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MAJOR ARTICLE

Maternal Bacteremia Caused by *Staphylococcus Aureus* With a Focus on Infective Endocarditis

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Background. Sepsis is an important cause of morbidity and mortality in the pregnant patient. Injection drug use in pregnant populations has 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 6-year period.

Methods. This was a retrospective review of pregnant patients hospitalized with *S. aureus* bacteremia between April 2013 and November 2019. Maternal in-hospital mortality and fetal in-hospital mortality were the primary outcomes measured; the secondary outcome was the rate of 6-month maternal readmission.

Results. Twenty-seven patients were included; 15 (56%) had IE. The median (interquartile range [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%) 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.

Conclusions. 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.

Keywords. bacteremia; infective endocarditis; injection drug use; pregnancy; *Staphylococcus aureus.*

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 ~2 in 1000 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 was to describe the characteristics and outcomes of *S. aureus* bacteremia in pregnant patients at our hospital over a 6-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

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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 *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 [11]. The Pitt bacteremia score was calculated using the scoring system based on available information from within 48 hours of the first positive blood culture [12]. Readmission and mortality data were collected by reviewing the electronic medical record for hospitalization after the initial *S. aureus* bacteremia diagnosis.

Descriptive and bivariate statistics were used to describe the patient population; categorical variables were compared using the Pearson chi-square or Fisher exact test, and continuous variables were compared by the Student *t* test or Mann-Whitney *U* test. All statistical analyses were performed using SPSS Software for MacIntosh, verison 26.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Twenty-seven patients met inclusion criteria. The demographic and clinical data of each patient are listed in Table 1. The median (interquartile range [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. Methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 81% infections. Valves involved in the IE patients included tricuspid (87%) and mitral (7%), and 1 (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

Table 1. Characteristics of Pregnant Patients With *Staphylococcus Aureus* Bacteremia

Variable	Patients (n = 27), No. (%) or Median (IQR)
Patient characteristics	
Age, y	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 d	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 multidrug-resistant organism colonization or infection, 1 y	7 (26)
Infection characteristics	
MRSA infection	22 (81)
Infectious diseases consult	26 (96)
Length of stay, d	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 h	5/11 (45)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

replacement, 2 while pregnant and 1 during the index hospitalization after delivery. Indications for valve replacement were due to the following: 1 patient had multiple tricuspid vegetations (ie, >2 cm) with severe tricuspid regurgitation, another patient had multiple mitral vegetations (ie, >1 cm) 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 1 set of twins. Three patients (11%) were lost to follow-up; 1 (4%) had a miscarriage at 17 weeks' gestation, and 1 patient (4%) underwent an elective abortion. Fifteen (68%) deliveries occurred prematurely before 36 weeks' gestation, and 17 (74%) babies required neonatal intensive care. Two (9%) infants died, and the overall infant 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 2 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 1 (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 0. 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.

Table 2. Patient and Fetal/Baby Outcomes

Characteristic	Patients (n = 27), No. (%)
Mother outcomes	
In-hospital death	1 (4)
Clinical worsening while on antibiotic therapy	2 (7)
6-mo readmission, all-cause	7 (26)
6-mo readmission, related to *S. aureus*	4/7 (57)
All-cause infection-related mortality, 12 mo	1 (4)
Loss to follow-up	3 (11)
Fetal/baby outcomes	
Alive on delivery	21/23 (91)
NICU requirement	17/23 (74)

Abbreviation: NICU, neonatal intensive care unit.

A comparison of the patients diagnosed with IE compared with the other *S. aureus* bacteremia sources was also performed. The patients in these groups are similar in age and have no differences in injection drug use, smoking, or hepatitis C seropositivity. Patients with IE more frequently required an intensive care unit (ICU) stay (P = .004) and mechanical ventilation (P = .008). There was not a significant difference in the use of vasopressors (P = .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 whom had previous pregnancies and aborted or lost fetuses. Ongoing 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]. Health care workers need to be cognizant of these normal changes but also need to be aware that they can be warning signs of sepsis even if fever is absent; only 19% of the patients in our cohort presented with fever. Using a scoring system such as the Sepsis in Obstetrics Score may help with early identification of pregnant women at risk for ICU admission from the emergency department 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 US 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 and 2017 were attributed to injection drug use, mostly among Caucasian women aged 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 health care or medication-assisted therapy [17].

Health care 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 >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 with our 20%. They found a significantly higher mortality rate in maternal IE compared with pregnant women without IE, at 5.3% [6]. 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 [12, 19]. The low mortality seen in our study is surprising, as *S. aureus* bacteremia carries a mortality of up to 30% in some reports [20]. 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 [3, 6]. Surgical valve replacement for IE in a pregnant woman was first described in 1976 [21]. Three (20%) of our 15 patients with IE had a valve replacement during their hospitalization, and 2 of these were completed while the patient was still pregnant. The risk of surgery to the patient and the fetus needs to be weighed against 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 [22].

Treatment of *S. aureus* bacteremia in pregnancy, especially in the presence of injection drug use, should be with a multidisciplinary approach, including establishing strategies to reduce harm in this patient population like addiction management, which can reduce infection recurrence from continued drug abuse [14]. 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 [23]. The role of the infectious diseases consultation in improving *S. aureus* bacteremia outcomes has also been established in previous publications [24]. 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 antibiotic 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 1 institution, but the study had a pragmatic student design given our research questions. Given the 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 pregnant 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.

CONCLUSIONS

This study highlights that *S. aureus* bacteremia, although rare, is an important cause of morbidity in pregnant women and has 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 ongoing injection drug use in this high-risk population are needed, such as developing and implementing treatment algorithms for early identification and treatment of *S. aureus* bacteremia in pregnancy.

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