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ORIGINAL RESEARCH

Compliance with Guidelines for Treatment of *Staphylococcus aureus* Bacteremia is Associated with Decreased Mortality in Patients Hospitalized for Community-Acquired Pneumonia with *Staphylococcus aureus* Bacteremia

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Abstract

Introduction: *Staphylococcus aureus* bacteremia has a minimum treatment duration of two weeks, while *S. aureus* community-acquired pneumonia (CAP) treatment is at least five days. Treatment failure, persistent bacteremia, and recurrence are common among patients with community-acquired *S. aureus* bacteremia. There is conflicting information in the current Infectious Diseases Society of America (IDSA) guidelines for the treatment of *S.aureus* bacteremia patients with CAP. Therefore, the appropriate treatment duration and modality for *S. aureus* CAP with bacteremia is unclear. The objective of this study was to compare outcomes among patients with *S. aureus* CAP and bacteremia treated in compliance *versus* non-compliance with IDSA *S. aureus* bacteremia guidelines.

Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) study database. Logistic regression was used to compare outcomes.

Results: A total of 117 patients with *S. aureus* CAP and bacteremia were included in the study. Compliance with *S. aureus* bacteremia guidelines was documented in 67 patients, and non-compliance was documented in 50 patients. Compliance with IDSA *S. aureus* bacteremia guidelines resulted in a decrease in odds of re-hospitalization of 30% after adjusting for confounding variables between the compliant and non-compliant groups (adjusted odds ratio (aOR) 0.70 [95% CI 0.29–1.70]; *P*=0.42). The 30-day mortality for the compliant group was 6% and for the non-compliant group was 10%; *P*=0.576. The 1-year mortality for the compliant group was 19% and for the non-compliant group was 44%; *P*=0.011.

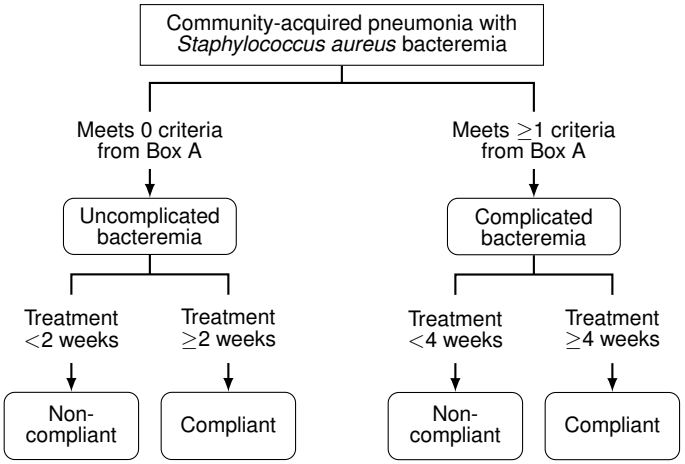
Conclusion: The present study demonstrated that when treated in compliance with IDSA guidelines for *S. aureus* bacteremia, there was decreased 1-year mortality for patients hospitalized for *S. aureus* CAP with bacteremia. In this case, the IDSA S. aureus bacteremia guidelines recommend treating uncomplicated *S. aureus* bacteremia with CAP for at least two weeks of antimicrobials and at least four weeks of antimicrobials for complicated *S. aureus* bacteremia with CAP.

Introduction

Staphylococcus aureus infections are associated with significant morbidity and mortality.[1] While *S. aureus* is responsible for less than 5% of microbiologically confirmed cases of community-acquired pneumonia (CAP), it is associated with an increased need for hospitalization, including intensive care unit (ICU) admission, increased length of hospital stay, and increased mortality compared to pneumococcal and other non-*S. aureus* causes of pneumonia.[2] Studies combining pneumonia, either acquired in the hospital or from the community, due to *S. aureus* with associated bacteremia have demonstrated mortality up to nearly 50% at 30 days.[3, 4] In addition, *S. aureus* bacteremia itself is often associated with other significant complications, such as intra-abdominal, iliopsoas, and epidural abscesses, as well as endovascular infections.[1]

The current Infectious Disease Society of America (IDSA) guidelines for CAP discuss a minimal treatment duration of five days.[5] A switch from intravenous to

Figure 1. Study population.



Box A. Complications of bacteremia

1. Temperature that did not drop below 100.5℉ during the first 3 days of antimicrobial therapy.
2. Echocardiogram revealing valvular pathology or a vegetation.
3. Prosthetic material or joints.
4. Immunocompromising condition or disease, such as organ transplantation, active neoplastic disease, autoimmune disease, or immunosuppressive therapy.
5. Metastatic sites of infection with *S. aureus*.
6. Persistent bacteremia, defined as having >1 positive blood culture for *S. aureus* when cultures drawn at least 30 minutes apart.

oral antimicrobial therapy is recommended when the patient is clinically stable and can tolerate and absorb oral antimicrobials.[5] However, there is no specific recommendation for *S. aureus* CAP complicated by bacteremia in the 2019 IDSA CAP guidelines. Therefore, the guidelines did not address this significant point and did not give specific recommendations on managing patients with *S. aureus* CAP complicated by bacteremia, thus being quite different from the IDSA guidelines for *S. aureus* bacteremia, which recommend a minimum treatment duration of 14 days for uncomplicated bacteremia and at least 4-6 weeks of intravenous antimicrobial therapy for complicated bacteremia.[6] Given the conflicting information in the current IDSA guidelines, the appropriate treatment duration and modality for *S. aureus* CAP with associated bacteremia remains unclear. A recent opinion piece addressed this conflict in treatment recommendations and suggested that in cases of *S. aureus* CAP associated with bacteremia, bacteremia itself should be the primary diagnosis guiding treatment.[7] However, more definitive data are needed to support this recommendation. The objective of this study was to compare outcomes among patients with *S. aureus* CAP with bacteremia treated in compliance *versus* non-compliance with IDSA *S. aureus* bacteremia guidelines.

Methods

Study design and subjects

The study design was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) study database. CAPO is a retrospective observational study of hospitalized adults with CAP in 130 institutions in 28 countries. Patients included in the study were hospitalized at four specific Louisville hospitals with CAP and at least one blood culture positive for *S. aureus*. Continuous patients were included from December 2012 to March 2018. Patients were excluded if they were pregnant, had a history of intravenous drug use, were younger than 18 years of age, had antimicrobials or medical care withdrawn during the study, did not have follow-up blood cultures, or left against medical advice. This study was approved by the University of Louisville Institutional Review Board (IRB number 11.0613).

Definitions

A patient was defined as having CAP when the following two criteria were met: 1) presence of a new pulmonary infiltrate on chest radiograph or chest computed tomography scan at the time of hospitalization and 2) at least one of the following: a) new cough or increased cough or sputum production, b) fever >37.8 °C (100.0 °F) or hypothermia <35.6°C (96.0°F), c) changes in leukocyte count (leukocytosis: >11,000 cells/mL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/mL).

A patient with CAP with *S. aureus* bacteremia was defined as a patient admitted to the hospital for CAP in whom *S. aureus* was isolated from a blood culture. Patients with hospital-acquired pneumonia (HAP) were omitted.

A patient was defined as being compliant or non-compliant with the IDSA *S. aureus* guidelines based on having complicated or uncomplicated bacteremia and on the duration of therapy (see **Figure 1**). A patient was defined as having complicated bacteremia when one or more of the following was present: 1) a temperature that did not drop below 100.5 °F during the first three days of antimicrobial therapy; 2) an echocardiogram revealing valvular pathology or vegetation; 3) prosthetic material or joints; 4) an immunocompromis-

Table 1. Patient Characteristics of *Staphylococcal aureus* CAP Bacteremia Patients as Non-Compliant and Compliant with IDSA *S. aureus* Bacteremia Guidelines.

	Non-compliant* (*n*=50)	Compliant* (*n*=67)	*P*	Missing (%)
Demographics				
Age	58 [49, 72]	59 [46, 70]	0.637	0
Male sex	23 (46)	32 (48)	0.999	0
African American	2 (4)	2 (3)	0.441	0
Laboratory findings				
Heart rate (beats/minute)	114 [104, 129]	112 [100, 125]	0.236	0
Respiratory rate (breaths/minute)	24 [20, 29]	24 [20, 30]	0.606	0
Systolic blood pressure (mmHg)	106 [88, 124]	104 [92, 119]	0.851	0
Diastolic blood pressure (mmHg)	50 [42, 59]	54 [45, 61]	0.470	0
Temperature (℃)	38 [37, 39]	38 [37, 39]	0.491	0
PaO_2 (mm Hg)	66 [56, 86]	88 [66, 103]	0.043	64.1
Blood urea nitrogen (mg/dL)	21 [17, 41]	29 [16, 36]	0.517	0
Serum glucose (mg/dL)	140 [111, 189]	143 [118, 199]	0.550	0.9
Serum sodium (mEq/L)	138 [134, 141]	135 [132, 139]	0.081	0
Hematocrit	33 [29, 36]	32 [28, 36]	0.589	0
Medical and social history				
Altered mental status	16 (32)	16 (24)	0.444	0
Alcohol abuse	3 (6)	2 (3)	0.737	0
Congestive heart failure	13 (26)	15 (22)	0.815	0
COPD	18 (36)	14 (21)	0.109	0
Diabetes mellitus type II	20 (40)	29 (43)	0.868	0
Neoplastic disease	8 (16)	5 (7)	0.248	0
Renal disease	13 (26)	21 (31)	0.672	0
Cerebrovascular disease	12 (24)	6 (9)	0.049	0
Renal failure	9 (18)	10 (15)	0.847	0
Suspicion of aspiration	3 (6)	3 (4)	1	0
Nursing home resident	8 (16)	8 (12)	0.719	0
Hospitalized >2 days in the prior 90 days	21 (42)	28 (42)	1	0
Home infusion therapy in the prior 30 days	8 (16)	4 (6)	0.144	0
Chronic dialysis in the prior 30 days	4 (8)	7 (10)	0.898	0
Home wound care	2 (4)	5 (7)	0.699	0
Family history of coronary artery disease	14 (28)	17 (25)	0.915	0
Coronary artery disease	13 (26)	17 (25)	1	0
Essential arterial hypertension	32 (64)	40 (60)	0.779	0
Hyperlipidemia	18 (36)	27 (40)	0.779	0
Prior myocardial infarction	10 (20)	8 (12)	0.349	0
Prior PTCA/CABG	7 (14)	11 (16)	0.921	0
Severity of disease				
Ventilatory support received	10 (20)	14 (21)	1	0
Vasopressors received	7 (14)	6 (9)	0.594	0.9
Direct admission to the ICU	16 (32)	22 (33)	1	0
Pneumonia severity index				
Risk class			0.725	
Risk Class I	4 (8)	4 (6)		
Risk Class II	9 (18)	12 (18)		
Risk Class III	6 (12)	9 (13)		
Risk Class IV	12 (24)	23 (34)		
Risk Class V	19 (38)	19 (28)		
Pneumonia severity index	116 [70, 150]	105 [74, 138]	0.405	

Abbreviations: ABX, antibiotics; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IQR, interquartile range; PTCA/CABG, percutaneous transluminal coronary angioplasty/coronary artery bypass grafting.

* Compliance defined as following IDSA Guideline reocmmended antimicrobial treatment. Data summarized as *n* (%) or median [IQR].

Table 2. Reasons for readmission within one year among patients with *Staphylococcus aureus* community-acquired pneumonia and bacteremia.

Diagnosis	*n* (%)
Bacteremia	16 (40)
Sepsis/septic shock	6 (15)
Pneumonia	5 (13)
Endocarditis	3 (8)
Line/port/vascular graft infection	3 (8)
Osteomyelitis	2 (5)
Cellulitis	2 (5)
Septic arthritis	1 (3)
Abscess	1 (3)

ing condition or disease, such as organ transplantation, active neoplastic disease, autoimmune disease, or immunosuppressive therapy; 5) metastatic sites of infection with *S. aureus*; or 6) persistent bacteremia, defined as having more than one blood culture positive for *S. aureus* when cultures were drawn at least 30 minutes apart. A patient who did not meet the criteria for complicated bacteremia was considered to have uncomplicated bacteremia.[7]

Patients were divided into two groups depending on the treatment received during hospitalization. Patients were included in the compliant group if antimicrobials were prescribed according to the IDSA guidelines for *S. aureus* bacteremia. Patients with uncomplicated bacteremia should receive two weeks of an intravenous antimicrobial. Any patient presenting with complicated bacteremia should receive at least four weeks of intravenous antimicrobial treatment. Patients with a shorter duration of therapy were included in the non-compliant group.

Outcomes evaluated were time to negative follow-up blood cultures, re-hospitalization within one year due to complications of *S. aureus* bacteremia, and 30-day, 6-month, and 1-year mortality. Death was considered as all-cause mortality. Readmission was defined as any subsequent admission within one year where *S. aureus* was isolated in culture and learned from the fluid. Echocardiogram results were collected from medical records to confirm valvular pathology or the presence of a vegetation.

Statistical analysis

Continuous variables were represented as medians and interquartile ranges. Categorical variables were represented as frequencies and percentages. Baseline categorical variables were compared using Chi-squared tests of independence, and continuous patient variables were compared using Mann-Whitney U tests. After adjusting for history of cerebrovascular disease and pneumonia severity index, logistic regression was used to compare mortality and readmission. Time to negative blood culture, readmission, and death were analyzed using Kaplan-Meier curves and compared using the log-rank test. A *P*-value less than 0.05 was considered significant.

Results

A total of 117 patients with *S. aureus* CAP and bacteremia met inclusion criteria. Compliance with *S. aureus* bacteremia guidelines was documented in 67 patients, and non-compliance was documented in 50 patients. Patient characteristics are shown in **Table 1**. *S. aureus*–related re-hospitalizations occurred in 23% of patients overall within one year. 21% *versus* 26% of patients were re-hospitalized within one year in the compliant and non-compliant groups, respectively. Reasons for readmission within one year among patients with *S. aureus* community-acquired pneumonia and bacteremia are shown in **Table 2**. Treatment compliance with IDSA guidelines for *S. aureus* bacteremia did not significantly influence re-hospitalization for either group; (adjusted odds ratio [aOR] 0.70 [95% CI: 0.29–1.70]; *P*=0.42; **Figure 2**).

Mortality

The 30-day mortality for the entire population was 7.7%. The 30-day mortality was 6% for the compliant group, and 10% for the non-compliant group. Adjusting for potential confounding variables, the difference in 30-day mortality between the compliant and non-compliant groups was not statistically significant (aOR 0.67 [95% CI 0.15–2.83]; *P*=0.576). (**Table 3**)

The 6-month mortality for the total population was 24%. For the compliant group, the 6-month mortality was 18%, and for the non-compliant group, it was 32%. Adjusting for potential confounding variables, the difference in 6-month mortality between the compliant and non-compliant groups was not statistically significant (aOR 0.51 [95% CI 0.19–1.36]; *P*=0.178). (**Table 3**)

The 1-year mortality for the total population was 30%. For the compliant group, the 1-year mortality was 19%, and for the non-compliant group, it was 44%. Adjusting for potential confounding variables, the compliant

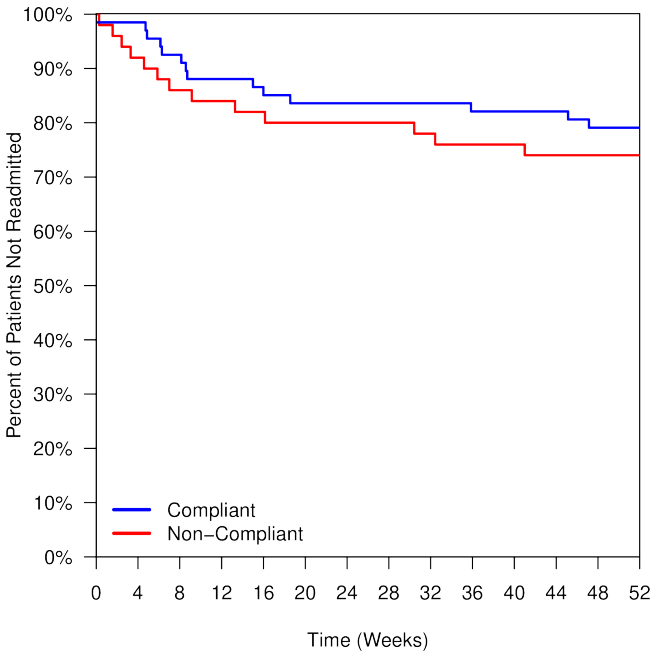


Figure 2. Kaplan–Meier curve for time to readmission within one year of hospitalization for community-acquired pneumonia with *S. aureus* bacteremia.

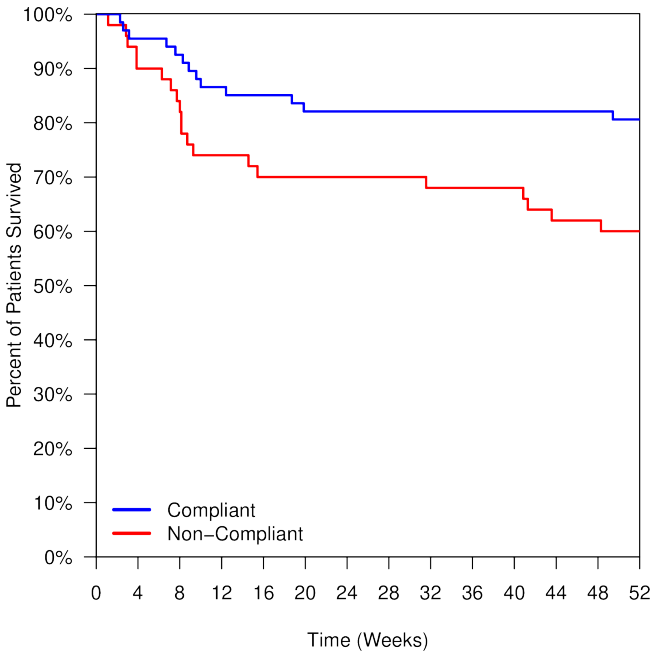


Figure 3. Kaplan–Meier curve for time to death over one year after hospitalization for community-acquired pneumonia with *S. aureus* bacteremia.

group had a 69% reduction in 1-year mortality compared to the non-compliant group (aOR 0.31 [95% CI 0.12–0.76]; *P*=0.011). (**Table 3** and **Figure 3**)

Time to negative blood culture (median [interquartile range]) in the compliant group was 3.6 [1.04, 4.18] days compared to 2.4 [2.34, 6.02] days in the non-compliant group; *P*=0.142 (**Table 4** and **Figure 4**).

Discussion

The present study demonstrated that patients with *S. aureus* CAP plus bacteremia, when treated according to the IDSA guidelines for *S. aureus* bacteremia (compliant) rather than the IDSA guidelines for CAP (non-compliant), had a 69% reduction in 1-year mortality (aOR 0.31 [95% CI 0.12–0.76]; *P*=0.011). Suggesting a longer course of antimicrobials for CAP beyond the 5-7 days recommended per the IDSA CAP guidelines may be necessary if *S. aureus* bacteremia is also present to reduce the risk of complications. Following the IDSA guidelines for *S. aureus* bacteremia may improve long-term mortality (1 year) for patients with *S. aureus* CAP who also have *S. aureus* bacteremia.

During readmission within one year after admission for CAP with *S. aureus* bacteremia, subsequent hospitalization due to *S. aureus* infection, such as bacteremia, sepsis, endocarditis, or pneumonia (as shown in **Table 2**) was seen in 40% of patients. These results show that *S. aureus* bacteremia with CAP is a severe infection with a higher subsequent hospitalization rate for complications. Furthermore, it is recommended to follow-up care of these patients upon hospital discharge.

The present study showed significantly lower mortality than previously described for *S. aureus* bacteremia in patients with HAP or CAP. De la Calle *et al.* reported 30-day total mortality for *S. aureus* bacteremia HAP and CAP as 46.9%.[3] *S. aureus* bacteremia HAP patients may be more likely to have multiple hospital-associated complications with subsequent higher mortality than *S. aureus* bacteremia CAP patients. However, even the 30-day mortality for *S. aureus* CAP with bacteremia has been reported as high as 37%.[3] Again, this may reflect that most of our patients were treated with a longer duration of intravenous antibiotic therapy, complying with IDSA guidelines for *S. aureus* bacteremia. Thus, providing adequate treatment of the bacteremia itself is the primary predictor of outcomes for CAP patients with *S. aureus* bacteremia.

In the present study, 30-day and 6-month mortality among the compliant and non-compliant groups was not statistically significant, but the 1-year mortality was; *P*=0.01. Hence, no improvement in outcomes will be appreciated when complying or not complying with the IDSA *S. aureus* bacteremia guidelines until one year. However, this is a benefit of reporting long-term outcomes—to show that certain management is associated with higher survival. Therefore, in this case,

Table 3. Mortality outcomes at 30 days, six months, and one year for patients hospitalized for community-acquired pneumonia with *S. aureus* bacteremia.

Mortality	Non-compliant	Compliant	Odds ratio [CI]	*P*
30-day	5 (10)	4 (6)	0.67 [0.16–2.83]	0.57568
6-month	16 (32)	12 (18)	0.51 [0.19–1.36]	0.17778
1-year	22 (44)	12.7 (19)	0.31 [0.062–0.50]	0.01142

Table 4. Time to negative blood culture for patients hospitalized for community-acquired pneumonia with *S. aureus* bacteremia.

	Time to negative blood culture, median [IQR]	*P*
		0.142
Compliant group (≥14-day treatment)	3.57 [1.04, 4.18]	
Non-compliant group (<14-day treatment)	2.42 [2.34, 6.02]	

Abbreviations: IQR, interquartile range.

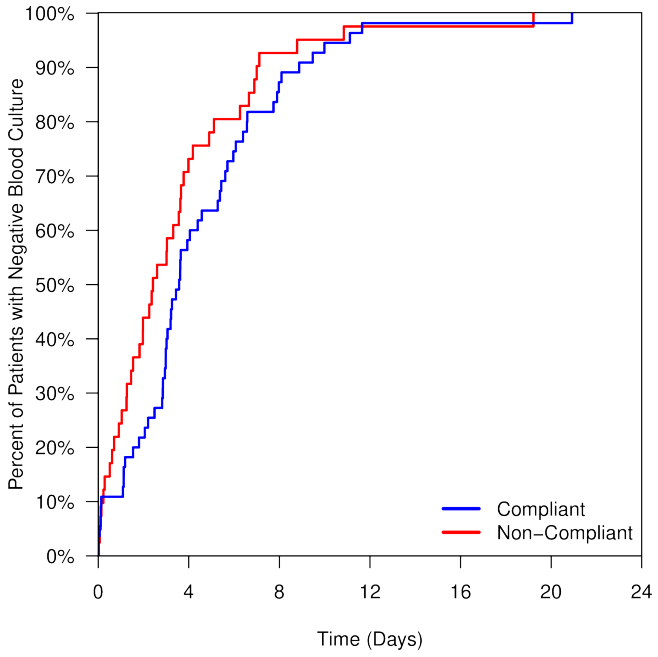


Figure 4. Kaplan–Meier curve for time to negative blood culture (in days) for patients hospitalized for community-acquired pneumonia with *S. aureus* bacteremia.

the IDSA *S. aureus* bacteremia guidelines dictate treating uncomplicated *S. aureus* bacteremia with CAP for at least two weeks of antimicrobials and at least four weeks of antimicrobials for complicated *S. aureus* bacteremia with CAP.

A study describing long-term outcomes for all *S. aureus* infections described a 42% mortality for patients within one year of diagnosis and further reported that 43% of the patients required re-hospitalization within that year.[8] While that study did not describe the differences in treatment among the different types of *S. aureus* infections, most of the patients were treated for skin and soft tissue infections.[8] The proportion of our patients who required re-hospitalization for our entire population was 23%. Perhaps this lower proportion was because a large proportion of the patients in our study had an infectious diseases consultation. Eighty percent of the patients included in the present study had an infectious diseases consultation, with 96% of those patients being treated in compliance with IDSA guidelines for *S. aureus* bacteremia. Infectious diseases consultation has demonstrated improved outcomes for patients with *S. aureus* bacteremia.[9] In addition, some studies found that at least 50% of patients with *S. aureus* bacteremia will develop complicated bacteremia [10], which supports appropriate management to prevent subsequent complications and hospitalizations.

Limitations of the present study primarily include its retrospective nature and relatively low number of patients (sample size of 117). Study strengths include an evaluation of long-term outcomes, including mortality as well as re-hospitalization. The two groups also had similar patient characteristics.

Overall, the present study suggests that adequate treatment of patients hospitalized for *S. aureus* CAP with bacteremia in compliance with IDSA *S. aureus* bacteremia guidelines decreases the odds of rehospitalization within the following year and improves long-term mortality. However, further research is needed to determine whether there is a difference in non-mortality outcomes, such as long-term complications.

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References

1. Que Y-A, Moreillon P. *Staphylococcus aureus* (including staphylococcal toxic shock syndrome). In: Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Eighth ed. Philadelphia, PA: W.B. Saunders, **2015**:2237-71.e5.

2. Self WH, Wunderink RG, Williams DJ, et al. *Staphylococcus aureus* community-acquired pneumonia: Prevalence, clinical characteristics, and outcomes. Clin Infect Dis **2016**; 63(3):300-9. doi: 10.1093/cid/ciw300. PMID: 27161775.

3. De la Calle C, Morata L, Cobos-Trigueros N, et al. *Staphylococcus aureus* bacteremic pneumonia. Eur J Clin Microbiol Infect Dis **2016**; 35(3):497-502. doi: 10.1007/s10096-015-2566-8. PMID: 26780692.

4. González C, Rubio M, Romero-Vivas J, González M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis **1999**; 29(5):1171-7. doi: 10.1086/313440. PMID: 10524959.

5. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med **2019**; 200(7):e45-e67. doi: 10.1164/rccm.201908-1581ST. PMID: 31573350.

6. 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. Clin Infect Dis **2011**; 52(3):e18-55. doi: 10.1093/cid/ciq146. PMID: 21208910.

7. Ramirez JA, File T, Musher D. Duration of antibiotic therapy for patients with bacteremic *Staphylococcus aureus* comunity-acquired pneumonia. Univ Louisville J Respir Infect **2018**; 2(1):Article 1. doi: 10.18297/jri/vol2/iss1/1.

8. Haessler S, Mackenzie T, Kirkland KB. Long-term outcomes following infection with meticillin-resistant or meticillin-susceptible *Staphylococcus aureus*. J Hosp Infect **2008**;

69(1):39-45. doi: 10.1016/j.jhin.2008.01.008. PMID: 18353493.

9. Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from *Staphylococcus aureus* bacteremia. Medicine (Baltimore) **2009**; 88(5):263-7. doi: 10.1097/MD.0b013e3181b8fccb. PMID: 19745684.

10. Guimaraes AO, Cao Y, Hong K, et al. A prognostic model of persistent bacteremia and mortality in complicated *Staphylococcus aureus* bloodstream infection. Clin Infect Dis **2019**; 68(9):1502-11. doi: 10.1093/cid/ciy739. PMID: 30165412.