Staphylococcus, Streptococcus, and *Enterococcus*

24

Amar Safdar and Donald Armstrong

Introduction

Gram-positive bacterial (GPB) infections are an important cause of serious illness in patients undergoing transplantation [1]. In recipients of hematopoietic stem cell transplantation (HSCT), GPB are by far the most common bacterial pathogens isolated. A relative decline in infections due to Gram-negative bacteria (GNB) has been attributed to a variety of factors: (1) frequently used antimicrobial prophylaxis with an emphasis on prevention of systemic infections resulting from these microorgansisms; (2) a rise in drug-resistance among disease-casuing GPB due to extensive exposure to healthcare environment and frequent use of broad-spectrum antibiotics that are often given as preventive or empiric therapy; (3) the necessity for maintenance of vascular access results in retention of intravascular devices for extended duration; (4) orointestinal mucositis associated with conventional preparatory regimens in patients undergoing allogeneic stem cell transplantation; (5) the presence of severe pre-engraftment neutropenia that may result in protracted courses of recovery in certain high-risk transplant groups, such as adults following conventional cord blood stem cell transplantation; (6) the emergence and widespread distribution of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) colonization and subsequent risk for invasive disease; (7) acute and chronic graft-versus-host disease (GVHD) involving the skin and orointestinal tract; and (8) hyposplenism noted in patients with chronic GVHD, which promotes the likelihood for serious, invasive pneumococcal disease and infections due to other encapsulated microorganisms [2–4].

Infection prevalance varies among patients undergoing solid organ transplantation (SOT), in most part the risk is a reflection upon the transplanted organ allograft and surgical procedure(s) involved. Deceased donor allograft-derived and organ perfusion fluid (PF)-associated GPB infections are a potential source for such infections. The risk of invasive bacterial infections reflects a proclivity for GPB in this group, and mostly related to surgical procedures that are often long and difficult. Prolonged tissue hypoperfusion, posttransplant allograft ischemia, and retransplantation procedures further increases the risk for bacterial infections. Furthermore, surgical drain(s) that are left in place for a long duration; external biliary tract drains like percutaneous transhepatic biliary catheter; percutaneous nephrostomy catheter, chest tube, and thoracic drains to name a few, promote risk for hospital-acquired bacterial infections; among such infections, GPB are common pathogens encountered. Postsurgical wound infections including wound dehiscence or other early complications following transplant surgery such as the development of primary or secondary hematoma or persistent seroma in the deep surgical bed may provide a nidus for bacterial infection; GPB are also prominent in such post -surgical complications. It is important to note that colonization with MRSA and vancomycin-resistant enterococci (VRE) poses a substantial burden due to a more noticeable risk for subsequent invasive bacterial disease and the risk for potential allograft compromise [5, 6].

Presence of extended-use intravascular access devices that are crucial in patients undergoing transplantation for supportive care that includes and not limited to fluid, electrolyte and mineral supplimentation, hyperalimentation, renal replacement therapy, plasma exchanges, blood and blood product transfusions, and administration of antibiotics among other medications needed to be given parenterally. These intravascular acess devices serve as a direct conduit between skin and blood vessels thereby promoting the risk

A. Safdar (✉)
Clinical Associate Professor of Medicine, Texas Tech University Health Sciences Center El Paso, Paul L. Foster School of Medicine, El Paso, TX, USA
e-mail: amar.safdar@cidimmunology.com

D. Armstrong
Infectious Disease Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Cornell University Medical College (ret), New York, NY, USA

Infectious Disease Society of America, Albuquerque, NM, USA

A. Safdar (ed.), *Principles and Practice of Transplant Infectious Diseases*, https://doi.org/10.1007/978-1-4939-9034-4_24

for bloodstream infections (BSIs). Skin commensals such as coagulase-negative staphylococci (CoNS) and *Corynebacterium jeikeium* are a well-recognized cause of catheter-related bloodstream infection (CR-BSI). Similar to HSCT recipients, patients undergoing SOT are also susceptible to serious invasive disease due to CA-MRSA. Allograft rejection and need for intensified drug-induced immune suppression further promote the risk for invasive disease due to conventional and opportunistic bacterial pathogens. In this regard, *Staphylococcus aureus*, viridans streptococci, and *Enterococcus* spp. are important pathogens [7–10].

Genetic susceptibility for GPB infections may be further accentuated in patients undergoing allograft transplantation. Minor genetic alternations such as single-nucleotide polymorphisms (SNPs) in the essential components of innate immune signaling pathways may become unmasked following trnspantation procedure and are thought to increase hosts' susceptibility for infections. Toll-like receptor 2 (TLR2) is an immune sensor for the components of GPB cell wall. Genetic alterations in the TLR2 gene may render this important pattern recognition receptor with impaired function, thereby enhanced susceptibility for GPB infections in such individuals. In a cohort of 694 liver transplant recipients, it was interesting to note that patients with TLR2 R753Q SNP (an amino acid substitution of arginine for glutamine at position 753) had similar frequency of GPB infections compared with those individuals without this TLR2 SNP. However, the presence of TLR2 R753Q SNP was identified in patients with higher rates of infection recurrence (28% vs. 12%, $P = 0.07$) and initial infection presentation with septic shock was significatly higher in subjects with this TLR2 mutation (11% vs. 1%, $P = 0.04$) versus those without. Important to note that presence of TLR2 R753Q SNP did not result in higher infection-related deaths among liver transplant recipients in this report [11].

Further studies are underway to assess clinical relevance for this and other genetic minor aberrations that may unmask minor immune dysfunction against commonly encountered pathogens, especially in individuals following allograft transplantation.

Staphylococcus Species

Staphylococci are the predominant GPB with the ability to cause serious illness in patients undergoing transplantation [12, 13]. Staphylococci can be divided into two main classes based on their ability to coagulate rabbit plasma. *Staphylococcus aureus* being coagulase positive and all other *Staphylococcus* species are referred to as coagulase-negative staphylococci (CoNS). Infections due to *S. aureus* may present as simple cellulitis or bacteremia versus a disseminated disease that features involvement of various organ systems. Patients with disseminated *S. aureus* infection usually present as life-threatening illness with sepsis or severe sepsis and even in non-transplant immunocompetent patients such infections may progress, in short order, to cause multiorgan dysfunction, disseminated intravascular coagulation, hemodynamic collapse and death. Probablity of severe illness is emphasized in transplant recipients with compromised immune defenses and compounded by dysregulation of hosts' immune-inflammatory response. The potential to cause pneumonia, endovascular and prosthetic device infections is an important ability of *S. aureus* and to a lesser extent by species belonging to the CoNS group. In general, infections due to CoNS are less severe, which is a reflection of low inherent virulence of these bacteria to cause disease in humans [14, 15].

Staphylococcus aureus

Epidemiology and Pathogenesis

S. aureus is a common commensal that can be isolated from 10% to 40% of individuals residing in various communities [16]. *S. aureus* has been well-established as a leading cause of both community-onset and nosocomial infections. Prior to the year 2000, a vast majority of MRSA infections were related directly, or indirectly, to the exposure to healthcare environment. *S. aureus* infections acquired in the community, almost exclusively were methicillin-susceptible strains of *S. aureus* (MSSA) [17]. The emergence and global spread of CA-MRSA have resulted in an increased prevalence of these pathogens among the general population and those undergoing transplantation procedures. MRSA colonization has been regarded as an important risk factor among HSCT recipients, and a precursor for subsequent invasive staphylococcal disease [18]. The risk for such infections now extends beyond healthcare exposure and must be entertained when assessing the possibility of illness due to staphylococci in the transplant population [19].

Most invasive *S. aureus* diseases in transplant recipients occur when mechanical defenses are breached, for example, due to break in the skin barrier resulting from catheter placement or bypassing upper airway defenses following insertion of an endotracheal tube [20]. The main risk factors include severe neutropenia, GVHD, allograft rejection, solid allograft retransplantation, treatment with systemic corticosteroids, and complicated allograft transplant surgery. *Staphylococcus aureus* infections are also encountered in a high frequency among patients requiring prolonged intensive care unit stay, mechanical assisted ventilatory support, renal replacement therapy, and those with severe pre-engraftment neutropenia. Diabetic patients with persistent hyperglycemia-induced neutrophil and macrophage dysfunction are also at risk for potentially severe staphylococcal disease [21, 22].

HSCT Recipients

A recent study from Europe in 15,181 neutropenic HSCT patients assessed 2,388 episodes of BSI. The annual incidence of BSI in this population was 16%; 62% had undergone allogeneic and 38% autologous stem cell graft transplants [23]. The authors noted an increase in enterococcal BSI from 2% in 2002 to 3% in 2014 ($P < 0.001$). Whereas the incidence of bacteremia due to CoNS declined from 8% to 5% ($P < 0.001$), in autologous stem cell recipients, this decline was even more pronounced, from 8% to 2% between 2002 and 2011, respectively ($P = 0.02$). No significant change in the trend for MRSA or vancomycin-resistant *Enterococcus* (VRE) bacteremia was evident during the study years. The case fatality rate among 2,388 bacteremia episodes was 3% and remained unchanged over the course of the study [23].

Myeloablative preparative conditioning regimen promotes the risk for bacterial infections. In a recent study of 460 patients, the risk of BSI was assessed during the first year after transplantation between 2008 and 2013. Thirty-four percent of patients who received myeloablative conditioning developed BSI, whereas, in patents, in whom nonmyeloablative stem cell transplantations were performed, BSIs were 17%. Sixty-eight percent of bacteremia episodes were due to GPB [24].

At a comprehensive cancer center in New York, the frequency of late HSCT *S. aureus* bacteremia was reported as 6 episodes per 100,000 patient-days. The median time of onset after transplantation was 137 days, and ranged between 55 and 581 days. Majority of these infections (84%), as expected, were acquired in the community [25]. Risk factors included ongoing acute GVHD, acute or chronic GVHD involving the skin ($P = 0.002$), use of systemic corticosteroids, liver dysfunction, and prolonged transplantation-related hospitalization ($P = 0.02$). *S. aureus* bacteremia in HSCT recipients at this large stem cell transplant center for the most part, occurred in patients with GVHD and/or those receiving systemic corticosteroids [25].

Solid Organ Transplant Recipients

Solid organ transplantation is a high-risk setting for MRSA and VRE colonization, and the carrier state is associated with a heightened risk for subsequent invasive bacterial disease. In a recent meta-analysis of 23 studies, including 17 with reference to liver transplants, the prevalence estimates for MRSA and VRE colonization prior to transplantation surgery were 8.5% and 12%, respectively. After transplantation, the prevalence estimates for MRSA were 9% and 16% for VRE. MRSA colonization significantly increased the risk for invasive bacterial disease both before and after transplantation (risk ratio [RR] 5.5 and RR 10.5, respectively). Similarly, VRE colonization was also associated with a significantly higher risk for subsequent invasive disease (RR 6.6 during pre-transplant and RR 7.9 after transplantation) [6]. In a small study of patients undergoing small bowel and multivisceral transplantation at the University of Nebraska, nearly one-third (36%) of *S. aureus* isolates associated with systemic infection were strains exhibiting resistance to several classes of antimicrobials [26].

Bacterial contamination of solid allograft perfusion fluid has been regarded as a potential source for organ graft contamination, which may result in early postsurgical allograft infection that carries a greater risk for systemic dissemination and sepsis during this period of high immune vulnerability. Microbiological data of 290 PF infections from a single center showed 35% PF had positive cultures for microorganisms, and of these, half (50%) were *Staphylococcus* species. However, it was important to note that invasive bacterial disease seldom resulted following PF contamination graft transplantation compared with patients in whom allografts were transported in PF with no evidence of contamination [27].

Donor-derived infection is an important concern in harvesting organs from donors with a recent history of, or ongoing high-grade *S. aureus* bacteremia, with or without evidence of endovascular infection. Transmission of such infections are well-established by sophisticated epidemiologic analysis and provides a pause for concern in assessing risk of exposure to potentially life-threatening *S. aureus* disease [28]. It is important to note that despite appropriate systemic antibiotics given after such allograft transplantation, patients remain at risk for these infections during or after the antibiotic prophylaxis has ended [29].

In living donor liver transplantation, the prominent risk factors for early bacterial infections were a high serum creatinine level (odds ratio [OR] 1.5), a long anhepatic arterial perfusion phase (OR 1), a reoperation (OR 6.4), young age (OR 1), and recipient who had no history of hepatocellular carcinoma (OR 2) [30].

In patients with cystic fibrosis (CF) undergoing lung transplantation, higher risk of infection is seen in a disease caused by mutations involving endosomal cystic fibrosis transmembrane conductance regulator (*Cftr*), pulmonary *S. aureus* colonization that occurs early in the course of illness and often, prior to colonization with pathogens such as *Pseudomonas aeruginosa.* These patients continue to remain susceptible to *S. aureus* infections as a result of intracellular survival of *S. aureus* in macrophages. In animal experiments, *S. aureus* after being internalized by *Cftr*-deficient macrophages are not killed due to a defect in the fusion of endosomal phagosomes with lysosomes [31]. This defect may persist in CF patients following pulmonary allograft transplant surgery.

A 5-year retrospective study from the University of Pittsburgh evaluated *S. aureus* infections within the first 90 days after lung transplantation [32]. In 596 patients following lung transplantation, 18% developed *S. aureus* infection, of these 38% were MRSA. The study observed an incremental increase in MRSA prevalence over the duration of the study.

Isolation of MRSA from the nares ($P < 0.0001$) or from respiratory tract samples ($P = 0.02$) at the time of transplantation was noted to significantly increase the risk for invasive MRSA disease within 3 months after transplantation [32].

Clinical experience at the University of Pittsburgh endorsed that *S. aureus* screening and decolonization for patients undergoing heart and heart-lung transplantation was fiscally beneficial, and averted 6.7 *S. aureus* infections (4.3 MRSA and 2.4 MSSA) leading to a cost saving of $240,602. The authors found that 89 patients were needed to be screened to prevent one *S. aureus* infection in this at risk organ transplant group [33].

The cross talk between bacterial communities and innate immune cells potentially determines the functional integrity of the transplanted lung allograft. In lung transplant recipients, long-term graft survival depends upon the balance between inflammation and tissue remodeling. Host-microbe interactions after lung transplant determines the immunologic tone of the airways and, consequently, may possibly, impact survival of the pulmonary allograft. In a French and Swiss study, the characteristics of the pulmonary microbiota aligned with distinct innate cell gene expression profiles provided evidence that bacterial dysbiosis could lead to proinflammatory or remodeling profiles in macrophages, whereas a congruous microbial community maintained homeostasis. Such an impact was associated with equitable distribution of bacterial communities with proinflammatory properties such as *Staphylococcus* spp. and *Pseudomonas* spp. versus bacteria like *Prevotella* and *Streptococcus* spp. with low immune-inflammation potential [34]. Further research is underway to assess the impact of host lung and respiratory tract microbiota and its impact on allograft survival.

Clinical Manifestations

S. aureus infections commonly involve the skin and skin structures, and clinical presentations include cellulitis and abscesses; systemic infections and end-organ disease are seen in both immunocompetent and immunocompromised patients [35, 36]. *S. aureus* is a leading cause of catheter-related bacteremia, prosthetic joint infections, and infections following a surgical procedure [15]. Suppurative complications such as infective endocarditis, pneumonia with concurrent bacteremia, osteomyelitis, spinal diskitis, native and prosthetic joint infections, and septic pulmonary emboli from subcutaneous abscesses may occur due to secondary bacterial seeding in patients with high-grade, persistent *S. aureus* bacteremia [37].

Bacteremia is a serious complication in patients undergoing HSCT. A recent 6-year single-center experience in patients with bacteremia following stem cell allograft transplantation, the 2-year overall survival was 46% compared with 60% survival noted among patients without BSI (HR 1.5; $P = 0.07$). *P. aeruginosa* and *E. coli* bacteremia were associated with highest mortality rates of 50% and 33%, respectively [38].

Late *S. aureus* BSIs occurred in HSCT recipients, and 40% involved a focal site of infection. Persistent bacteremia for more than 3 days despite removal of endovascular access was noted in more than 50% of cases. The median survival rate after *S. aureus* bacteremia was 135 days and ranged between 1 and 1,765 days [25].

In a kidney transplant unit in London, England, between 2012 and 2013, graft pyelonephritis was noted as a prominent cause of bacteremia (69%). Methicillin-sensitive *Staphylococcus aureus* was the most common pathogen isolated (26%), followed by, and expectedly, *Escherichia coli* (25%) [39].

Necrotizing pneumonia due to *S. aureus* in transplant patients usually occurs in critically ill patients with respiratory failure requiring prolonged assisted mechanical ventilation; as in general population, superimposed bacterial pneumonia may complicate the course during or after a viral upper respiratory tract infections due to influenza and other respiratory tract viruses [40].

The rise of CA-MRSA has been especially concerning given that CA-MRSA isolates can cause devastating disease including necrotizing fasciitis and necrotizing pneumonia even in otherwise healthy individuals; the potential for such complictions become more pronounced in the immunosuppressed patients undergoing transplantation [41, 42]. It is not uncommon to find *S. aureus* in patients with pyomyositis, septic arthritis, and septic bursitis, which may have occurred due to contiguous infection or from hematogenous bacterial seeding [43, 44].

Nosocomial pneumonia after lung and heart-lung transplantation was assessed between 2008 and 2010 at a surgical unit in France [45]. The authors reported their prospective evaluation of 79 lung or heart-lung transplant recipients, 35 (44%) of whom developed 64 episodes of nosocomial pneumonia. Pneumonia recurrence was seen in 40% of the cases; severities of illness and lung injury were the two main contributors for infection recurrence. *Staphylococcus aureus* accounted for 20% of these episodes, whereas *Enterobacteriaceae* (30%) and *Pseudomonas aeruginosa* (25%) were also common. It was interesting to note that ICU mortality did not greatly differ in patients with nosocomial pneumonia (14%), those with pneumonia recurrence (10%), and patients without pneumonia (11%; $P = 0.9$). It was however, unexpected that diagnosis of pneumonia had no impact on ICU mortality, especially in this high risk transplant group [45].

In 596 patients following lung transplantation at the University of Pittsburgh, *S. aureus* pneumonia (48%) was the most common presentation in 109 lung transplant recipients with *S. aureus* infection. Tracheobronchitis (26%), bacteremia (12%), intrathoracic infections (7%), and skin/soft tissue

infections (7%) were also noted. Risk factors included mechanical ventilation for >5 days and isolation of *S. aureus* from recipients' sterility surveillance cultures. Patients with these infections had prolonged hospitalization and intensive care unit stays ($P < 0.0001$). Further, in patients with *S. aureus* infections that occurred after undergoing lung transplantation; acute and chronic allograft rejection at 1 and 3 years ($P = 0.04$ and $P = 0.002$, respectively) and mortality at 1 and 3 years ($P = 0.05$ and $P = 0.009$, respectively) were significantly higher than in other patients in this series without *S. aureus* infection. Mortality rates of 7% on day 30 and 12% by day 90 after *S. aureus* infection was a sobering reminder regarding the severity of this infection in the vulnerable population [32].

In a large study from the Cleveland Clinic in Ohio 2,959 patients with *S. aureus* bacteremia were evaluated; 70 had undergone solid organ transplantation including 26 lung, 19 liver, 18 kidney, and 7 patients following heart allograft transplantation. The overall rate of *S. aureus* BSI was 22.9 per 1000 transplant patients. Early-onset bacteremia within 90 days after the transplant procedure was common in liver allograft recipients (79%) vs. 17% in patients having undergone renal allograft transplants. As expected, the duration of bacteremia was longer in SOT patients vs. non-solid organ transplant population (mean 3.8 days vs. 1.6 days; $P < 0.01$), and SOT recipients had significantly higher frequency of MRSA infection (86% vs. 52% in non-SOT population; $P < 0.0001$). The all-cause 30-day and 1-year mortality rates were 6% and 28% in patients following SOT, respectively. Pneumonia as a source of bacteremia was associated with a higher 30-day mortality (18% vs. 2% nonpulmonary source; $P = 0.04$). It was interesting to note that SOT status was independently associated with a lower risk of 30-day mortality (risk ratio [RR]: 0.37; $P = 0.02$) and may represent high vigilance and prompt institution of empiric antimicrobial therapy in this group [46].

At the University of Nebraska, the first *S. aureus* infection in a liver allograft recipient developed at a median of 29 days after undergoing transplantation. Just over half of these infections occurred during the first month after the liver transplant surgery [47]. As expected, 88% were hospital-acquired infections, 41% were polymicrobial, and nearly half (47%) were due to MRSA. Liver transplant patients with *S. aureus* infection were intubated more frequently (odds ratio [OR] 26.9; $P = 0.0006$), had an indwelling intravascular catheter (OR 11.6; $P = 0.02$), and underwent recent surgery (OR 26.9; $P = 0.0006$). Multivariate analysis revealed a 26.9 times higher risk of developing *S. aureus* infection in patients in whom surgery was performed within 2 weeks prior to infection diagnosis ($P = 0.0006$). Recent surgical procedure was the only significant independent risk factor for *S. aureus* infections after liver transplantation in this analysis [47].

Staphylococcus aureus infections in small bowel and multivisceral transplantation were assessed retrospectively in 22 cases at the University of Nebraska. The median age was 2 years; 43% of the first infection episodes were bacteremia, followed by pneumonia (30%), and surgical site infections (26%). As expected, the time to surgical site infections (41.0; range, 0–89 days) was significantly shorter than that to lung infections (266; range, 130–378 days; $P = 0.01$). When compared with other small bowel and visceral transplant recipients without *S. aureus* infection, the 22 cases studied had higher likelihood of CMV seromismatch (OR 3.0; $P = 0.08$); it was interesting to note that patients with CMV seromismatch had higher probability for developing *S. aureus* infection (OR, 2.9; $P = 0.085$). Patients in this transplant population with *S. aureus* infection were 2.2 times more likely to die ($P = 0.04$) and had a significantly shorter survival (28.5 months) compared with patients without *S. aureus* infection (45.8 months; $P = 0.04$) [26].

Diagnosis

These bacteria are hardy, grow well in enriched laboratory media, and are relatively easy to identify. The presence of *S. aureus* in specimens from sterile body sites in most instances represents microbiologic evidence of an infection. *S. aureus* contamination of blood cultures has been suggested [48]; in authors' view, this phenomenon occurs rarely and must not be entertained, especially in transplant population.

S. aureus has propensity to colonize various body sites, such as the oral and nasal cavities, upper respiratory tract, skin, and lower intestinal and genitourinary tracts. Therefore, isolation of *S. aureus* from endotracheal aspirate or urine sample obtained from an indwelling urinary catheter and even bronchial wash samples must be assessed in context of clinical presentation, pathogen-disease compatibility, and importantly, hosts' susceptibility along with pretest probability for such infections. However, these factors assist mainly in decision-making for individuals with intact immune function and may not necessarily enable determination regarding bacterial colonization versus locally invasive disease in severely immunosuppressed patients undergoing allograft transplantation.

Serologic or antigen assays have not proven to be clinically helpful in the diagnosis of *S. aureus* infection. The new diagnostic assessment including PCR for prompt determination of MRSA represents encouraging development [49]. A detailed review of the advancements in infection diagnosis is presented in the "Diagnoses and Prevention" section.

Treatment

Therapy for systemic *S. aureus* disease constitutes a comprehensive approach toward the patient, which involves (1) lowering the level of immune suppression; (2) identifying and addressing the source and/or primary focus of infection such

as (2a) removal of the infected or potentially infected foreign device, when feasible; (2b) surgical drainage of infected collections and debridement of necrotic tissue; and (3) selection of appropriate empiric antibiotic while awaiting culture and drug susceptibility results [50]. The importance of drainage of deep tissue infected collections and surgical removal of devitalized tissue cannot be overemphasized, as in many patients with localized infection, removal of the nidus and primary focus of infection alone may be curative and often supplemented with an abbreviated course of systemic antibiotic therapy [51]. In concert, if an infected foreign material, such as an indwelling intravascular catheter or an infected prosthetic joint, remains in place, then therapeutic success of antibiotic therapy alone tends to be suboptimal [52, 53].

Antibiotic treatment of *S. aureus* infection is complicated by emergence and speard of bacterial starins with extensive antimicrobial drug resistance. When the organism is sensitive, β-lactam antibiotics are the drugs of choice for *S. aureus* infections including nafcillin and oxacillin [54, 55]. Vancomycin is considered by most as optimal treatment for invasive MRSA infections, although increasing frequency of vancomycin treatment failures, especially in oncology and transplant population, have questioned this approach [56]. Treatment of MRSA bacteremia with vancomycin given as a single agent has been associated with a high rate of treatment failure evident as lack of clinical response and complete recovery, or early infection relapse, which may be observed in 15%–20% of the episodes; although overt vancomycin resistance by in vitro drug testing still remains an elusive phenomenon [57]. Failure to vancomycin therapy has motivated a search for alternative treatment options including newer drugs such as linezolid, tedizolid, tigecycline, ceftaroline, and daptomycin, to name a few.

Each of these agents, similar to vancomycin, has significant limitations. Proven treatment efficacy and superiority to vancomycin as a first-line agent for the treatment of systemic MRSA infections such as bacteremia, pneumonia, complicated intra-abdominal infections, and bone and joint infections need further clinical validation. It is imperative to take into account the potential for adverse events and systemic toxicity associated with vancomycin and these newer antibiotics including the following consideration: a) hosts' variables which may at times, influence drug clearance in patients undergoing transplantation; b) drug-drug interactions, with particular emphasis on pharmacokinetics and pharmacodynamics of drugs commonly use to treat allograft rejection GVHD; c) inherent or postexposure development of drug resistance, or selection of less drug susceptible bacterial strains, especially in at risk transplant population, in whom extensive prior exposure to the healthcare environment and the need for periodically given systemic broadspectrum antibiotics for recurrent or suspected infections are routinely priscribed both prior to, and following the transplantation procedure [58–69].

Selection of effective empiric antibiotic therapy for the treatment of glycopeptide-nonsusceptible staphylococci is difficult, as true resistance is rare and isolates exhibiting heterogeneous resistance or vancomycin tolerance may not become evident even after the drug susceptibility profiles are known. In patients undergoing SOT, use of vancomycin has been associated with low therapeutic efficacy and high rates of drug-induced renal impairment, which in part is a reflection of the cumulative nephrotoxicity resulting from standard practice antirejection drug regimens including calcineurin inhibitors given for prolong duration after the allograft transplant surgery.

A study from Spain during 2008 and 2010 enrolled 43 patients mostly after liver and kidney transplantation who received daptomycin for the treatment of GPB infections including CoNS catheter-related bacteremia (23.2%), *S. aureus* skin and skin structure infections (11.5%), and intra-abdominal abscess due to *Enterococcus faecium* (20.9%). The daily daptomycin dose was 6 mg/kg in 74% of the patients. On day 7 of daptomycin treatment, median estimated area under the curve was 1251 μg/mL/h. No changes were observed in tacrolimus serum levels. Daptomycin was not discontinued in any of these patients due to adverse events. Eighty-six percent clinical success with daptomycin therapy was noted in this small group of transplant recipients [63].

The potential role of antibiotics in modulating virulence among *S. aureus* is an intriguing phenomenon and needs further exploration, especially for the treatment of difficult-to-treat infections. The effects of antibacterial agents on pathogens' expression of virulence and on hosts' immune response are currently being explored. A recent review of the literature evaluated relevant articles that explored the effects of antibiotics on staphylococcal toxin production and the impact of these ancillary mechanisms on hosts' immune function. Most in vitro data pointed to a reduced level of expression of bacterial virulence following treatment with ribosomally active antibiotics such as linezolid and clindamycin, whereas cell wall-active antibiotics like beta-lactams were associated with amplified bacterial exotoxin production/release. In vivo studies confirmed the suppressive effect mediated by clindamycin and linezolid on the expression of bacterial virulence, supporting their utilization as a valuable management strategy to improve patient outcomes in cases of toxin-mediated staphylococcal disease [70].

The duration of therapy for *S. aureus* infection is highly individualized. A minimum of 2 weeks is recommended for patients with uncomplicated catheter-related bacteremia [71]. A longer course of antibiotic treatment is generally given ranging from 4 to 8 weeks in patients with complicated infections such as infective endocarditis, necrotizing pneumonia, empyema, septic arthritis, allograft pyelonephritis,

intra-abdominal deep tissue abscesses such as liver and splenic abscesses, and osteomyelitis. The antibiotics are usually given intravenous for more serious infections, whereas in select low-risk cases a transition to oral drugs that exhibit dependable enteral bioavailability may be considered as an option. Regardless of treatment duration, *S. aureus* systemic infection-related complications may arise during the course of therapy or long after the antibiotic therapy has ended. New suppurative foci may arise months after a successful resolution of acute *S. aureus* illness. Patients with serious *S. aureus* disease require a close and continued follow-up for the possibility of infection recurrence that may present as a suppurative focus, and may occur remote from the original site of infection; days to months after completing an appropriate course of concordant antibiotic therapy.

Coagulase-Negative Staphylococci

Epidemiology

Coagulase-negative staphylococci (CoNS) are part of the normal hosts' microflora; up to 90% of humans are colonized with these low-virulence environmental organisms [57]. Skin, orointestinal, and genitourinary mucosa are prominent sites of bacterial colonization. Unlike general population, patients undergoing transplantation are vulnerable to invasive disease due to CoNS. This is in most part attributed to breach in protective barriers resulting from (1) indwelling intravascular catheters; (2) surgical wounds; (3) various surgical drainage catheters including percutaneous nephrostomy tubes, external biliary tract catheters, and thoracic cavity drains, among others; (4) implantable left ventricular assist device in patients with advanced heart failure awaiting transplantation; (5) the presence of severe mucositis involving the orointestinal tract resulting from allogeneic HSCT preparatory conditioning regimens or in patients with post-HSCT GVHD; and (6) recently recognized periodontal disease as a risk factor for CoNS bacteremia in patients with pre-engraftment neutropenia following hematopoietic stem cell graft transplantation [23, 72, 73].

When species studies are performed, *S. epidermidis* is generally the leading cause of invasive CoNS infections in the immunosuppressed population [74]. *Staphylococcus lugdunensis* is an emerging member of the CoNS group, which has increasingly been recognized as a cause of severe endovascular infection. Such infections are clinically indistinguishable from that caused by *Staphylococcus aureus*. The potential for endocarditis due to this novel bacterial pathogen in transplant population needs further investigation. *Staphylococcus lugdunensis* has been associated with a variety of infections, especially osteoarticular infections, foreign body-associated infections, and bacteremia. Several putative virulence factors have been identified including adhesion factors, biofilm production, and proteolytic factors appears to proffer opportunistic potential of these newly recognized pathogens, which is in contrast to more insidious, less virulent species of bacteria grouped among CoNS [75]. In a recent retrospective analysis between 2011 and 2014, in only 45 of 2263 CoNS clinical isolates, *S. lugdunensis* was confirmed; skin and skin structure infections being the most common clinical presentation. It was interesting to note that patients with neutropenia did not appear to have a higher frequency of *S. lugdunensis* infections compared with patients with normal peripheral blood neutrophil count [76].

HSCT Recipients

Microbial contamination of hematopoietic stem cell graft derived from peripheral blood or bone marrow is uncommon, albeit, when this does occur, it may potentially lead to devastating systemic graft-acquired infection, especially in patients during pre-engraftment neutropenia. A microbiological evaluation of 291 peripheral blood and 39 bone marrow stem cell samples was conducted at a center in Poland between January 2012 and June 2013; bacterial contamination was demonstrated in nearly 3% of stem cell products. CoNS and *Micrococcus* species were the most frequent organisms detected in their air microbial contamination control environment. The risk for bacterial contamination increased with each step of cell processing, suggesting that least possible manipulation of the stem cells would improve microbial sterility of the transplant material. The authors also endorsed air contamination control environment as essential in the preparation of hematopoietic stem cells in order to reduce the risk for potential bacterial contamination [77].

SOT Recipients

Bacterial contamination of solid organ allograft preservation solution is not uncommon; in some studies, up to 44% of graft preservation fluid may exhibit bacterial and fungal contamination, or both; and as expected, CoNS is the most prevalent (64%) bacteria isolated in this setting [78]. It is important to recognize that only a small number of (~5%) infections after liver transplantation procedure were related to the organisms isolated in the preservation solution [78].

Disease Pathogenesis

The major CoNS diseases in transplant patients include bacteremia associated with an indwelling intravascular device and surgical site infections. The pathogenesis of device-related CoNS infection is thought to stem from bacterial capability to form biofilm on the foreign implanted material [79]. A recent study from Brazil showed that all CoNS strains isolated from patients with bacteremia were biofilm forming phenotypes and exhibited a high prevalence of atlE, indicting

an enhanced potential for autolysin/adhesin [80]. The investigators also showed that these blood-borne CoNS had an increased frequency of staphylococcal enterotoxin (SE) A gene and potential for exotoxin production. These heat-stable enterotoxins are a leading cause of gastroenteritis. In addition, SEs are powerful superantigens that stimulate nonspecific T-cell proliferation and indiscriminate lymphocyte activation bypassing the normal, highly regulated antigen presentation process; the resultant unrestraint systemic inflammatory response and hosts' organ damage is often lethal [81]. However, most reports of severe septicemia in transplant patients associated with SE-producing staphylococcus are attributed to *S. aureus* [82].

Clinical Manifestations/Diagnosis

Fever without an apparent focus of infection is the most common clinical presentation in transplant patients with catheter-related CoNS infection including those with a positive blood culture [83]. In the transplant patients, clinical evidence of catheter infection including insertion site inflammation, which is expected to present as pain, erythema, induration, and purulent drainage or an abscess formation along the catheter insertion site, subcutaneous reservoir pocket, or catheter tunnel is frequently absent. Diagnosis requires a high level of suspicion as patients may appear relatively asymptomatic withor without a nonspecific low-grade, persisent febrile illness [84]. Native valve infective endocarditis and hematogenous osteoarticular seeding has been noted in patients with CoNS catheter-related bacteremia, although these complications are far less frequent than those observed with *S. aureus* or GNB indwelling intravascular device infections with or without concurrent bacteremia.

In patients with prosthetic valves, especially those with persistent, recurrent, or relapsing CoNS bacteremia, secondary seeding of the prosthetic heart valves should be taken into consideration [85]. In patients with prosthetic valves, CoNS endocarditis similar to such infections caused by *S. aureus* may present with valve dysfunction and intracardiac abscesses, or both. In such cases, CoNS species evaluation becomes important, with an emphasis for *S. lugdunesis* as a potential pathogen.

Clinical presentation for infections involving nonvascular or non-articular prosthetic devices may also be clinically subtle and often vary based on the type of device used, organ system involved, and the degree of hosts' inflammatory immune response. Patients with CoNS cerebrospinal fluid shunt infection are sicker and have clinical features of bacterial meningitis; subtle clinical presentation such as low-grade fever, alteration in mental status, and shunt malfunction should also alert the treating physician for possible shunt infection; and CoNS are not uncommon pathogens for such device-related infections [86, 87]. The presence of pleocytosis in CSF has limited diagnostic value, as white cell counts in CSF may be either marginally increased or within the normal limits among patients with CoNS shunt infections. Patients with CoNS infection of prosthetic joints may not have significant clinical symptoms and rang from nominal joint discomfort rather than overt joint dysfunction, which is frequently seen in patients with *S. aureus* prosthetic joint septic arthritis. Such infections are less often accompanied with prominent, localized inflammatory response including joint effusion and adjacent tissue inflammation and swelling [88].

Diagnosis

The diagnosis of CoNS infection relies on isolation of the organism from appropriately obtained clinical sample. As expected, false-positive cultures due to bacterial colonization and contamination of the sterile-site samples such as blood cultures are not uncommon and leads to difficulty in interpretation and ascertaining true versus pseudobacteremia [89]. Reliability of blood cultures in reports of CoNS catheter-related bloodstream infections provides an outline for how to approach and determine clinical relevance of CoNS isolated in blood culture specimens [90]. In quantitative cultures, catheter-drawn blood samples exhibit (fourfold) higher number of bacterial colony-forming units compared with blood drawn from a peripheral site and hence regarded as an important diagnostic predictor for infected intrevascular catheter as the source of bacteremia [83]. Similarly, blood drawn through an infected catheter tend to become positive early (~2 h), a reflection on high bacterial inoculum size compared with blood culture samples drawn from a peripheral blood vessel [83, 91]. Isolation of these bacteria from a single blood culture sample or low-grade CoNS growth in quantitative blood cultures often reflects a poor preparation of the blood culture site resulting in inadvertent sample contamination. The diagnosis of CoNS infection from sources other than the blood needs to be considered based on the clinical setting with an understanding that these bacteria are the most common cause of culture contamination, while inversely, also a well-recognized cause of prosthetic joints and other implantable device infections.

Treatment

Removal of the infected device is regarded as the definite therapeutic intervention that is imperative for successful resolution of such infections and importantly, for reduce risk of early and late infection recurrence. The presence of bacteria-induced biofilm on the foreign surfaces and necrotic tissues such as chronically infected bones provides a niche for the bacteria to evade hosts' immune clearance, and commonly used antibiotic classes such as beta-lactams and glycopeptide have limited penetration and significantly

reduced antimicrobial activity against non-planktonic bacterial isolates frequently found in the biofilms [92].

Most CoNS isolates from healthcare-associated infections are resistant to β-lactam antibiotics [93]. Almost all clinical CoNS isolates are susceptible to vancomycin, although in vitro drug MICs have been increasing in the recent decades, and now a substantial number of clinical isolates exhibit vancomycin MICs between 1 and 2 μg/ml [94]. As true Vancomycin resistance still remains highly unlikely; most vancomycin clinical failures may result due to heteroresistance, vancomycin tolerance, or yet unknown other potential mechanism(s) at play [95].

Rifampin is active against the non-planktonic CoNS in the biofilms; for serious CoNS infections involving prosthetic heart valves and prosthetic joints that cannot be removed, salvage therapy with the addition of rifampin has been used, although prospective data for assessing efficacy for such intervention is not clear [96, 97]. CoNS are usually susceptible to new antimicrobials such as daptomycin, linezolid, and tedizolid, including recent addition of long-acting lipoglycopeptides like oritavancin and dalbavancin. Daptomycin has the lowest MICs against clinically important bacterial species grouped under CoNS [98].

With the exceptions of prosthetic valve endocarditis, CNS shunt and reservoir, ventricular assist device, and prosthetic joint infections, most CoNS infections respond readily to appropriate antimicrobial therapy. It is prudent and imperative that an infected device, when feasiable, must be removed; this recommendation is for mitigation of patient morbidity and cost of care incurred due to infection recurrence and relapse [99, 100]. Guidelines suggest that 7 days of appropriate concordant antibiotic therapy should be adequate for most uncomplicated CoNS catheter-related bacteremia in nonimmunocompromised patients. Longer treatment duration is suggested for patients with severe immune suppression and those with profound neutropenia; relapse rates of invasive CoNS infections are generally lower than those noted with systemic *S. aureus* disease [90].

Streptococci

The streptococci are a heterogeneous group of Gram-positive disease-causing bacteria with a wide-ranging nomenclature that continues to change [101]. Here we use the clinical microbiology laboratory approach toward these pathogens and consider them as follows: viridans group streptococcus (VGS), β-hemolytic streptococcus, and *Streptococcus pneumoniae*. Streptococci not outlined in these groups rarely cause invasive disease in the immunosuppressed patients undergoing transplantation procedure.

Viridans Group Streptococci

Epidemiology

Viridans group streptococci (VGS) are a diverse group of bacteria. They are often isolated from human orointestinal, upper respiratory, and female genital tracts [102]. Viridans, derived from *viridis*, refers to green color appearance in laboratory blood-enriched culture media due to the breakdown of hemoglobin also known as α-hemolysis. Among α-hemolytic streptococci, the most important pathogen is *Streptococcus pneumoniae*; for most non-*S. pneumoniae* α-hemolytic streptococci, further species determination is performed on request at most microbiology laboratories. The major VGS responsible for invasive disease in patients undergoing transplantation and patients with severe neutropenia belong to the *mitis* group and include *Streptococcus mitis*, *Streptococcus gordonii*, *Streptococcus oralis*, *Streptococcus sanguis*, and *Streptococcus parasanguis* [103–105]. Infections due to *Streptococcus anginosus* group are also seen, albeit less frequently and include *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*.

VGS are considered to have low intrinsic virulence, and in patients with intact immune function, they are mainly associated with endocarditis [106]. Similar to CoNS, VGS are far more likely to cause disease in neutropenic patients with cancer undergoing HSCT. In a recent study among children with cancer undergoing HSCT, diagnosis of leukemia and bacteremia due to *S. mitis* was common. It is important to note that 15% of these infection episodes were associated with Viridans Group Streptococcal Shock Syndrome, resulting in most patients (75%) requiring treatment in ICU, and half of the patients needing ICU care died with multiorgan failure [107].

VGS bacteremia occurs almost exclusively in patients receiving aggressive cytoreduction therapy for conditions such as acute leukemia and patients undergoing allogeneic HSCT preparatory conditioning regimen [108].

Treatment-induced mucosal dysruption of the orointestinal tract has been regarded as a major risk factor for systemic translocation of these low-virulence commensal bacteria, allowing them to gain access into the blood circulation [109]. It is also important to recognize that VGS breakthrough bacteremia are attributed to the widely priscribed antimicrobials for infection prophylaxis with drugs that are known to have limited activity against these organisms such as trimethoprim-sulfamethoxazole and fluorinated quinolones [110].

Clinical Presentation/Diagnosis

Most patients with invasive VGS disease present with fever in the setting of mucositis and profound neutropenia [111]. Approximately 25% of patients may present with a fulminant

septic shock syndrome characterized by hypotension, skin rash, and adult respiratory distress syndrome; *S. mitis* is the VGS species most commonly isolated from such patients [103, 111, 112]. This dramatic clinical presentation may represent a combination of hosts' susceptibility due to the underlying severe neutropenia additionally, bacterial exotoxin, which act as superantigen resulting in unrestraint activation of immune-inflammatory pathways resulting is rapidly progressive illness with a substantial risk for multiorgan failure and death [113].

Unlike general population, VGS bacteremia seldom leads to endocarditis in patients with neutropenia and those undergoing a stem cell transplantation procedure. The *risk* of endocarditis in patients following solid organ allograft transplantation who develop high-grade VGS bacteremia is not dissimilar to that observed in general population [114].

Group milleri streptococci (GMS) may cause chronic intra-abdominal and intrathoracic abscesses. Infections due to GMS were reported in 45 SOT recipients between 2001 and 2004. Patients following liver transplantation were prominently respresented (n = 34) in this cohort, followed by four kidney and pancreas; two small bowel; three combined liver and kidney; and combined kidney plus small bowel and a kidney allograft transplants, in one patient each. Most GMS infection episodes (42 cases) were intra-abdominal infections, pleural empyema in two, and one patient with soft tissue infection. It was interesting that unlike neutropenic cancer patients and those undergoing HSCT, only one patient had evidence of bacteremia. It was also of note that 61% of these infections were polymicrobial; recurrent cholangitis (38%) associated with anastomotic and nonanastomotic biliary strictures was the most common intra-abdominal infection, which required a need for repeated stenting or surgical intervention and prolonged antibiotic therapy. In one patient pancreatic allograft failed because of hemorrhagic erosion from bacterial abscess. There were no deaths attributed to MGS infections in the SOT recipients in this report [115].

Intrathoracic GMS infections after thoracic surgery, are an uncommon complication (4%). Most intrathoracic GMS infections present as empyema, infected pleural effusion, whereas bacterial mediastinitis is a rare complication. As seen in patients undergoing intra-abdominal allograft transplantation, GMS intrathoracic infections are frequently polymicrobial (64%), and infection recurrence (27%) may occur in nearly one-thrid of the cases [116].

Diagnosis

The diagnosis of VGS disease relies on isolating the organism from a sterile body site. The presence of VGS in blood cultures obtained adhering to the standard aseptic blood culture techniques may be regarded as a true pathogen. Isolation of VGS from the skin or mucosal sites, as expected, has limited clinical significance, as these organisms are part of the normal cutaneous and mucosal microbiota in humans. It is also important to take note of the possibility of blood cultures contaminated with VGS; however, their presence in blood samples must be considered clinically relevant, especially in high-risk patients such as those with antineoplastic chemotherapy-induced neutropenia and chemotherapy- or radiation-associated mucositis and patients with severe neutropenia and mucositis following condition preparatory regimens for allogenic stem cell transplantation [117]. Serologic or antigen tests have no diagnostic value for invasive VGS disease, even in the high-risk patients undergoing allograft transplantation.

Treatment

Therapy of VGS disease is limited by the high level of β-lactam antimicrobial resistance [118, 119]. The clinical samples isolated from patients with neutropenia, less than half (~40%) of the VGS isolates, exhibit in vitro susceptibility to penicillin [120]. However, for β-lactam-susceptible organisms, these drugs are considered first line of therapy. Vancomycin susceptibility among clinical VGS isolates is close to 100%. In cancer patients with mostly acute leukemia and those undergoing HSCT, nearly 30% of isolates were reported as penicillin resistant, whereas all isolates exhibited in vitro susceptibility to vancomycin [107].

An increasing level of resistance is observed for fluoroquinolone, especially in patients routinely given this class of antibiotics for prophylaxis; empiric therapy with fluoroquinolone to treat systemic or invasive VGS infections is therefore, not recommended [121, 122]. VGS bacteremia is generally treated for 10–14 days; patients with endovascular site of infection including endocarditis should receive treatment for 4 weeks. Patients with septic arthritis and osteomyelitis may be given intravenous antibiotics for 3–4 weeks followed by an oral agent for suppressive therapy for another 4–8 weeks or even longer duration, which depends on the hosts' risk factors, including cumulative immune suppression, severity of infection; and in cases where deferment of excision of necrotic or ischemic debridable tissue leaves the focus of infection unattended. The role of intravenous immunoglobulin and plasmapheresis has been explored for patients with exotoxin-mediated toxic shock syndrome and currently not considered as standard of care for severe VGS infections [113].

GMS were susceptible to penicillin G, carbapenems, and clindamycin, whereas cephalosporins and quinolones showed intermediate activity or resistance in some cases, and it is important to note that GMS bacteria in general tend to be resistant to aminoglycosides [115].

β-Hemolytic Streptococci

The β-hemolytic streptococci reflect upon their ability to cause full red blood cell lysis in the blood-enriched culture media. Group A β-hemolytic streptococci (GAS) or *Streptococcus pyogenes* is a common pathogen followed by group B β-hemolytic streptococci (GBS) or *Streptococcus agalactiae* and groups C and G β-hemolytic streptococci (GCS and GGS, respectively) also known as *Streptococcus dysgalactiae* subspecies *equisimilis* [123–125].

Epidemiology

β-Hemolytic streptococci are ubiquitous in the human and animal population; colonization of the skin and mucous membrane is a common event. They are also an important cause for locally invasive disease such as pharyngitis, lower urinary tract infection, and superficial skin and skin structure infections. Severe systemic disease may occur in the general population and those with immune dysregulation after undergoing allograft transplantation [126]. The oropharynx and skin are the main sites of GAS, GCS, and GGS colonization [127, 128], whereas GBS commonly colonize the perineal area [128–130]. In the general population, majority of β-hemolytic streptococcal infections are acquired and presented from the community [83]. Immunosuppressed patients, especially those undergoing antineoplastic chemotherapy and recipients of HSCT, have a much higher risk for invasive β-hemolytic streptococcal disease compared to the general population [131, 132]. Cancer patients with lymphedema due to cancer infiltration or surgical lymph node dissection or those with radiation-induced tissue scarring impeding lymphatic circulation are especially at risk for such infections [133]. GBS are the most common of the invasive β-hemolytic streptococci isolated from patients with cancer and those undergoing stem cell transplantation [134, 135]. The development of invasive GAS, although less common than GBS, may result in a devastating disease that carries high fatality rates in excess of 50% [125].

Clinical Manifestations

Most β-hemolytic streptococcal infections in immunosuppressed cancer and stem cell transplant patients present with cellulitis and subcutaneous abscesses. In patients undergoing solid organ transplantation procedure, surgical wound infection, deep surgical bed infection, secondary infections of postoperative seromas, and deep tissue hematomas may also be prominent clinical manifestations of β-hemolytic streptococci. It is important to note that number of these infections may accompany other pathogens; appreciation for polymicrobial aspect of such infections is the central tenet in planning and executing a comprehensive treatment approach for deep tissue, and body cavity infections following transplant surgery [136].

Disease may range from relatively uncomplicated cellulitis and superficial wound infection to necrotizing fasciitis with or without exotoxin-induced toxic shock syndrome. The latter two complications are almost exclusively associated with GAS infection. Cellulitis due to β-hemolytic streptococci tends to develop rapidly, spread quickly, and may be accompanied by systemic manifestations such as fatigue, severe prostration, chills, rigors, with high-grade fever [137]. Erysipelas is a form of superficial cellulitis, in which the disease is restricted to the dermis. These lesions are elevated and well-demarcated from the healthy surrounding tissues [138]. Recurrence of erysipelas is a concern and often seen in patients with impaired lymphatic circulation. Infections due to GAS, GCS, and GGS are the leading bacterial causes of pharyngitis in children; most infections are readily treatable, although peritonsillar abscess and cervical lymphadenitis may rarely occur [128].

Invasive, systemic β-hemolytic streptococcal disease causes serious morbidity in patients with a suppressed immune response. Adults with β-hemolytic streptococcal bacteremia, especially patients with advancing age, the risk of death from such infections is high [125]. β-hemolytic streptococcal skin lesions that are greater than 5 cm in diameter, presence of pain that is out of proportion to findings on physical examination, disproporte severity in pain to gentle touch, and signs of systemic toxicity, skin discoloration, and/or presence of bullae on the overlying skin should raise concern for deep tissue involvement; possibility of necrotizing fasciitis, pyomyositis, and compartment syndrome should be entertained in such patients [139]. β-hemolytic streptococci disease via exotoxin production, especially by GAS, leads to extensive destruction of hosts' tissue and usually spreads at an exceedingly fast pace. Streptococcal toxic shock syndrome has also been described in cancer patients with mortality rates exceeding 50% [135]. Patients with diabetes are susceptible to hematogenous bacterial seeding to the bones resulting in remote site acute osteomyelitis [140].

A higher incidence of GAS necrotizing fasciitis was recently observed in Montréal, Canada. The authors reported that varicella and the presence of *speC* gene in GAS strains were associated with necrotizing fasciitis. In patients undergoing transplantation, bacterial genetic factors and potential synergistic or additive effect of concurrent viral infections like varicella on risk of GAS-related necrotizing fasciitis is not known [141].

Diagnosis

β-Hemolytic streptococci are readily isolated from cultures that are appropriately obtained. Rapid antigen tests are reliable for the diagnoses of GAS pharyngitis in patients when such infections are suspected [142]. Recovery of β-hemolytic streptococci from sterile-site samples such as blood, joints,

deep tissue, and body cavity abscesses indicates a true infection. In contrast, isolation of β-hemolytic streptococcus species from mucous membranes and skin frequently reflects bacterial colonization.

An exception to the preceding stipulation is the isolation of GAS in mucosal site culture samples to assist in the diagnosis of toxic shock syndrome [143]. Serologic tests are not useful in patients with acute β-hemolytic streptococcal infections. Acute and convalescent serum for antibodies to streptolysin O or DNase can determine a recent infection due to GAS, although such serological tests are now seldom used in clinical practice [144].

Treatment

Penicillin and other β-lactam antibiotics are considered drugs of choice for the treatment of infections due to β-hemolytic streptococci [145]. For patients who cannot receive β-lactams, treatment with vancomycin is recommended. Carbapenems may also be an option in patients with non-life-threatening penicillin allergy [146]. Macrolide and lincosamide should not be used for serious infections as drug resistance is unpredictable and highly variable; these agents should only be used when susceptibility results are available, especially for outpatient transition of therapy [147]. Similarly, resistance to tetracyclines and trimethoprim-sulfamethoxazole warrants the use of these agents empirically to treat β-hemolytic streptococcal disease [148, 149]. Clinical experience with newer gram-positive drugs like daptomycin; the oxazolidinones, such as linezolid and tedizolid; tigecycline; and long-acting lipoglycopeptides such as dalbavancin and oritavancin is encouraging with good in vitro susceptibility data for β-hemolytic streptococcal clinical isolates [150, 151]. In cases of serious soft tissue infection, especially toxic shock syndrome, addition of clindamycin is strongly recommended to attenuate bacterial exotoxin production by slowly dying bacteria after exposure to beta-lactam antibiotics [152]. Uncomplicated bacteremia can be treated with a 10-day course of antibiotics, whereas fiat for complicated β-hemolytic streptococcal disease has traditionally been longer duration of antibiotic therapy. Surgical debridement of devitalized tissue and drainage of large purulent deep tissue collections is, as with any other bacterial or fungal infection, remains important for containment and resolution of infection [139].

Streptococcus pneumoniae

Epidemiology

S. pneumoniae is genetically similar to other bacteria in this category, although it is a prominent pathogen associated with a wide spectrum of invasive disease in immunocompromised patients and those in the general population.

Nasopharynx colonization due to pneumococci occurs more frequently in children (20–40%) compared with healthy adults (10–20%) [153]. *S. pneumoniae* is the leading cause of bacterial pneumonia that commences while patients are in the community [154]. Bacterial meningitis is also an important complication of *S. pneumoniae* in patients with community-onset meningitis [155]. Patients with chronic obstructive pulmonary disease, chronic kidney disease, and deficiencies in humoral immunity such as those following anti-CD20 and other B-cell targeted therapies and patients with chronic lymphocytic leukemia, B cell lymphoma, and plasma cell neoplasms like multiple myeloma; and those with hereditory hypogammaglobulinemia are especially susceptible to pneumococcal invasive disease. Similarly, patients with hyposplenism including those with sickle cell diseases and patients after splenectomy are at risk for, often severe disseminated infection due to *S. pneumoniae* [156]. Patients with chronic graft-versus-host disease following allogenic stem cell transplantation are vulnerable to infections due to encapsulated bacteria; *S. pneumoniae* is prominent in this regard [157].

It has also been suggested that prolonged exposure to systemic corticosteroids increases the risk for pneumococcal infection as is the extremes of age [158–160]. A high prevalence of *S. pneumoniae* in children less than 5 years of age is well recognized; young children with B-cell cancer or those undergoing anti-B-cell-targeted therapy for allogenic hematopoietic or solid organ transplantation are particularly susceptible to serious infection [156].

Clinical Presentation

S. pneumoniae is a major respiratory tract pathogen. Infections in adults involve lower respiratory tracts, and bacterial pneumonia is a common disease presentation; bronchitis and paranasal sinus infections may also occur [161], whereas in children, otitis media is not an uncommon presentation.

Community-onset pneumonia in the immunocompromised transplant recipients is a serious infection. Patients commonly present with chills, fever, and fatigue; cough is generally accompanied by purulent sputum and shortness of breath [162]. Patients with inflammation of the parietal pleural with or without bacterial empyema may present with pleuritic chest pain. Bacterial lung abscess due to *S. pneumoniae* is not an uncommon complication of invasive pulmonary pneumococcal disease and often associated with cavitary lung lesions [163].

In recent animal experiments, pneumococcal infection was shown to cause nonspecific ischemic cardiac alterations, myocardial necroptosis, and apoptosis in both acutely ill and convalescent nonhuman primates [164]. *S. pneumoniae* was detected in the myocardium of all animals with acute severe pneumonia. Furthermore, evidence of cardiac scar formation

was observed only in convalescent animals [164]. This study suggested a potential role of invasive pulmonary pneumococcal disease in the humans, with the possibility of subclinical bacterial invasion of the myocardium, resulting in cardiac injury from necroptosis and apoptosis, followed by cardiac scarring and remodeling after antibiotic therapy [164]. Clinical importance and cardiac impact in humans with invasive pneumococcal disease need further evaluation.

Patients with bacterial meningitis may often have concurrent bacteremia, whereas pneumonia may not be present. Fever and neck stiffness along with persistent and often severe headache are common clinical features of bacterial meningitis. In patients with advanced pneumococcal meningeal disease, altered sensorium, obtundation, and coma may be the initial presentation.

Other disease manifestations include septic arthritis, usually involving the native large joints. Pneumococcal septic arthritis involving the symphysis pubis is often misdiagnosed as osteitis pubis, a sterile inflammatory condition seen in women following urinary incontinence surgery and sports such as soccer and also in patients with pelvic malignancies. *Staphylococcus aureu*s was the major cause among athletes and *Pseudomonas aeruginosa* among intravenous drug users. Septic arthritis in patients with pelvic malignancies are usually polymicrobial infections involving the fecal flora. Antibiotics are recommended for 6 weeks, and surgical debridement is required in nearly half of the patients [165].

Osteomyelitis of spinal and paraspinal tissues caused by *Streptococcus pneumoniae* is an uncommon complication as reported by the group in Houston, Texas. These infections mostly occurred in the absence of recent surgical procedure or presence of a foreign device. The lumbar spine was the frequent site of infection. Such infections complicated by spinal epidural abscess or the presence of a phlegmon were accompanied by neurologic deficits and carried a higher risk for death. Antimicrobial therapy for 6 weeks was effective [166, 167].

In a report from Japan, 6% of patients with invasive pneumococcal disease had evidence of pneumococcal vertebral osteomyelitis. Most infections were acquired in the community and had no recent history of a surgical procedure or trauma. In their experience, the lumbar spine was involved in nearly two-thirds of patients, and the remaining patients had cervical spine involvement. Bacteremia in this group was nearly universal; none of the patients had a primary site of pneumococcal disease. Good response to intravenous beta-lactam therapy in this group was encouraging [168].

HSCT

In HSCT recipients, pneumococcal infections present as late-onset bacteremia. These late-onset BSIs were associated with worse outcomes including septic shock, ICU stays, and high risk for deaths [157, 169]. Early-onset bloodstream infections in patients undergoing HSCT are frequently associated with severe neutropenia, mucositis, and indwelling intravascular catheter infections. Whereas, late-onset BSIs are commonly seen in severely immunosuppressed allogeneic HSCT recipients with GVHD and those undergoing systemic corticosteroid therapy. Since majority of *S. pneumoniae* bacteremia occur during late transplantation period, effective preventive strategies such as immunization with newer, immunogenic conjugated pneumococcal vaccines and drug prophylaxis with agents that have activity against majority of *S. pneumoniae* isolates in the community are considered standard of care. Infection prevention is highly desirable as pneumococcal bacteremia in this population carries unacceptably high case fatality rates.

In patients after undergoing allogeneic HSCT, diagnosis of pneumonia and chronic GVHD was associated with high mortality and a significantly lower probability of survival; this was evident in patients even after a single episode of pneumonia [170]. Pneumococcus is an important bacterial pathogen in allogeneic stem cell transplant recipients and mostly noted as late bacterial pneumonia with or without bloodstream infection. Pneumonia during the first 100 days after allograft stem cell transplantation are significantly more invasive fungal lung disease among individuals with acute GVHD; in such patients acute respiratory failure, and presence of septic shock predicted high risk of death [170].

Memory B-cell defects in allogeneic HSCT recipients increases susceptibility for encapsulated bacterial infections, as effective containment and remedy for these organisms require intact opsonization to promote phagocytosis. In a recent study, circulating IgM memory B cells (CD19+, CD27+, IgM+); and switched memory B cells (CD19+, CD27+, IgM(−), which are indicators of normal B cell activation and development were evaluated in 37 allogeneic HSCT recipients and compared with 35 healthy controls [171]. Among other parameters assessed were T-lymphocyte subpopulations, serum immunoglobulin levels including IgG subclasses, and antibodies to pneumococcal polysaccharides. A significant deficiency in both switched memory and IgM memory B cells was evident in the stem cell transplant cohort compared with the individuals in the healthy control group [171]. This observation was noted throughout the period following transplantation procedure and possibly reflect a switch to impaired B-cell isotype(s) in germinal centers within lymph nodes and other secondary lymphoid tissue. As expected, presence of GVHD was associated with lower IgM memory B-cell counts and lower serum levels of IgG2, IgG4, IgA, and antipneumococcal antibodies. Allogeneic HSCT recipients are susceptible to pneumococcal disease, which in most part is a reflection on the underlying defects in memory B-cell function aggravated in the presence of chronic GVHD [171]. Furthermore, hyposplenism is a frequent feature in HSCT recipients with chronic

GVHD, which further enhances the risk for systemic infections due to encapsulated bacteria.

In a transplant unit in Canada, the probability for pneumococcal disease among HSCT recipients was 30-fold higher than the general population (regression ratio = 30.2; $P < 0.00001$). Serotypes 23F and 6B were most prevalent [172]. All infection-associated serotypes were included in pneumococcal polysaccharide vaccine, whereas only 69% were represented in the conjugate vaccines. It was also important to note that the level of resistance to trimethoprim-sulfamethoxazole was high among the *S. pneumoniae* isolated from the transplant population during this study [172].

At M.D. Anderson Cancer Center between 1989 and 2005, 47 of 7,888 HSCT recipients developed 54 episodes of *S. pneumoniae* infections, accounting for 7 infection episodes per 1000 stem cell transplants [157]. The incidence was significantly higher in the allogeneic vs. autologous stem cell graft recipients, nine vs. five infection episodes per 1000 HSCTs, respectively. Thirty-six percent had graft-versus-host disease, and as expected, 16 of 17 patients had chronic GVHD. The total of 54 episodes of *S. pneumoniae* infection occurred median 433 days after transplntation; 11% of these patients had infection recurrence [157]. All 50 late posttransplant episodes were community-acquired infections and seen 473 ± 671 days after transplantation. Bacteremic pneumonia was the most common presentation (61%), followed by pneumonia without bacteremia (19%) and uncomplicated bacteremia alone (15%) [157]. Regression analysis showed that treatment with corticosteroids significantly increased the risk for bacteremic pneumonia (OR, 11.7; $P \leq 0.025$). In bacterial isolates from 29 episodes, 93% of patients received concordant antimicrobial therapy. It was unexpected that only one of the six patients (13%) who died of *S. pneumoniae* infection had chronic GVHD. The probability of death was higher in patients receiving care in the ICU at the time of infection diagnosis (OR, 15.5; $P \leq 0.007$) and those with each unit increase in APACHE II score (OR, 1.9; $P \leq 0.008$). Vaccine-breakthrough *S. pneumoniae* infection occurred in 5 patients after a median of 546 days following immunization; most such patients (80%) had pneumonia and concurrent bacteremia [157]. It is noteworthy that there were no cases of extrapulmonary focus of pneumococcal disease in HSCT recipients presented in this report.

Nontropical pyomyositis is an uncommon infection, such severe bacterial infections occur mostly in patients with suppressed immune response. *S. aureus* is the prominent pathogen associated with this disease. Pyomyositis due to *S. pneumoniae* is rare [173]. A recent report of hematogenous pneumococcal pyomyositis in an allogeneic stem cell graft recipient involved erector spinae muscles that presented 34 months after the transplantation procedure. Patient had a favorable response to 4 weeks of intravenous benzyl penicillin therapy [173].

SOT

As in HSCT, patients undergoing solid organ transplantation are at a greater risk for IPD compared with general population. Invasive pneumococcal disease is mostly seen in the late posttransplant period, and infections commonly start in the community. A prospective, population-based surveillance from Toronto, Canada, assessed systemic pneumococcal infections in SOT recipients between 1995 and 2004 [174]. The incidence was 146 infections from sterile body sites per 100,000 persons per year compared with 11.5 per 100,000 persons per year in the general population (RR, 12.8; $P < 0.00001$). When they also included the isolates from the respiratory tract, the incidence rate in transplant patients rose to 419 per 100,000 persons per year. Serotypes 23F and 22F were most common; 85% of these infection-associated serotypes were included in the 23-valent pneumococcal vaccine [174]. The antimicrobial resistance in SOT population was similar to that observed in the pneumococcal isolates for the general population and was especially high for penicillin and TMP/SMX.

A large database of 4,458 pediatric heart transplant recipients between 1993 and 2014 showed that the risk of bacterial infection was highest in the first month after transplantation; 25% of patients developed bacteremia. It was not unexpected to notice that community-acquired *S. pneumoniae* (6%) and *Haemophilus influenzae* (3%) were prominent during the late transplant period, whereas within a month following transplant procedure, CoNS (16.97%), *Enterobacter* spp. (12%), and *Pseudomonas* spp. (12%) were the prominent bacterial pathogens [175]. A large proportion of the infections were caused by multidrug-resistant organisms. Patients at risk for bacterial infection following heart transplantation included young age and ventilator or extracorporeal membrane oxygenation during transplantation. Thirty-four percent died due to bacterial infections, and prior cardiac surgery and multiple sites of infection were independent predictors of death [175].

In the Netherlands, a prospective nationwide study between 2006 and the end of 2014 assessed the risk and frequency of community-acquired bacterial meningitis among 16-year-old or older solid organ transplant recipients [176]. Six SOT recipients had bacterial meningitis; interestingly all six had undergone renal allograft transplantation. The annual incidence of bacterial meningitis was sevenfold higher for renal transplant recipients as compared with the general population: 9.5 vs. 1.3 per 100,000 patients per year [176]. It is important to note that in majority of the patients (83%), classic presentation of bacterial meningitis such as fever, neck stiffness, and changes in mental status were not present. Further complicating early diagnosis and prompt institution of appropriate antibiotic therapy for this life-threatening disease in this susceptible population. Seizures were present in 33% of patients. *Streptococcus pneumoniae* and *Listeria*

monocytogenes were identified in two patients each, whereas, *Escherichia coli* and *Pseudomonas aeruginosa* were seen in one patient each. Another valuable observation in this report was the high incidence (67%) of unfavorable functional outcomes that probably were a reflection on the hosts' immunocompromised status and, importantly, atypical clinical presentation of bacterial meningitis in patients undergoing solid allograft transplantation [176].

A retrospective review from London, England, assessed long-term outcome in patients who underwent orthotopic cadaveric donor heart and lung transplantation between July 1986 and July 2006 [177]. The mean posttransplant follow-up was 5.4 ± 5.5 years. Bacterial meningitis was diagnosed in 39 adults after receiving 15 heart transplants, 12 lung including 4 bilateral lung transplants, and 12 heart-lung transplants. *Neisseria meningitidis* (54%) and *Streptococcus pneumoniae* (41%) were prominent pathogens followed by *Haemophilus influenzae* (5%). Hospital mortality rate was 10%, and none of these patients developed long-term complications after bacterial meningitis [177].

In a study from South Korea, 14 of 42 episodes of respiratory infections were noted after 1 month following lung transplantation [178]. Six were bacterial, four were viral, and two episodes were fungal infections. Among bacterial infections, two were due to MDR *Acinetobacter baumannii* and one each due to MDR *P. aeruginosa*, ESBL (+) *K. pneumoniae*, MRSA, and *Streptococcus pneumoniae*. Infection-related death occurred in 6 of the 14 episodes (43%) [178].

In a report from Barcelona, Spain, 138 episodes of spontaneous bacterial peritonitis (SBP) in 19 liver transplant recipients and 119 in nontransplant patients showed *Escherichia coli* (35.7%) and *Streptococcus pneumoniae* (21.4%) as the prominent pathogens [179]. It was interesting to note that pathogens associated with SBP were significantly more frequently identified in patients following transplantation (74%), whereas only 39% of nontransplant population with SBP had a positive culture ($P = 0.004$). As expected, renal failure (58% vs. 25%; $P = 0.004$) and hepatic encephalopathy (42% vs. 22%; $P = 0.08$) were more often seen in liver transplant recipients vs. the nontransplant group, respectively [179]. Similarly, deaths during the SBP episodes (53% vs. 13%; $P < 0.001$) and 6 months after the infection diagnosis (71% vs. 35%; $P = 0.005$) were significantly higher in the transplant population. The risk of death associated with the SBP was sixfold higher in patients with a high (>18) Model for End-Stage Liver Disease (MELD) score and fourfold higher in patients who had undergone liver transplantation. Mortality 6 months after SBP was fourfold higher in patients with hepatocellular carcinoma [179].

Orthotopic liver transplantation from a potential donors with active bacterial meningitis has been regarded as a contraindication for allograft procurement from such a donor. Due to a global shortage of liver allografts, in Birmingham, England, orthotopic liver transplants were performed from 33 donors with acute bacterial meningitis, 14 *Neisseria meningitidis*, 4 *Streptococcus pneumoniae*, 2 *Streptococcus* spp., and a single patient with *Haemophilus influenzae*. In 12 donors, a pathogen was not identified [180]. Of 34 recipients, 27 underwent elective and 7 had emergency transplantat surgery including 21 whole liver, 10 reduced-liver, and 3 split-liver allograft transplants. Adequate antimicrobial therapy before organ procurement and after transplant was administrated. The mean duration of follow-up after transplantation was 37 months (ranged from 1 day to 106 months). Overall patient (79% and 77%) and graft survival was; 72% and 65% at 1 and 60 months, respectively [180]. Patients who underwent elective liver transplant had significantly better survival compared with those who underwent emergency transplantation ($P < 0.05$). There was no difference in recipient and graft survival between the 34 patients who had received allograft from a donor with acute bacterial meningitis compared with recipient-matched groups. The authors observed no infectious complications in the recipient due to bacteria associated with meningitis after transplantation. Further data is needed before routine acceptance of liver allografts from donors with active bacterial meningitis becomes an acceptable practice, although study such as this, underscores that lifesaving procedure such as liver transplantation may be safly performed provided both donors and recipients are given adequate antimicrobial therapy. Furthermore, the optimum duration of antibiotic therapy in such recipients is not certain.

Diagnosis

Isolation of *S. pneumoniae* in blood, joint fluid, bronchial wash or lavage samples, and cerebrospinal fluid is regarded as diagnostic. Isolation of *S. pneumoniae* in sputum samples is a challenge, as diagnostic yield is significantly reduced in patients exposed to antibiotic(s) [181]. It has been estimated that only one-fourth of the patients with pneumococcal pneumonia will have a positive blood culture [182]. As with staphylococcal and other streptococcal infections, serologic studies have limited clinical use in assisting with the diagnosis of an acute infection episode. Detection of C-polysaccharide (BINAX-NOW) in the urine of adults with pneumococcal pneumonia is isolated in 75–85% of the patients; this test has high specificity and reliable negative predictive value [183]. Polymorphonuclear-predominant pleocytosis, low glucose, and high protein in the cerebrospinal fluid are the hallmarks of bacterial meningitis that are as expected to be present in most patients with pneumococcal meningitis. Gram-stain, bacterial antigen assays and culture of cerebrospinal fluid obtained promptly prior to extensive antibiotic exposure are essential for establishing the correct diagnosis [182].

Treatment

S. pneumoniae penicillin susceptibility and laboratory breakpoints have been reevaluated as to include the site of infection and the route by which the antibiotics may be administered [184]. For all pneumococcal infections other than the central nervous system, organisms demonstrating in vitro penicillin susceptibility of ≤2 μg/ml, reflecting approximately 95% of clinical pneumococcal cases in the United States, have good probability for attaining a clinical response to high-dose penicillin given intravenously [184]. For treatment of pneumococcal meningitis, penicillin MIC of <0.06 μg/ml is considered susceptible, and others with MIC ≥ 0.12 μg /ml are regarded as resistant bacterial strains; nearly 75% of pneumococci isolated in patients with meningitis in the United States fall in the susceptible category [184]. Pneumococcal isolates are universally susceptible to vancomycin. Respiratory fluorinated quinolones such as levofloxacin and moxifloxacin retain susceptibility for most pneumococcal isolates, although due to limited clinical experience and unpredictable response, authors recommend not to use these agents alone to treat patients with *S. pneumoniae* CNS infections [185, 186]. In *S. pneumoniae* isolated from respiratory specimens in the United States, resistance to macrolides, clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines ranged from 20% to 40% [187]. In the authors' opinion, these drugs should not be used for the treatment of invasive pneumococcal disease in the transplant population.

Linezolid is an effective and safe treatment option for patients with *S. pneumoniae* infections [188]. Linezolid was shown to be effective and well tolerated in severely immunocompromised children with an underlying malignancy including those at young age [189]. The increased susceptibility to bacterial respiratory tract infection following a viral infection was associated with a substantial increase in local and systemic IFN-γ concentrations. Linezolid was shown to reduce IFN-γ and TNF-α production in stimulated peripheral blood mononuclear cells. In mice, linezolid recently showed protection from post influenza pneumococcal infection, and this reversal of immune hyporesponsiveness was attributed to the drug's ability to mitigate exaggerated postviral IFN-γ and TNF-α immune responses [190]. This ancillary immune modulatory effect of linezolid, especially in patients that are susceptibile for postviral superimposed bacterial pneumonia, is intriguing and needs further evaluation.

Daptomycin should not be used to treat lung infections, especially bronchogenic pneumonia because of limited drug diffusion in the alveolar space and inactivation of daptomycin by pulmonary surfactant [191].

Mortality for invasive pneumococcal disease remains around 15% within the first week of hospitalization, and most infections respond to a relatively short course of antibiotic therapy; extended therapy for over 2 weeks is recommended for patients with meningitis, empyema, bone and joint infections, and deep tissue abscesses that are not evacuated and patients with complicated bacteremia with an endovascular focus of infection [182].

S. pneumoniae is the only Gram-positive bacteria for which there are licensed vaccines available globally. The role of pneumococcal vaccine in transplant population is discussed in Chap. 63.

Enterococcus

Epidemiology

Enterococci, not dissimilar to CoNS and VGS, cause a disproportionately higher number of infections in the immunosuppressed cancer and transplant patients compared with the general population [192]. Most enterococcal infections are associated with prolonged exposure to healthcare environment. Enterococci are prominent bacteria in human intestinal microbiome. *E. faecalis* and *E. faecium* are two most frequently isolated species from infections in humans [193]. Patients with cancer and those undergoing transplantation have especially high rates of intestinal colonization and subsequent risk for invasive disease due to vancomycin-resistant enterococci (VRE). The factors promoting selection and persistence for VRE colonization in certain high-risk individuals with cancer and those undergoing transplantation procedure remain unclear, although prior exposure to m antibiotics has been proposed. It was interesting that a recent report indicated transplant unit reconstruction had interrupted endemic transmission of VRE, which resumed with novel enterococcal strains upon reopening of the unit. It was hypothesized that endemic VRE transmission in this transplant unit probably reflected VRE contamination of shared equipment and environmental surfaces [194]. This provides further insight into the possible reason that VRE has been an unabating challenge at certain transplant units, whereas less of a problem in patients undergoing a similar transplantation procedures at other institutions. This hypothesis was further emphasized in a recent study from Buffalo, New York, that active surveillance and contact precautions for VRE colonization were not effective in preventing VRE bacteremia in patients undergoing stem cell transplantation at their institution [195], whereas, a group from Salt Lake City, Utah reported in 2016 that VRE transmission from room surfaces appeared to be an infrequent event, thereby concluding that adherence to VRE surveillance, disinfection strategies, and contact isolation protocols are needed to be adhered to and may reduce VRE colonization rates in patients with hematologic malignancies and those undergoing HSCT [196].

HSCT

A single-center experience among patients admitted for induction chemotherapy or those undergoing HSCT from 2006 to 2014 showed that the incidence of VRE bacteremia was 6.5% of admissions or 2.7 VRE bacteremia per 1000 bloodstream infection at-risk days [192]. Mortality and length of stay were significantly higher in patients in whom VRE bacteremia were to occur. Patients with prior VRE colonization had eightfold higher probability for VRE bacteremia; similarly, patients with renal insufficiency (twofold), aminoglycoside use (~fivefold), and antibiotics with anaerobic activity (~threefold) had significantly higher risk for VRE bacteremia. The authors also reported using a predictive model, which identified severe neutropenia and prior beta-lactam antibiotic use were among prominent risk factors for VRE bloodstream invasion and infection [192].

A recent report from Salt Lake City, Utah, showed that VRE bacteremia after stem cell engraftment and resolution of neutropenia in HSCT recipients was associated with a much higher mortality compared with VRE bacteremia during the neutropenic pre-engraftment period [197]. Pre-engraftment bacteremia from any organism resulted in an increase length of hospitalization and higher cost of care. Mortality was similar for pre-engraftment VRE bacteremia and bacteremia due to other organisms in this neutropenic phase following stem cell transplantation. The authors pointed out that a high VRE bacteremia mortality rate observed during the post-engraftment period was largely associated with severe graft-versus-host disease and relapsed leukemia [197]. It was also interesting to note that frequently VRE strains switched phenotypes when isolated from patients before and after the transplantation procedure [197].

A contrasting review of patients undergoing HSCT at the Mayo Clinic in Rochester, Minnesota concluded that VRE colonization was a surrogate marker and not an independent predictor of mortality in HSCT recipients [198]. They observed high morbidity in their transplant patients with VRE bacteremia, although this had no significant impact on posttransplant survival. The data was generated between 2004 and 2014 by conducting twice-weekly perirectal swab PCR screening for vanA and vanB. In 73 of 203 patients, VRE colonization was noted prior to HSCT and in 11% VRE colonization occurred within the first 100 days after transplantation [198]. There was no significant difference in overall survival based on pretransplant VRE colonization status. However, patients that developed VRE colonization within the first 100 days after HSCT had a significantly worse survival. During the first 30 days following transplant, 91% had screened positive for VRE colonization prior to developing bacteremia. On multivariable analysis, advanced age (≥60 years), high HSCT comorbidity score, and prior VRE colonization were independent risk factors for VRE bacteremia. It was notable that only one patient had died with VRE bacteremia during the first 100 days after HSCT [198].

The findings from a center in Cleveland, Ohio, were in concert with the report from the Mayo Clinic; they found that between 1997 and 2011, the incidence of VRE-B had increased in 800 adult allogeneic HSCT recipients. Seventy-six patients developed VRE-vanB bacteremia after a median of 46 days following transplantation. Multivariable analysis showed that the risk for VRE-vanB bacteremia was higher in patients with high HSCT comorbidity score, with diagnosis of acute lymphoblastic leukemia, and recipients of unrelated donor and umbilical cord blood stem cell allograft transplantation. A fourfold higher probability of death in patients with VRE-vanB bacteremia was a significant finding on multivariate analysis; however, only 6% of 67 deaths within 5 weeks after transplantation were attributed to VRE infection [199], drawing attention to the clinical relevance of VRE bacteremia in high-risk transplant patients as a potential surrogate marker for poor prognosis during the early posttransplant period.

The preceding observation was also noted in a review of 247 adult patients in whom 28% had VRE colonization after allogeneic HSCT between 2008 and 2009 [200]. This report from Memorial Sloan Kettering Cancer Center in New York reported VRE bacteremia (54%) as the leading cause of bloodstream infection within 30 days after HSCT at their institution. Only 57% of patients with VRE bacteremia had VRE colonization during pretransplant screening [200]. Attributable mortality to VRE infection was low (9%), reflecting VRE bacteremia as a surrogate marker for altered host intestinal tract microbiota and perhapse an indicator for a subgroup of high-risk individuals undergoing allogeneic stem cell graft transplantation.

In patients undergoing autologous stem cell transplantation, despite having a high rate of VRE colonization, the risk for invasive bacterial disease is low. High rates of VRE colonization in this group may potentially serve as a reservoir for transmission to other higher-risk patients in a transplant unit or center [201].

In patients following allogeneic stem cell graft transplantation, donor-derived T cells recognize host tissues as foreign and orchestrating an assault on the recipient tissues, clinically known as GVHD. The intestinal tract is the most common site of GVHD, and in recent years, an interest in the composition of gut microbiota and its relationship with the development of GVHD was explored. The loss of intestinal bacterial diversity is common in patients undergoing HSCT due to prophylactic, preemptive, and empiric use of broad-spectrum antibiotics. This loss in intestinal biodiversity and overgrowth of opportunistic pathogens belonging to the phylum *Proteobacteria* and genus *Enterococcus* in patients following HSCT have been linked to enhance the risk for treatment-related mortality including GVHD, systemic

infections, and organ failure [202]. In animal experiments, interventions to mitigate alternations in selective intestinal bacterial overgrowth with the use of prebiotic and probiotic strategies have shown favorable results on the risk and severity of GVHD [202]. Further clinical studies are needed to explore these and other interventions that may restore healthy intestinal microbiota, especially in patients undergoing allogeneic stem cell to promote.

In patients undergoing HSCT, 2% chlorhexidine bathing was effective in regards to VRE colonization and infection [203], whereas no similar benefits were noted in protection against MDR-GNB, especially for infections due to *P. aeruginosa.*

A review of 822 autologous and allogeneic HCST recipients at Northwestern Memorial Hospital between 2004 and 2008 noted a 10% incidence in *Clostridium difficile*-associated diarrhea (CDAD) [204]. A significant association became apparent between CDAD and VRE colonization among other prominent risk factors for CDAD such as febrile neutropenia; exposure to ciprofloxacin, vancomycin, and aztreonam; prolonged duration of antibiotic therapy, and allogeneic stem cell transplantation [204].

Experiments have shown the protective significance of the normal microbiota; VRE colonization serves as a surrogate, representing alteration in the intestinal microbiome, especially following the influential perturbation during and after prolonged, broad-spectrum antibiotic therapy. Exogenously administered VRE was shown to efficiently and nearly completely displace the normal microbiota of the small and large intestines in mice after antibiotic therapy [205]. Furthermore, investigators from a comprehensive cancer center in New York showed that VRE colonization preceded bacteremia and sepsis in patients undergoing allogeneic HSCT [205].

SOT

Enterococcus species are recognized for nearly three decades as a potential pathogen in patients undergoing liver and other abdominal visceral transplants. Early on at the Mayo Clinic in Rochester, Minnesota, 405 consecutive liver transplantations were conducted between 1985 and 1993, a selective bowel decontamination prophylaxis regimen was routinely given [206]. In 52 patients (13%), 70 episodes of bacteremia were seen; most infections were due to *Enterococcus faecalis* (n = 50), and 18 isolates of *Enterococcus faecium*; vancomycin resistance in clinical enterococcal isolates was not an issue during the study years. It was important to note that nearly half (49%) of these infections were polymicrobial and one-third (34%) of the patients had complications involving the biliary tract. Not dissimilar to the observation in allogeneic HSCT recipients, most deaths (73%; 11 of 15) were not associated with enterococcal bacteremia. Significant risk factors in this group for enterococcal bacteremia included Roux-en-Y choledochojejunostomy (P = 0.005), a cytomegalovirus-seropositive donor (P = 0.013), prolonged transplantation time (P = 0.02), and strictures in the biliary tract (P = 0.016). On univariate analysis, diagnosis of primary sclerosing cholangitis (P = 0.009) and symptomatic cytomegalovirus infection (P = 0.008) was significantly present in patients in whom bacteremia due to *Enterococcus* spp. was observed [206]. Further underpinning the significance of isolation of these low-virulence pathogens in blood culture samples among patients undergoing liver transplantation, as a potential surrogate for identifying a highly susceptible subgroup of patients who have undergone abdominal visceral allograft transplantation surgery.

Selective bowel decontamination prophylactic regimens were suggested for mitigation of intestinal colonization due to MDR microorganisms. The Mayo Clinic reported isolation of VRE in early 1995 from surveillance cultures obtained from patients undergoing liver and kidney transplantation. By the end of 1997, 52 patients had VRE colonization, importantly with a single vanB clone [207]. VRE infection was observed in six patients (11%) [207].

In a longitudinal study from Pittsburgh, Pennsylvania, between 1990 and 1999, 165 patients underwent liver transplantation. Fifty-one (31%) patients developed posttransplant infection due to one or more MDR bacteria. A substantial number of bacteria (69%) were MDR pathogens. A high level of drug resistance was noted in *S. aureus* (91%) and enterococcal isolates (50%) [208]. During the decade-long study, a significant trend emerged for infections due to MDR bacteria mainly due to GPB infections like MRSA (P = 0.0001) and VRE (P = 0.04). In contrast, no significant increase was reported among MDR-GNB infections during the course of this study [208].

Patients undergoing solid organ transplantation are at an increased risk for colonization due to MRSA and VRE, an observation similar to patients undergoing allogeneic stem cell transplantation. As pointed out in a number of studies, bacterial colonization is an important precursor for invasive disease, especially those undergoing abdominal visceral allograft transplantation. A meta-analysis involving 23 published studies assessed the burden of MRSA and VRE colonization in patients undergoing solid organ transplantation; 17 of these studies were in liver transplant population [6]. The pooled prevalence estimates before transplantation were 8.5% for MRSA and 11.9% for VRE. However, MRSA colonization estimate was lower (4.0%) in studies involving 200 or more patients. The prevalence estimates for bacterial colonization after the transplantation procedure were 9.4% and 16.2% for MRSA and VRE, respectively. The risk for MRSA infection was significantly higher in patients with MRSA colonization before transplantation (RR 5.5) and also for patients in whom colonization occurred after the

transplantation procedure (RR 10.56). In concert with the risk for subsequent MRSA infection, VRE colonization before (RR 6.6) and after transplantation (RR 7.9) were associated with significantly higher risk of invasive VRE disease [6].

Most early posttransplant VRE infections are a result of complications arising from transplant surgery, a need for extended stay in transplant or surgical critical unit and prolonged exposure to broad-spectrum antibiotics. Bacteremia, intra-abdominal infections, urinary tract infections, and surgical site infections are common clinical presentation. VRE endovascular infections including endocarditis in the SOT population is rarely seen [114, 209]. Complications involving the biliary tract, such as strictures and biliary leaks, and importantly the interventions to ameliorate these compilations are important risk factors for VRE infection in patients undergoing liver transplantation [209, 210].

In kidney transplant recipients, VRE infections are prominent in patients with HCV infection, those undergoing multivisceral transplantation such as kidney and pancreas allograft surgery, patients requiring renal replacement therapy after transplantation surgery; nephrostomy tube placement, and patients taken back to the operation room for re-exploration surgery [211].

Left ventricular assist devices (LVAD) are used as a bridge to cardiac transplantation in patients with severe life-threatening heart failure awaiting transplant surgery. Pretransplant infection of LVAD increases the risk for post-transplant infections including infections due to VRE. Patients with LVAD infections commonly present as primary bacteremia, pocket and tunnel infection, endovascular infections including LVAD endocarditis, and infections involving the mediastinum. In a report from Rush University Medical Center in Chicago, IL 46 LVAD-related infections were diagnosed in half of patients who underwent LVAD implantation as a bridge to transplantation. Twenty-nine episodes of LVAD-related bacteremia included five patients with LVAD endocarditis; presence of diabetes appeared to increase the risk for bacteremia. VRE infection was diagnosed in six patients with LVAD-related infection who had undergone transplantation surgery; four of these six patients died. It was interesting to note that VRE infections were not seen in patients without pretransplant LVAD-related infection [212].

Diagnosis

Culture is the mainstay of diagnosis, with serologic or antigen tests having no value. The isolation of enterococci from non-sterile specimens such as urine, sputum, or external wound drainage usually represents colonization or subclinical infection rather than infection that requires treatment. Prescribing antibiotics in this situation generally fails to eradicate the organism while promoting the risk for development of antimicrobial resistance and exposing the patient to adverse events and toxicicty plus potentil for drug-drug interactions [213]. Even when isolated from sterile sites such as the abdominal cavity, enterococci are usually present along with one or more other organisms [136], and treatment of more virulent pathogens has been shown to cure such infections even in the absence of targeted anti-enterococcal therapy [214]. This concept is illustrated by the highly effective nature of cephalosporins in treating intra-abdominal infections despite having limited activity against enterococci [215].

Treatment

Treatment of enterococcal infection is complicated; bacterial species and drug resistance profile are the main influence in selection of drug(s) for a specific type of infection. Most clinical *E. faecalis* isolates show in vitro susceptibility to common beta-lactam drugs such as penicillin, ampicillin, amoxicillin, and piperacillin and to carbapenems like imipenem. Nafcillin is not effective against *E. faecalis*. It is important to remember that *E. faecalis* isolates are intrinsically resistant to cephalosporins [216]. In contrast, *E. faecium* isolates exhibit a high level of penicillin resistance, which in most cases exceeds 50% [216]. Macrolides, TMP-SMX, and fluoroquinolones are generally not effective against enterococci [217]. Vancomycin is regarded as the drug of choice for treating enterococci infections in patients with serious hypersensitivity to beta-lactams and those with beta-lactam-resistant isolates. However, with the emergence and spread of vancomycin nonsusceptible strains, the choice(s) of optimum effective therapy remains uncertain [213]. Enterococci may exhibit tolerance to β-lactam antibiotics, meaning that bacterial growth is inhibited in vitro following exposure at low drug concentrations, however bacterial killing induced by autolytic cellular pathways is not achievable following exposure to, even high antibiotic levels that could be given at physiologic doses [218]. Beta-lactam tolerance is an important mechanism underlying treatment failure and/or infection recurrence in severely immunosuppressed patients with neutropenia and those with endovascular infections [213]. A bactericidal effect may be achieved against some isolates by the addition of an aminoglycoside [218]. The bacterial killing after the addition of aminoglycosides only occurs in isolates that show in vitro susceptibility to these drugs, and as expected, no synergistic benefit should be expected among bacterial strains that are tolerant to beta-lactam drugs and also resistant to aminoglycosides [218].

Linezolid, tedizolid, daptomycin, and seldom-used quinupristin/dalfopristin are the drugs active against VRE. Quinupristin/dalfopristin lacks efficacy against *E. faecalis*. Enterococcal bloodstream infection and with rare hematogenous seeding of the meninges resulting in bacterial meningitis that may occasionally occur in severely immunocompromised patients including those undergoing HSCT;

linezolid monotherapy was reported to be effective, although clinical experience is limited [219]. Furthermore, linezolid resistance has emerged as a daunting concern, especially in patients undergoing HSCT. In a study in Essen, Germany, conducted between 2014 and 2015, 20 patients had linezolid-resistant VRE, and 18 of these patients underwent HSCT [220]. Twenty-five percent of patients developed bloodstream infection. Ten patients had bacterial colonization at the time of hospitalization. Eighty percent of patients with hospital-onset linezolid-resistant VRE had prior therapy with linezolid [220]. The authors report no clear evidence of patient-to-patient or environment-to-patient transmission within the transplant unit. It was interesting to note that a single genotype in six patients was noted, and all such patients were referred for the same hospital.

A report from the University of Illinois in Chicago conducted between 2000 and 2008 assessed 48 hospitalized patients being treated with linezolid and reported reduced susceptibility to VRE in these clinical isolates [221]. A significantly high risk for such infections was seen in patients undergoing allogeneic stem cell or solid organ allograft transplantation (OR: 2.6), treatment with immunosuppressive agents (OR: 2.4), both systemic corticosteroids (OR: 2.4) and noncorticosteroid immunosuppressive drugs (OR: 2.3), and exposed to linezolid with 1 year prior to infection diagnosis (OR: 34.5). Multivariable analysis showed that the risk of reduced susceptibility to linezolid among clinical VRE isolates was 32-fold greater in individuals who had received linezolid within 1 year of infection diagnosis. It is important to note that in this report most patients with VRE infections due to reduced linezolid susceptibility had not been treated with linezolid in the year prior and reduced linezolid susceptibility did not impact patient outcomes, which included clinical or microbiological cure, length of hospitalization, and all-cause mortality [221]. Further studies are needed to understand the clinical relevance and potential for treatment failure in patients with the emerging reduced linezolid susceptibility VRE infections and how best to manage such infections.

The in vitro susceptibility data for daptomycin and tigecycline are encouraging. Emergence of daptomycin resistance among clinical VRE isolates, especially in patients undergoing HSCT is of grave concern [222]. Reports of clinical failures with these agents in the setting of high in vitro drug MICs have underscored the potential threat [223]. However, in a recent report among adults with VRE bacteremia following HSCT and those with hematologic malignancies, the duration of bacteremia and microbiological failure rates did not differ by daptomycin MICs [224]. Multivariable analysis indicated an interesting trend that all-cause 30-day mortality was low in patients with VRE bacteremia due to bacterial strains that had high daptomycin MICs (3–4 micrograms/L) [224]. This trend, however, did not reach a level of statistical significance [224]. If this were to be a valid and significant finding, such an observation would put "disease-causing fitness" of such bacterial strains into question and, as mentioned earlier in various reports, and place emphsis on the surrogate nature of enterococcal infections, especially in high-risk patients following allogenic stem cell or solid organ allograft transplantation.

Summary

Gram-positive bacteria (GPB) are an important cause of serious systemic disease in the immunocompromised patients, especially patients after undergoing allograft transplantation. A rise in infections due to GPB in the last two decades has been attributed to a variety of reasons that prominently include antimicrobial prophylaxis with a focus on the prevention of Gram-negative bacterial infections and common use of indwelling intravascular access devices. In solid organ transplant recipients, postsurgical wound and deep tissue infections resulting from tissue ischemia, prolonged and complicated surgical procedures, allograft rejection, and severity of iatrogenic drug-induced immune suppression are important contributing factors. Severe orointestinal mucositis, prolonged pre-engraftment neutropenia, and graft-versus-host disease involving the skin and orointestinal tract are important consideration to promote risk among patients undergoing hematopoietic stem graft transplants. Community-acquired methicillin-resistant *Staphylococcus aureus* is now frequently encountered. Similarly, drug resistance among various pathogenic *Staphylococcus*, *Streptococcus*, and *Enterococcus* species has a substantial impact on selection of empiric antibiotic therapy in this population with suspected bacterial infection. Early diagnosis, prompt institution of appropriate therapy, assessment for outcome prognosticators, and recognizing the potential for early and late infection- and treatment-related complications forms the bases for providing optimum management of GPB infections in the transplant population.

References

1. Berenger BM, Doucette K, Smith SW. Epidemiology and risk factors for nosocomial bloodstream infections in solid organ transplants over a 10-year period. Transpl Infect Dis. 2016;18(2):183–90.
2. Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: neutropenia, humoral, and splenic defects. Clin Infect Dis. 2011;53(8):798–806.
3. Safdar A, Armstrong D. Infectious morbidity in critically ill patients with cancer. Crit Care Clin. 2001;17(3):531–70.

4. Oliveira-Cunha M, Bowman V, di Benedetto G, Mitu-Pretorian MO, Armstrong S, Forgacs B, et al. Outcomes of methicillin-resistant Staphylococcus aureus infection after kidney and/or pancreas transplantation. Transplant Proc. 2013;45(6):2207–10.
5. Moore C, Davis NF, Burke JP, Power R, Mohan P, Hickey D, et al. Colonisation with methicillin-resistant Staphylococcus aureus prior to renal transplantation is associated with long-term renal allograft failure. Transpl Int. 2014;27(9):926–30.
6. Ziakas PD, Pliakos EE, Zervou FN, Knoll BM, Rice LB, Mylonakis E. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. Am J Transplant. 2014;14(8):1887–94.
7. Nesher L, Chemaly RF, Shah DP, Mulanovich VE, Hosing C, Rolston KV. Utility of routine surveillance blood cultures in asymptomatic allogeneic hematopoietic stem cell transplant recipients with indwelling central venous catheters at a comprehensive cancer center. Am J Infect Control. 2014;42(10):1084–8.
8. Lukenbill J, Rybicki L, Sekeres MA, Zaman MO, Copelan A, Haddad H, et al. Defining incidence, risk factors, and impact on survival of central line-associated blood stream infections following hematopoietic cell transplantation in acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant. 2013;19(5):720–4.
9. Toro JJ, Morales M, Loberiza F, Ochoa-Bayona JL, Freytes CO. Patterns of use of vascular access devices in patients undergoing hematopoietic stem cell transplantation: results of an international survey. Support Care Cancer. 2007; 15(12):1375–83.
10. Laura R, Degl'Innocenti M, Mocali M, Alberani F, Boschi S, Giraudi A, et al. Comparison of two different time interval protocols for central venous catheter dressing in bone marrow transplant patients: results of a randomized, multicenter study. The Italian Nurse Bone Marrow Transplant Group(GITMO). Haematologica. 2000;85(3):275–9.
11. Lee SO, Brown RA, Kang SH, Abdel-Massih RC, Razonable RR. Toll-like receptor 2 polymorphism and Gram-positive bacterial infections after liver transplantation. Liver Transpl. 2011;17(9):1081–8.
12. Kanamaru A, Tatsumi Y. Microbiological data for patients with febrile neutropenia. Clin Infect Dis. 2004;39(Suppl 1):S7–S10.
13. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis. 2003;36(9):1103–10.
14. Archer GL, Climo MW. Staphylococcus epidermidis and other coagulase-negative staphylococci. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2352–9.
15. Moreillon P, YQue YA, Glauser MP. Staphylococcus aureus (including staphylococcal toxic shock). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2321–51.
16. Kuehnert MJ, Kruszon-Moran D, Hill HA, McQuillan G, McAllister SK, Fosheim G, et al. Prevalence of Staphylococcus aureus nasal colonization in the United States, 2001–2002. J Infect Dis. 2006;193(2):172–9.
17. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2008;46(Suppl 5):S344–9.
18. Kato N, Tanaka J, Mori A, Tutumi Y, Yonezumi M, Chiba K, et al. The risk of persistent carriage of methicillin-resistant Staphylococcus aureus in hematopoietic stem cell transplantation. Ann Hematol. 2003;82(5):310–2.
19. Navarro MB, Huttner B, Harbarth S. Methicillin-resistant Staphylococcus aureus control in the 21st century: beyond the acute care hospital. Curr Opin Infect Dis. 2008;21(4):372–9.
20. 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;198(3):336–43.
21. Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015;144(2):171–85.
22. Djaldetti M, Salman H, Bergman M, Djaldetti R, Bessler H. Phagocytosis—the mighty weapon of the silent warriors. Microsc Res Tech. 2002;57(6):421–31.
23. Weisser M, Theilacker C, Tschudin Sutter S, Babikir R, Bertz H, Götting T, et al. Secular trends of bloodstream infections during neutropenia in 15,181 haematopoietic stem cell transplants: 13-year results from a European multicenter surveillance study (ONKO-KISS). Clin Microbiol Infect. 2017;23(11):854–9.
24. Gjaerde LI, Moser C, Sengeløv H. Epidemiology of bloodstream infections after myeloablative and non-myeloablative allogeneic hematopoietic stem cell transplantation: a single-center cohort study. Transpl Infect Dis. 2017;19(5).
25. Mihu CN, Schaub J, Kesh S, Jakubowski A, Sepkowitz K, Pamer EG, et al. Risk factors for late Staphylococcus aureus bacteremia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant. 2008;14(12):1429–33.
26. Florescu DF, Qiu F, Vivekanandan R, Mercer DF, Langnas AN, Kalil AC. Risk factors and outcomes of Staphylococcus aureus infections after small bowel and multivisceral transplantation. Pediatr Infect Dis J. 2012;31(1):25–9.
27. Ranghino A, Diena D, Simonato F, Messina M, Burdese M, Piraina V, et al. Clinical impact of bacterial contamination of perfusion fluid in kidney transplantation. Springerplus. 2016;5:7.
28. Altman DR, Sebra R, Hand J, Attie O, Deikus G, Carpini KW, et al. Transmission of methicillin-resistant Staphylococcus aureus via deceased donor liver transplantation confirmed by whole genome sequencing. Am J Transplant. 2014;14(11):2640–4.
29. Doucette KE, Al-Saif M, Kneteman N, Chui L, Tyrrell GJ, Kumar D, et al. Donor-derived bacteremia in liver transplant recipients despite antibiotic prophylaxis. Am J Transplant. 2013;13(4):1080–3.
30. Soong RS, Chan KM, Chou HS, Wu TJ, Lee CF, Wu TH, et al. The risk factors for early infection in adult living donor liver transplantation recipients. Transplant Proc. 2012;44(3):784–6.
31. Li C, Wu Y, Riehle A, Ma J, Kamler M, Gulbins E, et al. Staphylococcus aureus survives in cystic fibrosis macrophages, forming a reservoir for chronic pneumonia. Infect Immun. 2017;85(5):e00883–16.
32. Shields RK, Clancy CJ, Minces LR, Kwak EJ, Silveira FP, Abdel Massih RC, et al. Staphylococcus aureus infections in the early period after lung transplantation: epidemiology, risk factors, and outcomes. J Heart Lung Transplant. 2012;31(11):1199–206.
33. Clancy CJ, Bartsch SM, Nguyen MH, Stuckey DR, Shields RK, Lee BY. A computer simulation model of the cost-effectiveness of routine Staphylococcus aureus screening and decolonization among lung and heart-lung transplant recipients. Eur J Clin Microbiol Infect Dis. 2014;33(6):1053–61.
34. Bernasconi E, Pattaroni C, Koutsokera A, Pison C, Kessler R, Benden C, et al. Airway microbiota determines innate cell inflammatory or tissue remodeling profiles in lung transplantation. Am J Respir Crit Care Med. 2016;194(10):1252–63.
35. Cordonnier C, Buzny A, Leverger G, Herbrecht R, Hunault M, Leclercq R, et al. Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. Clin Infect Dis. 2003;36(2):149–58.

36. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA. 2007;298(15):1763–71.
37. Takeda K, Tanaka K, Kumamoto T, Nojiri K, Mori R, Taniguchi K, et al. Septic pulmonary embolism originated from subcutaneous abscess after living donor liver transplantation: a pitfall of postoperative management. Clin J Gastroenterol. 2013;6(5):378–82.
38. Malagola M, Rambaldi B, Ravizzola G, Cattaneo C, Borlenghi E, Polverelli N, et al. Bacterial blood stream infections negatively impact on outcome of patients treated with allogeneic stem cell transplantation: 6 years single-centre experience. Mediterr J Hematol Infect Dis. 2017;9(1):e2017036.
39. Melzer M, Santhakumaran T, Welch C. The characteristics and outcome of bacteraemia in renal transplant recipients and non-transplant renal patients. Infection. 2016;44(5):617–22.
40. Mulcahy ME, McLoughlin RM. Staphylococcus aureus and influenza A virus: partners in coinfection. MBio. 2016;7(6):e02068–16.
41. Obed A, Schnitzbauer AA, Bein T, Lehn N, Linde HJ, Schlitt HJ. Fatal pneumonia caused by Panton-Valentine Leucocidine-positive methicillin-resistant Staphylococcus aureus (PVL-MRSA) transmitted from a healthy donor in living-donor liver transplantation. Transplantation. 2006;81(1):121–4.
42. Audard V, Pardon A, Claude O, Jablonski M, Remy P, Desvaux D, et al. Necrotizing fasciitis during de novo minimal change nephrotic syndrome in a kidney transplant recipient. Transpl Infect Dis. 2005;7(2):89–92.
43. Hachisuka H, Kimori K, Tsuge K. Methicillin-resistant Staphylococcus aureus arthritis of the wrist treated with arthrodesis using vascularized fibular transfer: a case report. J Reconstr Microsurg. 2007;23(5):289–94.
44. Ross JJ. Septic arthritis of native joints. Infect Dis Clin North Am. 2017;31(2):203–18.
45. Dudau D, Camous J, Marchand S, Pilorge C, Rézaiguia-Delclaux S, Libert JM, et al. Incidence of nosocomial pneumonia and risk of recurrence after antimicrobial therapy in critically ill lung and heart-lung transplant patients. Clin Transplant. 2014;28(1):27–36.
46. Malinis MF, Mawhorter SD, Jain A, Shrestha NK, Avery RK, van Duin D. Staphylococcus aureus bacteremia in solid organ transplant recipients: evidence for improved survival when compared with nontransplant patients. Transplantation. 2012;93(10):1045–50.
47. Florescu DF, McCartney AM, Qiu F, Langnas AN, Botha J, Mercer DF, et al. Staphylococcus aureus infections after liver transplantation. Infection. 2012;40(3):263–9.
48. Denniston S, Riordan FA. Staphylococcus aureus bacteraemia in children and neonates: a 10 year retrospective review. J Infect. 2006;53(6):387–93.
49. Malhotra-Kumar S, Haccuria K, Michiels M, Ieven M, Poyart C, Hryniewicz W, et al. Current trends in rapid diagnostics for methicillin-resistant Staphylococcus aureus and glycopeptide-resistant enterococcus species. J Clin Microbiol. 2008;46(5):1577–87.
50. Moellering RC Jr. Current treatment options for community-acquired methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis. 2008;46(7):1032–7.
51. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339(8):520–32.
52. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351(16):1645–54.
53. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001;32(9):1249–72.
54. Ruotsalainen E, Kardén-Lilja M, Kuusela P, Vuopio-Varkila J, Virolainen-Julkunen A, Sarna S, et al. Methicillin-sensitive Staphylococcus aureus bacteraemia and endocarditis among injection drug users and nonaddicts: host factors, microbiological and serological characteristics. J Infect. 2008;56(4):249–56.
55. Chang FY, Peacock JE Jr, Musher DM, Triplett P, MacDonald BB, Mylotte JM, et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore). 2003;82(5):333–9.
56. Safdar A, Rolston KV. Vancomycin tolerance, a potential mechanism for refractory gram-positive bacteremia observational study in patients with cancer. Cancer. 2006;106(8):1815–20.
57. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N Engl J Med. 2007;357(4):380–90.
58. Metzger R, Bonatti H, Sawyer R. Future trends in the treatment of serious Gram-positive infections. Drugs Today (Barc). 2009;45(1):33–45.
59. Liebenstein T, Schulz LT, Viesselmann C, Bingen E, Musuuza J, Safdar N, et al. Effectiveness and safety of tigecycline compared with other broad-spectrum antimicrobials in abdominal solid organ transplant recipients with polymicrobial intraabdominal infections. Pharmacotherapy. 2017;37(2):151–8.
60. Durante-Mangoni E, Andini R, Parrella A, Mattucci I, Cavezza G, Senese A, et al. Safety of treatment with high-dose daptomycin in 102 patients with infective endocarditis. Int J Antimicrob Agents. 2016;48(1):61–8.
61. Matono T, Nagashima M, Mezaki K, Motohashi A, Kutsuna S, Hayakawa K, et al. Molecular epidemiology of β-lactamase production in penicillin-susceptible Staphylococcus aureus under high-susceptibility conditions. J Infect Chemother. 2018;24(2):153–5.
62. Pea F. Daptomycin in solid organ transplantation: consideration of dosage adjustments in renal impairment. Transpl Infect Dis. 2014;16(5):868–9.
63. Len O, Montejo M, Cervera C, Fariñas MC, Sabé N, Ramos A, Cordero E, et al. Daptomycin is safe and effective for the treatment of gram-positive cocci infections in solid organ transplantation. Transpl Infect Dis. 2014;16(4):532–8.
64. Torre-Cisneros J, Martín-Dávila P, Azanza JR, Pahissa A, Gavaldà J, DAPTOSOT(Daptomycin in Solid Organ Transplantation) Study Group. Daptomycin is safe and effective for the treatment of gram-positive cocci infections in solid organ transplantation. Transpl Infect Dis. 2014;16(4):532–8.
65. Wood ME, Sherrard LJ, Ramsay KA, Yerkovich ST, Reid DW, Kidd TJ, et al. Methicillin-resistant Staphylococcus aureus acquisition in healthcare workers with cystic fibrosis: a retrospective cross-sectional study. BMC Pulm Med. 2016;16(1):78.
66. Samanipour A, Dashti-Khavidaki S, Abbasi MR, Abdollahi A. Antibiotic resistance patterns of microorganisms isolated from nephrology and kidney transplant wards of a referral academic hospital. J Res Pharm Pract. 2016;5(1):43–51.
67. Tessier JM, Puzio T, Young A, Wolfe L, Han J, Duane TM. Thrombocytopenia associated with linezolid therapy in solid organ transplant recipients: a retrospective cohort study. Surg Infect (Larchmt). 2015;16(4):361–7.
68. Radunz S, Juntermanns B, Kaiser GM, Treckmann J, Mathe Z, Paul A, et al. Efficacy and safety of linezolid in liver transplant patients. Transpl Infect Dis. 2011;13(4):353–8.
69. Vernadakis S, Saner FH, Rath PM, Kaiser GM, Mathe Z, Treckmann J, et al. Successful salvage therapy with daptomycin after linezolid and vancomycin failure in a liver transplant recipient with methicillin-resistant Staphylococcus aureus endocarditis. Transpl Infect Dis. 2009;11(4):346–8.
70. Hodille E, Rose W, Diep BA, Goutelle S, Lina G, Dumitrescu O. The role of antibiotics in modulating virulence in Staphylococcus aureus. Clin Microbiol Rev. 2017;30(4):887–917.
71. Kim AI, Adal KA, Schmitt SK. Staphylococcus aureus bacteremia: using echocardiography to guide length of therapy. Cleve Clin J Med. 2003;70(6):517, 520-1, 525-6.

72. Raber-Durlacher JE, Laheij AM, Epstein JB, Epstein M, Geerligs GM, Wolffe GN, et al. Periodontal status and bacteremia with oral viridans streptococci and coagulase negative staphylococci in allogeneic hematopoietic stem cell transplantation recipients: a prospective observational study. Support Care Cancer. 2013;21(6):1621–7.
73. Zakhour R, Chaftari AM, Raad II. Catheter-related infections in patients with haematological malignancies: novel preventive and therapeutic strategies. Lancet Infect Dis. 2016;16(11):e241–50.
74. Persson L, Strid H, Tidefelt U, Söderquist B. Phenotypic and genotypic characterization of coagulase-negative staphylococci isolated in blood cultures from patients with haematological malignancies. Eur J Clin Microbiol Infect Dis. 2006;25(5):299–309.
75. Argemi X, Hansmann Y, Riegel P, Prévost G. Is Staphylococcus lugdunensis significant in clinical samples? J Clin Microbiol. 2017;55(11):3167–74.
76. Nesher L, Tarrand J, Chemaly RF, Rolston KV. Staphylococcus lugdunensis infections, filling in the gaps: a 3-year retrospective review from a comprehensive cancer center. Support Care Cancer. 2017;25(4):1063–9.
77. Kozlowska-Skrzypczak M, Bembnista E, Kubiak A, Matuszak P, Schneider A, Komarnicki M. Microbial contamination of peripheral blood and bone marrow hematopoietic cell products and environmental contamination in a stem cell bank: a single-center report. Transplant Proc. 2014;46(8):2873–6.
78. Garcia-Zamora C, Segura J, Lopez-Lopez V, Salvador C, Cascales Campos PA, Pons Miñano JA, et al. Clinical significance of contamination of the preservation solution in liver transplantation. Transplant Proc. 2015;47(8):2322–3.
79. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infect Dis. 2002;2(11):677–85.
80. Pedroso SHSP, Sandes SHC, Luiz KCM, Dias RS, Filho RAT, Serufo JC, et al. Biofilm and toxin profile: a phenotypic and genotypic characterization of coagulase-negative staphylococci isolated from human bloodstream infections. Microb Pathog. 2016;100:312–8.
81. Paniagua-Contreras GL, Monroy-Pérez E, Vaca-Paniagua F, Rodríguez-Moctezuma JR, Vaca S. Expression of enterotoxin-coding genes in methicillin-resistant Staphylococcus aureus strains isolated from Mexican haemodialysis patients. Ann Clin Microbiol Antimicrob. 2014;13:55.
82. Paterson DL, Singh N, Gayowski T, Marino IR. Rapidly fatal bacteremia due to Staphylococcus aureus producing both enterotoxins A and B in a liver transplant recipient. Clin Infect Dis. 1997;25(6):1481–2.
83. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis. 2007;7(10):645–57.
84. Yusuf SW, Ali SS, Swafford J, Durand JB, Bodey GP, Chemaly RF, et al. Culture-positive and culture-negative endocarditis in patients with cancer: a retrospective observational study, 1994–2004. Medicine (Baltimore). 2006;85(2):86–94.
85. Cecchi E, Chirillo F, Castiglione A, Faggiano P, Cecconi M, Moreo A, et al. Clinical epidemiology in Italian Registry of Infective Endocarditis(RIEI): focus on age, intravascular devices and enterococci. Int J Cardiol. 2015;190:151–6.
86. Arnell K, Cesarini K, Lagerqvist-Widh A, Wester T, Sjölin J. Cerebrospinal fluid shunt infections in children over a 13-year period: anaerobic cultures and comparison of clinical signs of infection with Propionibacterium acnes and with other bacteria. J Neurosurg Pediatr. 2008;1(5):366–72.
87. Adams DJ, Rajnik M. Microbiology and treatment of cerebrospinal fluid shunt infections in children. Curr Infect Dis Rep. 2014;16(10):427.
88. Barrett L, Atkins B. The clinical presentation of prosthetic joint infection. J Antimicrob Chemother. 2014;69(Suppl 1):i25–7.
89. Beekmann SE, Diekema DJ, Doern GV. Determining the clinical significance of coagulase-negative staphylococci isolated from blood cultures. Infect Control Hosp Epidemiol. 2005;26(6):559–66.
90. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001;32(9):1249–72.
91. Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C, Muñoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis. 2007;44(6):820–6.
92. de Oliveira A, Cataneli Pereira V, Pinheiro L, Moraes Riboli DF, Benini Martins K, Ribeiro de Souza da Cunha Mde L. Antimicrobial resistance profile of planktonic and biofilm cells of Staphylococcus aureus and coagulase-negative staphylococci. Int J Mol Sci. 2016;17(9):pii:E1423.
93. Mutnick AH, Kirby JT, Jones RN. CANCER resistance surveillance program: initial results from hematology-oncology centers in North America. Chemotherapy Alliance for Neutropenics and the Control of Emerging Resistance. Ann Pharmacother. 2003;37(1):47–56.
94. García de la Mària C, Cervera C, Pericàs JM, Castañeda X, Armero Y, Soy D, et al. Epidemiology and prognosis of coagulase-negative staphylococcal endocarditis: impact of vancomycin minimum inhibitory concentration. PLoS One. 2015;10(5):e0125818.
95. Decousser JW, Desroches M, Bourgeois-Nicolaos N, Potier J, Jehl F, Lina G, et al. Susceptibility trends including emergence of linezolid resistance among coagulase-negative staphylococci and meticillin-resistant Staphylococcus aureus from invasive infections. Int J Antimicrob Agents. 2015;46(6):622–30.
96. Chu V, Miro JM, Hoen B, Cabell CH, Pappas PA, Jones P, et al. Coagulase-negative staphylococcal prosthetic valve endocarditis: a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study. Heart. 2009;95(7):570–6.
97. Karchmer AW, Archer GL, Dismukes WE. Rifampin treatment of prosthetic valve endocarditis due to Staphylococcus epidermidis. Rev Infect Dis. 1983;5(Suppl 3):S543–8.
98. Stuart JI, John MA, Milburn S, Diagre D, Wilson B, Hussain Z. Susceptibility patterns of coagulase-negative staphylococci to several newer antimicrobial agents in comparison with vancomycin and oxacillin. Int J Antimicrob Agents. 2011;37(3):248–52.
99. Ortega M, Ortega M, Rovira M, Almela M, Marco F, de la Bellacasa JP, Martínez JA, et al. Bacterial and fungal bloodstream isolates from 796 hematopoietic stem cell transplant recipients between 1991 and 2000. Ann Hematol. 2005;84(1):40–6.
100. Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis. 1997;25(2):247–59.
101. Facklam R. What happened to the streptococci: overview of taxonomic and nomenclature changes. Clin Microbiol Rev. 2002;15(4):613–30.
102. Johnson CC, Tunkel AR. Viridans group streptococci, groups C and G streptococci, and Gemella morbilliform. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2434–50.
103. Han XY, Kamana M, Rolston KV. Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. J Clin Microbiol. 2006;44(1):160–5.
104. Husain E, Whitehead S, Castell A, Thomas EE, Speert DP. Viridans streptococci bacteremia in children with malignancy: relevance of species identification and penicillin susceptibility. Pediatr Infect Dis J. 2005;24(6):563–6.

105. Lyytikainen O, Rautio M, Carlson P, Anttila VJ, Vuento R, Sarkkinen H, et al. Nosocomial bloodstream infections due to viridans streptococci in haematological and non-haematological patients: species distribution and antimicrobial resistance. J Antimicrob Chemother. 2004;53(4):631–4.
106. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, et al. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA. 2005;293(24):3012–21.
107. Nielsen MJ, Claxton S, Pizer B, Lane S, Cooke RP, Paulus S, et al. Viridans group streptococcal infections in children after chemotherapy or stem cell transplantation: a 10-year review from a Tertiary Pediatric Hospital. Medicine (Baltimore). 2016;95(9):e2952.
108. Almyroudis NG, Fuller A, Jakubowski A, Sepkowitz K, Jaffe D, Small TN, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis. 2005;7(1):11–7.
109. Richard P, Amador Del Valle G, Moreau P, Milpied N, Felice MP, Daeschler T, et al. Viridans streptococcal bacteraemia in patients with neutropenia. Lancet. 1995;345(8965):1607–9.
110. Prabhu RM, Piper KE, Litzow MR, Steckelberg JM, Patel R. Emergence of quinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving quinolone antimicrobial prophylaxis. Eur J Clin Microbiol Infect Dis. 2005;24(12):832–8.
111. Marron A, Carratala J, Gonzalez-Barca E, Fernandez-Sevilla A, Alcaide F, Gudiol F. Serious complications of bacteremia caused by viridans streptococci in neutropenic patients with cancer. Clin Infect Dis. 2000;31(5):1126–30.
112. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis. 1992;14(6):1201–7.
113. Ohuoba EF, Kansal RG, Hayden RT, Kotb M, Adderson EE. Failure of viridans group streptococci causing bacteremia in pediatric oncology patients to express superantigens. J Pediatr Hematol Oncol. 2006;28(9):627–9.
114. Paterson DL, Dominguez EA, Chang FY, Snydman DR, Singh N. Infective endocarditis in solid organ transplant recipients. Clin Infect Dis. 1998;26(3):689–94.
115. Stelzmueller I, Berger N, Wiesmayr S, Eller M, Tabarelli W, Fille M, et al. Group milleri streptococci: significant pathogens in solid organ recipients. Transpl Int. 2007;20(1):51–6.
116. Stelzmueller I, Biebl M, Berger N, Eller M, Mendez J, Fille M, et al. Relevance of group Milleri streptococci in thoracic surgery: a clinical update. Am Surg. 2007;73(5):492–7.
117. Richter SS, Beekmann SE, Croco JL, Diekema DJ, Koontz FP, Pfaller MA, et al. Minimizing the workup of blood culture contaminants: implementation and evaluation of a laboratory-based algorithm. J Clin Microbiol. 2002;40(7):2437–44.
118. Huang WT, Chang LY, Hsueh PR, Lu CY, Shao PL, Huang FY, et al. Clinical features and complications of viridans streptococci bloodstream infection in pediatric hemato-oncology patients. J Microbiol Immunol Infect. 2007;40(4):349–54.
119. Collin BA, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. Clin Infect Dis. 2001;33(7):947–53.
120. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis. 2002;34(11):1524–9.
121. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34(6):730–51.
122. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R. Bacteremia due to viridans group streptococci with diminished susceptibility to levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. Clin Infect Dis. 2002;34(11):1469–74.
123. Sylvetsky N, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM. Bacteremia due to beta-hemolytic Streptococcus group G: increasing incidence and clinical characteristics of patients. Am J Med. 2002;112(8):622–6.
124. Nielsen HU, Kolmos HJ, Frimodt-Moller N. Beta-hemolytic streptococcal bacteremia: a review of 241 cases. Scand J Infect Dis. 2002;34(7):483–6.
125. Colford JM Jr, Mohle-Boetani J, Vosti KL. Group B streptococcal bacteremia in adults. Five years' experience and a review of the literature. Medicine (Baltimore). 1995;74(4):176–90.
126. Bisno AL, Ruoff KL. Streptococcus pyogenes. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2362–79.
127. Peter G, Smith AL. Group A streptococcal infections of the skin and pharynx (second of two parts). N Engl J Med. 1977;297(7):365–70.
128. Peter G, Smith AL. Group A streptococcal infections of the skin and pharynx (first of two parts). N Engl J Med. 1977;297(6):311–7.
129. Edwards MS, Rench MA, Palazzi DL, Baker CJ. Group B streptococcal colonization and serotype-specific immunity in healthy elderly persons. Clin Infect Dis. 2005;40(3):352–7.
130. McDonald MI, Towers RJ, Andrews RM, Benger N, Currie BJ, Carapetis JR. Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian aboriginal communities where acute rheumatic fever is hyperendemic. Clin Infect Dis. 2006;43(6):683–9.
131. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, et al. Epidemiology of severe Streptococcus pyogenes disease in Europe. J Clin Microbiol. 2008;46(7):2359–67.
132. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. JAMA. 2008;299(17):2056–65.
133. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. Am J Med. 1992;93(5):543–8.
134. Awada A, van der Auwera P, Meunier F, Daneau D, Klastersky J. Streptococcal and enterococcal bacteremia in patients with cancer. Clin Infect Dis. 1992;15(1):33–48.
135. Ekelund K, Skinhoj P, Madsen J, Konradsen HB. Invasive group A, B, C and G streptococcal infections in Denmark 1999–2002: epidemiological and clinical aspects. Clin Microbiol Infect. 2005;11(7):569–76.
136. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. Clin Infect Dis. 2007;45(2):228–33.
137. Gabillot-Carre M, Roujeau JC. Acute bacterial skin infections and cellulitis. Curr Opin Infect Dis. 2007;20(2):118–23.
138. Bonnetblanc JM, Bedane C. Erysipelas: recognition and management. Am J Clin Dermatol. 2003;4(3):157–63.
139. Wong CH, Wang YS. The diagnosis of necrotizing fasciitis. Curr Opin Infect Dis. 2005;18(2):101–6.
140. Solis-Garcia del Pozo J, Martinez-Alfaro E, Abad L, Solera J. Vertebral osteomyelitis caused by Streptococcus agalactiae. J Infect. 2000;41(1):84–90.
141. Minodier P, Bidet P, Rallu F, Tapiero B, Bingen E, Ovetchkine P. Clinical and microbiologic characteristics of group A streptococcal necrotizing fasciitis in children. Pediatr Infect Dis J. 2009;28(6):541–3.
142. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of

group A streptococcal pharyngitis. Infectious Diseases Society of America. Clin Infect Dis. 2002;35(2):113–25.
143. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA. 1993;269(3):390–1.
144. Shet A, Kaplan EL. Clinical use and interpretation of group A streptococcal antibody tests: a practical approach for the pediatrician c. Pediatr Infect Dis J. 2002;21(5):420–6; quiz 427–30.
145. Kaplan EL. Recent evaluation of antimicrobial resistance in beta-hemolytic streptococci. Clin Infect Dis. 1997;24(Suppl 1):89–92.
146. Sodhi M, Axtell SS, Callahan J, Shekar R. Is it safe to use carbapenems in patients with a history of allergy to penicillin? J Antimicrob Chemother. 2004;54(6):1155–7.
147. Martin JM, Green M, Barbadora KA, Wald ER. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. N Engl J Med. 2002;346(16):1200–6.
148. Ayer V, Tewodros W, Manoharan A, Skariah S, Luo F, Bessen DE. Tetracycline resistance in group A streptococci: emergence on a global scale and influence on multiple-drug resistance. Antimicrob Agents Chemother. 2007;51(5):1865–8.
149. Traub WH, Leonhard B. Comparative susceptibility of clinical group A, B, C, F, and G beta-hemolytic streptococcal isolates to 24 antimicrobial drugs. Chemotherapy. 1997;43(1):10–20.
150. King A, Phillips I. The in vitro activity of daptomycin against 514 Gram-positive aerobic clinical isolates. J Antimicrob Chemother. 2001;48(2):219–23.
151. Jones RN, Ross JE, Castanheira M, Mendes RE. United States resistance surveillance results for linezolid (LEADER Program for 2007). Diagn Microbiol Infect Dis. 2008;62(4):416–26.
152. Russell NE, Pachorek RE. Clindamycin in the treatment of streptococcal and staphylococcal toxic shock syndromes. Ann Pharmacother. 2000;34(7–8):936–9.
153. Garcia-Rodriguez JA, Fresnadillo Martinez MJ. Dynamics of nasopharyngeal colonization by potential respiratory pathogens. J Antimicrob Chemother. 2002;50(Suppl S2):59–73.
154. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
155. Scarborough M, Gordon SB, Whitty CJ, French N, Njalale Y, Chitani A, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med. 2007;357(24):2441–50.
156. Torda A, Chong Q, Lee A, Chen S, Dodds A, Greenwood M, et al. Invasive pneumococcal disease following adult allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2014;16(5):751–9.
157. Youssef S, Rodriguez G, Rolston KV, Champlin RE, Raad II, Safdar A. Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989–2005. Medicine (Baltimore). 2007;86(2):69–77.
158. Kyaw MH, Rose CE Jr, Fry AM, Singleton JA, Moore Z, Zell ER, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis. 2005;192(3):377–86.
159. Kulkarni S, Powles R, Treleaven J, Riley U, Singhal S, Horton C, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. Blood. 2000;95(12):3683–6.
160. Engelhard D, Cordonnier C, Shaw PJ, Parkalli T, Guenther C, Martino R, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. Br J Haematol. 2002;117(2):444–50.
161. Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL, AGEDD Adult Pneumococcal Burden Study Team, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One. 2013;8(4):e60273.
162. Principi N, Marchisio P, Rosazza C, Sciarrabba CS, Esposito S. Acute otitis media with spontaneous tympanic membrane perforation. Eur J Clin Microbiol Infect Dis. 2017;36(1):11–8.
163. Nicolini A, Cilloniz C, Senarega R, Ferraioli G, Barlascini C. Lung abscess due to Streptococcus pneumoniae: a case series and brief review of the literature. Pneumonol Alergol Pol. 2014;82(3):276–85.
164. Reyes LF, Restrepo MI, Hinojosa CA, Soni NJ, Anzueto A, Babu BL, et al. Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent cardiac remodeling. Am J Respir Crit Care Med. 2017;196(5):609–20.
165. Ross JJ, Hu LT. Septic arthritis of the pubic symphysis: review of 100 cases. Medicine (Baltimore). 2003;82(5):340–5.
166. Siddiq DM, Musher DM, Darouiche RO. Spinal and paraspinal pneumococcal infections-a review. Eur J Clin Microbiol Infect Dis. 2014;33(4):517–27.
167. Kutas LM, Duggan JM, Kauffman CA. Pneumococcal vertebral osteomyelitis. Clin Infect Dis. 1995;20(2):286–90.
168. Suzuki H, Shichi D, Tokuda Y, Ishikawa H, Maeno T, Nakamura H. Pneumococcal vertebral osteomyelitis at three teaching hospitals in Japan, 2003–2011: analysis of 14 cases and a review of the literature. BMC Infect Dis. 2013;13:525.
169. Gudiol C, Garcia-Vidal C, Arnan M, Sánchez-Ortega I, Patiño B, Duarte R, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. Bone Marrow Transplant. 2014;49(6):824–30.
170. Aguilar-Guisado M, Jiménez-Jambrina M, Espigado I, Rovira M, Martino R, Oriol A, et al. Pneumonia in allogeneic stem cell transplantation recipients: a multicenter prospective study. Clin Transplant. 2011;25(6):E629–38.
171. D'Orsogna LJ, Wright MP, Krueger RG, McKinnon EJ, Buffery SI, Witt CS, et al. Allogeneic hematopoietic stem cell transplantation recipients have defects of both switched and igm memory B cells. Biol Blood Marrow Transplant. 2009;15(7):795–803.
172. Kumar D, Humar A, Plevneshi A, Siegal D, Franke N, Green K, et al. Invasive pneumococcal disease in adult hematopoietic stem cell transplant recipients: a decade of prospective population-based surveillance. Bone Marrow Transplant. 2008;41(8):743–7.
173. Kurosawa S, Doki N, Sekiya N, Senoo Y, Ikuta S, Takaki Y, et al. Pyomyositis caused by Streptococcus pneumoniae after allogeneic hematopoietic stem cell transplantation. J Infect Chemother. 2017;23(4):250–2.
174. Kumar D, Humar A, Plevneshi A, Green K, Prasad GV, Siegal D, et al. Invasive pneumococcal disease in solid organ transplant recipients–10-year prospective population surveillance. Am J Transplant. 2007;7(5):1209–14.
175. Rostad CA, Wehrheim K, Kirklin JK, Naftel D, Pruitt E, Hoffman TM, et al. Bacterial infections after pediatric heart transplantation: Epidemiology, risk factors and outcomes. J Heart Lung Transplant. 2017;36(9):996–1003.
176. van Veen KE, Brouwer MC, van der Ende A, van de Beek D. Bacterial meningitis in solid organ transplant recipients: a population-based prospective study. Transpl Infect Dis. 2016;18(5):674–80.
177. Bahrami T, Vohra HA, Shaikhrezai K, Tadjkarimi S, Banner N, Amrani M, et al. Intrathoracic organ transplantation from donors with meningitis: a single-center 20-year experience. Ann Thorac Surg. 2008;86(5):1554–6.
178. Kim SY, Shin JA, Cho EN, Byun MK, Kim HJ, Ahn CM, et al. Late respiratory infection after lung transplantation. Tuberc Respir Dis (Seoul). 2013;74(2):63–9.

179. Pérez-Cameo C, Vargas V, Castells L, Bilbao I, Campos-Varela I, Gavaldà J, et al. Etiology and mortality of spontaneous bacterial peritonitis in liver transplant recipients: a cohort study. Liver Transpl. 2014;20(7):856–63.
180. Satoi S, Bramhall SR, Solomon M, Hastings M, Mayer AD, de Goyet JV, et al. The use of liver grafts from donors with bacterial meningitis. Transplantation. 2001;72(6):1108–13.
181. Le Monnier A, Carbonnelle E, Zahar JR, Le Bourgeois M, Abachin E, Quesne G, et al. Microbiological diagnosis of empyema in children: comparative evaluations by culture, polymerase chain reaction, and pneumococcal antigen detection in pleural fluids. Clin Infect Dis. 2006;42(8):1135–40.
182. Musher DM. Streptococcus pneumoniae. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2392–410.
183. Klugman KP, Madhi SA, Albrich WC. Novel approaches to the identification of Streptococcus pneumoniae as the cause of community-acquired pneumonia. Clin Infect Dis. 2008;47(Suppl 3):S202–6.
184. Centers for Disease Control and Prevention (CDC). Effects of new penicillin susceptibility breakpoints for Streptococcus pneumoniae–United States, 2006–2007. MMWR Morb Mortal Wkly Rep. 2008;57(50):1353–5.
185. Fernandez J, Hilliard JJ, Morrow BJ, Melton JL, Flamm RK, Barron AM, et al. Efficacy of a new fluoroquinolone, JNJ-Q2, in murine models of Staphylococcus aureus and Streptococcus pneumoniae skin, respiratory, and systemic infections. Antimicrob Agents Chemother. 2011;55(12):5522–8.
186. Hameed N, Tunkel AR. Treatment of drug-resistant Pneumococcal Meningitis. Curr Infect Dis Rep. 2010;12(4):274–81.
187. Sahm DF, Brown NP, Draghi DC, Evangelista AT, Yee YC, Thornsberry C. Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001–2005. Postgrad Med. 2008;120(3 Suppl 1):8–15.
188. San Pedro GS, Cammarata SK, Oliphant TH, Todisco T, Linezolid Community-Acquired Pneumonia Study Group. Linezolid versus ceftriaxone/cefpodoxime in patients hospitalized for the treatment of Streptococcus pneumoniae pneumonia. Scand J Infect Dis. 2002;34(10):720–8.
189. Moschovi M, Trimis G, Tsotra M, Chatzi F, Karamolegou K, Santou A, et al. Efficacy and safety of linezolid in immunocompromised children with cancer. Pediatr Int. 2010;52(5):694–8.
190. Breslow-Deckman JM, Mattingly CM, Birket SE, Hoskins SN, Ho TN, Garvy BA, et al. Linezolid decreases susceptibility to secondary bacterial pneumonia postinfluenza infection in mice through its effects on IFN-γ. J Immunol. 2013;191(4):1792–9.
191. Baltz RH. Daptomycin: mechanisms of action and resistance, and biosynthetic engineering. Curr Opin Chem Biol. 2009;13(2):144–51.
192. Webb BJ, Healy R, Majers J, Burr Z, Gazdik M, Lopansri B, et al. Prediction of bloodstream infection due to vancomycin-resistant Enterococcus in patients undergoing leukemia induction or hematopoietic stem-cell transplantation. Clin Infect Dis. 2017;64(12):1753–9.
193. Ghanem G, Hachem R, Jiang Y, Chemaly RF, Raad I. Outcomes for and risk factors associated with vancomycin-resistant Enterococcus faecalis and vancomycin-resistant Enterococcus faecium bacteremia in cancer patients. Infect Control Hosp Epidemiol. 2007;28(9):1054–9.
194. Ford CD, Gazdik Stofer MA, Coombs J, Lopansri BK, Webb BJ, Motyckova G, et al. Decrease in vancomycin-resistant Enterococcus colonization after extensive renovation of a unit dedicated to the treatment of hematologic malignancies and hematopoietic stem-cell transplantation. Infect Control Hosp Epidemiol. 2017;38(9):1055–61.
195. Almyroudis NG, Osawa R, Samonis G, Wetzler M, Wang ES, McCarthy PL, et al. Discontinuation of systematic surveillance and contact precautions for Vancomycin-Resistant Enterococcus (VRE) and its impact on the incidence of VRE faecium bacteremia in patients with hematologic malignancies. Infect Control Hosp Epidemiol. 2016;37(4):398–403.
196. Ford CD, Lopansri BK, Gazdik MA, Webb B, Snow GL, Hoda D, et al. Room contamination, patient colonization pressure, and the risk of vancomycin-resistant Enterococcus colonization on a unit dedicated to the treatment of hematologic malignancies and hematopoietic stem cell transplantation. Am J Infect Control. 2016;44(10):1110–5.
197. Ford CD, Gazdik MA, Lopansri BK, Webb B, Mitchell B, Coombs J, et al. Vancomycin-resistant Enterococcus colonization and bacteremia and hematopoietic stem cell transplantation outcomes. Biol Blood Marrow Transplant. 2017;23(2):340–6.
198. Hefazi M, Damlaj M, Alkhateeb HB, Partain DK, Patel R, Razonable RR, et al. Vancomycin-resistant Enterococcus colonization and bloodstream infection: prevalence, risk factors, and the impact on early outcomes after allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. Transpl Infect Dis. 2016;18(6):913–20.
199. Tavadze M, Rybicki L, Mossad S, Avery R, Yurch M, Pohlman B, et al. Risk factors for vancomycin-resistant enterococcus bacteremia and its influence on survival after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2014;49(10):1310–6.
200. Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, et al. The changing epidemiology of vancomycin-resistant Enterococcus (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Biol Blood Marrow Transplant. 2010;16(11):1576–81.
201. Ford CD, Lopansri BK, Gazdik MA, Snow GL, Webb BJ, Konopa KL, Petersen FB. The clinical impact of vancomycin-resistant Enterococcus colonization and bloodstream infection in patients undergoing autologous transplantation. Transpl Infect Dis. 2015;17(5):688–94.
202. Staffas A, Burgos da Silva M, van den Brink MR. The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease. Blood. 2017;129(8):927–33.
203. Mendes ET, Ranzani OT, Marchi AP, Silva MT, Filho JU, Alves T, et al. Chlorhexidine bathing for the prevention of colonization and infection with multidrug-resistant microorganisms in a hematopoietic stem cell transplantation unit over a 9-year period: Impact on chlorhexidine susceptibility. Medicine (Baltimore). 2016;95(46):e5271.
204. Trifilio SM, Pi J, Mehta J. Changing epidemiology of Clostridium difficile-associated disease during stem cell transplantation. Biol Blood Marrow Transplant. 2013;19(3):405–9.
205. Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, et al. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest. 2010;120(12):4332–41.
206. Patel R, Badley AD, Larson-Keller J, Harmsen WS, Ilstrup DM, Wiesner RH, et al. Relevance and risk factors of enterococcal bacteremia following liver transplantation. Transplantation. 1996;61(8):1192–7.
207. Patel R, Allen SL, Manahan JM, Wright AJ, Krom RA, Wiesner RH, et al. Natural history of vancomycin-resistant enterococcal colonization in liver and kidney transplant recipients. Liver Transpl. 2001;7(1):27–31.
208. Singh N, Gayowski T, Rihs JD, Wagener MM, Marino IR. Evolving trends in multiple-antibiotic-resistant bacteria in liver transplant recipients: a longitudinal study of antimicrobial susceptibility patterns. Liver Transpl. 2001;7(1):22–6.

209. Papanicolaou GA, Meyers BR, Meyers J, Mendelson MH, Lou W, Emre S, et al. Nosocomial infections with vancomycin-resistant Enterococcus faecium in liver transplant recipients: risk factors for acquisition and mortality. Clin Infect Dis. 1996;23(4):760–6.
210. McNeil SA, Malani PN, Chenoweth CE, Fontana RJ, Magee JC, Punch JD, et al. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. Clin Infect Dis. 2006;42(2):195–203.
211. Linares L, Cervera C, Cofán F, Ricart MJ, Esforzado N, Torregrosa V, et al. Epidemiology and outcomes of multiple antibiotic-resistant bacterial infection in renal transplantation. Transplant Proc. 2007;39(7):2222–4.
212. Simon D, Fischer S, Grossman A, Downer C, Hota B, Heroux A, et al. Left ventricular assist device-related infection: treatment and outcome. Clin Infect Dis. 2005;40(8):1108–15.
213. Murray BE. Vancomycin-resistant enterococcal infections. N Engl J Med. 2000;342(10):710–21.
214. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore). 1988;67(4):248–69.
215. Fry DE. Third generation cephalosporin antibiotics in surgical practice. Am J Surg. 1986;151(2):306–13.
216. Weinstein MP. Comparative evaluation of penicillin, ampicillin, and imipenem MICs and susceptibility breakpoints for vancomycin-susceptible and vancomycin-resistant Enterococcus faecalis and Enterococcus faecium. J Clin Microbiol. 2001;39(7):2729–31.
217. Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. Diagn Microbiol Infect Dis. 2007;58(2):163–70.
218. Kristich CJ, Rice LB, Arias CA. Enterococcal infection—treatment and antibiotic resistance. In: Gilmore MS, Clewell DB, Ike Y, Shankar N, editors. Enterococci: from commensals to leading causes of drug resistant infection [Internet]. Boston: Massachusetts Eye and Ear Infirmary; 2014. Available from http://www.ncbi.nlm.nih.gov/books/NBK190420/PubMed.
219. Frasca KL, Schuster MG. Vancomycin-resistant enterococcal meningitis in an autologous stem cell transplant recipient cured with linezolid. Transpl Infect Dis. 2013;15(1):E1–4.
220. Krull M, Klare I, Ross B, Trenschel R, Beelen DW, Todt D, et al. Emergence of linezolid- and vancomycin-resistant Enterococcus faecium in a department for hematologic stem cell transplantation. Antimicrob Resist Infect Control. 2016;5:31.
221. Santayana EM, Grim SA, Janda WM, Layden JE, Lee TA, Clark NM. Risk factors and outcomes associated with vancomycin-resistant Enterococcus infections with reduced susceptibilities to linezolid. Diagn Microbiol Infect Dis. 2012;74(1):39–42.
222. Wudhikarn K, Gingrich RD, de Magalhaes Silverman M. Daptomycin nonsusceptible enterococci in hematologic malignancy and hematopoietic stem cell transplant patients: an emerging threat. Ann Hematol. 2013;92(1):129–31.
223. Grim SA, Hong I, Freeman J, Edwards C, Clark NM. Daptomycin for the treatment of vancomycin-resistant enterococcal infections. J Antimicrob Chemother. 2009;63(2):414–6.
224. Chong PP, van Duin D, Bangdiwala A, Ivanova A, Miller WC, Weber DJ, et al. Vancomycin-resistant Enterococcal bloodstream infections in hematopoietic stem cell transplant recipients and patients with hematologic malignancies: impact of daptomycin MICs of 3 to 4 mg/L. Clin Ther. 2016;38(11):2468–76.