American Journal of Transplantation 2013; 13: 50–58
Wiley Periodicals Inc.



doi: 10.1111/ajt.12098

Special Article

# Methicillin-Resistant, Vancomycin-Intermediate and Vancomycin-Resistant *Staphylococcus aureus* Infections in Solid Organ Transplantation

**C. Garzoni[a,b,*], P. Vergidis[c] and the AST Infectious Diseases Community of Practice**

[a] *Department of Internal Medicine and Infectious Diseases, Clinica Luganese, Lugano, Switzerland*
[b] *Clinic for Infectious Diseases, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland*
[c] *Division of Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, PA*
* *Corresponding author: Christian Garzoni, christian.garzoni@gmail.com*

**Key words: Antibiotic resistance, bacterial infection, multidrug resistance, posttransplant infection**

**Abbreviations: CA-MRSA, community-associated MRSA; CLSI, Clinical and Laboratory Standards Institute; EARSS, European Antimicrobial Resistance Surveillance System; HA-MRSA, healthcare-associated MRSA; HIV, human immunodeficiency virus; hVISA, heteroresistant VISA; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; MALDI-TOF, matrix-assisted laser desorption ionization-time-of-flight mass spectrometry; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, Methicillin-susceptible *S. aureus*; PCR, polymerase chain reaction; PNA-FISH, fluorescent *in situ* hybridization employing peptide nucleic acid probes; PVL, Panton-Valentine leukocidin; SSC*mec*, staphylococcal chromosome cassette *mec*; SSTIs, skin and soft-tissue infections; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant enterococci; VRSA, vancomycin-resistant *S. aureus*.**

## Epidemiology and Risk Factors

*Staphylococcus aureus* is a major cause of infection among solid-organ transplant recipients. After years of rising incidence, methicillin-resistant *S. aureus* (MRSA) infections have been decreasing. In the United States, the incidence of MRSA catheter-associated bloodstream infections has declined (1) as have rates of invasive healthcare-associated MRSA infections (2). Data from Europe are even more encouraging (3). According to the European Antimicrobial Resistance Surveillance System (EARSS), invasive MRSA infections are decreasing in nine countries (4). According to the HELICS surveillance network, the incidence of MRSA infections has decreased in the intensive care setting (5). Those data support the use of aggressive policies in infection prevention and control. Despite those positive data, MRSA still accounts for more than 25% of bacteremias caused by *S. aureus* in many European countries (4). However, among central venous catheter-associated bloodstream infections caused by *S. aureus* in United States intensive care units (ICUs), more than 50% are caused by MRSA (6). Thus, further efforts to decrease infection are needed.

*S. aureus* is a Gram-positive organism frequently causing infection following transplantation. It is commonly encountered within the first 3 posttransplant months. A significant number of those infections are caused by MRSA. *S. aureus* is one of the leading causes of Gram-positive bacteremia among transplant recipients reported in up to 25% of all isolated bacterial pathogens (7–10). *S. aureus* is a common cause of pneumonia after lung transplantation with rates of MRSA infection ranging from 40% to 80% in staphylococcal pneumonia (11–13). Surgical site infections following transplantation are also commonly caused by *S. aureus*. The true extent of MRSA colonization and incidence of infection after transplantation in adults and children varies among transplant centers reflecting the type of transplanted organs and the prevalence of carriage and infection in the nontransplant patient population.

Risk factors associated with MRSA infection include prolonged hospital stay, exposure to broad-spectrum antibiotics, admission to an ICU or burn unit, recent surgery, close contact to other patients with MRSA, presence of foreign bodies such as central venous catheters, and MRSA colonization (14). Factors specifically noted in liver transplant recipients include surgery within 2 weeks prior to infection, cytomegalovirus seronegativity or primary infection, extended posttransplant ICU stay, presence of other major posttransplant infections, peritonitis and increased prothrombin time (15–17). Patients on the waiting list and transplant recipients have an increased risk of becoming colonized with MRSA because of their illness and contact with the healthcare system. High rates of colonization have been reported for those undergoing hemodialysis (18) and patients with cystic fibrosis (19). Patients can become colonized following transplantation, as shown among liver

transplant recipients (20). MRSA acquisition is dependent on the local MRSA prevalence, infection control policies and the recipient's general state of illness (21).

Methicillin-susceptible and -resistant *S. aureus* colonization has been shown to increase the risk of subsequent infection (22), which is usually caused by the same strain. Among transplant patients specific data exist only for liver recipients. Liver transplant recipients colonized with MRSA on admission are at risk for subsequent MRSA infection. The reported incidence of infection in MRSA carriers ranges from 24 to 87% (15,23–25). MRSA carriage among liver transplant recipients does not seem to significantly affect mortality (24,25). In contrast, MRSA infection is associated with increased mortality (15,25). The incidence of MRSA infection seems to be higher in newly colonized patients than in chronic carriers (26), although data on transplant recipients are lacking. Donor-derived MRSA infection transmitted from a healthy living donor has been reported (27).

The increasing incidence of community-associated MRSA (CA-MRSA) is becoming a public health problem of great concern (28,29). CA-MRSA strains were originally isolated in patients who did not have contact with the healthcare system and were distinguished from healthcare-associated MRSA (HA-MRSA) through epidemiologic and antimicrobial resistance patterns. Most CA-MRSA strains carry staphylococcal chromosome cassette (SCC*mec*) type IV and genes for the exotoxin Panton-Valentine leukocidin (PVL) (30). CA-MRSA has a worldwide distribution, but its prevalence varies geographically. In a study conducted in 12 US emergency departments, the prevalence of MRSA was 59% among all skin and soft-tissue infections (SSTIs) and clone USA300 accounted for almost all isolates (31). Clone USA300 also causes an increasing proportion of hospital-onset invasive MRSA infections (28,29,32,33). CA-MRSA prevalence is lower in Europe and currently the most important risk factor is traveling to or origin from high-prevalence countries (34,35). Isolated cases and small outbreaks caused by different clones have been documented in many European countries (3,36). Furthermore, CA-MRSA is spreading from the community into hospitals, and the incidence of CA-MRSA infections and outbreaks in hospitalized patients is increasing (28,36,37). An increasing prevalence of CA-MRSA colonization in livestock with the potential of human spread has also been reported (3,28,29,36).

CA-MRSA can be transmitted from person to person. In US studies, the following groups were found to be at risk for colonization or infection: neonates and children; athletes who participate in contact sports; injection drug users; men who have sex with men; military personnel; persons living in correctional facilities, nursing homes, or shelters; adults 65 years or older; veterinarians; pet owners; pig and horse farmers. HIV infection, cystic fibrosis and household contact with a person known to be colonized or infected with MRSA are additional risk factors. The presence of SSTI or a history of recent severe pneumonia should raise the suspicion of CA-MRSA colonization (28,38). In the general population, CA-MRSA is typically associated with uncomplicated SSTIs but can also cause severe disease, such as necrotizing fasciitis or necrotizing pneumonia (28,29,38). Certain strains, notably USA300, often produce PVL, whose role in the virulence of MRSA remains controversial. Infection with CA-MRSA has been reported among transplant patients; very few epidemiologic data exist (27,39) but possibly follow the trends of the general population. In a single-center study from Canada, among 17 cases of MRSA colonization and/or infection, all strains were found to be hospital-associated (13). Considering the increasing incidence, infection with CA-MRSA should be suspected even in low-prevalence areas.

The prevalence of vancomycin-intermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA) is increasing worldwide with major regional differences (40,41). Lacking a standardized detection method, findings on prevalence depend on study methodology. Data on transplant recipients are sparse. In a French study, heterogeneous glyocopeptide intermediate *S. aureus* strains were found in 13 (27%) of 48 patients (42). Vancomycin-resistant *S. aureus* (VRSA) has been shown to occur through transfer of the *vanA* gene from vancomycin-resistant enterococci (VRE) to MRSA. Few cases of VRSA have been reported to date in the United States (43) and Asia (44,45); none among transplant recipients. Factors that have been associated with VRSA infection are colonization or infection with MRSA or VRE, prior use of vancomycin, presence of chronic cutaneous ulcers and diabetes mellitus (43). Transplant recipients have multiple comorbidities and are potentially at risk for VRSA infection.

## Diagnosis

*S. aureus* infections occurring in the first 3 posttransplant months are typically related to the surgical procedure and use of medical devices such as intravenous catheters and endotracheal tubes (7,9,10,46). MRSA most commonly causes bloodstream, lower respiratory tract, wound and intraabdominal infections. Diagnosis is established by isolation of the organism from affected sites. In general, isolation of *S. aureus* from a normally sterile body site or blood culture is diagnostic of infection. Depending on the clinical context, MRSA isolated in sputum, wound culture or fluid obtained from a drainage catheter may represent infection or mere colonization. In the absence of consistent clinical symptoms, signs and/or radiographic findings, isolation of the pathogen is more likely to represent colonization than infection and antibiotic treatment is not required.

Detection of Gram-positive cocci in clusters on Gram stain of the direct specimen provides an early clue to diagnosis. Rapid diagnostic assays, such as real-time PCR (47), fluorescent *in situ* hybridization employing peptide

nucleic acid probes (PNA-FISH) (48) and matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF) (49) can expedite the characterization of Gram-positive cocci in blood cultures. For infection control purposes, surveillance cultures may be obtained from the anterior nares, throat, axillae, rectum or open wound areas. Traditional culture techniques provide results within 24–72 h. Chromogenic agar can be used to detect MRSA with a very high negative predictive value after only 24 h of incubation. A longer incubation period of 48 h slightly increases the sensitivity of the assay (50). Molecular techniques targeting DNA sequences within *SCCmec*, a mobile element carrying the methicillin-resistance gene *mecA*, allow for MRSA detection within 2–6 h (51).

Isolates with oxacillin MIC $\geq$4 μg/mL or methicillin MIC $\geq$16 μg/mL are considered methicillin-resistant. A 30 μg cefoxitin disk is more sensitive in detecting methicillin resistance than a 1 μg oxacillin disk (52). Molecular methods can be used to detect the *mecA* gene which codes for penicillin binding protein 2a and has been associated with resistance to beta lactams. In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered the vancomycin breakpoints for MRSA. Current breakpoints are $\leq$2 μg/mL for susceptible, 4–8 μg/mL for intermediate and $\geq$16 μg/mL for resistant isolates (53). Vancomycin has been considered the drug of choice for MRSA infections (I). However, strains with reduced susceptibility have emerged. VISA strains are homogeneous bacterial populations with MIC of 4–8 μg/mL. hVISA strains are susceptible using standard broth microdilution, but contain a small subpopulation of bacteria ($1/10^5$–$10^6$) that show intermediate susceptibility to vancomycin. VISA and hVISA strains are difficult to detect with automated standard MIC methodology and disk diffusion testing. E-test can improve the detection of VISA. Routine use of alternative methods for hVISA detection is not routinely recommended. Clinicians and microbiology laboratory personnel should be aware of this pitfall, as those strains have been associated with treatment failures (54). For an insufficient or failed response to vancomycin, particularly with strains at the upper end of the susceptible range (2 μg/mL), hVISA and VISA should be suspected. This should be communicated to the microbiology laboratory. If necessary, the strain can be further tested at a reference laboratory. A more detailed review is beyond the scope of this text; please refer to IDSA Guidelines (55), Centers for Disease Control VISA/VRSA guide (56) and recent reviews (40,54,57). Finally, pulse field gel electrophoresis and/or genotyping of the *SCCmec* gene can be performed to differentiate CA-MRSA from HA-MRSA and is mainly used for epidemiologic and research purposes.

## Treatment

Clinical practice guidelines for the treatment of MRSA infections have been published by the Infectious Diseases Society of America (55). A summary of antimicrobial agents used in the management of staphylococcal infections, with an emphasis on transplantation issues, is provided in Table 1. Vancomycin is the drug of choice for serious infections caused by MRSA (I). Vancomycin is a bactericidal agent that inhibits bacterial cell wall synthesis. For methicillin-susceptible *S. aureus* (MSSA) the rate of bacterial killing is slower compared to β-lactams.

Guidelines have been published on the therapeutic use of vancomycin (58). Dosages should be calculated based on actual body weight. Target trough concentrations were selected with the aim of optimizing pharmacodynamics and efficacy and to minimize selection of resistant strains. For complicated MRSA infections, such as endocarditis, bacteremia, meningitis and pneumonia, serum trough concentrations of 15–20 μg/mL are advised (III). In most patients with normal renal function, these concentrations are achieved with a dose of 15–20 mg/kg every 8–12 h. In seriously ill patients, a loading dose of 25–30 mg/kg should be considered (58) (III).

In the case of isolates with an MIC value of 2 μg/mL, therapeutic serum levels cannot be achieved even with trough concentrations of 15–20 μg/mL. As demonstrated in a meta-analysis of 22 studies, vancomycin MIC values of $\geq$1.5 μg/mL were associated with higher mortality rates, particularly among patients with bloodstream infections (59). Higher MIC values were also predictive of treatment failure. The optimal treatment in case of high MIC and vancomycin failure is controversial, as there are currently no data to support better survival rates with the use of alternative antimicrobial agents, even though this practice has been recommended by several experts (60–66) (III). Infectious disease consultation is strongly advised (II-2).

Daptomycin, a bactericidal agent, is approved for use in complicated SSTIs, bacteremia and right-sided endocarditis (67). Further data are needed to extend the experience in the treatment of left-sided endocarditis (68). Daptomycin should not be used to treat pulmonary infections as it is inactivated by the lung surfactant. For prolonged bacteremia or documented microbiological failure while on daptomycin therapy, susceptibility testing should be repeated because of the risk of emergence of resistance. Of note, nonsusceptibility to daptomycin has been seen in isolates with increased MIC to vancomycin (69). The standard dose for treatment of bacteremia in patients with normal renal function is 6 mg/kg/day. Dosages of 8–10 mg/kg/day may be safe and effective in patients with severe complicated infections and have been suggested by some experts (61).

Linezolid, a bacteriostatic agent, is approved for use in uncomplicated and complicated SSTIs and nosocomial MRSA pneumonia. The drug is not approved for use in *S. aureus* bacteremia or endocarditis. Adverse events include thrombocytopenia, lactic acidosis, peripheral and optic neuropathy, particularly after prolonged use (more than 28 days).

**Table 1:** Therapeutic options for methicillin-resistant *Staphylococcus aureus* (MRSA) infections (please see the text for details)

| Antimicrobial | Dosing | Comments |
|---|---|---|
| Vancomycin | 15–20 mg/kg (actual body weight) q12h. For younger patients consider dosing q8h. Do not exceed 2 g/dose<br>Consider 25–30 mg/kg load for serious infections and in critically ill patients<br>$Cr_{cl}$ 20–49: 15–20 mg/kg q24h<br>$Cr_{cl}$ ≤20: redose based on serum concentrations<br>Initial load for critically ill with renal impairment should not be reduced<br>IHD: loading 15–25 mg/kg, then 5–10 mg/kg or 500–1000 mg after each dialysis session (3 times per week) | • Treatment of choice for susceptible MRSA (I)<br>• Dosing should be adjusted based on serum trough concentrations; obtain trough at steady-state conditions (just before the fourth dose)<br>• Target trough concentrations for bacteremia, endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia: 15–20 μg/mL (III)<br>• If no adequate clinical/microbiological response despite adequate debridement, or MIC >2 μg/mL, an alternative drug is recommended. ID consultation is advised (II-2)<br>• Nephrotoxicity mostly if concomitant use of other nephrotoxic medications, preexisting renal impairment, dehydration, advanced age<br>• Red person syndrome may be reduced by prolonging infusion rate and premedication with antihistamine |
| Daptomycin | $Cr_{cl}$ ≥30: 4 mg/kg q24h for complicated SSTI; 6 mg/kg q24h for bacteremia, endocarditis, bone/joint infection<br>Some experts advocate 8–10 mg/kg for endocarditis and complicated bacteremia<br>$Cr_{cl}$ <30, IHD: 4 mg/kg q48h for complicated SSTI; 6 mg/kg q48h for bacteremia, endocarditis, bone/joint infection<br>Not evaluated in severe hepatic impairment (Child–Pugh class C) | • Do not use for pneumonia. Inactivated by surfactant<br>• Reduced susceptibility can emerge during therapy; recheck MIC if inadequate response. Risk factors: previous vancomycin therapy and high vancomycin MIC. Observed especially in left-side endocarditis and deep-seated infections<br>• Can cause myopathy. Monitor creatine phosphokinase at least weekly during therapy. Avoid concomitant use of statins |
| Linezolid | 600 mg PO/IV q12h<br>No renal adjustment required<br>Metabolites may accumulate in patients with renal impairment but clinical significance unknown<br>Not adequately evaluated in severe hepatic impairment (Child–Pugh class C) | • Indicated in SSTI and nosocomial pneumonia<br>• Myelosuppression (mainly if used for >2 weeks). Monitor complete blood count weekly<br>• Lactic acidosis<br>• Peripheral and optic neuropathy (in long-term therapy)<br>• Serotonin syndrome (avoid use with SSRIs, triptans) |
| Trimethoprim-sulfamethoxazole | One double strength (DS) tablet contains 160 mg of trimethoprim<br>8–10 mg/kg daily based on trimethoprim component in 2 divided doses (usually 1–2 DS tab twice daily)<br>$Cr_{cl}$ 10–30: 50% of usual dose<br>$Cr_{cl}$ <10, IHD: avoid or use 1 DS tab q48h | • Indicated for SSTI. Unlabeled use: osteomyelitis, septic arthritis<br>• Avoid use in bacteremia, endocarditis<br>• May reduce serum concentration of cyclosporine<br>• Rare but life-threatening adverse events: hepatotoxicity, severe dermatologic reactions, hematologic dyscrasias<br>• Do not use in third trimester of pregnancy |
| Clindamycin | 300–600 mg po/iv q8h<br>No renal adjustment required<br>Use caution with severe hepatic impairment | • Indicated for SSTI. Unlabeled use: pneumonia, osteomyelitis, septic arthritis<br>• Avoid use in bacteremia, endocarditis<br>• May decrease serum concentration of mycophenolate<br>• Diarrhea, including *Clostridium difficile* infection<br>• Myelosuppression<br>• Hepatotoxicity |
| Tigecycline | 100 mg load, then 50 mg q12h<br>No renal adjustment required<br>Child–Pugh class C: 100 mg load, then 25 mg q12h | • Indicated for SSTI, intraabdominal infections, community acquired pneumonia caused by MSSA. Not approved for MRSA pneumonia<br>• Avoid use in bacteremia and endocarditis<br>• May increase serum concentration of cyclosporine<br>• Nausea and vomiting are common adverse events<br>• Do not use in pregnancy and children <8 years |
| Doxycycline | 200 mg load, then 100 mg twice daily<br>No renal adjustment required | • Unlabeled use: cellulitis due to community-associated MRSA<br>• Do not use in pregnancy and children <8 years |
| Ceftaroline | 600 mg q12h<br>$Cr_{cl}$ 31–50: 400 mg q12h<br>$Cr_{cl}$ 15–30: 300 mg q12h<br>$Cr_{cl}$ <15, IHD: 200 mg q12h | • Indicated for complicated SSTI. Not approved for healthcare-associated pneumonia<br>• No data for bacteremia<br>• Use with caution in patients with penicillin allergy |
| Quinupristin-dalfopristin | 7.5 mg/kg q12h for complicated SSTI<br>7.5 mg/kg q8h for bacteremia<br>No renal adjustment required | • Unlabeled use: persistent bacteremia associated with vancomycin failure<br>• Quinupristin may increase the serum concentration of cyclosporine<br>• Severe myalgias and arthralgias limit drug use<br>• Phlebitis when infused via peripheral line<br>• Hyperbilirubinemia |
| Telavancin | $Cr_{cl}$ ≥50: 10 mg/kg q24h<br>$Cr_{cl}$ 30–50: 7.5 mg/kg q24h<br>$Cr_{cl}$ 10–29: 10 mg/kg q48h<br>$Cr_{cl}$ <10 or IHD: no data available. Use caution or avoid<br>Not evaluated in severe hepatic impairment | • Indicated for complicated SSTI<br>• Combination with tacrolimus may cause $QT_c$ prolongation<br>• Women of childbearing age should have serum pregnancy test prior to use |
| Rifampin | Prosthetic-valve endocarditis: 300 mg three times daily<br>Device-associated osteoarticular infection: 600 mg once daily or 300–450 mg twice daily<br>$Cr_{cl}$ <10 or IHD: give 50–100% of usual dose | • Use only in combination with other antistaphylococcal agent if hardware retention (I)<br>• Rifampin may significantly increase the metabolism of tacrolimus, sirolimus, cyclosporine and corticosteroids (use caution, monitor concentrations). Avoid combination with mycophenolate mofetil |

$Cr_{cl}$ = creatinine clearance in mL/min, IHD = intermittent hemodialysis; MIC = minumum inhibitory concentration; MSSA = methicillin-susceptible *S. aureus*; SSRI = selective serotonin re-uptake inhibitor; SSTI = skin and soft tissue infection; VISA = vancomycin-intermediate *S. aureus*.

Renal insufficiency can increase drug toxicity. Concomitant use of selective serotonin reuptake inhibitors should be avoided to prevent serotonin toxicity. In a retrospective study, linezolid appeared to be safe and effective for the treatment of gram-positive infections in liver transplant recipients despite those patients' increased risk of thrombocytopenia (70). In a single randomized controlled trial, linezolid demonstrated greater clinical efficacy compared to vancomycin for the treatment of nosocomial MRSA pneumonia, even though 60-day mortality was similar between the two drugs (71).

Trimethoprim-sulfamethoxazole (TMP-SMX), a bactericidal agent, is used in the treatment of SSTIs and osteomyelitis. Due to its use for prophylaxis in transplant recipients, susceptibility may not be universal. TMP-SMX can increase the myelotoxicity of methotrexate and nephrotoxicity of cyclosporine. TMP-SMX may decrease the renal excretion of creatinine and thus increase serum creatinine levels without causing actual renal impairment. Clindamycin, a bacteriostatic agent, has a role in complicated SSTIs, pneumonia and osteomyelitis. Susceptibility to MRSA may vary by geographic region. TMP-SMX and clindamycin are not recommended for the treatment of bacteremia or endocarditis. Tigecycline, a bacteriostatic agent, is approved for use in complicated SSTIs (72). Because of a rapid decline of the drug serum concentration between dose intervals (73), tigecycline is not recommended in the treatment of serious infections, such as bacteremia or endocarditis In a meta-analysis of randomized controlled trials, tigecycline was associated with increased mortality compared to active comparator antibiotics (74). Doxycycline and minocycline are alternative oral agents. Quinupristin-dalfopristin is bactericidal if the organism is susceptible to both drug components. The drug is approved for use in complicated SSTIs. Its use has been limited by severe arthralgias and myalgias.

Ceftaroline and telavancin are two recently approved bactericidal agents with activity against MRSA. Their role in invasive MRSA infections remains to be determined. Ceftaroline, a fifth-generation cephalosporin, is approved for complicated SSTIs (75) and community-acquired pneumonia (76). For pneumonia, it has been approved for MSSA but not MRSA. Telavancin, a semisynthetic lipoglycopeptide, is approved only for complicated SSTIs (77). Teicoplanin and fusidic acid are antimicrobials with activity against MRSA which are marketed in several countries but are not currently available in the United States.

Combination treatment is considered in certain infections. For prosthetic valve endocarditis (II-3) and device-associated osteoarticular infection with hardware retention (I), rifampin is typically combined with other antistaphylococcal agents (55,78). In transplant recipients receiving rifampin, immunosuppressive drug serum concentrations should be monitored closely due to the potential drug–drug interactions, especially with calcineurin inhibitors (III). Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve endocarditis (II-1). Aminoglycosides may be used in combination with vancomycin as synergistic agents for prosthetic valve endocarditis (III); however, the potential for nephrotoxicity, especially with calcineurin inhibitors, should be considered. For severe necrotizing pneumonia, combination therapy that includes toxin-suppressing agents (clindamycin or linezolid) has been suggested in nontransplant patients based on *in vitro* studies (79) (III).

Duration of treatment depends on the type of infection. For uncomplicated SSTIs treatment for 5–10 days is generally recommended. Abscesses should be drained and complicated deep-seated infections should be debrided. Pneumonia should be treated for 7–14 days depending on the extent of the infection and patient's clinical response. Longer courses are generally advised for necrotizing pulmonary infection. Patients meeting the criteria for uncomplicated bacteremia (exclusion of endocarditis; no implanted prostheses; clearance of bacteremia within 2–4 days; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection) should be treated for a minimum of 2 weeks (55). Patients who do not meet the above criteria have complicated bacteremia and should be treated for 4–6 weeks. Infective endocarditis is also treated for 4–6 weeks (80). There are no data to support longer antibiotic treatment courses for MRSA in transplant recipients compared to immunocompetent patients. Reducing immunosuppressive therapy is advised in the case of severe infection (III).

In patients with persistent bacteremia, endovascular infection must be excluded. Patients should undergo evaluation for endocarditis with transesophageal echocardiography. Septic thrombophlebitis should be considered in the presence of intravenous catheters. If possible, indwelling devices should be removed. Appropriate imaging studies can identify a potential metastatic focus of infection. Serial blood cultures should be obtained to document clearance of bacteremia and determine duration of treatment.

## Prevention/Infection Control

Several studies have demonstrated the positive impact of infection control measures for the prevention of MRSA infection. Transplant recipients are at high risk for MRSA infection due to surgical procedure, ICU stay, multiple comorbidities and immunocompromised status. Few studies have specifically addressed the issue of prevention in the transplant population and data on efficacy of infection control strategies are often extrapolated from studies conducted in other high-risk groups. Published guidelines provide the framework for the prevention of nosocomial transmission of MRSA (81–84), VISA and VRSA (56). Infection control strategies, aimed to reduce transmission of MRSA and other multidrug-resistant bacteria, include active surveillance, contact isolation, hand hygiene,

environmental cleaning, decolonization of carriers and antimicrobial stewardship. Each transplant program should adopt infection control practices based on the local epidemiology and available resources.

Universal active surveillance screening for MRSA colonization has been a matter of debate and not generally recommended (II-1). The approach can be considered in facilities with unacceptably high MRSA transmission rates despite optimized prevention practices (81) Using a reporting system, healthcare workers should be notified of patients with known MRSA colonization or recent infection. These patients should be isolated until their status can be confirmed or disproved (II-2).

In the hospital setting, healthcare workers are the main source of patient-to-patient MRSA spread. Hand hygiene is the most important measure for limiting the spread of resistant organisms, and programs that increase adherence and compliance with hand washing or use of alcohol-based sanitizers should be implemented (85) (II-1). To reduce MRSA spread to noncolonized patients, contact precautions are recommended for patients who are known to be colonized or infected, especially those with draining wounds or infected airways (II-1). Contact precautions include placement of patients in private rooms or in rooms with other similarly colonized individuals (cohorting), gloving and use of impermeable gowns for every patient contact, and additional barrier protection (e.g. masks, face shields and eye protection) if exposure to contaminated body fluids is anticipated (II-1). Medical equipment and patient care surfaces should be cleaned and disinfected (II-1). Whenever possible, the dedicated use of noncritical equipment for the affected patient is preferable, as well as cleaning and disinfecting of shared equipment before use in patients not known to be colonized with MRSA (III).

The efficiency of universal decolonization of hospitalized patients in preventing transmission has been a matter of debate. MRSA colonization has been associated with subsequent development of infection in patients undergoing surgical procedures. Decolonization has been associated with a decrease in postoperative *S. aureus* infections (86,87) (I). Pretransplant identification of colonized patients and subsequent eradication of MRSA may be a valuable strategy for limiting infection. However, decolonization may not be permanent; hence it is difficult to determine when to decolonize a patient awaiting transplantation. The benefit of decolonization may vary depending on the type of transplanted organ. For instance, Gram-positive organisms may play a greater role in surgical site infections among cardiothoracic transplant patients. Colonized patients can be identified by using nasal/cutaneous swab cultures or a rapid identification method such as PCR or chromogenic agar. A typical decolonization protocol includes the intranasal application of 2% topical mupirocin twice daily for 5 days combined with chlorhexidine baths for 7 days (88) (II-1). Long-term use of antistaphylococcal agents is not recommended for decolonization (II-2). Patients with known MRSA colonization or previous infection without documented eradication should receive perioperative prophylaxis against MRSA (89) (II-2).

Liver transplant candidates and recipients colonized with MRSA are at increased risk of infection (24,25). Transmission of MRSA to patients not previously colonized may occur after transplantation (20). In a single institution study, isolated nasal decolonization of liver transplant candidates was not shown to reduce posttransplant infections due to MRSA (90). In a more recent study, active surveillance, cohorting, contact isolation precautions and nasal decolonization reduced MRSA infection rates among liver transplant recipients (21) . Eradication measures are most successful when implemented in patients with a limited extent of colonization (i.e. the absence of open wounds colonized with MRSA) shortly before surgery (82) (II-2).

Antimicrobial stewardship programs that promote judicious antibiotic use are critical in reducing selective pressure and limiting the spread of resistant pathogens (II-2). Consequently, it is preferable to limit empirical antimicrobial therapy, avoid unnecessary prolonged regimens for perioperative prophylaxis, favor narrow spectrum antibiotics, adopt narrow spectrum antibiotics once a specific pathogenic organism is identified, and avoid excessive duration of treatment (84).

## Acknowledgment

This manuscript was modified from a previous guideline written by Christian Garzoni published in the *American Journal of Transplantation* 2009; 9(Suppl 4): S41–S49, and endorsed by American Society of Transplantation/Canadian Society of Transplantation.

The authors wish to thank Tamar Barlam, MD, from Boston University for reviewing the manuscript, and Andriana Renzoni, PhD, from Geneva University Hospital for her helpful comments.

## Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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