Maternal Bacteremia Caused by *Staphylococcus aureus* with a Focus on Infective Endocarditis

Morgan K. Morelli, MD, Michael P. Veve, PharmD, MPH, Mahmoud A. Shorman, MD

1University of Tennessee Medical Center, Knoxville, TN, 37920, USA
2Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Knoxville, TN, 37920, USA
3Department of Internal Medicine, University of Tennessee Graduate School of Medicine, Knoxville, TN, 37920 USA

#Address correspondence to Mahmoud A. Shorman, E-mail: mshorman@utmck.edu

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Abstract

**Background:** Sepsis is an important cause of morbidity and mortality in the pregnant patient. Injection drug use in pregnant populations have led to increased cases of bacteremia and infective endocarditis (IE) due to *Staphylococcus aureus*. We describe all cases of *S. aureus* bacteremia and IE among admitted pregnant patients at our hospital over a six-year period.

**Methods:** Retrospective review of hospitalized pregnant patients with *S. aureus* bacteremia was analyzed between 4/2013-11/2019. Maternal and fetal in-hospital mortality were primary outcomes measured; secondary outcome was the rate of 6-month maternal readmission.

**Results:** Twenty-seven patients were included; 15 (56%) had IE. The median (IQR) age was 29 (25-33) years; 22 (82%) patients had methicillin-resistant *S. aureus*. Infection onset occurred at a median (IQR) of 29 (23-34) weeks gestation. Twenty-three (85%) mothers reported active injection drug use, and 21 (78%) had were hepatitis C seropositive. Fifteen (56%) mothers required intensive care unit (ICU) care. Twenty-two (81%) patients delivered 23 babies; of the remaining 5 mothers, 3 (11%) were lost to follow up and 2 (7%) terminated pregnancy. Sixteen (73%) babies required neonatal ICU care, and 4/25 (16%) infants/fetuses died during hospitalization. One (4%) mother died during hospitalization, and 7/26 (27%) mothers were readmitted to the hospital within 6-months for infectious complications.

**Conclusion:** Injection drug use is a modifiable risk factor for *S. aureus* bacteremia in pregnancy. Fetal outcomes were poor, and mothers were frequently readmitted secondary to infection. Future targeted interventions are needed to curtail injection drug use in this population.

**Key words:** Pregnancy, *Staphylococcus aureus*, bacteremia, infective endocarditis, injection drug use
Introduction

Maternal sepsis in the United States continues to be a common cause of mortality and morbidity, accounting for up to 15% of all maternal deaths and up to 5% of intensive care unit (ICU) admissions.\(^1\) It is generally caused by *Escherichia coli* or other common sources of genitourinary infections.\(^2\) Throughout the years, there has been an increase in published case reports on *Staphylococcus aureus* bacteremia and infective endocarditis (IE) in pregnant patients.\(^3\)\(^-\)\(^5\) There are few cohorts describing patient characteristics, ideal treatment, or maternal and fetal outcomes beyond these case reports.\(^6\)

Recent increases in the incidence of people who inject drugs (PWID), even among pregnant patients, have led to subsequent infection-related complications such as hepatitis C, skin and soft tissue infections, IE, and death.\(^7\) The incidence of bacteremia in the pregnant population has been found to be around 2 in 1,000 live births.\(^2\)\(^,\)\(^8\)\(^,\)\(^9\) The incidence of IE in pregnant women, although rare (1 in 100,000), can lead to devastating complications including increased maternal and fetal morbidity and mortality.\(^10\) Additional data are needed to identify best practice recommendations in pregnant patients with infections, particularly *S. aureus* bacteremia.

The purpose of this study is to describe characteristics and outcomes of *S. aureus* bacteremia in pregnant patients at our hospital over a six-year period.

Methods

A retrospective case series of hospitalized pregnant patients with *S. aureus* bacteremia was analyzed between April 2013 and November 2019 at an academic medical center in Knoxville, Tennessee. Data collected for descriptive analysis were demographic, obstetric, microbiologic,
radiologic, substance use status, treatment, and mortality through chart review of the electronic medical record. A list of female patients under age 50 with the discharge diagnosis “bacteremia” was cross matched with patients with a diagnosis of “pregnancy” to narrow search results. The University of Tennessee Graduate School of Medicine institutional review board approved the study.

Hospitalized adult patients were included if they i) had culture confirmed \textit{S. aureus} isolated from blood cultures and ii) had a confirmed pregnancy diagnosis. The source of bacteremia was determined from review of electronic medical records. For patients with multiple infections, the following cascade was used as a means to quantify primary disease by severity: endocarditis > osteoarticular infection > other bacteremia. Patients with IE were confirmed to be definite by the modified Duke criteria.\textsuperscript{11} The Pitt bacteremia score was calculated using the scoring system based on available information from 48 hours within the first positive blood culture.\textsuperscript{12} Readmission and mortality data were collected by reviewing the electronic medical record for hospitalization after the initial \textit{S. aureus} bacteremia diagnosis.

Descriptive and bivariate statistics were used to describe the patient population; categorical variables were compared by Pearson’s chi-square or Fisher’s exact test and continuous variables were compared by the student’s t-test or the Mann-Whitney U-test. All statistical analyses were performed using SPSS Software for Macintosh v.26.0 (IBM Corp, Armonk, NY).

\textbf{Results}

Twenty-seven patients met inclusion criteria. Demographic and clinical data of each patient is listed in Table 1. The median (IQR) age was 29 (25-33) years, and the median (IQR) duration of pregnancy at the time of infection diagnosis was 28 (9-38) weeks. The median (IQR) length of stay was
13 (8-31) days. Twenty-three (85%) patients reported active injection drug use, and 7 (30%) had a history of or active medication assisted therapy use. Twenty-one (78%) patients were hepatitis C virus seropositive, and 21 (78%) reported concomitant tobacco use during pregnancy. Eleven (41%) patients lived in a rural location based on ZIP code; 16 (60%) patients had a documented history of receiving prenatal care. Ten (37%) patients were previously hospitalized within 90 days before the index admission.

Only 5 (19%) patients presented with a fever on admission. Fifteen (56%) mothers required intensive care while hospitalized; the documented rationale of escalation of care to ICU included severe sepsis or shock (10, 68%), respiratory failure (4, 26%), and pregnancy-related care (1, 7%) due to concerns for intrauterine fetal demise and hemorrhage. The median (IQR) duration of ICU stay was 4 (3-10) days. All patients had previous pregnancies, and the median (IQR) number of pregnancies was 3 (2-4); the median (IQR) number of previously aborted or lost fetuses was 2 (1-2).

The primary sources of bacteremia included IE (56%), skin and soft tissue infection (19%), bone and joint infection (11%), endometritis (7%), and unknown source (7%). Five (33%) of the patients diagnosed with IE were also found to have a concomitant source including septic arthritis and empyema. MRSA accounted for 81% infections. Valves involved in the IE patients included tricuspid (87%), mitral (7%), and one (7%) patient had both tricuspid and aortic valve involvement. Nine (60%) IE patients underwent anesthesia for a trans-esophageal echocardiogram. All 15 of patients with IE had evidence of septic emboli.

Eleven (41%) patients had a procedure performed to obtain source control for their bacteremia, which included percutaneous drain placement, debridement, and/or arthrocentesis. Five (45%) of these
procedures were completed within the first 72 hours of admission. Three (20%) IE patients underwent valve replacement, two while pregnant and one during the index hospitalization after delivery.

Indications for valve replacement were due to the following: 1 patient had multiple tricuspid vegetations (i.e., >2cm) with severe tricuspid regurgitation, another patient had multiple mitral vegetations (i.e., >1cm) with severe mitral regurgitation, and the last patient had worsening aortic insufficiency secondary to IE).

Twenty-two (81%) patients delivered a baby at a median (IQR) of 34 (32-37) weeks gestation. Outcomes of mother and infant are outlined in Table 2. Twenty-three babies were born due to one set of twins. Three patients (11%) were lost to follow-up; 1 (4%) had a miscarriage at 17 weeks gestation, and one patient (4%) underwent an elective abortion. Fifteen (68%) deliveries occurred prematurely prior to 36 weeks gestation, and 17 (74%) babies required neonatal intensive care. Two (9%) infants died, and the overall infants or fetal mortality was 4/25 (16%).

All patients received intravenous antibiotic therapy with in vitro activity against S. aureus within 1 hour of positive blood cultures. The most common antibiotic therapies were: vancomycin (10, 37%), cefazolin (5, 19%), daptomycin (4, 15%), anti-MRSA combination therapy (4, 15%), and other (4, 15%). One patient only had antibiotics for two days according to the treating physician plan; she did not have an infectious disease consultation during her hospital stay. The median (IQR) duration of antibiotic therapy was 6 (4-6) weeks; the majority of patients received intravenous therapy, and 1 (4%) patient was transitioned to oral linezolid for uncomplicated S. aureus bacteremia.

Only one (4%) mother died while hospitalized secondary to IE; this patient had a Pitt bacteremia score of 10, while all other patients presented with a median score of zero. Twenty-one of 26 (81%)
surviving mothers were treated in the hospital or discharged to receive care at a skilled nursing facility; 5 (19%) patients left the hospital against medical advice (AMA). Seven of 26 (27%) mothers were readmitted to the hospital within 6 months for infectious complications; 4/7 (57%) due to *S. aureus* infections and 3/7 (43%) due to different bacteria (Table 2). Two out of 7 (29%) had recurrent *S. aureus* bacteremia.

A comparison of the patients diagnosed with IE compared to the other *S. aureus* bacteremia sources was also performed. The patients in these groups are similar in age and have no differences in PWID, smoking, or were hepatitis C seropositive. Patients with IE more frequently required an intensive care unit (ICU) stay (*P*=0.004) and mechanical ventilation (*P*=0.008). There was not a significant difference in the use of vasopressors (*P*=0.182).

Discussion

This study found high rates of poor outcomes in pregnant patients, as well as their infants, who presented with *S. aureus* bacteremia. Importantly, injection drug use was common among mothers, all of which had previous pregnancies and aborted or lost fetuses. On-going injection drug use in women of child-bearing age represents a serious public health concern and likely leads to unplanned pregnancies or other complications involving fetal outcomes. Additionally, maternal sepsis can be difficult to initially diagnose as some symptoms such as tachycardia and tachypnea can be normal physiologic changes of pregnancy. Because of this, there may be delays in appropriate management, especially with antibiotic administration.¹ Healthcare workers need to be cognizant of these normal changes but also be aware that they can be warning signs of sepsis even if fever was absent; only 19% of the patients in our cohort presented with fever. Using a scoring system such as Sepsis in Obstetrics Score may help in early identification of pregnant women at risk for ICU admission from the ED for sepsis.¹
There are no case series or literature reviews dedicated to *S. aureus* bacteremia in pregnant women to our knowledge. In our cohort, only 19% of cases were caused by MSSA; MRSA was the overwhelming cause of disease and is likely reflective of the prevalence of community-acquired MRSA in the southeast United States. Other studies investigating maternal bacteremia found *S. aureus* to be the cause in only 3-4% of cases.\(^8,9\) Our rates of MRSA infection are higher than even what is seen in the general United States population, with an estimated 40% of *S. aureus* bacteremia being due to MRSA.\(^13\) One recent study found that 24% of the MRSA bloodstream infections in Tennessee between 2015-2017 were attributed to injection drug use, mostly among Caucasian women between 18-49 years. PWID are at higher risk of MRSA infection due to skin trauma, shared needles or other uncleaned equipment and close contact between colonized or infected persons.\(^14\) Injection drug use is a well-documented risk factor for *S. aureus* infections in the general population, so it is logical to translate this to our pregnant population.\(^15,16\) Additionally, 41% of our patients came from a rural area based on their ZIP code. It is known that people from more rural areas and of lower socioeconomic status have higher rates of injection drug use and higher risk of community acquired MRSA infections, and generally lack access to routine healthcare or medication assisted therapy.\(^17\)

Healthcare exposure is common in the pregnant population and is a known risk factor for MRSA infections. This was also observed in our cohort, as 37% of the patients were hospitalized within 90 days of admission.\(^13\) The shared characteristics of PWID, hepatitis C seropositivity, and tobacco use in our patients are unique to what has been published in obstetrics literature previously. It is known that the prevalence of opioid use and PWID has increased in pregnant women.\(^18\)
Infective endocarditis is a major complication of *S. aureus* bacteremia and in a recent cohort study of maternal IE across Canada, Schwartz et al. reviewed a database of 475 cases. *Staphylococcus* species accounted for 69% of the cases, and patients tended to be over 35 years old, Caucasian, and of lower-income. Our IE patients had a median age of 29 years and all were Caucasian. Twelve percent of their patients received valve replacements compared to our 20%. They found a significantly higher mortality rate in maternal IE compared to pregnant women without IE at 5.3%. Only 1 patient died in our cohort during index hospitalization, her Pitt bacteremia score was 10. This tool has been validated and used as a predictor of mortality in bacteremia, but it has not been proven specifically in *S. aureus* bacteremia. The low mortality seen in our study is surprising, as *S. aureus* bacteremia carries a mortality of up to 30% in some reports. However, the majority of these patients were young and received care at an institution where invasive staphylococcal infections are common. In our study, 80% of patients presenting with IE needed ICU admission from presenting with severe sepsis and shock or respiratory failure requiring intubation, and 7 patients were readmitted due to infectious complications within 6 months. This highlights the importance of early identification and treatment of this severe infection with a combination of both medical and surgical therapy preferably at a high-level medical center. Surgical valve replacement for IE in a pregnant woman was first described in 1976. Three (20%) of our 15 patients with IE had a valve replacement during their hospitalization, and two of these were completed while the patient was still pregnant. The risk of surgery to the patient and the fetus needs to be weighed with the benefits. It has been suggested that medical therapy alone is sufficient during pregnancy, and valve surgery can be safely deferred until after delivery as long as the patient is stable and responding well to antibiotics.

Treatment of *S. aureus* bacteremia in pregnancy especially in the presence of PWID should be with a multi-disciplinary approach, including establishing strategies to reduce harm in this patient’s
population like addition management, which can reduce infection recurrence from continued drug abuse. A multidisciplinary task force was formed in our institution with representatives from psychiatry, infectious diseases, pharmacy, cardiac surgery, infection control, and hospital leaders. The task force aimed to standardize diagnostic and treatment algorithm plans for PWID patients to improve outcomes. The role of the infectious diseases consultation in improving *S. aureus* bacteremia outcomes has also been established in previous publications. Infectious diseases consultations were obtained in 96% of the patients in our cohort, and in the only patient who did not receive an infectious diseases consultation, antibiotics were administered for 2 days and the patient was lost to follow up after hospital discharge. Antimicrobial stewardship programs can oversee the challenges of prescribing prolonged IV antibiotics courses for *S. aureus* bacteremia in this high-risk patient population, especially in the case of continued injection drug use and risk of abusing IV access and risk of patients leaving AMA.

While this case series dedicated to *S. aureus* as a cause of maternal bacteremia shows the importance of emphasizing this pathogen in this patient population, there are limitations that should be highlighted. We are limited by the retrospective nature of this study done at one institution, but represent a pragmatic student design given our research questions. Given limitations of our sample size, we were unable to detect meaningful exposures or other risk factors associated with poor maternal and fetal outcomes. However, *S. aureus* bacteremia in the pregnancy population represents a serious public health issue that should be researched. These findings may not be comparable to other centers that have a lower prevalence of PWID in their communities; in east Tennessee, invasive infections due to MRSA are common.
Conclusion

This study highlights that *S. aureus* bacteremia, although rare, is an important cause of morbidity in pregnant women and poor fetal outcomes. Continued injection drug use is an important modifiable risk factor for *S. aureus* bacteremia in pregnancy, and mothers were frequently readmitted secondary to infection. Future targeted interventions to curtail on-going injection drug use in this high-risk population, such as developing and implementing treatment algorithms for early identification and treatment of *S. aureus* bacteremia in pregnancy.
References

1. Albright CM, Has P, Rouse DJ, Hughes BL. Internal Validation of the Sepsis in Obstetrics Score to Identify Risk of Morbidity From Sepsis in Pregnancy. Obstetrics and gynecology. 2017;130(4):747-755.
2. Drew RJ, Fonseca-Kelly Z, Eogan M. A Retrospective Audit of Clinically Significant Maternal Bacteraemia in a Specialist Maternity Hospital from 2001 to 2014. Infectious diseases in obstetrics and gynecology. 2015;2015:518562.
3. Kebed KY, Bishu K, Al Adham RI, et al. Pregnancy and postpartum infective endocarditis: a systematic review. Mayo Clinic proceedings. 2014;89(8):1143-1152.
4. Campuzano K, Roque H, Bolnick A, Leo MV, Campbell WA. Bacterial endocarditis complicating pregnancy: case report and systematic review of the literature. Archives of gynecology and obstetrics. 2003;268(4):251-255.
5. Yuan SM. Infective Endocarditis during pregnancy. Journal of the College of Physicians and Surgeons—Pakistan : JCPSP. 2015;25(2):134-139.
6. Schwartz J, Czuoj-Shulman N, Moss E, Abenhaim HAJAJoO, Gynecology. 608: Incidence, risk factors and mortality associated with infective endocarditis in pregnancy. 2020;222(1):S389-S390.
7. Prasad M, Jones M. Medical complications of opioid use disorder in pregnancy. Seminars in perinatology. 2019;43(3):162-167.
8. Surgers L, Valin N, Carbonne B, et al. Evolving microbiological epidemiology and high fetal mortality in 135 cases of bacteremia during pregnancy and postpartum. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2013;32(1):107-113.
9. O'Higgins AC, Egan AF, Murphy OC, Fitzpatrick C, Sheehan SR, Turner MJ. A clinical review of maternal bacteremia. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2014;124(3):226-229.
10. Montoya ME, Karnath BM, Ahmad M. Endocarditis during pregnancy. Southern medical journal. 2003;96(11):1156-1157.
11. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;30(4):633-638.
12. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumonaeae bacteremia: implicatons of extended-spectrum beta-lactamase production in nosocomial infections. Annals of internal medicine. 2004;140(1):26-32.
13. Rasmussen RV, Fowler VG, Jr., Skov R, Bruun NE. Future challenges and treatment of Staphylococcus aureus bacteremia with emphasis on MRSA. Future microbiology. 2011;6(1):43-56.
14. Parikh MP, Octaria R, Kainer MA. Methicillin-Resistant Staphylococcus aureus Bloodstream Infections and Injection Drug Use, Tennessee, USA, 2015-2017. Emerging infectious diseases. 2020;26(3):446-453.
15. Laupland KB, Church DL, Mucenski M, Sutherland LR, Davies HD. Population-based study of the epidemiology of and the risk factors for invasive Staphylococcus aureus infections. The Journal of infectious diseases. 2003;187(9):1452-1459.
16. Bassetti S, Battegay M. Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies. Infection. 2004;32(3):163-169.
17. Miller LG, Kaplan SL. Staphylococcus aureus: a community pathogen. Infectious disease clinics of North America. 2009;23(1):35-52.
18. Krans EE, Patrick SWJO, gynecology. Opioid use disorder in pregnancy: health policy and practice in the midst of an epidemic. 2016;128(1):4.

19. Roth JA, Tschudin-Sutter S, Dangel M, Frei R, Battegay M, Widmer AF. Value of the Pitt Bacteraemia Score to predict short-term mortality in Staphylococcus aureus bloodstream infection: a validation study. *Swiss medical weekly*. 2017;147:w14482.

20. Kobayashi D, Yokota K, Takahashi O, Arioka H, Fukui T. A predictive rule for mortality of inpatients with Staphylococcus aureus bacteraemia: A classification and regression tree analysis. *Eur J Intern Med*. 2014;25(10):914-918.

21. Nazarian M, McCullough GH, Fielder DL. Bacterial endocarditis in pregnancy: successful surgical correction. *The Journal of thoracic and cardiovascular surgery*. 1976;71(6):880-883.

22. Caliskan S, Besli F, Sag S, Gungoren F, Baran I. Can infectious endocarditis during pregnancy be cured with only drug treatment? *The heart surgery forum*. 2015;18(1):E33-35.

23. Walker B, Heidel E, Shorman M. Clinical Characteristics and Outcome of Staphylococcus aureus Prostate Abscess, Ten-Year Experience at a Tertiary Care Center. *Open forum infectious diseases*. 2019;6(10).

24. 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.
Table 1: Characteristics of pregnant patients with *Staphylococcus aureus* bacteremia.

| Variable                                    | Patients n=27 |
|---------------------------------------------|---------------|
| **Patient Characteristics**                 |               |
| Age, years                                  | 29 (25-33)    |
| Rural living residence based on ZIP Code    | 11 (41%)      |
| Race, Caucasian                             | 27 (100%)     |
| Weeks into pregnancy, time of admission     | 29 (23-34)    |
| **Insurance Status**                        |               |
| Uninsured                                   | 1 (4%)        |
| Private                                     | 1 (4%)        |
| Medicaid                                    | 25 (93%)      |
| Recent hospitalization, 90 days             | 10 (37%)      |
| History of or active injection drug use     | 23 (85%)      |
| Use of Medication Assisted Therapy          | 7/23 (30%)    |
| Current smoker            | 21 (78%) |
|--------------------------|----------|
| Hepatitis C virus seropositive | 21 (78%) |
| Previous history of infective endocarditis | 1 (4%) |
| Previous multi-drug resistant organism colonization or infection, 1 year | 7 (26%) |

**Infection Characteristics**

| MRSA infection          | 22 (81%) |
|-------------------------|----------|
| Infectious Diseases Consult | 26 (96%) |
| Length of stay, days    | 13 (8-31) |
| Admitted to ICU         | 15 (56%) |
| Vasopressor use         | 6 (22%)  |
| Pitt bacteremia score   | 0 (0-2)  |
| Bacteremia Source        |       |
|-------------------------|-------|
| Infective Endocarditis  | 15 (56%) |
| ABSSSI                  | 5 (19%)  |
| Bone and Joint          | 3 (11%)  |
| Endometritis            | 2 (7%)  |
| Unknown                 | 2 (7%)  |

| Septic emboli           | 15 (56%) |
| Other source control obtained within 72 hours | 5/11 (45%) |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; ABSSSI, acute bacterial skin and skin structure infections.
Table 2. Patient and fetal/baby outcomes.

| Characteristic                                        | Patients n=27 |
|------------------------------------------------------|---------------|
| **Mother Outcomes**                                  |               |
| In-hospital death                                    | 1 (4%)        |
| Clinical worsening while on antibiotic therapy       | 2 (7%)        |
| 6-month readmission, all-cause                       | 7 (26%)       |
| 6-month readmission, related to *S. aureus*          | 4/7 (57%)     |
| All-cause infection-related mortality, 12-months     | 1 (4%)        |
| Loss to follow-up                                    | 3 (11%)       |
| **Fetal/baby Outcomes**                              |               |
| Alive on delivery                                    | 21/23 (91%)   |
| NICU requirement                                     | 17/23 (74%)   |

Abbreviations: NICU, neonatal intensive care unit