staphylococcus aureus is the most common bacterial pathogen in hospitalized patients, and is a leading cause of bacteremia. Current guidelines recommend when the etiology of infection is known or suspected, the antimicrobial most cost-effective, least toxic, and most narrow in spectrum be used. To evaluate treatment of PSSA bacteremia with penicillin versus other antibiotics, a retrospective cohort study was conducted at a tertiary care center in Western Massachusetts using data collected from 2003 to 2013. One-hundred and eight patients with PSSA bacteremia were included. The primary exposure was defined as treatment with penicillin within 3 days of the first positive culture. The primary outcome was duration of bacteremia, with length of hospital stay and 30-day readmission as secondary outcomes. Data were abstracted from administrative databases and medical records, and multivariable and propensity-score-adjusted analyses were conducted. Overall, there was no difference in duration of bacteremia according to treatment (p=0.77), and a non-significant 25% increase in length of stay post-culture was observed in patients not receiving penicillin (p=0.34). Propensity-score-adjusted analyses also did not yield significant differences in clinical outcomes. The results of this

study suggest no significant associations between treatment with penicillin versus other antibiotics and clinical outcomes. Given the low cost and decreased risk of developing multidrug-resistant bacteria, PSSA bacteremia should be treated preferentially with penicillin. However, given the small sample size, and the potentially wide range of antibiotics used in place of penicillin, caution should be exercised in interpreting these results. Larger multi-site studies are needed to address these associations.

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CHAPTER 1

INTRODUCTION

Staphylococcus aureus is a common cause of infection, particularly in healthcare settings, and is a leading cause of bacteremia. The prevalence of both community-acquired and nosocomial infections has been steadily increasing over the past two decades.[1,4] Although more commonly associated with skin and soft tissue infections, *S. aureus* has been observed to be the most common cause of nosocomial pneumonia and surgical site infections,[1] and is also the most common bacterial pathogen among clinical isolates in hospitalized patients.[22] In 2006, Kuehnert et al. conducted a study among 9622 individuals who were part of the National Health and Nutrition Examination Survey (NHANES).[3] The authors observed that about one-third of the United States population had *S. aureus* colonization, although carriage rates can be as high as 50% among high-risk populations, such as injection drug-users, insulin-dependent diabetics, and patients with intravascular catheters.[2]

The first strains of *S. aureus* to be resistant to penicillin were observed in the 1940's, shortly after penicillin was introduced.[2] Initially, these strains were rare, however, as the use of penicillin became more widespread, the prevalence of penicillin-resistant strains began to increase. It was first observed in Denmark that by 1966, 85% - 90% of hospital isolates were resistant to penicillin. Resistant strains are also common in the community. In the US, by the 1970's, 70% - 85% of community isolates were resistant to penicillin.[2] A review article by Lowy in 1998 described that less than 5% of isolates remained susceptible to penicillin.[4]

The development of antibiotic resistance has been ushered in by two key factors; overuse and misuse of antibiotics. Frequently, antibiotics are prescribed for an indication that is not warranted, or is not ideal.[6] It has been reported that a large proportion (~75%) of ambulatory antibiotic prescriptions are for conditions such as otitis media, sinusitis, bronchitis, and upper respiratory infections. Antibiotic therapy is frequently unnecessary, because the etiologies of these conditions are predominantly viral.[21]

Appropriate antibiotic therapy is generally defined as treatment with an agent to which the causative pathogen is susceptible *in vitro*. Inappropriate therapy has been associated with poor clinical outcomes, such as increased risk of mortality or increased length of hospital stay.[7,8] The Infectious Diseases Society of America (IDSA) guidelines recommend that when an etiologic diagnosis is known or suspected, the antimicrobial agent that is the most cost-effective, least toxic, and most narrow in spectrum be used.[9]

Recent evidence has suggested that there is a resurgence of penicillin-susceptible *S. aureus* (PSSA).[11-13] The reason for this increase of PSSA is unclear; however, Crane posits that a focus on more resistant strains, such as methicillin-resistant *S. aureus* (MRSA), has created an opportunity for penicillin-susceptible strains to resurface.[12] In 2013, Nissen et al, describes that PSSA accounted for one-fifth of cases of SAB in Denmark.[11] In an editorial response to this study, Crane observed a similar resurgence of PSSA at 417-bed hospital in Buffalo, New York. PSSA accounted for 13 to 15% of all cases of *S. aureus* among patients. Similarly, according to the 2012 antibiogram at Baystate Medical Center in Springfield, Massachusetts, approximately 20% of all methicillin-susceptible *S. aureus* tested were also susceptible to penicillin.[13] Based on data indicating superior potency of penicillin over other penicillinase-resistant β-lactams,

it is recommended that penicillin should be considered as the drug of choice for treating PSSA.[11]

A common consequence of *S. aureus* infection is *S. aureus* bacteremia (SAB). SAB can be a serious condition with high mortality rates ranging from 11 to 43%.[4,10] Bacteremia is defined as presence of *S. aureus* in the bloodstream as confirmed by a positive blood culture result. Factors associated with mortality in SAB include age over 50 years, inadequate source control of infection, and serious underlying cardiac, neurologic, or respiratory disease.[4]

There is a paucity of literature investigating PSSA, and the associations between treatment with penicillin versus other antibiotics and clinical outcomes. There has only been one study to date where this was the focus, although only the endpoint of 30-day mortality was evaluated.[11] Three studies have considered duration of bacteremia as an outcome[14,15,24]; however, these studies were evaluating other therapies versus standard care in methicillin-resistant and susceptible *S. aureus* isolates[24], or where the susceptibilities were not specified[14,15]. One of these studies was conducted over 30 years ago.[15] To date, there have been no studies that investigated the association of penicillin treatment with readmission as an outcome.

Therefore, we proposed to conduct a retrospective cohort study comparing the effectiveness of treatment with penicillin versus other antibiotics among patients hospitalized with PSSA at Baystate Medical Center in Springfield, Massachusetts. We hypothesized that among hospitalized patients with PSSA bacteremia, after adjusting for patient characteristics, those whose antibiotics were appropriately switched to penicillin

will have a shorter duration of bacteremia, shorter length of stay, and lower rates of 30-day readmission as compared to patients who were treated with other antibiotics.

CHAPTER 2

METHODS

2.1 Study Population

Baystate Medical Center in Springfield, Massachusetts is a tertiary care facility serving an ethnically and socioeconomically diverse population. Patients aged 18 years or older who were admitted between January 2003 and January 2013 with a confirmed diagnosis of PSSA bacteremia were included in this study. PSSA bacteremia was defined as at least one positive blood culture for *S. aureus* that was susceptible to penicillin. The initial study sample consisted of 6455 *S. aureus* cultures drawn at Baystate between 2003 and 2013.

Of the original sample of 6455 cultures, exclusion criteria consisted of duplicate cultures (n=1250), coagulase-negative *Staphylococci* (n=2319), and penicillin-resistant *S. aureus* (n=2545). Additionally, to ensure the same patient was not included more than once in the study, repeat cultures drawn within six weeks of the index culture (n=166) were excluded. Patients were also excluded if a subsequent negative culture was not available (n=22), and if there was documentation of a penicillin allergy (n=16). Patients under 18 years of age were also excluded (n=29). This left a sample size of 108 unique patients for analysis. Additional exclusion criteria were necessary for the analysis of each outcome. Analyses for duration of bacteremia excluded patients whose duration was less than 3 days. For total and LOS post-culture analyses, patients with an LOS post-culture of less than 3 days were excluded. Also, analyses for 30-day readmission required that 10 deaths, as well as patients with LOS post-culture less than 3 days be excluded (Figure 1).

2.2 Data Collection

Data for our study were abstracted from MedMined and McKesson databases, as well as electronic medical records. MedMined Data Mining Surveillance program (CareFusion Corporation, San Diego, CA) was designed to identify clinically meaningful patterns in data sets, relying on microbiologic and patient location data.[16] McKesson is a large administrative database maintained for billing purposes. Using MedMined, microbiological data such as *S. aureus* drug sensitivities and results of blood cultures were extracted. Demographic and other clinical data were abstracted from McKesson and electronic medical records. Data from these three sources were then merged to construct a de-identified data set for our study which is in compliance with established Health Insurance Portability and Accountability Act (HIPAA) regulations.

The primary exposure was treatment with penicillin, and was assessed through McKesson, a database maintained for billing purposes. All antibiotics a patient would have received during their admission are reflected in this database. We defined treatment with penicillin as having received penicillin within 3 days of the first positive blood culture. Patients receiving another antibiotic, or receiving penicillin more than 3 days after the first positive culture were defined as receiving no or late penicillin. Treatment groups were defined this way because patients' antibiotics would not have been switched to penicillin until approximately 48 hours after the initial blood culture is drawn, as this is the time required for susceptibility tests to be completed. Defining treatment with penicillin as within 3 days of the culture not only captures if a patient was treated with penicillin, but if the timing of treatment was appropriate; in other words, within 24 hours of the when results were available to clinicians.

The primary outcome of interest was duration of bacteremia, which was defined as the time interval from the first positive blood culture to the first negative culture. Results and dates of the first positive culture were extracted from MedMined, while results and dates of the first negative blood culture were abstracted from medical records. Duration of bacteremia was then calculated as the difference between these dates, in days. Secondary outcomes included length of stay (LOS) in days, and all-cause 30-day readmission, which were available through McKesson. Length of stay was further divided into total LOS, LOS before the positive culture, and LOS post-culture.

Covariates were selected based on inclusion in prior literature and potential for confounding. Data on covariates were assessed through McKesson, or abstraction from electronic medical records. The following covariates were assessed via McKesson: age, sex, race, Charlson Comorbidity Index (CCI), transfer to ICU during hospitalization, admission in previous 90 days, admission source, discharge disposition, and community acquired infection. The CCI was defined as two levels of comorbidity categories: low/intermediate (CCI score = 0-2), and high (CCI score $\geq$3), and was calculated from secondary diagnoses compiled from McKesson using the International Classification of Diseases, 9th revision (ICD-9). Admission source was categorized as home, transfer from skilled nursing facility (SNF), emergency department, MD/referral, and other. Discharge disposition was categorized as long-term care, death, home, acute/short-term care, and other. Community acquired infection was defined as LOS before positive culture $\leq$3 days.

Covariates that were abstracted from electronic medical records included: diabetes mellitus, malignancy, current chemotherapy, requirement for dialysis, illicit injection

drug use, presence of a surgical wound, presence of an indwelling catheter, site of infection, and infectious disease consult. Site of infection was categorized as catheter related, respiratory, endocarditis, osteomyelitis, dialysis access, other, and unknown.

2.3 Statistical Analysis

The distribution of all variables was examined. Demographic data and other categorical variables were reported as frequencies and percentages. Continuous variables were reported with means and standard deviations, medians, range and quartiles. Distribution of duration of bacteremia by covariates was examined, and significance testing was performed using Spearman's rank correlation for continuous and ordinal variables, and ANOVA for categorical variables. Length of stay is right skewed; therefore, bivariate distributions of total LOS and LOS post-culture by covariates were analyzed using non-parametric tests. Significance testing for continuous and ordinal variables was performed using Spearman's rank correlation, and Kruskal-Wallis was used for categorical variables. Bivariate distribution of 30-day readmission by covariates was also examined. Significance testing was performed using independent t-tests for continuous variables, Wilcoxon's rank-sum for ordinal variables, and Fisher's exact test for categorical variables. Ten deaths were excluded in all analyses of 30-day readmission, as well as patients whose LOS post-culture was less than 3 days, leaving 69 individuals available for analysis.

For the primary outcome of duration of bacteremia, a multiple linear regression model was used to estimate beta coefficients, and adjust for patient characteristics as potential confounders. For consistency with LOS analyses, duration of bacteremia was

log-transformed prior to fitting the linear regression model. Covariates selected for this model included sex, current chemotherapy, and where the patient was admitted from. To select for covariates, variables with a *p*-value of ≤0.25 from the bivariate analysis of duration of bacteremia were included in the initial model. After running the initial model, variables with a Wald *p*-value >0.10 were evaluated individually by removing that variable from the model. If the coefficient for treatment with penicillin changed by >15%, the variable was retained in the model. Treatment with penicillin was defined as receiving penicillin within 3 days of the positive culture; therefore, it was necessary to exclude patients if their bacteremia resolved during those 3 days. This left a sample size of 79 for the multivariable analysis of duration of bacteremia.

Linear regression models were also used to estimate beta coefficients for total LOS and LOS post-culture. Because LOS is right skewed, data were log-transformed prior to fitting the multivariable models. Covariates selected for the total LOS model included race, transfer to ICU during admission, community acquired infection, and admission source. Covariates selected for the LOS after culture model included age, injection drug use, transfer to ICU during hospitalization, community acquired infection, previous admission within 90 days, admission source, and infectious disease consult. Covariates were selected in the same manner as previously described for duration of bacteremia. As with the duration of bacteremia model, patients with an LOS post-culture of less than 3 days were excluded from the analysis in order to avoid including patients who were discharged before treatment with penicillin was begun. This exclusion left a sample size of 75 for the LOS post-culture and total LOS multivariable analyses.

Survival functions for each group were also compared using Kaplan-Meier estimates for total LOS and LOS post-culture. Survival functions that diverge early and meet late are indicative of inherent differences between the two groups that may not be observed when comparing means or medians. Kaplan-Meier plots were constructed to verify findings observed from comparison of means and medians.

Logistic regression was used to estimate odds ratios and adjust for patient characteristics for the multivariable analysis of 30-day readmission. As previously noted, 10 deaths were excluded, leaving a sample size of 98 individuals for the analysis. The logistic regression model for 30-day readmission was adjusted for admission within previous 90 days. Variables with a *p*-value of ≤ 0.25 from the bivariate analysis of duration of bacteremia were included in the initial model. Starting with variables with the highest p-values from the Wald test, a formal log-likelihood ratio test was conducted to determine inclusion of variables in the final model. Those with log-likelihood ratio test p-values <0.05 were included in the final model, or if removal of a variable resulted in a >15% change in the coefficient for treatment with penicillin.

To address the concern of confounding by indication, we estimated a propensity score from logistic regression models. The propensity model to estimate the probability that a patient will receive treatment with penicillin was developed based on a non-parsimonious multivariable logistic regression model using variables previously described in the covariate assessment section. Variables included in estimation of the propensity score were previous admission within the past 90 days, year of admission, ICU transfer, sex, race, age, illicit injection drug use, surgical wound, indwelling catheter, dialysis requirement, infectious disease consult, diabetes mellitus, and the

Charlson Comorbidity Index. Of these, variables marginally associated with treatment at a *p*-value ≤ 0.25 were injection drug use, indwelling catheter, dialysis requirement, and diabetes. However, to consider as many patient characteristics as possible in the propensity score, all variables were retained in the model.

In order to assess fitness of our propensity score model, we conducted a Hosmer-Lemeshow goodness of fit test. The results of this test yielded a *p*-value of 0.25, indicating that this model adequately fits our data. The area under the receiver operating characteristic (ROC) curve was also analyzed to determine if this model exhibited acceptable discrimination between treatment groups. The area under the ROC was 0.80 (95% CI, 0.68 – 0.92), indicating acceptable discrimination; in other words, 80% of the time, this model will correctly discriminate between patients who received penicillin and those who did not, or received penicillin late. The fitness of the propensity score model indicates that the estimated propensity score should adequately address potential confounding by indication. Therefore, in separate analyses to account for patient characteristics that may influence whether or not a patient is treated with penicillin, the propensity score was used as a covariate in a multivariable model.

Sensitivity analyses were conducted by redefining the primary exposure variable as receiving penicillin within 4 days of the positive culture, or receiving another antibiotic or penicillin after 4 days of the culture. Similar to our primary analyses, patients with outcomes occurring prior to 4 days post-culture were excluded from the analyses. Multivariable analyses for all outcomes were then repeated.

Two-sided p-values <0.05 were considered statistically significant. All analyses were performed using Stata 13.1 (College Station, Tx).

CHAPTER 3

RESULTS

After initial exclusion criteria, 108 unique patients were available for analysis. The average age of the population was 64 years, and the majority were male (69%) and white (81%). There were 16 patients who received penicillin within 3 days, and 92 who either received another antibiotic or received penicillin after 3 days. Table 1 depicts baseline characteristics of the study population by treatment group. Fifteen percent of the study population received penicillin within an appropriate time frame, and 85% did not receive penicillin or received penicillin more than 3 days post-culture. Variables at least marginally associated with treatment ($p \leq 0.25$) included diabetes mellitus, injection drug use, transfer to ICU during hospitalization, site of infection, infectious disease consult, and discharge disposition.

Tables 2 and 3 describe the distribution of outcomes for the study population. After exclusion of patients with duration of bacteremia less than 3 days, 79 patients were left for analysis. The mean duration was 4.6 days and ranged from 3 to 9 days. After excluding patients with an LOS post-culture less than 3 days, 75 patients were available for all LOS analyses. Median total length of stay was 14 days, and ranged from 4 to 71 days. Length of stay after the positive culture had a median of 9 days, and a range from 3 to 49 days. LOS outcomes are characteristically right skewed, as illustrated in Figures 3 and 5. After excluding 10 deaths and patients with LOS post-culture less than 3 days, 15 patients (22%) were readmitted within 30-days, and 54 (78%) were not.

Tables 4, 5 and 6 show the distribution of outcomes by covariates for the study population. For duration of bacteremia, variables that were at least marginally associated ($p \leq 0.25$) were age, diabetes mellitus, and current chemotherapy (Table 4). Variables associated with LOS post-culture were sex, injection drug use, ICU transfer during admission, admission source, infectious disease consult, and discharge disposition. For total LOS, associated variables included age, sex, race, malignancy, ICU transfer during admission, site of infection, community acquired infection, and admission source, and infection disease consult (Table 5). The distribution of patients readmitted within 30 days by covariates is depicted in Table 6. Variables associated with 30-day readmission with a p-value ≤ 0.25 included, the Charlson Comorbidity Index, and admission in the previous 90 days.

The distribution of outcomes by treatment group is described in Table 7. Briefly, patients who received penicillin had a mean duration of bacteremia of 4.7 days, median LOS post-culture of 8 days, and median total LOS for patients receiving penicillin was 14 days. For patients receiving a different antibiotic or penicillin late, the mean duration of bacteremia was 4.6 days, median LOS post-culture was 9 days, and median total LOS was 14 days. Four (50%) patients were readmitted within 30 days in the penicillin group, and 11 (18%) were readmitted among patients not receiving or receiving penicillin late (Table 8). All differences in outcomes between the treatment groups were non-significant. To further analyze differences in LOS, Kaplan-Meier plots were constructed for both total LOS (Figure 4) and LOS after culture (Figure 5). As depicted in the figures, the survival curves for both total LOS and LOS post-culture follow similar patterns between the treatment groups.

Unadjusted and adjusted multivariable analyses for the primary outcome of duration of bacteremia are shown in Table 9. As described previously, because of our methods of defining treatment exposure, patients with duration of bacteremia of less than 3 days were excluded, leaving 79 patients available for the analysis. Duration of bacteremia was log-transformed; therefore, the beta coefficients can be interpreted as a percent change in the dependent variable for a categorical change in the independent variable. Fifteen (19%) received penicillin within 3 days, and 64 (81%) did not, or received penicillin after 3 days. In the unadjusted analysis, patients in the no/late penicillin treatment group exhibited a non-significant 2% decrease in duration of bacteremia compared to those in the penicillin group (β = -0.02; 95% CI, -0.19 – 0.16). After adjusting for age, presence of diabetes mellitus, and current chemotherapy, patients in the no/late penicillin group exhibited a non-significant 3% increase in duration of bacteremia as compared to patients receiving penicillin within 3 days, (β = 0.03; 95% CI, -0.15 – 0.20).

Table 10 shows the results of multivariable analyses for LOS post-positive culture as well as total LOS. After excluding patients who were discharged within 3 days of the culture, 75 patients were left for the LOS analyses. The primary LOS outcome of interest is LOS post-culture, because this would be the period of time when a patient's antibiotics would have been switched to penicillin in response to the results of the blood culture. Nine patients (12%) received penicillin, and 66 (88%) were in the no/late penicillin group. For the unadjusted analysis, patients who did not receive or received penicillin late showed a non-significant 3.1% increase in LOS post-culture as compared to those receiving penicillin within 3 days (β = 0.031; 95% CI, -0.46 – 0.52). After adjusting for

injection drug use, site of infection, admission source infectious disease consult, and discharge disposition, patients in the no/late penicillin group exhibited a non-significant 25% increase in LOS after culture as compared to those in the penicillin group. However, the increase was not statistically significant ($\beta = 0.25$; 95% CI, -0.27 – 0.78). Total length of stay was also analyzed; the unadjusted analysis shows that patients in the no/late penicillin group had a non-significant 9% increase in total LOS as compared to those receiving penicillin ($\beta = 0.09$; 95% CI, -0.34 – 0.53). After adjusting for sex, race, community acquired infection, admission source, and infectious disease consult, patients in the no/late penicillin group had a non-significant 17% increase in total LOS as compared to those in the penicillin group ($\beta = 0.17$; 95% CI, -0.23 – 0.58).

The results of the multivariable analyses for 30-day readmission are depicted in Table 11. After exclusion of 10 deaths and patients who were discharged within 3 days of the positive culture, 69 individuals were available for this analysis. Eight (12%) of whom received penicillin within 3 days of the positive culture, and 61 (88%) did not, or received penicillin late. In the unadjusted analysis, patients in the no/late penicillin group had a marginally significant reduction in the risk of readmission within 30 days as compared to patients in the penicillin group (OR = 0.22; 95% CI, 0.05 – 1.01). After adjustment for admission within the previous 90 days, the reduction in risk was statistically significant; patients in the no/late penicillin group had a significant reduction in risk of readmission within 30 days as compared to those who received penicillin within 3 days (aOR = 0.08; 95% CI, 0.01 – 1.63).

Propensity score adjusted analyses resulted in no significant differences in clinical outcomes between the treatment groups. Table 12 shows the propensity score adjusted

analysis for duration of bacteremia. Patients in the no/late penicillin group had a non-significant 4% decrease in duration of bacteremia as compared to patients in the penicillin group, after adjusting for propensity score (β = -0.04; 95% CI, -0.24 – 0.15). Table 13 depicts results of propensity score adjusted analyses for LOS post-culture and total LOS. Patients not receiving or receiving penicillin late had a non-significant 4% decrease in LOS post-culture (β = -0.04; 95% CI, -0.60 – 0.52) as compared to patients receiving penicillin after adjusting for propensity score; there was virtually no difference in total LOS (β = 0.003; 95% CI, -0.49 – 0.50). For the analysis of 30-day readmission, adjustment for propensity score resulted in an attenuation of the association between penicillin treatment and 30-day readmission (Table 14). Receiving another antibiotic or penicillin late was associated with a non-significant 75% decrease in the risk of readmission within 30 days as compared to patients receiving penicillin within 3 days while adjusting for propensity score (OR = 0.25; 95% CI, 0.04 – 1.59).

Sensitivity analyses were conducted by redefining our exposure variable as receiving penicillin within 4 days of the first positive culture. In these analyses, patients who were discharged, or whose duration of bacteremia was less than 4 hours were excluded. Table 15 shows the results of the sensitivity analysis for duration of bacteremia; the results were similar to our primary analysis. Sensitivity analyses for LOS post-culture and total LOS yielded similar results (Table 16). The results of our sensitivity analysis for 30-day readmission were also similar to the primary analysis (Table 17).

CHAPTER 4

DISCUSSION

In this study of 108 patients admitted at Baystate Medical Center with a confirmed diagnosis of PSSA bacteremia, our results suggest that there are no large differences in clinical outcomes in patients who were treated appropriately with penicillin within an appropriate time window, and patients who were treated with a different antibiotic or received penicillin more than 3 days after the first positive culture. After performing separate analyses adjusting for patient characteristics and propensity score, we observed that duration of bacteremia, and LOS post-culture for both groups were similar and non-significant. The propensity-score-adjusted odds ratio for risk of 30-day readmission suggested that patients who received another antibiotic or penicillin late, may have had a decreased risk of readmission; however, these results were also statistically non-significant.

There has only been one other study that has evaluated the effectiveness of penicillin versus other antibiotics for the treatment of PSSA bacteremia.[11] Nissen et al. conducted a retrospective cohort study in Denmark, reviewing charts of 588 PSSA bacteremia cases in five centers from January 1995 to December 2010. The primary outcome in this study was 30-day mortality rate. The authors observed that therapy with cefuroxime was associated with an increased risk in 30-day mortality as compared to treatment with penicillin (HR = 2.54; 95% CI, 1.49 – 4.32). No significant difference in risk of 30-day mortality was observed between patients treated with penicillin and those treated with dicloxacillin.

Two studies within the past 10 years have explored duration of bacteremia as an outcome, although it was not considered the primary outcome for either study.[14, 24] In 2011, Lemonovich et al. conducted a retrospective cohort study to examine the association between combination therapy with an aminoglycoside for *S. aureus* endocarditis or bacteremia and risk of recurrent bacteremia.[14] The primary outcome was recurrent bacteremia; duration of bacteremia in days was considered as a secondary outcome. The investigators observed that for subjects receiving combination therapy with an aminoglycoside, the risk of recurrent bacteremia was significantly lower than those who did not receive an aminoglycoside (OR = 0.26; 95% CI, 0.07 – 0.98). However, there was no significant difference in the median days of duration of bacteremia ($p = 0.49$). In 2006, Fowler et al. conducted a randomized controlled trial evaluating treatment of *S. aureus* bacteremia and endocarditis with daptomycin versus standard therapy.[24] In the secondary analyses for duration of bacteremia, the investigators observed that for both methicillin-resistant and methicillin-susceptible *S. aureus*, the median duration of bacteremia did not differ significantly between the treatment groups ($p = 0.25$ and 0.28, respectively).

Generally, the results of our primary analysis of duration of bacteremia were similar to the results of the two more recent studies that considered this as an outcome. As with these two studies, the results or our multivariable and propensity-score-adjusted analyses suggested that there was no difference in duration of bacteremia between the two treatment groups. However, neither of these previous studies focused on penicillin-susceptible *S. aureus*, nor were they evaluating penicillin as a treatment. Nissen et al. conducted the only study evaluating the effectiveness of penicillin in patients with

confirmed PSSA bacteremia, but the only outcome investigated was 30-day mortality. Thus, the results of this study may not be directly comparable with our study. It does suggest, however, that for PSSA bacteremia, penicillin or other penicillin-class antibiotics (such as dicloxacillin) are associated with improved clinical outcomes. The results of our multivariable and propensity-score-adjusted analyses for LOS also suggested that there were no significant differences between treatment groups. The only statistically significant association observed was with risk of 30-day readmission. In our multivariable analysis, we found that patients who did not receive, or received penicillin late were significantly less likely to be readmitted within 30-days as compared to patients treated with penicillin within 3 days post-culture. However, there were only 69 patients available for this analysis, and furthermore, there were very few patients who received penicillin and were readmitted in this analysis. Consequently, the validity of this result may be questionable. Propensity-score-adjusted analysis of 30-day readmission resulted in a non-significant decreased risk of 30-day readmission,

This study has several limitations that should be addressed. A substantial limitation of this study is the small sample size; particularly after patients with duration of bacteremia less than 3 days and patients who were discharged within 3 days of the positive culture were excluded. Furthermore, there were a small number of patients included in the penicillin group. This could have precluded us from detecting any differences between treatment groups due to inadequate power. Also, antibiotics given in place of penicillin in the no or late penicillin group were not classified. Patients not receiving penicillin were likely prescribed an antibiotic that was also effective against PSSA. Consequently, these patients may have fared just as well as those who received

penicillin in the appropriate time frame, thereby biasing our results towards the null. This could be a plausible explanation for why patients who were treated with penicillin versus those treated with other antibiotics exhibited no difference in duration of bacteremia.

As with any study evaluating a treatment, confounding by indication is a potential for bias in this study. Physicians may be more likely to treat a patient with a particular antibiotic if they present with certain diagnoses or comorbidities. To minimize the impact of this bias, propensity scores were estimated. The propensity score is a conditional probability of a patient receiving a particular treatment, given patient characteristics.[23] Fitness of the propensity score model as assessed with the Hosmer-Lemeshow goodness of fit test and area under the ROC curve indicated that the model was adequate, and was able to mitigate the effects of confounding by indication. The propensity score was then used as a covariate in a multivariable analysis; the results of these analyses were similar to our primary analysis.

Since we defined the primary exposure as treatment with penicillin within 3 days of the first positive culture, there was a potential for immortal time bias. Immortal time bias can occur when there are outcomes during a period of time before an individual is considered to be exposed. This would create a disproportionate number of unexposed individuals who experienced an outcome, thereby introducing a systematic bias that would underestimate the association.[25] In the context of our study, to minimize the impact of immortal time bias, patients whose bacteremia resolved, or were discharged within 3 days after the first positive culture were excluded from the multivariable analyses. If these patients were not excluded, there would be patients who experienced

outcomes before there was an opportunity to be treated with penicillin, which would have biased our results away from the null.

To the best of our knowledge this is the first study to consider duration of bacteremia, LOS, and 30-day readmission as outcomes in evaluating treatment with penicillin for treatment of PSSA bacteremia. Although this study was limited by a small sample size and lack of statistical power, steps were taken to minimize the impact of potential biases. Furthermore, this patient population represents 10 years of admissions at Baystate Medical Center, and exclusion criteria were decided on in order to ensure a patient population consisting of unique patients with confirmed cases of PSSA bacteremia.

CHAPTER 5

CONCLUSION

In conclusion, the results of this study suggest that there is no association between treatment with penicillin and clinical outcomes. Given the low cost and decreased risk of developing multidrug-resistant bacteria, PSSA bacteremia should be treated preferentially with penicillin. However, given the small sample size, and the potentially wide range of antibiotics that may be used in place of penicillin, caution should be exercised in interpreting these results. Directions for further research should include larger multi-site studies to address these associations.

Table 1. Characteristics of Study Population by Treatment Group: PSSA at Baystate Medical Center, 2003-2013

		Patient Treatment Group		
	All (n=108)	Penicillin [n=16 (15%)]	No/Late Penicillin [n=92 (85%)]	*p*-value †
Age, years; [$\bar{X}$ (SD)]	64 (16.2)	63 (16.9)	64 (16.2)	0.96
Sex				0.42
Male	64 (59%)	8 (50%)	56 (61%)	
Race				0.76
White	88 (81%)	14 (88%)	74 (80%)	
Black	14 (13%)	1 (6%)	13 (14%)	
Other	6 (6%)	1 (6%)	5 (5%)	
Charlson Comorbidity Index				0.98
0-2	28 (26%)	4 (25%)	24 (26%)	
≥ 3	80 (74%)	12 (75%)	68 (74%)	
Diabetes Mellitus				0.25
Yes	33 (31%)	7 (44%)	26 (28%)	
Malignancy				0.36
Yes	11 (10%)	0 (0%)	11 (12%)	
Chemotherapy				1.00
Yes	5 (5%)	0 (0%)	5 (5%)	
Requirement for Dialysis				0.29
Yes	20 (19%)	1 (6%)	19 (20%)	
Injection Drug Use				0.16
Yes	5 (5%)	2 (13%)	3 (3%)	
Surgical Wound				0.46
Yes	17 (16%)	1 (6%)	16 (17%)	
Indwelling Catheter				0.28
Yes	46 (43%)	9 (56%)	37 (40%)	
ICU during Hospitalization				0.23
Yes	31 (28%)	7 (43%)	24 (26%)	
Site of Infection				0.09
Catheter Related	13 (12%)	0 (0%)	13 (14%)	
Respiratory	8 (7%)	0 (0%)	8 (9%)	
Endocarditis	9 (8%)	4 (25%)	5 (5%)	
Osteomyelitis	10 (9%)	2 (13%)	8 (9%)	
Dialysis Access	7 (6%)	0 (0%)	7 (8%)	
Other	20 (19%)	4 (25%)	16 (17%)	
Unknown	41 (38%)	6 (38%)	35 (38%)	
Community Acquired Infection				
Yes	36 (33%)	5 (31%)	31 (34%)	1.00
Admission in Previous 90 Days				1.00
Yes	28 (26%)	4 (25%)	24 (26%)	
Admission Source				0.51
Home	66 (61%)	9 (56%)	57 (62%)	
Transfer from SNF	13 (12%)	4 (25%)	9 (10%)	
Emergency Department	14 (13%)	2 (13%)	12 (13%)	
MD/Ref	9 (8%)	1 (6%)	8 (9%)	
Other	6 (6%)	0 (0%)	6 (7%)	
Infectious Disease Consult				0.08
Yes	73 (68%)	14 (88%)	59 (64%)	
Discharge Dispostion				0.09
Longterm Care	35 (32%)	4 (25%)	31 (33%)	
Death	10 (9%)	2 (13%)	8 (9%)	
Home	45 (42%)	4 (25%)	41 (45%)	
Acute/Short-term Care	14 (13%)	5 (31%)	9 (10%)	
Other	4 (4%)	1 (6%)	3 (3%)	

† Significance testing perfomed using independent t-test for continuous variables, Wilcoxon's Rank-Sum for ordinal variables, and Fisher's Exact test for categorical variables

Table 2. Distribution of Duration of Bacteremia, Total Length of Stay, and Length of Stay Post-Positive Culture: PSSA at Baystate Medical Center, 2003-2013

	$\bar{X}$ (SD)	Median	Min	25th%	75th%	Max
Duration of bacteremia, days* (n=79)†	4.6 (1.5)	4	3	3	6	9
Total length of stay, days (n=75)‡	18.1 (13.2)	14	4	10	23	71
Length of stay before positive culture, days (n=75)	6.7 (8.3)	4	0	2	8	56
Length of stay post-positive culture, days (n=75)	11.4 (9.0)	9	3	5	15	49

* Duration of bacteremia defined as time from first positive culture to time of first negative culture

† Excluded patients if duration of bacteremia less than 3 days

‡ Excluded patients if LOS post-culture less than 3 days

Table 3. Distribution of 30-day Readmisson: PSSA at Baystate Medical Center, 2003-2013

N=69*	N (%)
30-day Readmission	
No	54 (78%)
Yes	15 (22%)

* Excluded 10 deaths and if LOS post-culture less than 3 days

Table 4. Distribution of Duration of Bacteremia by Covariates: PSSA at Baystate Medical Center, 2003-2013

	Duration of Bacteremia (days)				
n=79*	$\bar{x}$ (SD)	Median	25th %	75th %	*p*-value†
Age, years (Spearman's rho)	ρ = -0.199	---	---	---	0.08
Sex					0.31
Male	4.7 (1.5)	4	4	6	
Female	4.3 (1.5)	4	3	5	
Race					0.88
White	4.5 (1.5)	4	3	6	
Black	4.9 (1.7)	4	4	6	
Other	4.8 (1.6)	4	4	6	
Charlson Comorbidity Index					0.46
0-2	4.7 (1.3)	4	4	6	
≥ 3	4.5 (1.5)	4	3	6	
Diabetes Mellitus					0.09
Yes	5.0 (1.7)	4.5	3.5	6	
No	4.4 (1.3)	4	3	5	
Malignancy					0.33
Yes	4.1 (1.2)	4	3	5	
No	4.6 (1.5)	4	3	6	
Chemotherapy					0.06
Yes	3.0 (0.0)	3	3	3	
No	4.6 (1.5)	4	3	6	
Requirement for Dialysis					0.72
Yes	4.7 (1.4)	4.5	3.5	6	
No	4.6 (1.5)	4	3	6	
Injection Drug Use					0.38
Yes	4.0 (1.2)	4	3	4	
No	4.6 (1.5)	4	3	6	
Surgical Wound					0.55
Yes	4.3 (1.2)	4	3.5	5	
No	4.6 (1.5)	4	3	6	
Indwelling Catheter					0.29
Yes	4.4 (1.5)	4	3	5	
No	4.7 (1.5)	4.5	3	6	
ICU during Hospitalization					0.66
Yes	4.5 (1.5)	4	3	5.5	
No	4.6 (1.5)	4	3	6	
Site of Infection					0.81
Catheter Related	4.4 (1.1)	3	5	5	
Respiratory	4.2 (0.8)	4	4	5	
Endocarditis	4.2 (1.2)	4	3	5	
Osteomyelitis	5.1 (2.3)	4	3	7	
Dialysis Access	4.4 (1.7)	4	3	5	
Other	4.9 (1.4)	4.5	4	6	
Unknown	4.5 (1.5)	4	3	6	
Community Acquired Infection					0.50
Yes	4.7 (1.3)	5	4	6	
No	4.5 (1.6)	4	3	6	
Admission in Previous 90 Days					0.78
Yes	4.7 (1.4)	4.5	3.5	5.5	
No	4.5 (1.5)	4	3	6	
Admission Source					0.60
Home	4.7 (1.5)	4	4	6	
Transfer from SNF	4.1 (1.9)	3	3	5	
Emergency Department	4.4 (1.3)	4.5	3	5.5	
MD/Ref	4.2 (0.9)	4.5	3	5	
Other	5.2 (1.5)	5.5	4	6	
Infectious Disease Consult					0.90
Yes	4.6 (1.6)	4	3	6	
No	4.6 (1.3)	5	3	5	
Discharge Dispostion					0.60
Longterm Care	4.3 (1.4)	4	3	6	
Death	4.6 (1.4)	4.5	3.5	5.5	
Home	4.7 (1.5)	5	3	6	
Acute/Short-term Care	5.0 (1.9)	4	3	7	
Other	3.6 (0.6)	4	3	4	

* Excluded patients if duration of bacteremia less than 3 days

† Significance testing perfomed using Spearman's Rank Correlation for continuous and ordinal variables and ANOVA for categorical variables.

Table 5. Distribution of Total Length of Stay and Length of Stay Post-Positive Culture by Covariates: PSSA at Baystate Medical Center, 2003-2013

	Length of Stay Post-Positive Culture(days)					Total Length of Stay (days)				
N=75*	$\bar{X}$ (SD)	Median	25th %	75th %	*p*-value†	$\bar{X}$ (SD)	Median	25th %	75th %	*p*-value†
Age, years (Spearman's rho)	ρ = -0.065	---	---	---	0.58	ρ = -0.136	---	---	---	0.24
Sex					0.18					0.18
Male	12.9 (10.6)	10	5	15		20.3 (15.6)	14	10	23	
Female	9.4 (6.0)	7	5	10		15.2 (8.7)	14	8	20	
Race					0.34					0.13
White	12.1 (9.5)	9.5	6	15		19.4 (14.1)	14.5	10	25	
Black	8.6 (4.6)	7	5	12		13.2 (6.3)	12	8	18	
Other	8.5 (8.2)	5	4	8		11.8 (8.4)	9.5	8	12	
Charlson Comorbidity Index					0.97					0.71
0-2	11.7 (9.1)	8.5	4	15.5		18.4 (12.6)	16	9	22.5	
≥ 3	11.3 (9.1)	9	5	15		17.9 (13.6)	13	10	23	
Diabetes Mellitus					0.29					0.43
Yes	9.2 (5.5)	7.5	4.5	13		15.3 (8.7)	13.5	9.5	19	
No	12.4 (10.2)	9	6	15		19.4 (14.8)	14	10	24	
Malignancy					0.41					0.07
Yes	12.2 (7.1)	11.5	7	19		21.8 (10.4)	20	17	28	
No	11.2 (9.3)	8	5	15		17.5 (13.6)	13	10	21	
Chemotherapy					0.95					0.26
Yes	10.0 (6.4)	8.5	5.5	14.5		22.3 (9.9)	25.5	15.5	29	
No	11.5 (9.1)	9	5	15		17.8 (13.4)	14	10	21	
Requirement for Dialysis					0.69					0.46
Yes	13.5 (12.5)	10	4	16		21.0 (16.4)	15.5	10	28	
No	10.9 (8.1)	8	5	15		17.4 (12.5)	14	9	22	
Injection Drug Use					0.18					0.46
Yes	18.0 (14.3)	12.5	9	27		25.0 (22.8)	15.5	12.5	37.5	
No	11.0 (8.6)	8	5	15		17.7 (12.6)	14	9	23	
Surgical Wound					0.84					0.79
Yes	10.6 (7.7)	8.5	5	15		18.9 (17.0)	13	9	22	
No	11.6 (9.4)	9	5	15		17.9 (12.4)	14	10	23	
Indwelling Catheter					0.85					0.93
Yes	11.8 (10.7)	8	4	15		19.4 (15.9)	13	9	24	
No	11.1 (7.8)	9	5	15		17.1 (11.1)	14	10	21	
ICU during Hospitalization					0.24					0.13
Yes	11.7 (6.4)	10	7	17.5		20.5 (14.5)	16	11	23.5	
No	11.3 (10.1)	8	5	13		16.9 (12.5)	13	9	21	
Site of Infection					0.08					0.24
Catheter Related	8.4 (6.6)	6	4	12		14.7 (9.5)	12	7	20	
Respiratory	17.4 (6.3)	19	17	20		25.2 (10.2)	23	23	24	
Endocarditis	19.2 (17.6)	10	10	21		26.8 (21.1)	16	14	28	
Osteomyelitis	15.7 (11.6)	12	8	21		20.2 (17.9)	15	11	21	
Dialysis Access	9.4 (4.3)	10	9	10		14.8 (7.5)	13	10	13	
Other	10.5 (10.9)	7	4	13		15.2 (11.3)	10	9	17	
Unknown	9.8 (5.6)	8	5	15		18.1 (13.8)	14	9	26	
Community Acquired Infection					0.32					<0.001
Yes	11.5 (7.9)	9.5	7	15		13.1 (8.1)	10.5	8	15	
No	11.3 (9.9)	8	4	15		22.2 (15.2)	17	11	28	
Admission in Previous 90 Days					0.33					0.28
Yes	12.8 (10.5)	9.5	7	15		19.4 (13.0)	14	12	27	
No	10.8 (8.4)	8	5	15		17.5 (13.4)	14	9	22	
Admission Source					0.12					0.12
Home	10.0 (8.7)	7	5	12		15.4 (10.9)	11	9	17	
Transfer from SNF	11.2 (5.2)	10	8	15		22.0 (18.4)	15	13	28	
Emergency Department	10.7 (7.9)	8	4	19		17.0 (11.7)	13	8	24	
MD/Ref	17.7 (15.6)	12	6	24		28.1 (19.4)	27	12	42	
Other	15.3 (5.9)	15	13	17		20.2 (7.7)	20	17	28	
Infectious Disease Consult					0.04					0.02
Yes	10.2 (8.5)	8	5	12		15.4 (10.4)	12.5	9	17	
No	13.7 (9.7)	12	7	15		23.3 (16.7)	18	12	28	
Discharge Dispostion					0.23					0.49
Longterm Care	12.6 (11.4)	8	5	15		18.9 (13.5)	14	10	22	
Death	12.3 (7.8)	9	7	20		21 (12.7)	18.5	10	28	
Home	9.5 (7.9)	7	4	11		15.6 (11.4)	13	8	17.5	
Acute/Short-term Care	13.6 (6.9)	13.5	9	15		22.7 (18.9)	15.5	12	23	
Other	12.0 (5.7)	12	8	16		14.5 (3.5)	14.5	12	17	

* Excluded patients if LOS post-culture less than 3 days

† Significance testing performed using Spearman's Rank Correlation for continuous and ordinal variables, and Kruskal-Wallis for categorical variables.

Table 6. Distribution of 30-day Readmission by Covariates: PSSA at Baystate Medical Center, 2003-2013

	30-day Readmission		
N=69*	Yes [n=15 (22%)]	No [n=54 (78%)]	*p* -value †
Age, years; [$\bar{x}$ (SD)]	64 (17.4)	60 (15.7)	0.44
Sex			0.77
Male	8 (53%)	32 (59%)	
Race			0.57
White	11 (73%)	44 (81%)	
Black	2 (13%)	7 (13%)	
Other	2 (13%)	3 (6%)	
Charlson Comorbidity Index			0.17
0-2	2 (13%)	17 (31%)	
≥ 3	13 (87%)	37 (69%)	
Diabetes Mellitus			0.36
Yes	7 (47%)	17 (31%)	
Malignancy			0.36
Yes	3 (20%)	5 (9%)	
Chemotherapy			1.00
Yes	0 (0%)	3 (6%)	
Requirement for Dialysis			0.72
Yes	2 (13%)	11 (20%)	
Injection Drug Use			0.53
Yes	1 (7%)	2 (4%)	
Surgical Wound			0.46
Yes	4 (27%)	9 (17%)	
Indwelling Catheter			0.77
Yes	7 (47%)	22 (41%)	
ICU during Hospitalization			1.00
Yes	4 (27%)	16 (30%)	
Site of Infection			0.99
Catheter Related	3 (20%)	8 (15%)	
Respiratory	0 (0%)	3 (6%)	
Endocarditis	1 (7%)	3 (6%)	
Osteomyelitis	1 (7%)	6 (11%)	
Dialysis Access	1 (7%)	4 (7%)	
Other	4 (27%)	11 (20%)	
Unknown	5 (33%)	19 (35%)	
Community Acquired Infection			1.00
Yes	5 (33%)	28 (34%)	
Admission in Previous 90 Days			< 0.001
Yes	11 (73%)	11 (20%)	
Admission Source			0.64
Home/Self-Referred	7 (47%)	33 (61%)	
Transfer from SNF	2 (13%)	7 (13%)	
Emergency Department	3 (20%)	5 (9%)	
MD/Ref	2 (13%)	4 (7%)	
Other	1 (7%)	5 (9%)	
Infectious Disease Consult			0.75
Yes	11 (73%)	36 (67%)	
Discharge Dispostion			0.38
Longterm Care	6 (40%)	19 (35%)	
Home	5 (33%)	27 (50%)	
Acute/Short-term Care	3 (20%)	7 (13%)	
Other	1 (7%)	1 (2%)	

* Excluded 10 deaths and if LOS post-culture less than 3 days

† Significance testing perfomed using independent t-test for continuous variables, Wilcoxon's Rank-Sum for ordinal variables, and Fisher's Exact test for categorical variables

Table 7. Distribution of Outcomes According to Antibiotic Treatment: PSSA at Baystate Medical Center, 2003-2013

	Antibiotic Treatment												
	Penicillin [n=15 (19%)]						No/Late Penicillin [n=64 (81%)]						
n = 79*	$\bar{X}$ (SD)	Median	Min	25th %	75th %	Max	$\bar{X}$ (SD)	Median	Min	25th %	75th %	Max	*p* -value†
Duration of Bacteremia (days)	4.7 (1.8)	4	3	4	6	9	4.6 (1.4)	4	3	3	6	8	0.78
	Penicillin [n=9 (12%)]						No/Late Penicillin [n=66 (88%)]						
n = 75**	$\bar{X}$ (SD)	Median	Min	25th %	75th %	Max	$\bar{X}$ (SD)	Median	Min	25th %	75th %	Max	*p* -value†
Total Length of Stay (days)	14.3 (5.2)	14	7	12	15	26	18.6 (13.9)	14	4	9	23	71	0.82
Length of Stay Before Culture (days)	4.8 (3.7)	4	0	2	7	11	6.9 (8.7)	4	0	2	8	56	0.81
Length of Stay Post-Culture (days)	9.6 (4.7)	8	5	6	10	19	11.6 (9.5)	9	3	5	15	49	1.00

* Excluded patients if duration of bacteremia less than 3 days

** Excluded patients if LOS post-culture less than 3 days

† Significance testing performed using independent t-test for duration of bacteremia, and Wilcoxon's rank sum for total LOS, LOS before, and after culture

Table 8. Distribution of 30-day Readmisson by Antibiotic Treatment: PSSA at Baystate Medical Center, 2003-2013

N=69*	Penicillin [n=8 (12%)]	No/Late Penicillin [n=61 (88%)]	*p* -value†
30-day Readmission, N (%)			0.06
No	4 (50%)	50 (82%)	
Yes	4 (50%)	11 (18%)	

† Significance testing performed using Fisher's exact test

* Excluded 10 deaths and if LOS post-culture less than 3 days

Table 9. Unadjusted and Adjusted Multivariable Analysis of Log-Transformed Duration of Bacteremia: PSSA at Baystate Medical Center, 2003-2013

		Duration of Bacteremia					
		Unadjusted			Adjusted†		
N=79*	N(%)	Beta (SE)	95% CI	*p*- value	Beta (SE)	95% CI	*p*- value
Antibiotic Treatment							
Penicillin	15 (19%)	Referent	------		Referent	------	
No/Late Penicillin	64 (81%)	-0.02 (0.09)	-0.19 , 0.16	0.86	0.03 (0.08)	-0.15 , 0.20	0.77

† Adjusted for age, diabetes mellitus and current chemotherapy

* Excluded subjects if duration of bacteremia was less than 3 days

Table 10. Unadjusted and Adjusted Multivariable Analysis of Log-Transformed Total Length of Stay and Length of Stay Post-Positive Culture: PSSA at Baystate Medical Center, 2003-2013

		Length of Stay Post-Positive Culture (N=75)*							Total Length of Stay (N=75)*					
		Unadjusted			Adjusted†				Unadjusted			Adjusted‡		
	N(%)	Beta (SE)	95% CI	*p*- value	Beta (SE)	95% CI	*p*- value	N(%)	Beta (SE)	95% CI	*p*- value	Beta (SE)	95% CI	*p*- value
Antibiotic Treatment														
Penicillin	9 (12%)	Referent	-----		Referent	-----		9 (12%)	Referent	-----		Referent	-----	
No/Late Penicillin	66 (88%)	0.031 (0.24)	-0.46 , 0.52	0.90	0.25 (0.26)	-0.27 , 0.78	0.34	66 (88%)	0.09 (0.22)	-0.34 , 0.53	0.67	0.17 (0.20)	-0.23 , 0.58	0.40

† Adjusted for injection drug use, site of infection, admission source, ID consult, and discharge disposition

‡ Adjusted for sex, race, site of infection, community aquired infection, admission source, and ID consult

* Excluded subjects if length of stay post-culture less than 3 days

Table 11. Unadjusted and Adjusted Multivariable Analysis of 30-day Readmission: PSSA at Baystate Medical Center, 2003-2013

		Unadjusted			Adjusted†		
N=69*	N(%)	Crude OR	95% CI	*p*- value	aOR	95% CI	*p*- value
Antibiotic Treatment							
Penicillin	8 (12%)	1.00	Referent		1.00	Referent	
No/Late Penicillin	61 (88%)	0.22	0.05, 1.01	0.05	0.08	0.01, 0.63	0.02

† Adjusted for admission within previous 90 days

* Excluded 10 deaths and if LOS post-culture less than 3 days

Table 12. Propensity Score Adjusted Analysis of Log-Transformed Duration of Bacteremia: PSSA at Baystate Medical Center, 2003-2013*

		Duration of Bacteremia		
N=79†	N(%)	Beta (SE)	95% CI	*p*- value
Antibiotic Treatment				
Penicillin	15 (19%)	Referent	--	
No/Late Penicillin	64 (81%)	-0.04 (0.10)	-0.24 , 0.15	0.67

* Variables included in propensity score estimator: admission in previous 90 days, year of admission, ICU during admission, sex, race, age, injection drug use, presence of surgical wound, indwelling catheter, dialysis requirement, id consult, diabetes mellitus, and CCI

† Excluded subjects if duration of bacteremia was less than 3 days

Table 13. Propensity Score Adjusted Analysis of Log-Transformed Total Length of Stay and Length of Stay Post-Positive Culture: PSSA at Baystate Medical Center, 2003-2013*

	Length of Stay Post-Positive Culture, days (N=75)†				Total Length of Stay, days (N=75)†			
	N(%)	Beta (SE)	95% CI	*p*-value	N(%)	Beta (SE)	95% CI	*p*-value
Antibiotic Treatment								
Penicillin	9 (12%)	Referent	-----		9 (12%)	Referent	-----	
No/Late Penicillin	66 (88%)	-0.04 (0.28)	-0.60 , 0.52	0.93	66 (88%)	0.003 (0.24)	-0.49 , 0.50	0.98

* Variables included in propensity score estimator: admission in previous 90 days, year of admission, ICU during admission, sex, race, age, injection drug use, presence of surgical wound, indwelling catheter, dialysis requirement, id consult, diabetes mellitus,
† Excluded subjects if length of stay post-culture less than 3 days

Table 14. Propensity Score Adjusted Analysis of 30-day Readmission: PSSA at Baystate Medical Center, 2003-2013*

N=69†	N(%)	OR	95% CI	*p*-value
Antibiotic Treatment				
Penicillin	8 (12%)	1.00	Referent	
No/Late Penicillin	61 (88%)	0.25	0.04 , 1.59	0.14

* Variables included in propensity score estimator: admission in previous 90 days, year of admission, ICU during admission, sex, race, age, injection drug use, presence of surgical wound, indwelling catheter, dialysis requirement, id consult, diabetes mellitus, and CCI
† Excluded 10 deaths and if LOS post-culture less than 3 days

Table 15. Sensitivity Analysis of Log-Transformed Duration of Bacteremia: PSSA at Baystate Medical Center, 2003-2013‡

		Duration of Bacteremia		
		Adjusted†		
N=55*	N(%)	Beta (SE)	95% CI	*p*-value
Antibiotic Treatment				
Penicillin	19 (34%)	Referent	------	
No/Late Penicillin	36 (65%)	0.09 (0.08)	-0.06 , 0.25	0.22

† Adjusted for sex, chemotherapy, and admission source
‡ Exposure defined as penicillin treatment within 4 days
* Excluded subjects if duration of bacteremia was less than 4 days

Table 16. Sensitivity Analysis of Log-Transformed Total Length of Stay and Length of Stay Post-Positive Culture: PSSA at Baystate Medical Center, 2003-2013*

	LOS Post-Positive Culture, days (N=69)**					Total LOS, days (N=69)**		
		Adjusted‡				Adjusted†		
	N(%)	Beta (SE)	95% CI	*p*- value	N(%)	Beta (SE)	95% CI	*p*- value
Antibiotic Treatment								
Penicillin	16 (23%)	Referent	-----		16 (23%)	Referent	-----	
No/Late Penicillin	53 (77%)	0.36 (0.24)	-013 , 0.85	0.14	53 (77%)	0.22 (0.21)	-0.18 , 0.64	0.27

† Adjusted for race, icu during admission, community aquired infection, and admission source

‡ Adjusted for age, injection drug use, icu during hospitalization, community acquired infection, previous admission within 90 days, admission source, and ID consult

* Exposure defined as penicillin treatment within 4 days

** Excluded subjects if length of stay post-culture less than 4 days

Table 17. Sensitivity Analysis of 30-day Readmission: PSSA at Baystate Medical Center, 2003-2013‡

		Adjusted†		
N=63*	N(%)	aOR	95% CI	*p*- value
Antibiotic Treatment				
Penicillin	15 (23%)	1.00	Referent	
No/Late Penicillin	48 (76%)	0.09	0.01 , 0.71	0.02

† Adjusted for admission within previous 90 days

‡ Exposure defined as penicillin treatment within 4 days

* Excluded 10 deaths and if LOS post-culture less than 4 days

Figure 1. Exclusion Criteria; PSSA at Baystate Medical Center, 2003-2013

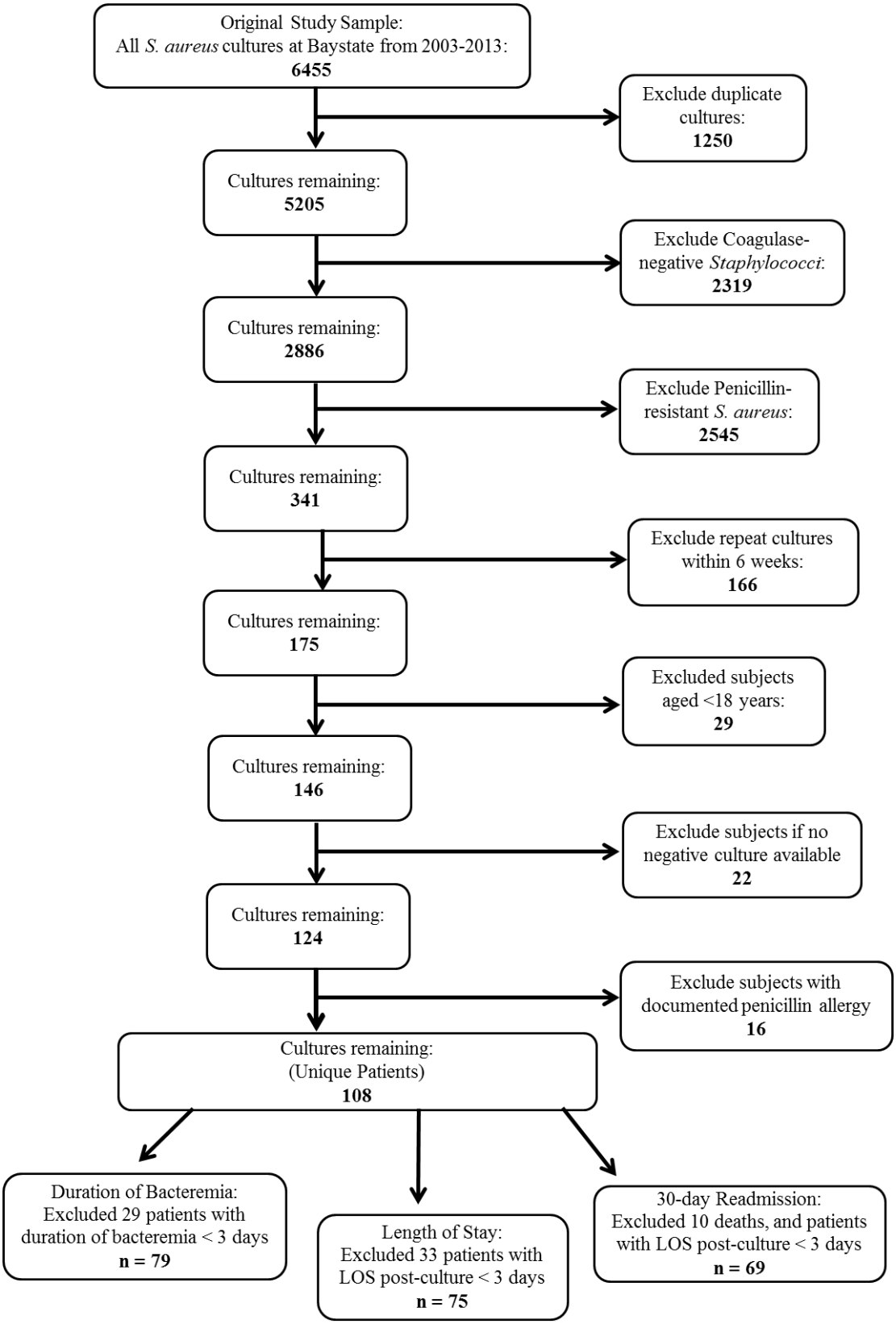


Figure 2. Histogram of Duration of Bacteremia; PSSA at Baystate Medical Center, 2003-2013

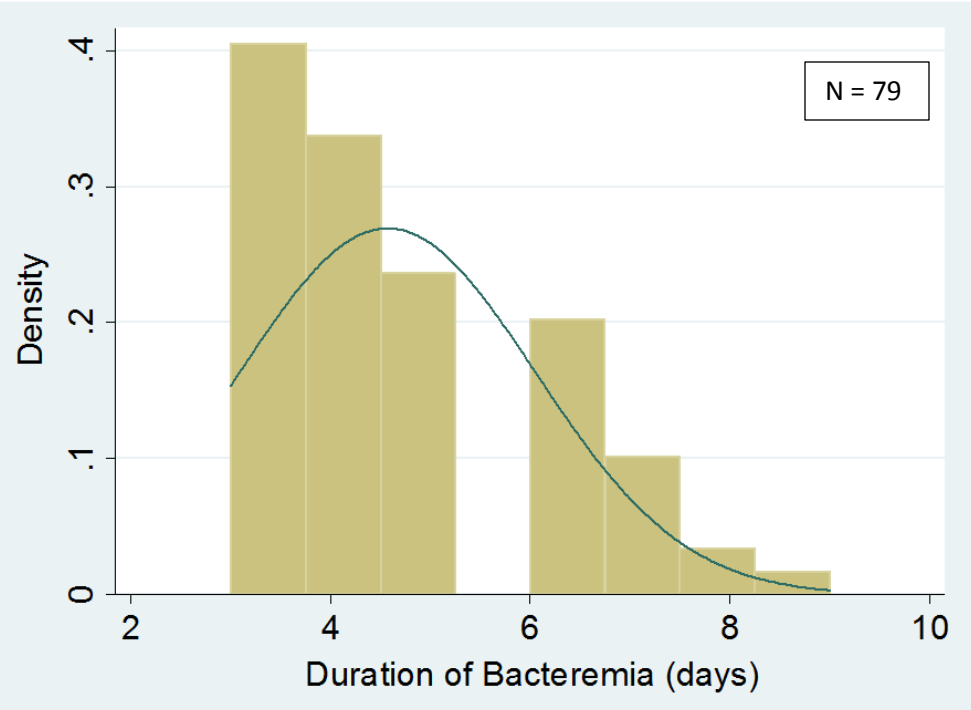


Figure 3. Histogram of Total Length of Stay; PSSA at Baystate Medical Center, 2003-2013

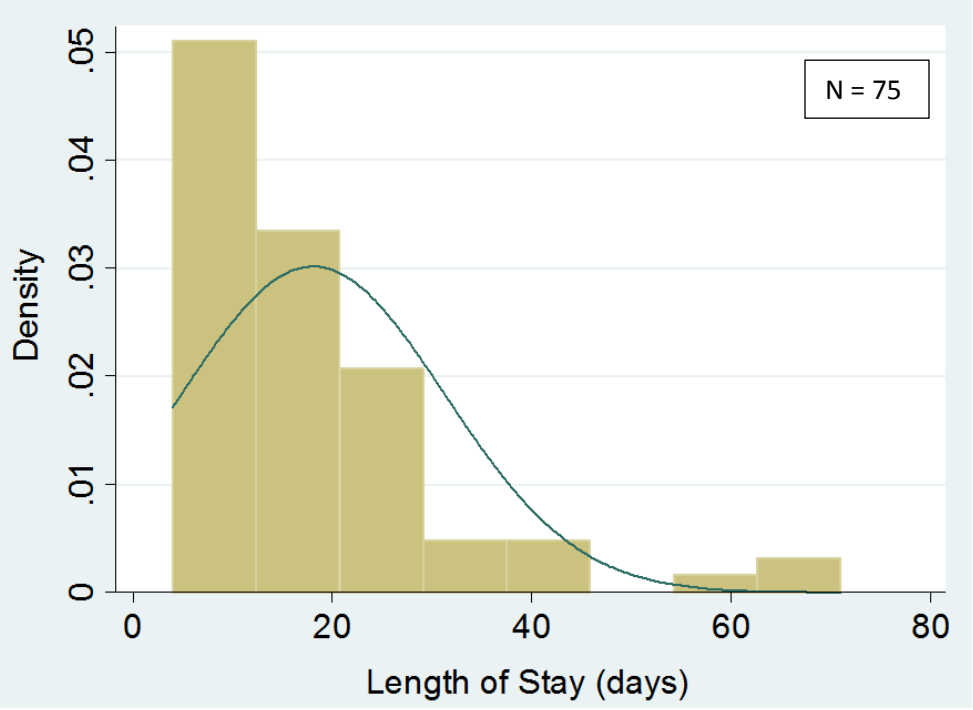


Figure 4. Kaplan-Meier Plot for Total Length of Stay; PSSA at Baystate Medical Center, 2003-2013

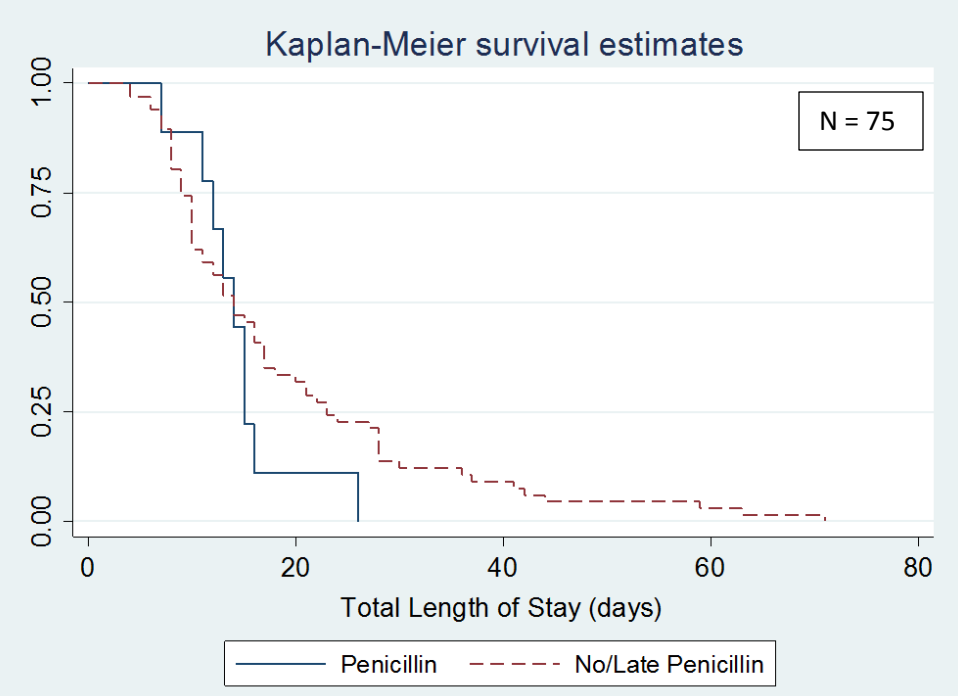


Figure 5. Histogram of Length of Stay After Positive Culture; PSSA at Baystate Medical Center, 2003-2013

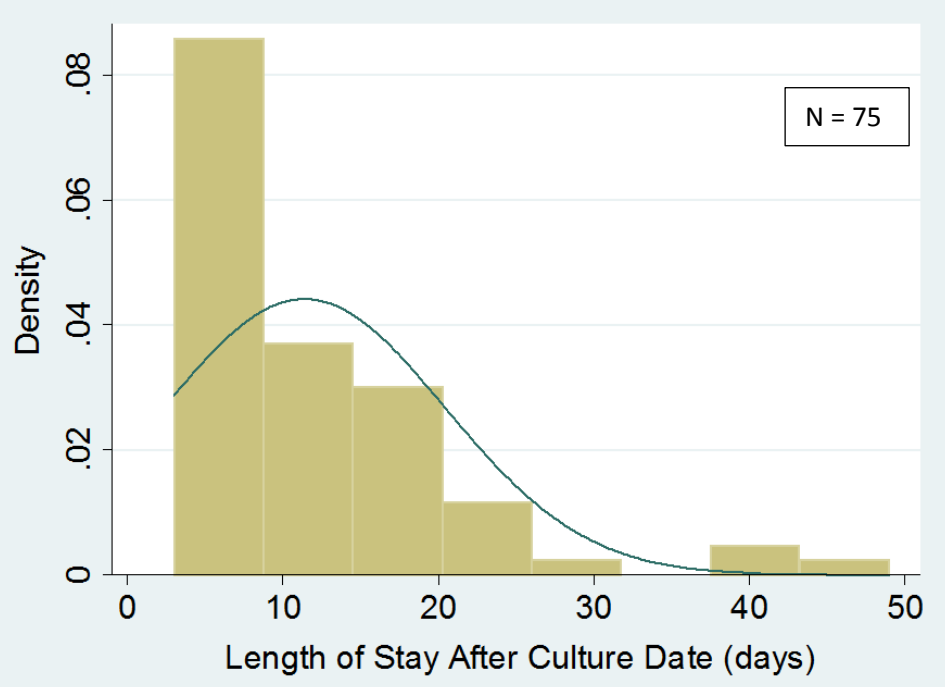
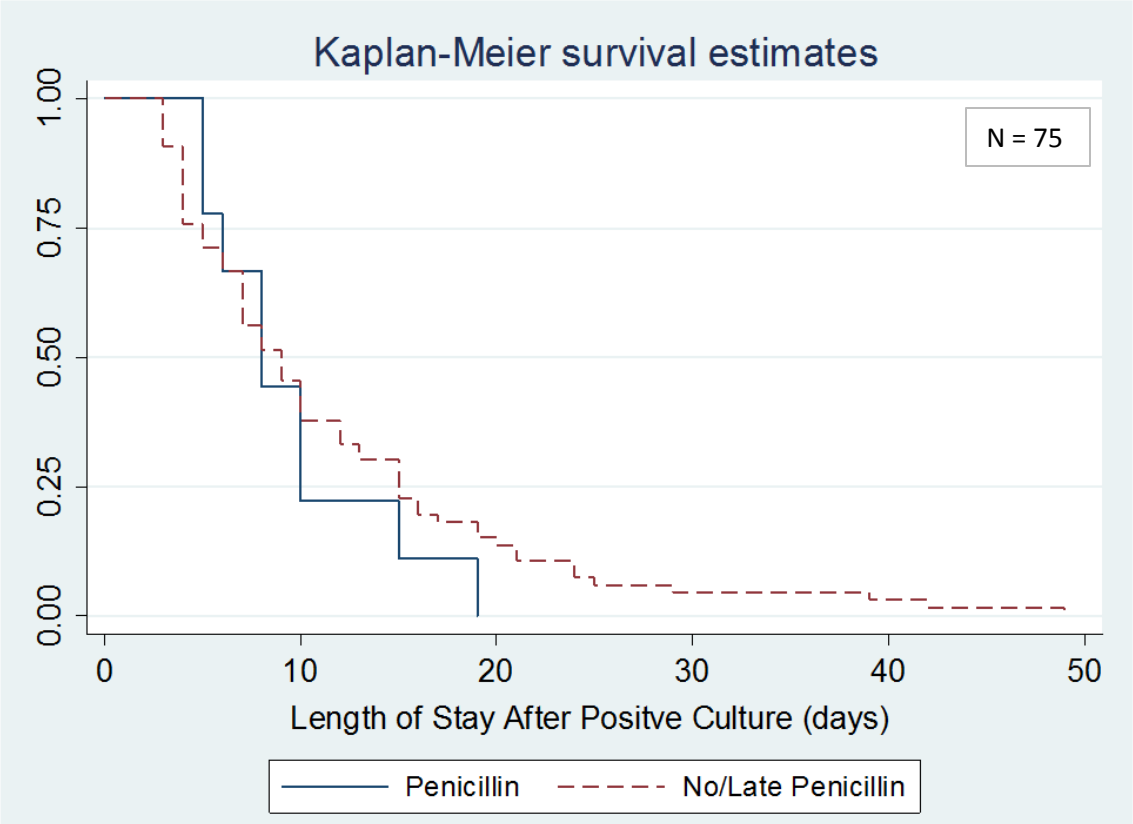


Figure 6. Kaplan-Meier Plot for Length of Stay After Positive Culture; PSSA at Baystate Medical Center, 2003-2013



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