ORIGINAL RESEARCH PAPER

Internal Medicine

KEY WORDS: Staphylococcus aureus bacteremia, Disseminated Methicillin-Sensitive Staphylococcus aureus, diabetes mellitus, pyelonephritis, osteomyelitis, recurrent infections, abscess formation, antibiotic therapy

STAPHYLOCOCCUS AUREUS MSSA YET DISSEMINATED

Ashwini Prakash* Department Of Internal Medicine KMC Hospital, Dr B.R Ambedkar Circle, Mangalore, Karnataka India. *Corresponding Author

Haroon H Department Of Internal Medicine Kasturba Medical College Mangalore, Manipal Academy Of Higher Education, Manipal, Karnataka, India.

Aakanksha Shetty Department Of Internal Medicine KMC Hospital, Dr. B. R. Ambedkar Circle, Mangalore, Karnataka, India.

ABSTRACT

Introduction: Staphylococcus Aureus Bacteremia (SAB) is a major cause of bloodstream infections, associated with high morbidity and mortality. Methicillin-Sensitive Staphylococcus aureus (MSSA) can cause invasive and disseminated infections, particularly in patients with comorbidities. Managing disseminated MSSA is challenging due to its potential to form abscesses, recurrent bacteremia, and involve multiple organ systems. **Case Report:** We report the case of a 44-year-old male with poorly controlled Type 2 Diabetes Mellitus and recurrent MSSA bacteremia. The patient initially presented with fever, anorexia, and significant weight loss. Imaging and laboratory findings revealed Pyelonephritis with microabscesses and Diabetic Ketoacidosis. During subsequent admissions, he presented with a right foot ulcer, Osteomyelitis, and recurrent urinary tract infections (UTIs), requiring multiple hospitalizations. After blood and urine cultures confirmed MSSA, broad-spectrum antibiotics were initiated and later tailored to Cloxacillin and Clindamycin. Bilateral Double-J stenting was performed to relieve Hydroureteronephrosis, and surgical debridement of the foot ulcer. The patient showed clinical improvement after a six-week antibiotic course. **Discussion:** This case underscores the challenges in managing disseminated MSSA infections in a diabetic patient with recurrent hospitalizations. Infections such as pyelonephritis and osteomyelitis often require prolonged antibiotic therapy, source control through surgical intervention, and close monitoring to prevent recurrence. Diabetic patients are at an increased risk of invasive MSSA due to compromised immunity, which requires a multifaceted approach for successful management. **Conclusion:** Effective management of disseminated MSSA infections in high-risk patients requires timely diagnosis, comprehensive antimicrobial therapy, and vigilant follow-up. Involvement of infectious disease specialists and adherence to antibiotic protocols improve outcomes, particularly in patients with comorbidities.

INTRODUCTION

Staphylococcus aureus is a gram-positive bacterium commonly found on human skin and mucous membranes, recognized as a major pathogen responsible for a wide spectrum of infections, from mild skin and soft tissue infections to life-threatening systemic diseases. Infections caused by S. aureus are categorized into two main types based on their susceptibility to antibiotics: Methicillin-Resistant Staphylococcus aureus (MRSA) and Methicillin-Sensitive Staphylococcus aureus (MSSA). MRSA strains emerged in the early 1960s with adaptations that made them resistant to Methicillin and other beta-lactam antibiotics, creating additional treatment challenges. Meanwhile, MSSA strains remain prevalent, with approximately 20-30% of the population carrying MSSA asymptomatically, typically in regions such as the nasopharynx, skin, gastrointestinal tract, and perineum . Both MSSA and MRSA bacteremia share risk factors, including immunosuppression, organ transplantation, cancer, dialysis dependency, and diabetes mellitus [1].

Classification of Staphylococcus Aureus Bacteremia (SAB)

1. Community-Acquired SAB: This occurs in individuals without prior healthcare exposure and is common among intravenous drug users and individuals with spontaneous osteoarticular infections, such as vertebral osteomyelitis or epidural abscess. Patients with community-acquired SAB are often more prone to multiple complications at presentation, including endocarditis, acute renal failure, shock, acute respiratory distress syndrome, or disseminated intravascular coagulation [2][3].

2. Healthcare-Associated, Community-Onset SAB: This type is seen in patients with frequent healthcare interactions, such as those recently hospitalized, receiving intravenous therapy or wound care at home, residing in nursing facilities, or undergoing dialysis or chemotherapy [4].

3. Healthcare-Associated, Hospital-Onset SAB: Acquired during hospital stays, which includes central-line associated bloodstream infections, ventilator-associated pneumonia, and surgical site infections. Hospital-onset SAB is more often linked to MRSA and is a leading cause of nosocomial bloodstream infections, with an increased incidence due to the growing use of intravascular devices like hemodialysis lines and peripherally inserted central catheters.

Classification of SAB Severity: Complicated vs. Uncomplicated

It influences the diagnostic workup, duration of antibiotic therapy, and prognosis. The Infectious Diseases Society of America (IDSA) criteria for uncomplicated SAB include ruling out infective endocarditis via echocardiography, absence of prosthetic devices, negative follow-up blood cultures 2-4 days after the initial positive culture, fever resolution within 72 hours of effective antibiotic therapy, and no signs of metastatic infection [5]. Patients who do not meet these criteria are classified as having complicated SAB [6].

MSSA Pathogenesis and Clinical Impact

MSSA can cause both localized and disseminated infections, the latter leading to bacteremia and potentially affecting multiple organ systems, including the lungs, bones, joints, kidneys, and heart valves. This may result in severe conditions such as pneumonia, osteomyelitis, pyelonephritis, and endocarditis. Risk factors for invasive S. aureus infections include diabetes mellitus, immunosuppression, chronic kidney disease, and the presence of indwelling devices.

Disseminated MSSA infections pose significant clinical challenges, as they can form abscesses and cause recurrent bacteremia. Effective management requires prolonged antibiotic therapy, source control, and sometimes surgical intervention to drain abscesses and remove infected devices.

Case Report

A 44-year-old male with a known history of Type 2 Diabetes Mellitus and Hypertension presented with a 2-week history of fever, anorexia, cough, and unintentional weight loss of approximately 5 kg. His medical history included a previous admission in March 2023 for a 10-day history of fever, cough, anorexia, and significant weight loss (8 kg). During that admission, he was diagnosed with Diabetic Ketoacidosis (DKA), pyelonephritis, anemia, and community-acquired pneumonia (CAP). Blood cultures at that time revealed Staphylococcus aureus, while urine cultures showed no growth. CT abdomen scan demonstrated left-sided pyelonephritis with multiple microabscesses. He was treated with intravenous Piperacillin-Tazobactam and cloxacillin for 10 days, with no requirement for urological intervention.

In July 2024, the patient was re-admitted with a 7-day history of fever, abdominal pain, and a wound on the right foot. He was diagnosed with anemia, urinary tract infection (pyelonephritis), hyperuricemia, a trophic ulcer, and acute kidney injury (AKI). CT of the kidneys, ureters, and bladder (CT KUB) revealed bilateral pyelonephritis with hydronephrosis, but the patient declined the recommended double J (DJ) stenting. Urine cultures grew Staphylococcus aureus sensitive to oxacillin. He was treated with intravenous piperacillin-tazobactam and linezolid for 7 days, along with three pints of packed red blood cell (PRBC) transfusion. The peak creatinine during this admission was 2.5 mg/dL, which improved to 1.3 mg/dL at discharge. He was discharged on oral Faropenem for 7 days.

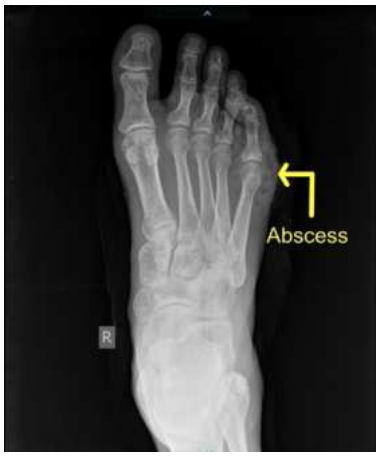
Current Admission

The patient presented to our hospital with history of persistent fever for two weeks associated with easy fatiguability and weight loss of approximately six kg in two weeks. On examination, patient was found to have pallor, a temperature of 101°F, blood pressure of 140/90 mmHg, pulse rate of 74/min, respiratory rate of 20/min, and oxygen saturation of 99% on room air. Lung auscultation revealed bilateral crepitations, while cardiac examination was normal. Examination of the right foot showed swelling, erythema, increased local temperature on the lateral aspect and firm skin. An infected trophic ulcer was noted over the right fifth toe at the metatarsophalangeal (MTP) joint, extending to the metatarsal head and accompanied by abscess formation.

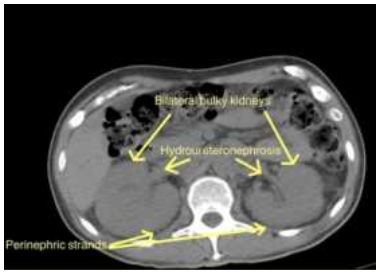
Investigations and Management

Laboratory investigations indicated anemia (hemoglobin of 9.1 g/dL), leukocytosis (31,060 cells/μL with 94% neutrophils), elevated C-reactive protein (CRP) of 271 mg/dL, and a creatinine level of 3.96 mg/dL. Urinalysis revealed glucose 3+, protein 1+, leukocytes 3+, and 817 pus cells per high-power field. Random blood sugar was noted at 508 mg/dL, and uric acid at 5.8 mg/dL. Blood glucose levels were initially managed with insulin infusion, which was later transitioned to subcutaneous short-acting insulin.

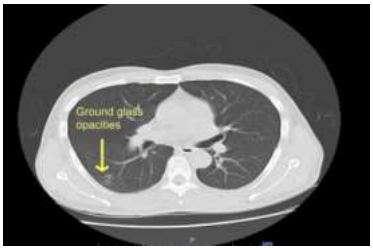
A chest X-ray was unremarkable, X-ray of the foot indicated osteomyelitis [Figure 1].Blood, urine, and pus cultures were sent. In view of patient having recurrent infections and repeated hospitalisation, initially MRSA was suspected and was started on intravenous Meropenem, Clindamycin and Teicoplanin for broad-spectrum coverage. Ultrasound with Doppler of the right foot showed cellulitis of the ankle and foot, along with a fibrotic nodular lesion on the right lateral aspect of the foot, callus formation, and underlying inflammation, with no evidence of deep vein thrombosis (DVT). Abscess debridement was performed by a plastic surgeon followed by daily sterile dressings. An abdominal ultrasound indicated bilateral pyelonephritis with hydroureteronephrosis and chronic cystitis. CT urogram [Figure 2] showed bilateral enlarged kidneys with mild hydroureteronephrosis, perinephric fat stranding, thickening of the posterior pararenal and lateral conal fascia, and minimal perinephric fluid on the right, suggestive of pyelonephritis, Cystitis with periureteritis was also noted. High-Resolution Computed Tomography (HRCT) of the chest revealed subpleural ground-glass opacities in the superior segment of the right lower lobe, suggestive of an infective etiology [Figure 3].



[Figure 1] X-ray of the foot indicated osteomyelitis



[Figure 2] CT urogram - Bilateral pyelonephritis with Hydroureteronephrosis



[Figure 3] HRCT chest showing ground-glass opacities in the superior segment of the right lower lobe

Bilateral double-J stenting (DJ) was performed by Urologist. Blood and urine cultures grew Methicillin-Sensitive Staphylococcus aureus (MSSA) sensitive to Oxacillin. Intravenous Meropenem and Teicoplanin were discontinued, and intravenous Cloxacillin was initiated while continuing intravenous Clindamycin. Infectious Disease (ID) consult was taken for the further management. Ultrasound of the neck and axilla revealed reactive lymphadenopathy, and Quantiferon TB Gold test was negative. A Transthoracic Echocardiogram (TTE) followed by Transesophageal Echocardiography (TEE) was performed to rule out valvular vegetations, and a Positron Emission Tomography-Computed Tomography (PET-CT) was conducted, showing hypermetabolic soft tissue density thickening in the right foot, suggestive of active infective/inflammatory etiology; hypermetabolic lung lesion; focal hypermetabolism involving the right renal cortex indicative of pyelonephritis; and mildly hypermetabolic, enlarged, reactive retroperitoneal lymph nodes and no evidence of infective endocarditis.

The patient showed clinical improvement after initiation of Cloxacillin, with a reduction in inflammatory markers (white

blood cell count reduced to 18,720 cells/μL and CRP to 70 mg/dL). Creatinine levels improved to 2.17 mg/dL. The patient remained afebrile from day 6, and subsequent blood, urine, and pus cultures were sterile. He was discharged with intravenous Cloxacillin and Clindamycin via a central line to complete a 6-week course, along with iron supplements and short-acting insulin.

Follow-Up

At the follow-up visit in the outpatient department, the patient remained afebrile with a white blood cell count of 4,820 cells/μL, hemoglobin of 8.2 g/dL, and serum creatinine of 2 mg/dL. A pelvic ultrasound performed on day 14 showed bilaterally enlarged kidneys with signs of cystitis. Subsequent blood and urine cultures showed no growth. The DJ stent was removed on day 15. The patient was continued on intravenous Cloxacillin and Clindamycin for a total of six weeks, received injections of erythropoietin twice weekly, and maintained well-controlled blood glucose levels with insulin. Regular wound dressings for the right foot were performed, and on examination, the wound appeared healthy.

DISCUSSION

Staphylococcus aureus bacteremia (SAB) remains a prominent global cause of bloodstream infections, with rising rates of community-onset MSSA bacteremia. S.aureus produces various molecules that drive its pathogenesis and virulence. Disseminated infection and abscess formation are facilitated by coagulase and von Willebrand factor binding protein (vWbp), which induce coagulation and alter normal hemostasis to evade host defenses. These proteins activate prothrombin, disrupting host control mechanisms, while surface agglutinins bind fibrinogen and convert it to fibrin. High levels of vWbp and coagulase accumulate at abscess peripheries, forming a pseudocapsule or fibrous capsule that prevents phagocytosis by host immune cells. Additional secreted factors attract and destroy immune cells, transforming abscesses into purulent exudate, which allows S. aureus to disseminate and create new lesions. These virulence factors are central to SAB pathogenesis and abscess formation [7]. Key mortality predictors include age, comorbidities, infection source and spread, persistence duration, and failure to eliminate identifiable infection sources[8].

Positive blood cultures for S. aureus necessitate a prompt clinical assessment and immediate empiric antibiotic therapy. A comprehensive history and physical examination are essential for identifying the bacteremia source and any signs of metastatic infection. Symptom-driven imaging studies should be used to assess possible metastatic disease, with transthoracic echocardiography (TTE) often employed to evaluate endocarditis in high-risk cases. The routine use of transesophageal echocardiography (TEE) remains debated due to cost, availability, and risk considerations.

The primary treatment approach for MSSA bacteremia and metastatic infections involves semi-synthetic, Penicillinase-stable beta-lactam antibiotics, such as Nafcillin or Cloxacillin. Cefazolin offers comparable effectiveness to Nafcillin and serves as an alternative option. Vancomycin, less effective for MSSA, should be reserved for MRSA, with de-escalation to beta-lactams recommended once susceptibility data is available, as Vancomycin use can result in slower bacterial clearance and higher mortality. For uncomplicated SAB, a minimum 14-day antibiotic course is recommended, while deep-seated infections typically require 4 to 6 weeks. Optimal management of metastatic infections requires adequate antibiotic coverage and, when feasible, removal or drainage of the infection source [9].

Accepted SAB management guidelines include:1) determining whether the infection is uncomplicated or complicated, 2) identifying and removing infection sources, and 3) selecting appropriate antibiotics in terms of type, dosage, and duration.

Disseminated MSSA infections are associated with specific host and clinical factors that predispose individuals to systemic bacterial spread. Poorly controlled diabetes, for instance, compromises immune function, fostering S. aureus proliferation and increasing bacteremia risk. Chronic kidney disease (CKD), particularly in dialysis patients, elevates the risk due to frequent vascular access and impaired immunity [10]. Immunosuppressed individuals, including those with HIV/AIDS, malignancies, or on immunosuppressive therapies, face a higher risk for systemic infections due to diminished immune capacity.

Indwelling medical devices, such as central venous catheters, prosthetic joints, pacemakers, or urinary catheters, provide direct bloodstream entry points for MSSA, facilitating systemic infection. Intravenous drug use further heightens risk, as repeated use of non-sterile needles introduces MSSA directly into circulation, leading to severe infections such as bacteremia and infective endocarditis. Recent surgical procedures or trauma also present MSSA entry points, while chronic skin conditions weaken skin barriers, increasing bacterial invasion susceptibility. Prolonged hospitalization, particularly in intensive care units, raises the risk of healthcare-associated MSSA infections, potentially leading to bacteremia and systemic complications.

Infectious Disease Consultations (IDC) have shown to improve SAB outcomes by reducing mortality, complications, and relapse by involving thorough evaluation, including follow-up blood cultures to confirm bacterial clearance, increased echocardiography use, timely infection source removal, extended treatment durations for complicated SAB cases, and appropriate antibiotic selection for MSSA infections[11][12].

Early recognition and intervention are crucial to prevent localized MSSA infections from becoming disseminated. Comprehensive physical examination is essential to identify findings patients, particularly those with diabetic neuropathy, may not report, as illustrated in this case, where a leg abscess was diagnosed despite a lack of pain. For disseminated MSSA infection cases, detailed evaluations, including high-resolution chest CT (HRCT), bronchoscopy, and TEE, are important to rule out pulmonary involvement and infective endocarditis. An ophthalmologic examination should assess for Roth's spots, while PET-CT may help identify infection foci.

In this patient, poorly controlled diabetes and incomplete treatment of prior MSSA infections were significant risk factors. Regular follow-up with blood, urine, and pus cultures is essential for monitoring therapeutic progress. Ensuring completion of a full six-week antibiotic course is vital to achieving a successful outcome and preventing recurrence.

CONCLUSION

SAB remains a significant global health issue, with a notable rise in community-onset MSSA cases. Effective management of SAB requires early identification, accurate classification, and timely initiation of appropriate treatment. Antimicrobial Stewardship Programs (ASP) and Infectious Disease Consultations (IDC) play essential roles in optimizing antibiotic selection, reducing response times, and managing complications, ultimately improving patient outcomes.

Staphylococcus aureus possesses various mechanisms to evade immune defenses and resist antibiotics, including biofilm formation, intracellular survival, and toxin production. These virulence factors complicate treatment and may necessitate prolonged antibiotic therapy, removal of infected devices, and, in some cases, surgical intervention.

This case highlights the complexities of managing

disseminated MSSA infections in a patient with poorly controlled diabetes, recurrent infections, and neuropathy. A delay in diagnosis during previous admissions led to abscess formation, emphasizing the importance of comprehensive evaluation, imaging, and timely intervention with targeted antibiotic therapy and surgical debridement. Recovery was achieved through a multidisciplinary approach, emphasizing the necessity of close monitoring and follow-up to prevent recurrence and improve outcomes in high-risk patients.

Rigorous management of both MSSA and MRSA SAB through effective antimicrobial therapy and vigilant monitoring is essential to mitigate the challenges posed by these infections and to enhance patient prognosis.

REFERENCES

[1] Laupland KB, Ross T, Gregson DB. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. J Infect Dis. 2008 Aug 1;198(3):336-43. doi: 10.1086/589717. PMID: 18522502.

[2] Abraham L, Bamberger DM. Staphylococcus aureus Bacteremia: Contemporary Management. Mo Med. 2020 Jul-Aug;117(4):341-345. PMID: 32848271; PMCID: PMC7431060.

[3] Willcox PA, Rayner BL, Whitelaw DA. Community-acquired Staphylococcus aureus bacteraemia in patients who do not abuse intravenous drugs. QJM. 1998 Jan;91(1):41-7. doi: 10.1093/qjmed/91.1.41. PMID: 9519211.

[4] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002 Nov 19;137(10):791-7. doi: 10.7326/0003-4819-137-10-200211190-00007. PMID: 12435215.

[5] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011 Feb 1;52(3):285-92. doi: 10.1093/cid/cir034. PMID: 21217178.

[6] Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603-661. doi:10.1128/CMR.00134-14

[7] Kobayashi SD, Malachowa N, DeLeo FR. Pathogenesis of Staphylococcus aureus abscesses. Am J Pathol. 2015 Jun;185(6):1518-27. doi: 10.1016/j.ajpath.2014.11.030. Epub 2015 Mar 4. PMID: 25749135; PMCID: PMC4450319.

[8] Van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012 Apr;25(2):362-86. doi: 10.1128/CMR.05022-11. PMID: 22491776; PMCID: PMC3346297.

[9] Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME, Walker S, Wertheim HF, Wilson P, Llewelyn MJ; UK Clinical Infection Research Group. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect Dis. 2011 Mar;11(3):208-22. doi: 10.1016/S1473-3099(10)70285-1. PMID: 21371655.

[10] Fayed MH, Iftikhar H, Anjum S, Khyatt O, Najam M. A Severe Case of Disseminated Multifocal Methicillin-Susceptible Staphylococcal Infection in a Diabetic Patient. Cureus. 2022 Mar 25;14(3):e23483. doi:10.7759 /cureus.23483. PMID: 35494918; PMCID: PMC9038576.

[11] Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from Staphylococcus aureus bacteremia. Medicine (Baltimore). 2009 Sep;88(5):263-267. doi: 10.1097/MD. 0b013e3181b8fccb. PMID: 19745684; PMCID: PMC2881213.

[12] Nagao M, Iinuma Y, Saito T, Matsumura Y, Shirano M, Matsushima A, Takakura S, Ito Y, Ichiyama S. Close cooperation between infectious disease physicians and attending physicians can result in better management and outcome for patients with Staphylococcus aureus bacteraemia. Clin Microbiol Infect. 2010 Dec;16(12):1783-8. doi: 10.1111/j.1469-0691.2010.03156.x. PMID: 21077985.