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Staphylococcus aureus Bacteremia in Adults

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Abstract

Staphylococcus aureus is an important cause of bacteremia, and *S. aureus* bacteremia constitutes a serious condition with high morbidity and mortality, secondary to multiple complications including infective endocarditis and embolization. The incidence of bacteremia with *S. aureus* is increasing with more frequent use of medications that lower immune system response, and with the utilization of more invasive medical procedures. In addition, the emergence of resistant *S. aureus* isolates is becoming more common and can negatively affect the outcome of an individual if not diagnosed and managed properly. Health care workers encounter *S. aureus* bloodstream infections on a routine basis, and in certain situations, it becomes a very challenging infection to control. Because of the impact this entity has on health care costs and the increased use of resources, it is necessary to highlight the causes, clinical presentation, associated complications, and treatment measures. In this chapter, we will cover each of these points, with somewhat more emphasis on methicillin-resistant *S. aureus* that is prevalent in both community and hospital settings and is more commonly associated with worsening prognosis and higher mortality.

Keywords: *Staphylococcus aureus*, Bacteremia, Sepsis, methicillin susceptible, methicillin resistant, community acquired, hospital acquired

1. *Staphylococcus aureus* infections: introduction

Staphylococcus aureus is a Gram-positive staphylococci that can exist commensally with humans as a colonizer but can also exist as a pathogen. It is a major pathogen in bacteremia whether community acquired or hospital acquired. It has proven its versatility by continuing to be an important infectious pathogen that has contributed to increasing morbidity and mortality of patients over the years. Despite the advances in antibiotic therapy targeting this pathogen, *S. aureus* remains a multipotent organism that causes infection using toxin production and nontoxin-mediated pathways. This organism causes a wide array of

infections, from a simple skin infection to more dangerous situations such as bacteremia, endocarditis, pneumonia, bone and joint infections, and many others that may jeopardize the life of the patient. Bacteremia is one major cause of morbidity in both the inpatient and outpatient setting, and *S. aureus* is notorious for causing invasive infections that lead to bacteremia.

Patients with *S. aureus* bacteremia can be at risk for many complications that may increase morbidity, with mortality rates of 20–40% that have been described. The higher the level of resistance, the higher the mortality rates. This is why methicillin-resistant *S. aureus* (MRSA) is expected to have a higher morbidity/mortality, longer hospital stays, and higher health care costs when compared with methicillin-sensitive *S. aureus* (MSSA) bacteremia [1]. Also, in cases of infection with MRSA, there is a higher rate of treatment failure that may include death within 30 days of receiving therapy, persistent positive blood cultures for more than 10 days after therapy, or recurrence of septicemia within 60 days after finishing therapy.

2. *S. aureus* colonization

S. aureus is a part of the normal human flora; up to 50% of healthy individuals may be persistently colonized with it. Colonization with *S. aureus* can be persistent in up to 20% of cases, intermittent in 60%, and always absent in up to 20% of people. In a study performed on the general US population that looked at colonization rates in the nares with *S. Aureus*, it was found that the prevalence of MRSA colonization was 0.8% between 2001 and 2002, and went up to 1.5% between 2003 and 2004. The anterior nares is felt to be the major site of *S. aureus* colonization, but some people can be colonized with *S. aureus* outside the nares in areas such as the throat, axilla, inguinal region, and perirectal area. Several conditions may increase the rate of colonization such as diabetes mellitus, HIV infection, underlying skin diseases, and end stage renal disease requiring hemodialysis. Colonization typically precedes *S. aureus* infection. These conditions can place the subject at a higher risk of invasive staphylococcal infections such as bacteremia, which is why much of infection control and prevention efforts target colonization with *S. aureus*.

Nasal carriage of *S. aureus* colonization has been associated with the development of infections. A substantial proportion of cases of *S. aureus* bacteremia appear to be of endogenous origin as they originate from colonies in the nasal mucosa. This is one reason why strategies to prevent systemic *S. aureus* infections by eliminating nasal carriage need to be supported.

3. Epidemiology

Since methicillin-resistant *S. aureus* constitutes a major burden on health care systems we will focus mainly on it. There are several terms for classifying MRSA infections, namely bacteremia. The first category is the health care-associated MRSA (also called nosocomial)

that occurs more than 48 hours into hospitalization. The second category is community-onset health care-associated MRSA, which includes two factions: (1) patients in whom infection occurs less than 48 hours into hospitalization and (2) patients in the community who have had a prior hospitalization in the last 12 months (including for surgery or dialysis) or those who are residents of long-term care facilities. The third category is community-associated MRSA infections occurring outside of health care settings among individuals who do not have prior health care exposures. Several outbreaks of MRSA have occurred in the community without exposure to health care facilities. This reflects a great change in the epidemiology of MRSA-related infections. Once solely a hospital pathogen and only seen among individuals with prior health care exposures, now MRSA is seen in populations without health care exposures. Poor hygiene conditions, close contact, contaminated material, and damaged skin were found to be some of the risk factors for spread of MRSA infection in the community. In the United States, the most common MRSA community-acquired strain is the USA300 strain based on pulsed-field gel electrophoresis. This community-based clone mostly causes skin and soft tissue infections, but it may cause more invasive infections such as bacteremia in 5–10% of people. This clone is causing more nosocomial infections as well.

Besides being an important cause of community-acquired bacteremia such as in cases of intravenous drug use leading to endocarditis, or cases of intravenous home infusion therapy, *S. aureus* is a leading cause of nosocomial bacteremia. It ranks second after coagulase negative staphylococci as a cause of primary bacteremia. In the hospital setting, a higher prevalence of methicillin-resistant isolates is seen. Most of the time, bacteremia develops from *S. aureus* strains colonizing the host; however, this infection can be transmitted through contact with other colonized individuals or contaminated surfaces such as hands of health care workers or environmental spaces. Spread of staphylococci in aerosols of respiratory secretions from colonized patients has also been reported.

4. *S. aureus* virulence factors leading to bacteremia

In observing individual responses to MRSA infection, some hosts become severely ill while others have only mild symptoms. It is unclear why certain factors are directly linked to this discrepancy in response. There are several virulence factors of *S. aureus* that may be structural and secreted products that could cause the pathogenesis of the disease with *S. aureus*. Microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) are surface proteins that mediate adherence of *S. aureus* to host tissues. These molecules bind molecules belonging to different surfaces such as fibronectin, collagen, and fibrinogen. The MSCRAMMs help establish invasive and serious infections like endovascular infections, bone and joint infections, and prosthetic-device infections. **Figure 1** represents a schema of the structural and secreted products that *S. aureus* uses in order to achieve a high virulence level, and serious infections like blood stream infection. **Table 1** listed a few selected virulence factors [2].

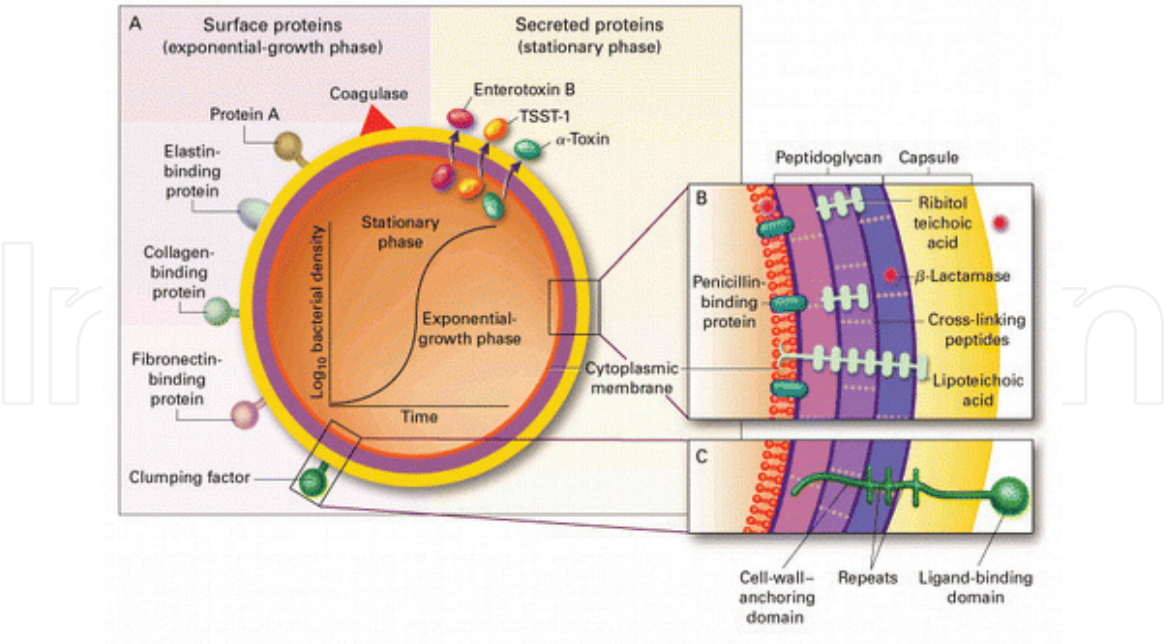


Figure 1. Pathogenic factors of *Staphylococcus aureus* with structural and secreted products both playing roles as virulence factors. (A) Surface and secreted proteins. (B and C) Cross sections of the cell envelope. TSST-1, toxic shock syndrome toxin-1. Source: With permission from the Massachusetts Medical Society. Copyright 1998 Massachusetts Medical Society.

Type of virulence factors	Selected factors ^a	Associated clinical syndromes
Involved in attachment	MSCRAMMs (e.g., clumping factors, fibronectin-binding proteins, collagen, and bone sialoprotein-binding proteins)	Endocarditis, osteomyelitis, septic arthritis, and prosthetic-device and catheter infections
Involved in persistence	Biofilm accumulation (e.g., polysaccharide intercellular adhesion), small-colony variants, and intracellular persistence	Relapsing infections, cystic fibrosis, and syndromes as described above for attachment
Involved in evading/destroying host defenses	Leukocidins (e.g., PVL and γ-toxin), capsular polysaccharides (e.g., 5 and 8), protein A, CHIPS, Eap, and phenol-soluble modulins	Invasive skin infections and necrotizing pneumonia (CA-MRSA strains that cause these are often associated with PVL) abscesses (associated with capsular polysaccharides)
Involved in tissue invasion/penetration	Proteases, lipases, nucleases, hyaluronate lyase, phospholipase C, and metalloproteases (elastase)	Tissue destruction and metastatic infections
Involved in toxin-mediated disease and/or sepsis	Enterotoxins, toxic shock syndrome toxin-1, exfoliative toxins A and B, α-toxin, peptidoglycan, and lipoteichoic acid	Food poisoning, toxic shock syndrome, scalded skin syndrome, bullous impetigo, and sepsis syndrome
With poorly defined role in virulence	Coagulase, ACME, and bacteriocin	

Table 1. Selected *Staphylococcus aureus* virulence factors.

5. Pathogenicity

Several mechanisms lead to blood stream infection with *S. aureus*. After adhering to tissues or prosthetic materials, *S. aureus* is capable of growing in various ways. It can evade host defenses and the activity of antibiotics by forming biofilms on host and prosthetic surfaces. Additionally, *S. aureus* may escape the defense mechanisms by surviving inside several types of cells (such as endothelial cells) as in the situation of bacteremia and endocarditis. Another mechanism of survival is that *S. aureus* can form small-colony variants (SCVs) that can hide in host cells thus keeping them protected against defense mechanisms and leading to persistent and recurrent infection. The production of an antiphagocytic microcapsule is another method of defense escape used by *S. aureus* and can cause abscess formation. *S. aureus* can further halt host defenses by blunting neutrophil extravasation and chemotaxis to the infected area by producing chemotaxis inhibitory protein. Moreover, it produces leukocidins that destroy leucocytes by inflicting holes in the cell membrane.

Additional methods that help *S. aureus* in creating invasive blood stream infection exist and include the secretion of numerous enzymes that hydrolyze tissues. This causes invasion, destruction and further spread of the pathogen to distant organs via the blood stream. Septic shock can thus result through the activation of the individual's immune system and coagulation pathways.

Pathogenesis of *S. aureus* is also affected by regulation of the expression of virulence factors. It appears that expression of these factors in a coordinated manner reduces the metabolic demands of the pathogen. Thus, MSCRAMM proteins that get secreted early in the infectious process help the establishment of the infection in tissue sites, while the later production of toxins facilitates the spread of the infection. The accessory gene regulator (*agr*) is a quorum-sensing system that plays a critical role in the regulation of staphylococcal virulence.

Besides virulence factors of *S. aureus*, it appears that patients were sicker when they developed an infection in the setting of negative colonization status. Noncarriers of the organism seem to have less protective immunity than those who are carriers. The formation of antibodies may also protect against the development of toxic shock syndrome.

Based on the above fact, *S. aureus* has many mechanisms to produce disease, namely bacteremia, while evading host defenses.

6. Bacteremia caused by *S. aureus*

Bacteremia is defined as the presence of bacteria in normally sterile blood. Typically more than one bottle in the set will be positive for growth; however, only one positive bottle is needed to diagnose bacteremia. Risk factors associated with *S. aureus* bacteremia include the presence of prosthetic devices, surgical site infections, or skin conditions such as chronic ulceration, injection drug use (IDU), and host factors that incur predisposition to recurrent infections. Prosthetic devices include any intravascular catheter such as hemodialysis catheter or central venous catheter. Patients on hemodialysis are at a higher risk for staphylococcal endocarditis and constitute a relatively new at-risk group. Other factors include defects of

polymorphonuclear leukocytes and congenital syndromes that are associated with more risk of *S. aureus* infections, such as the cases of neutropenia, chronic granulomatous disease, as well as Job's, Chediak-Higashi, and Wiskott-Aldrich [3].

Clinical manifestations of *S. aureus* bacteremia typically involve systemic responses such as fever and hypotension. When bacteremia occurs secondarily to infection at a primary site, clinical symptoms associated with that organ system may also be present. Cellulitis, chronic ulceration, or trauma to skin and soft tissue may serve as portals of entry for the bacteria and the primary source of a *S. aureus* bacteremia. Tenderness or erythema surrounding a vascular catheter may also serve as a clinical manifestation of underlying bacteremia [4], though absence does not rule out the diagnosis. Patients with *S. aureus* pneumonia can develop bacteremia and have accompanying upper respiratory symptoms. *S. aureus* bacteriuria without the presence of a urinary catheter may be an indicator of *S. aureus* bacteremia [5]. *S. aureus* meningitis, though less common, may also occur in the setting of complication due to *S. aureus* bacteremia [6] and in addition to fever can demonstrate confusion and nuchal rigidity associated with acute bacterial meningitis.

Clinical approach to a patient with *S. aureus* bacteremia should include a detailed history, thorough physical exam, and if required, additional imaging with possible infectious disease consultation. History should involve questions as to the presence or absence of potential portals of entry such as wounds and also determine the presence of prosthetic devices including hardware (orthopedic or cardiac) and intravascular catheters. Questions related to localization of pain may help determine if metastatic spread has occurred such as in cases of vertebral osteomyelitis/diskitis or endocarditis. Physical exam should include an extensive evaluation of the skin and mucous membranes to look for sites of bacterial entry. Cardiac evaluation should assess for the presence of murmurs associated with infective endocarditis. Other stigmata of endocarditis should be sought through fundoscopic exam and exam of the digits for the appearance of emboli in skin. Baseline mental status should be noted and carefully monitored for signs of deterioration which may be concomitant with development of additional complications.

Complications of *S. aureus* bacteremia range from colonization after a treatment to infective endocarditis. Infective endocarditis is one of the most severe complications, with *S. aureus* now recognized as the most common cause in the industrialized world [7]. Pathogenesis is due to a combination of adhesion factors (as discussed earlier) on the surface of *S. aureus* and bacterial-induced platelet aggregation, which cause adhesion damage to heart valves [8]. Risk factors for IE in the setting of *S. aureus* bacteremia include prosthetic heart valve or predisposing cardiac abnormalities, IVDU, intravascular catheter infection, or persistent bacteremia [9]. Specific clinical manifestations associated with *S. aureus* infective endocarditis include sepsis syndrome involving fever, tachycardia, and hypotension, cardiac failure due to valve destruction, and sequelae from septic emboli. Within the heart, once *S. aureus* adheres to and colonizes the valve its intrinsic procoagulant activity triggers deposition of platelets and fibrin which leads to the formation of a vegetation. The structural abnormality is typically associated with regurgitation, and if untreated can progress to cardiac failure. Transthoracic echocardiography should be used as the initial diagnostic test in a patient with suspected endocarditis, as its specificity approaches 100% [10], however, specificity is lower being at most 75%. Transthoracic echocardiography is not 100% specific for infective endocarditis due

to potential false positives, however, given a sensitivity greater than 90%, it is the better of the two for identification of valvular vegetations. Vascular phenomena occur when septic emboli dislodge from the vegetation and occlude arteries in the periphery as well as centrally affecting vital organs. Peripheral manifestations including skin lesions (Janeway spots, Osler's nodes) and retinal lesions (Roth's spots), while splenic vein thrombosis can lead to infarction of the spleen. Neurological complications include cerebral infarctions, intracerebral or sub-arachnoid hemorrhage, meningitis, cerebritis, and encephalomalacia.

7. Bacteremia treatment

Treatment of *S. aureus* bacteremia should first be approached by seeking out a potential focus of infection and determining whether or not it can be removed. Though no specific guidelines exist regarding duration of treatment, the general consensus advocates a 14-day treatment course for *S. aureus* bacteremia in cases where the source such as an intravascular catheter or prosthetic device can be removed, or an abscess can be drained [11]. In cases where removal of an intravascular catheter is not possible, antibiotic lock therapy may be used in an attempt to salvage the line, which includes filling the catheter lumen with high concentrations of antibiotics and leaving them in place for several hours to days [12]. Longer treatment courses extending for 4–6 weeks are required for deeper wound infections such as endocarditis and osteomyelitis. Methicillin-resistant *S. aureus* coverage should be included in empiric therapy with de-escalation to a beta-lactam agent if methicillin-susceptible *S. aureus* is later identified.

Once *S. aureus* susceptibility is determined, antibiotic therapy may be directed toward either MSSA or MRSA. Beta-lactams such as penicillins and cephalosporins, and if needed, glycopeptides, are antibiotics classes used for the treatment of MSSA. Beta-lactams inhibit bacterial cell wall assembly by binding to membrane bound enzymes called penicillin-binding proteins that perform cross-linking. The beta-lactam ring binds to the penicillin-binding proteins and prevents the cross-linking component of cell wall assembly, causing cell death via autolysis of osmotic instability [13]. In cases where beta-lactams cannot be used to treat MSSA, such as with history of anaphylaxis to penicillin, the class of antibiotics known of as glycopeptides (which includes vancomycin) may be used. It should not be used as primary treatment for MSSA, however, if drug intolerance is not an issue.

Since MRSA bacteremia constitutes a great deal of infection in this day and constitutes a major cause of increasing morbidity and mortality, we decided to elaborate more about its treatment in different settings and to discuss the newer treatment options that are available.

8. Management of MRSA bacteremia and infective endocarditis in adults

MRSA was described in 1961, shortly after methicillin was introduced. Unlike penicillin resistance, which is achieved via the bacteria-produced enzyme penicillinase, methicillin resistance is mediated by a newly acquired penicillin-binding protein (called PBP2A) and encoded for by the *mecA* gene. The *MecA* gene is located on a mobile genetic element called

staphylococcal chromosome cassette (SCCmec) [14]. If methicillin-resistant *S. aureus* bacteremia is identified, vancomycin and daptomycin are generally recommended for treatment based on current guidelines. Glycopeptides are a class of antibiotics that include vancomycin and work by binding to bacterial cell wall precursors and interfering with penicillin-binding protein enzymes, causing cessation of cell wall synthesis and later cell death. Daptomycin is a lipopeptide that is approved for the treatment of *S. aureus*-complicated skin or soft tissue infection, bacteremia and right-sided infective endocarditis [15]. Daptomycin diffuses through the peptidoglycan layer of Gram-positive organisms to the plasma membrane where it caused rapid depolarization resulting in the loss of membrane potential leading to loss of protein, DNA, and RNA synthesis and resulting in cell death [16].

In the case of uncomplicated bacteremia that is determined by the absence of endocarditis, artificial hardware, multiple sites of infection, and for which repeated blood cultures do not grow MRSA and patients are clinically well, vancomycin or daptomycin 6 mg/kg/dose IV once daily can be given for at least 2 weeks. However, in the case of complicated bacteremia, a duration of 4–6 weeks of therapy is recommended, depending on the extent of infection. Sometimes, higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily may be needed.

When MRSA bacteremia becomes complicated with infective endocarditis, IV vancomycin or daptomycin 6–10 mg/kg/dose IV once daily for 6 weeks is recommended. It is not recommended to add gentamicin or rifampin to vancomycin for bacteremia or native valve infective endocarditis.

It is also important to identify the source and extent of the infection with removal and debridement or drainage of other sites of infection to decrease the bulk of the infection. Blood cultures need to be collected every 2–4 days after initial positive cultures until documentation of the clearance of bacteremia. And echocardiography is recommended for all adult patients with bacteremia to eliminate the possibility of associated endocarditis; transesophageal echocardiography (TEE) being preferred over transthoracic echocardiography (TTE). In the cases of large vegetations that exceed 10 mm in diameter, occurrence of more than one embolic event during the first 2 weeks of therapy, severe valvular insufficiency, valvular perforation or dehiscence, decompensated heart failure, perivalvular or myocardial abscess, new heart block, or persistent fevers or bacteremia, evaluation for replacement of the affected valve should be considered in consultation with cardiothoracic surgery.

In conditions that are characterized by MRSA bacteremia complicated with infective endocarditis of a prosthetic valve, administration of IV vancomycin plus rifampin 300 mg PO/IV every 8 h for at least 6 weeks plus gentamicin 1 mg/kg/dose IV every 8 h for 2 weeks is recommended, along with early evaluation for valve replacement surgery to decrease the risk of embolization.

9. Antimicrobial therapy that may be used for MRSA bacteremia

9.1. Clindamycin

Clindamycin is not specifically approved for treatment of MRSA infection, but it has been used for skin infections and invasive susceptible community-acquired MRSA infections in children. It is bacteriostatic and, as such, is not recommended for bacteremia, endovascular

infections like infective endocarditis or septic thrombophlebitis. Clindamycin has excellent tissue penetration, particularly in bone and abscesses, but has poor penetration into the CSF. Community-acquired MRSA infections are more susceptible to Clindamycin than hospital-acquired isolates. It is important to have a D-zone test to look for inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible isolates. Side effects include diarrhea and *Clostridium difficile*-associated disease. Clindamycin is pregnancy category B.

9.2. Daptomycin

This is a lipopeptide class antibiotic that destroys cell membrane function through calcium-dependent binding, leading in a bactericidal activity in a concentration-dependent manner. It is FDA approved for adults with *S. aureus* bacteremia, right-sided infective endocarditis, and complicated skin infections. It is not supposed to be given in nonhematogenous MRSA pneumonia because its activity is inhibited by pulmonary surfactant. The susceptibility breakpoint for daptomycin for *S. aureus* is ≤ 1 $\mu\text{g/mL}$. It appears that prior use of vancomycin and elevated vancomycin minimal inhibitory concentrations (MICs) has been associated with increases in daptomycin MICs and the emergence of nonsusceptible isolates. Monitoring creatinine phosphokinase (CPK) while on daptomycin is necessary to avoid rhabdomyolysis, which is seen with higher doses. Therapy with daptomycin may be complicated with daptomycin-induced eosinophilic pneumonia. Daptomycin is pregnancy category B.

9.3. Linezolid

Linezolid is a synthetic oxazolidinone and inhibits initiation of protein synthesis at the 50S ribosome. It is FDA-approved for treatment of skin infections and nosocomial pneumonia due to MRSA. It has a 100% oral bioavailability. Resistance to linezolid is rare, but has been reported. An outbreak with linezolid-resistant and methicillin-resistant *S. aureus* in an intensive care unit has been reported in Spain. Resistance to linezolid was mediated by the *cfr* gene, as all isolates ended up carrying this gene. It is not approved for the treatment of MRSA bacteremia, although it has been used for this condition on several occasions. Long-term use is not advisable as it may be complicated with hematologic toxicity, thrombocytopenia, anemia, neutropenia, peripheral and optic neuropathy, and lactic acidosis. Peripheral and optic neuropathy may not be reversible. Since it is a weak, nonselective, reversible inhibitor of monoamine oxidase, it may cause serotonin syndrome in patients taking concurrent selective serotonin-receptor inhibitors. It is considered pregnancy category C.

9.4. Tedizolid

Tedizolid is an oxazolidinone drug. It has the advantage of oral and parenteral formulations, similar to linezolid. It was approved for the treatment of acute bacterial skin and skin structure infections in 2014 and is administered once daily. Its use in bacteremia has not been recommended at this point.

9.5. Quinupristin-dalfopristin

Quinupristin-dalfopristin is constituted of two streptogramin antibiotics and inhibits protein synthesis. It is FDA approved for skin and soft tissue infections in adults and children >16

years of age. It has been used as salvage therapy for invasive MRSA infections in the setting of vancomycin treatment failure. It can have several side effects such as arthralgias, myalgias, and infusion-related reactions that may limit its use. Quinupristin-dalfopristin is considered pregnancy category B.

9.6. Rifampin

Rifampin is bactericidal against *S. aureus* and achieves high intracellular levels and good penetration in biofilms. It cannot, however, be used as monotherapy and is recommended to be used in combination with another antibiotic. It can be given at doses ranging from 600 mg daily in a single dose or in two divided doses to 900 mg daily in two or three divided doses. Rifampin is usually used in the setting of a *S. aureus* hardware infection.

9.7. Telavancin

Telavancin is an intravenous lipoglycopeptide. It inhibits cell wall synthesis by binding to peptidoglycan chain precursors and causing cell membrane depolarization. It has bactericidal activity against MRSA, vancomycin intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA). It is FDA approved for complicated skin and soft tissue infections in adults and is pregnancy category C. Nephrotoxicity was more commonly reported among patients treated with telavancin than among those treated with vancomycin, however, unlike vancomycin, there is no need to monitor telavancin levels in the serum. It may be given in bacteremia, but would be an off label use.

9.8. Tetracyclines

Doxycycline is a tetracycline that is approved for the treatment of skin and soft tissue infections due to *S. aureus*. There is lack of data to support its use in more invasive infections like bacteremia. Tetracycline and doxycycline resistance in CA-MRSA is associated with *tetK* gene, but does not affect minocycline susceptibility. Minocycline is available in oral and parenteral formulations. A newer tetracycline named tigecycline is a glycylcycline and is a derivative of the tetracyclines. It is FDA approved in adults for skin and soft tissue infections and intraabdominal infections. It has a bacteriostatic activity against MRSA, thus it is not used in bacteremia; however, it was found that its use was associated with an increase in all-cause mortality. Tetracyclines are pregnancy category D and are not recommended for children <8 years of age due to the potential for tooth enamel discoloration and decreased bone growth.

9.9. Trimethoprim-sulfamethoxazole

TMP-SMX is not FDA-approved for the treatment of any staphylococcal infection, but since the majority of community-acquired MRSA strains are susceptible to it *in vitro*, it has become widely used for skin and soft tissue infections. It may also be used in bone and joint infections. For more invasive cases such as staphylococcal bacteremia and endocarditis, it can be used, though not as a first line drug. In addition, its use in the elderly must be done in conjunction

with close monitoring of creatinine and potassium levels. It is not recommended in pregnant women in the third trimester (pregnancy category C/D).

9.10. Ceftaroline

Ceftaroline is a fifth-generation cephalosporin. It is bactericidal against Gram-positive and Gram-negative pathogens and has activity against MRSA and VISA strains. It is recommended for skin and skin tissue infections and community-acquired pneumonia. Its use in cases of *S. aureus* bacteremia is still under investigation.

9.11. Dalbavancin

Dalbavancin is a semisynthetic lipoglycopeptide that inhibits cell wall synthesis. Its half-life is 147-258 hours, which allows use at once weekly dosing. It was approved in 2014 for treatment of acute bacterial skin and skin structure infections due to Gram-positive organisms, including MRSA. It is not yet approved for cases of *S. aureus* bacteremia.

9.12. Oritavancin

Oritavancin is a semisynthetic glycopeptide that also inhibits cell wall synthesis. Its half-life is 100 hours, allowing for single dose therapy. It was approved for treatment of acute bacterial skin and skin structure infections in 2014.

9.13. Vancomycin

Vancomycin has been the mainstay of parenteral therapy for MRSA infections; it has slow bactericidal activity. There is evidence of emerging resistant strains. Vancomycin kills staphylococci more slowly than β -lactams do *in vitro* and is inferior to β -lactams for MSSA bacteremia and infective endocarditis. Tissue penetration is highly variable and depends upon the degree of inflammation. Vancomycin's minimum inhibitory concentration breakpoints were changed in 2006 to improve the detection of intermediate susceptible strains (susceptible: MIC of 2 μ g/mL or lower; intermediate: MIC of 4–8 μ g/mL; and resistant: MIC 16 μ g/mL or greater). The concept of MIC creep has arisen due to decrease in susceptibility to vancomycin among *S. aureus* isolates. *S. aureus* strains have been reported to “creep” up and approach the breakpoint of 2 with increasing frequency. This has been associated with worse clinical outcomes when vancomycin is used as therapy, when the MRSA isolate has a higher MIC to vancomycin. Vancomycin is considered pregnancy category C.

10. Management of persistent MRSA bacteremia and vancomycin treatment failures in adult patients

In cases of persistent positive blood cultures for *S. aureus*, it is necessary to look for deep-seated infections and hidden foci that continually send particles of infection into the blood stream. Removal of these infectious foci by either drainage or surgical debridement is recommended.

When vancomycin is used but the bacteremia persists, high-dose daptomycin (10 mg/kg/day), if the isolate is susceptible, in combination with another agent such as gentamicin 1 mg/kg IV every 8 h, rifampin 600 mg PO/IV daily, or 300–450 mg PO/IV twice daily, linezolid 600 mg PO/IV BID, TMP-SMX 5 mg/kg IV twice daily should be considered. But in case of reduced susceptibility to vancomycin and daptomycin, quinupristin-dalfopristin 7.5 mg/kg/dose IV every 8 h, TMP-SMX 5 mg/kg/dose IV twice daily, linezolid 600 mg PO/IV twice daily, or telavancin 10 mg/kg/dose IV once daily may be other options.

11. Recommendations for vancomycin dosing

In case of bacteremia, the dose of IV vancomycin is 15–20 mg/kg/day divided in two or three doses in order to conserve normal renal function. For seriously ill patients such as those with sepsis, meningitis, pneumonia, or infective endocarditis with suspected MRSA infection, a loading dose of 25–30 mg/kg (actual body weight) may be considered. Monitoring of vancomycin trough levels is necessary to guide the dosing of this antibiotic. Serum trough levels should be measured prior to the fourth or fifth dose. For serious infections such as bacteremia, infective endocarditis, meningitis, pneumonia, and necrotizing fasciitis due to MRSA, vancomycin trough concentrations of 15–20 µg/mL are recommended. Vancomycin trough monitoring is recommended for serious infections, patients who are morbidly obese have renal dysfunction or have fluctuating volumes of distribution. For isolates with a vancomycin MIC ≤ 2 , the patient's clinical response should determine the continued use of vancomycin; however, if the patient has not had a clinical or microbiologic response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC. For the isolates with a vancomycin MIC >2 µg/mL (e.g., VISA or VRSA), an alternative to vancomycin should be used.

12. Prevention

Decolonization is important to achieve prevention of *S. aureus* bacteremia and other infections. The role of decolonization in controlling the spread of *S. aureus* is still unclear. It is also unclear what the optimal regimen is. Options include agents for nasal decolonization such as mupirocin and topical body decolonization with an agent such as chlorhexidine gluconate to target the extra nasal sites. Systemic oral antibiotics can be used for decolonization; however, there are issues that are very important to consider for decolonization, recolonization, and development of resistance. The current guidelines suggest that decolonization be considered in patients with recurrent skin infections or ongoing transmission occurring among household contacts despite optimizing wound care and hygiene measures. Hand hygiene consists of soap and water or an alcohol-based hand rub before and after contact with infected areas. Sharing personal items is discouraged.

As for hospitals, infection control and prevention strategies should include hand hygiene, active surveillance to identify *S. aureus* colonization, and environmental cleaning. Patient bathing with chlorhexidine gluconate in intensive care units leads to a reduction in *S. aureus* colonization and infection. It is felt that bathing with chlorhexidine gluconate is a measure for source control that may lead to less contamination of health care worker hands, thus less contamination of the environment and the spread of infection to other patients. One additional infection control strategy for years has been to create a vaccination against *S. aureus*. So far, attempts have been unsuccessful, but there is much research in this area.

13. Future perspective

S. aureus has had a steady increase in incidence over the last several decades. The higher frequency of artificial catheters, cardiac devices, joints being placed, of skin and surgical site wounds becoming infected, and intravenous drug use all serve as nidus for infection, particularly bacteremia. The cost and resource burden on health care systems is projected to continue to grow as the number of risk factors increase. There is also the problem to consider of how MRSA initially was only seen in health care settings but now makes up a large percentage of community-based infections.

What are some of the ways the medical community is working on not only treating but also preventing a much more widespread and resistant phenomenon? The approval of several newer antibiotics to combat serious MRSA infections shown in 2014, and there are a number of prospective antibiotics being studied with the potential to come to market [17]. A concerted effort among medical centers to make improvements at the level of the diagnostic stage (using transesophageal imaging more regularly) will be necessary in order to improve outcomes. In a different approach, the relationship among host immunologic factors in conjunction with environmental factors would be an additional avenue for exploration and possibly result in additional, nonantibiotic regimens. Continued use and awareness of infection prevention measures such as use of isolation inpatient and basic hand hygiene are both effective strategies in the greater attempt to not allow the bacteria to morph any and to prevent basic spread of the organism. Finally, there may be a time in the future when the ultimate means of infection control—a vaccination—would become available.

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