Abstract  
Gram-positive bacteria are a diverse group of organisms that are a major source of morbidity and mortality in patients with cancer. The increasing use of long-term indwelling central catheters and cytotoxic chemotherapies has contributed to the emergence of Gram-positive bacteria as the leading cause of bacteremia in cancer patients. These organisms are also among the foremost causes of pneumonia, skin and soft-tissue infections, osteomyelitis, and central nervous system infections in cancer patients. Gram-positive organisms have a remarkable ability to develop resistance to many of the currently available antimicrobials, but the predilection to become antimicrobial resistant varies substantially for particular organisms and for individual antimicrobial agents. Therefore physicians treating cancer patients need to be familiar with the common clinical manifestations, complications, and treatment options for a wide variety of diseases caused by Gram-positive bacteria.

Keywords  
Staphylococcus aureus • Streptococcal, pneumococcal, and enterococcal Infections • Cancer • Antibiotic resistance

Historical Perspective

Historically, Gram-negative rods were the predominant bacterial pathogens causing invasive disease in patients with cancer [1, 2]. However, a major rise in the incidence of Gram-positive infections occurred in the mid- to late-1980s such that Gram-positive organisms now cause the majority of invasive bacterial disease in patients with cancer (Fig. 35.1) [3–13]. Reasons for the increase in Gram-positive infections include, but are not limited to, antimicrobial prophylaxis strategies, increased use of long-term in-dwelling catheters, and advances in chemotherapeutic regimens [5, 14, 15]. Regardless of the causal factors for the escalation of Gram-positive infections, physicians caring for patients with cancer need to be familiar with the epidemiology and clinical manifestations of, and the treatment options for, infections due to Gram-positive bacteria. In this chapter, we will examine the major Gram-positive bacterial genera that cause invasive disease in cancer patients (Table 35.1).

Staphylococci

Staphylococci are the predominant Gram-positive pathogens causing serious infections in patients with cancer (Fig. 35.2) [16–19]. Staphylococci can be divided into two main classes depending on their ability to coagulate rabbit plasma, with Staphylococcus aureus being coagulase positive and the remainder of species grouped together as coagulase-negative staphylococci (CNS). S. aureus has the ability to cause a broad array of serious diseases, whereas CNS are plainly less virulent pathogens [20, 21].

Staphylococcus aureus

Epidemiology

S. aureus is a common commensal that can be isolated at any given time from 20 to 40% of humans [22, 23]. S. aureus is a leading cause of both community-onset and nosocomial infections and is commonly divided into methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) depending on sensitivity to β-lactam antimicrobials [24]. Prior to 2000, a reasonable rule of thumb was that MSSA caused disease in the community whereas MRSA caused nosocomial infections [25]. The rise of community-associated MRSA (CA-MRSA), however, in many parts of the world means that MRSA now causes the majority of S. aureus disease in...
both the community and healthcare settings, including patients with cancer [26–28].

Most invasive *S. aureus* disease in patients with cancer occurs when mechanical defense barriers are breached, for example due to breaks in the skin resulting from catheter placement or bypassing of airway defenses by the insertion of an endotracheal tube [29]. Compared to the general population, patients with cancer have a nearly 13-fold increase of invasive disease due to *S. aureus* with major additional risk factors including graft-versus-host disease, receipt of corticosteroids, surgery, mechanical ventilation, neutropenia, diabetes mellitus, and hemodialysis [29–31].

Clinical Manifestations/Diagnosis

Although many *S. aureus* infections are confined to the skin and soft-tissue, a considerable number of patients, especially

### Table 35.1 Summary of major Gram-positive pathogens causing invasive infections in patients with cancer

| Bacteria                     | Risk factors                                                                 | Typical infections                                                                 | Treatment options                          | Comments                                      |
|------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------|
| *Staphylococcus aureus*      | Breaks in skin, mechanical ventilation, and indwelling venous catheters      | Skin and soft-tissue infection, pneumonia, osteomyelitis, and catheter-related bacteremia | β-lactams, vancomycin                      | Surgical intervention often necessary         |
| Coagulase-negative staphylococci | Indwelling venous catheters and prosthetic devices                        | Catheter-related bacteremia and prosthetic device infection                    | Vancomycin                                 | Generally cause healthcare related infections |
| Viridans group streptococci | Neutropenia and mucositis                                                   | Septicemia and pneumonia                                                          | β-lactams, vancomycin                      | Cause of septic shock in neutropenic patients |
| β-hemolytic streptococci     | Breaks in skin and chronic disease                                          | Skin and soft-tissue infection, septic shock, and osteomyelitis                  | Penicillin                                  | Surgical intervention needed for necrotizing soft tissue infections |
| *Streptococcus pneumoniae*   | Chronic medical diseases, impaired immunoglobulin production                | Pneumonia and meningitis                                                          | β-lactams, vancomycin, and fluoroquinolones | Consider vaccination                          |
| Enterococci                  | Broad-spectrum antimicrobials, surgery, and prolonged hospital stay         | Catheter-related bacteremia and catheter-related urinary tract infections        | β-lactams, vancomycin; Q/D, a and daptomycin for VRE a | Low virulence pathogens                      |

a* Q/D quinupristin/dalfopristin
b* VRE vancomycin resistant enterococci

---

**Fig. 35.1** Data demonstrating percent of infection in patients with neutropenia caused by Gram-negative (gray bars) and Gram-positive (black bars) bacteria. Note the increase in Gram-positive infection beginning in mid-1980s. Data graphs are single organism bacteremias in International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer trials of febrile neutropenia. Reprinted with permission from ref. [3]
Management of Gram-Positive Bacterial Disease

those who are immune-compromised, develop more invasive disease [4, 24]. *S. aureus* is a leading cause of catheter-related bacteremia, prosthetic joint infections, and postsurgical infections [21]. Among patients with cancer, suppurative complications such as infective endocarditis, bacteremic pneumonia, and osteomyelitis often result from *S. aureus* bacteremia [32, 33]. Necrotizing pneumonia due to *S. aureus* in patients with malignancy usually occurs in mechanically-ventilated patients, but can affect healthy patients in the community especially following an antecedent influenza infection or in patients with long-term in-dwelling catheters (Fig. 35.3) [34, 35]. The rise of CA-MRSA has been especially concerning given that CA-MRSA isolates can cause devastating invasive infection such as necrotizing fascitis and necrotizing pneumonia even in otherwise healthy hosts and more so in patients with cancer [36]. *S. aureus* is commonly isolated from cancer patients with pyomyositis, septic arthritis, and septic bursitis either as a result of contiguous infection or hematogenous seeding [32].

The diagnosis of *S. aureus* infection is relatively straightforward as the organism is hardy, grows well in the microbiology laboratory, and is easily identified. The isolation of *S. aureus* from a sterile site should almost always be taken as evidence of invasive disease with the exception that, on occasion, *S. aureus* may contaminate blood cultures [37]. In light of the propensity of *S. aureus* to colonize, the isolation of *S. aureus* from nonsterile samples such as an endotracheal aspirate does not, in and of itself, indicate an infectious process [38]. Serologic or antigen assays have not proven to be clinically helpful in the diagnosis of an *S. aureus* infection.

### Treatment

Therapy of *S. aureus* disease consists of a combination approach involving antimicrobials and surgical drainage when indicated [39]. The importance of drainage of pus and/or surgical removal of dead tissue cannot be overemphasized as many patients will respond to surgery alone, whereas few patients will be cured with antimicrobials alone when pus is undrained or nonviable tissue is present [40, 41]. Similarly if foreign-material, such as an indwelling venous catheter or an infected prosthetic joint, remains in place, then therapeutic success rates are markedly reduced [42, 43].

Antibiotic treatment of *S. aureus* infection is complicated by extensive antimicrobial resistance. When the organism is sensitive, β-lactam antibiotics are the drugs of choice for *S. aureus* infections with typically used agents including nafcillin, oxacillin, and cefazolin [44–46]. Optimal treatment for invasive MRSA infections is an area of intense debate with the most experience having been accumulated with vancomycin [47]. Treatment of bacteremic MRSA infection with vancomycin is associated with a substantial failure rate – perhaps 15–20%, although overt vancomycin resistance is not responsible [48]. These failures have motivated a search for alternative anti-MRSA agents [49, 50] and, during the past decade, new drugs active against MRSA have been developed including quinupristin-dalfopristin, linezolid, tigecycline, and daptomycin [49–52]. Each of these agents has significant limitations and none has been proven superior to vancomycin in a clinical trial setting.

The duration of therapy for *S. aureus* infection is highly individualized, but a minimum of 2 weeks is typical given for uncomplicated catheter-related bacteremia [53]. Patients with complicated disease such as infective endocarditis, necrotizing pneumonia, septic arthritis, and osteomyelitis are generally treated with between 4 and 8 weeks of antimicrobials [54, 55]. The therapy is usually all intravenous for more serious infections whereas some portion of treatment may be oral for nonlife threatening infections such as lower
extremity osteomyelitis [56]. Regardless of treatment duration, complications, such as a new suppurative focus, may arise during therapy or for a significant period of time thereafter meaning that patients with serious *S. aureus* infections need to be closely monitored [57].

**Coagulase Negative Staphylococci**

**Epidemiology**

CNS are part of the normal flora of the human mucosa and skin with up to 90% of persons being colonized with CNS at any given time [58]. In contrast to patients without cancer, patients with cancer are especially vulnerable to CNS infection as a result of their damaged immune response, extensive contact with the healthcare system, and high frequency of use of medical devices [17, 18]. When species studies are performed, *Staphylococcus epidermidis* is generally the leading cause of invasive CNS in patients with cancer [59].

The major CNS diseases in cancer patients are bloodstream infections in patients with indwelling catheters and postsurgical infections (Fig. 35.2) [60, 61]. The pathogenesis of device-related CNS infection is thought to stem from their capacity to form biofilms on indwelling catheters [62]. CNS are also the leading cause of cerebrospinal fluid (CSF) shunt infections which are a significant issue for cancer patients with primary or metastatic central nervous system tumors [63].

**Clinical Manifestations/Diagnosis**

Catheter-related bacteremia due to CNS generally presents as fever without an apparent site of infection [64]. Infected catheters may have little to no evidence of purulence or surrounding erythema, and patients with CNS bacteremia may appear relatively asymptomatic [65]. Complications of CNS catheter-related bacteremia include infective endocarditis and hematogenous osteomyelitis among others, but complications of CNS-related bacteremia are rare compared to more virulent organisms such as *S. aureus* or Gram-negative rods [66]. CNS are the leading cause of prosthetic valve endocarditis, and endocarditis must be considered in all patients with a prosthetic valve and CNS bacteremia [67]. Prosthetic valve endocarditis due to CNS often presents with valve dysfunction or intracardiac abscess [68].

The clinical presentation of CNS infection of prosthetic devices other than venous catheters depends on the device involved and the level of the inflammatory response. For example, CNS infection of CSF shunt may present with overt meningitis, but often the presentation is more subtle with only low-grade temperature, alteration in mental function, or shunt-malfunction [63]. Pleocytosis of the CSF may be mild or the cell count may even be normal. Similarly, CNS infection of prosthetic joints may present with symptoms ranging from mild pain or joint dysfunction to a prominent, localized inflammatory response [42].

The diagnosis of CNS infection relies on isolation of the organism from appropriately obtained specimens. Because CNS are present on the skin of patients and healthcare workers, false-positive cultures from blood and other sterile sites are exceedingly common and lead to substantial difficulty in physician interpretation [69]. Good data on the reliability of blood cultures come from studies of CNS catheter-related bacteremia [43]. If a catheter is the source of infection, then quantitative cultures generally show fourfold higher numbers of colony forming units for blood drawn through the catheter compared to peripheral blood [64]. Similarly, cultures of blood drawn through an affected catheter tends to turn positive in automated blood culture systems at least 2 h earlier compared to those obtained from peripheral blood [64, 70]. The diagnosis of CNS infection from sources other than blood needs to be considered on a patient-specific basis with full knowledge that CNS is both the most common culture contaminant and a leading cause of prosthetic device infection.

**Treatment**

Because of the propensity of CNS to adhere to foreign material, optimal treatment of CNS infection includes removal of the infected device when possible [71]. The vast majority of CNS causing healthcare-associated infections are resistant to β-lactams [72]. Vancomycin is the drug for which most experience is available for CNS infection [73]. Because rifampin is active against CNS in the biofilm state, rifampin may be added for serious CNS infections such as prosthetic valve endocarditis although there is no clear proof of its efficacy [68, 74]. CNS are usually susceptible to recently developed antimicrobials such as quinupristin/dalfopristin, linezolid, and daptomycin [60]. With the exceptions of prosthetic valve endocarditis and prosthetic joint infection, most CNS infections respond readily to antimicrobials especially when the infected device is removed [10, 75]. Guidelines suggest that 7 days is adequate treatment for uncomplicated CNS catheter-related bacteremia after catheter removal and relapse rates are generally lower than those observed for *S. aureus* [43].

**Streptococci**

The streptococci are a heterogeneous group of pathogens with a confusing and oft-changing nomenclature [76]. For the purposes of this chapter, we will follow the approach of
the clinical microbiology laboratory, stratifying streptococci into viridans group streptococci (VGS), β-hemolytic streptococci, and Streptococcus pneumoniae. Streptococci not classified into these groups rarely cause invasive disease in patients with cancer and thus will not be discussed further herein.

**Viridans Group Streptococci**

**Epidemiology**

VGS are a diverse group of bacteria that commonly colonize the human oropharynx, upper respiratory tract, gastrointestinal tract, and female genital tract [77]. Viridans, derived from Latin, viridis, means green and refers to the tendency of these organisms to break down hemoglobin in blood or chocolate agar plates (α-hemolysis) causing a greenish color to appear. Most clinical microbiology laboratories do not routinely speciate α-hemolytic streptococci beyond determining whether S. pneumoniae is present, with non-S. pneumoniae α-hemolytic streptococci being broadly labeled as VGS. The major VGS responsible for invasive disease in cancer patients belong to the *mitis* group and include *S. mitis*, *S. oralis*, *S. sanguis*, and *S. parasanguis* [78–80].

VGS are considered to have low intrinsic virulence and rarely cause disease other than endocarditis in immunocompetent individuals [81]. Similar to CNS, VGS are far more likely to cause disease in patients with cancer, and these organisms are consistently identified as among the leading if not the most common cause of bloodstream infection in neutropenic individuals (Fig. 35.2) [82–84]. VGS bacteremia occurs almost exclusively in patients receiving aggressive cytoreduction therapy for such conditions as acute leukemia or following bone marrow transplantation [85, 86]. It is believed that the development of mucositis allows for translocation of colonizing VGS from the oropharynx or gastrointestinal tract into the bloodstream [87]. VGS bacteremia has been correlated with the use of prophylactic antimicrobials that have limited anti-VGS activity such as trimethoprim-sulfamethoxazole and fluoroquinolones [88].

**Clinical Presentation/Diagnosis**

Most patients with invasive VGS disease present with fever in the setting of mucositis and profound neutropenia [89]. Approximately 25% of patients present with a fulminant septic shock syndrome characterized by hypotension, rash, and adult respiratory distress syndrome (Fig. 35.4); *S. mitis* is the VGS species most commonly isolated from these patients [78, 89, 90]. Whether the dramatic clinical presentation in such patients is due to host susceptibility, *S. mitis* toxin elaboration or a combination of both is not currently understood. VGS bacteremia only rarely leads to endocarditis in patients with neutropenia, perhaps because of concomitant thrombocytopenia [65, 81].

The diagnosis of VGS disease relies on culturing the organism from a sterile site, usually the bloodstream. Isolating VGS from the skin or mucosal sites has no diagnostic significance given that these organisms are common colonizers. VGS may contaminate blood cultures [91]. But should be considered true pathogens in the appropriate clinical setting, i.e. in patients with neutropenia, mucositis, and fever. Serologic or antigen tests have no utility in diagnosing invasive VGS disease.

**Treatment**

Therapy of VGS disease is hampered by increasing resistance to β-lactam antimicrobials [92, 93]. When isolated from patients with neutropenia, VGS susceptibility to penicillin may be as low as 40% [86]. β-lactams remain the drugs of choice for invasive VGS disease if the organisms are susceptible. VGS isolates are uniformly susceptible to vancomycin, and vancomycin is commonly prescribed when invasive VGS is suspected [94]. Isolates from VGS infections that develop in patients receiving fluoroquinolone prophylaxis are often fluoroquinolone resistant [88, 95]. VGS bacteremia is generally treated for 10–14 days with longer course reserved for complicated cases, such as endocarditis. Whether agents such as intravenous immunoglobulin would help patients with fulminant VGS sepsis is not known [96].
**β-Hemolytic Streptococci**

The β-hemolytic streptococci are so-called because of their ability to fully lyse red blood cells during growth on blood agar plates. Most cancer-related β-hemolytic streptococcal infections are caused by group A β-hemolytic streptococci (*S. pyogenes*), group B β-hemolytic streptococci (*S. agalactiae*), and groups C and G β-hemolytic streptococci (*S. dysgalactiae* subspecies *equisimilis*) [97–99]. For purpose of clarity, herein we will call these organisms GAS, GBS, GCS, and GGS for group A, B, C, and G *Streptococcus* respectively.

**Epidemiology**

β-hemolytic streptococci are ubiquitous colonizers of the human skin and mucous membranes and a major cause of invasive disease in patients with and without cancer [100]. The main sites of GAS colonization in humans are the oropharynx and skin [101, 102]. GBS commonly colonizes the perineal area, whereas GCS and GGS can be isolated from the throat and skin [103, 104]. The vast majority of infections due to these organisms have a community onset [64]. Having a malignancy markedly increases the risk of invasive disease due to β-hemolytic streptococci compared to the general population [105, 106]. The risk of cellulitis due to β-hemolytic streptococci is even further increased in patients with cancer who have had disruption of lymphatic drainage by, for example, a lymph node dissection [107]. Limited systematic studies have suggested that GBS is the most common of the invasive β-hemolytic streptococci isolated from persons with cancer followed by GAS, GCS, and GGS [108, 109]. The development of invasive GAS disease, however, carries an especially poor prognosis with mortality rates of >50% [110].

**Clinical Manifestations/Diagnosis**

Most β-hemolytic streptococcal infections in adult cancer patients are skin and soft-tissue related. Disease may range from relatively uncomplicated cellulitis to necrotizing fasciitis and toxic shock syndrome especially when the etiologic agent is GAS. Cellulitis due to β-hemolytic streptococci tends to develop rapidly, spread quickly, and be accompanied by systemic manifestations such as chills and fever [111]. Erysipelas is a form of cellulitis caused by β-hemolytic streptococci in which disease is restricted to the dermis. Lesions are raised above the level of the surrounding tissue, and there is a clear demarcation of involved from uninvolved tissue [112]. This infection tends to occur – and, importantly – to recur in areas of damaged lymphatic drainage, which explains the propensity for recurrent infection in the ipsilateral arm after breast resection and lymph node dissection. Among children, GAS along with GCS and GGS are the leading bacterial causes of pharyngitis which is usually uncomplicated, although invasive disease, such as peritonsillar abscesses and cervical lymphadenitis, may occur [102].

Although less common than uncomplicated cellulitis or pharyngitis, infection of deeper tissues by β-hemolytic streptococci causes substantial morbidity and mortality in cancer patients [110]. Large skin lesions (>5 cm), pain out of proportion to abnormal findings on physical examination, systemic toxicity, skin discoloration, and the development of bullae all raise concern for deep tissue involvement and mandate consideration of invasive β-hemolytic infection [113]. Toxin elaboration by β-hemolytic streptococci, especially GAS, leads to profound tissue destruction and rapidly expanding disease. Streptococcal toxic shock syndrome has also been described among cancer patients with mortality rates exceeding 50% [109]. Hematogenous osteomyelitis is a common presentation of invasive GBS disease, especially among patients with diabetes mellitus [114].

Culture is the mainstay of diagnosis for β-hemolytic streptococcal infection. Rapid antigen tests when positive are reliable in diagnosing GAS pharyngitis when the ordered in patients with a high pretest probability of having the disease [115]. Recovery of β-hemolytic streptococci from a sterile site should be taken as indication of a true infection, whereas the isolation of β-hemolytic streptococci from mucous membranes and skin are often without clinical significance. An exception to this rule is toxic shock syndrome, which can occur in the absence of invasive disease; thus a diagnosis of GAS-related toxic shock syndrome can be supported by isolation of the organism from a mucosal site [116]. Serologic tests are not useful in the acute setting in diagnosing disease due to β-hemolytic streptococci. Acute and convalescent serum for antibodies to streptolysin O or DNase can be sent to determine whether an infection with GAS has occurred although these tests are rarely used in a clinical setting [117].

**Treatment**

β-hemolytic streptococci remain susceptible to penicillin and other β-lactam antibiotics, and these agents remain the drugs of choice for the treatment of infections due to β-hemolytic streptococci [118]. For patients who cannot receive β-lactams vancomycin is recommended although consideration should also be given to carbapenems if the penicillin allergy is not life threatening [119]. Macrolide and lincosamide resistance rates are highly variable, and these agents should not be used for serious infections without knowing strain susceptibility [120]. Many isolates are resistant to tetracyclines and trimethoprim-sulfamethoxazole [121, 122]. Experience with newer Gram-positive agents such as
daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline is limited although in vitro data are promising [123, 124]. In cases of serious soft tissue infection, especially toxic shock syndrome, clindamycin is added to reduce toxin production by slowly dying GAS [125]. Uncomplicated bacteremia due to β-hemolytic streptococci can be treated with a 10-day course of antibiotics whereas complicated disease mandates longer therapy. Surgical debridement of devitalized tissue is mandatory when these agents cause necrotizing soft-tissue infections [113].

**Streptococcus pneumoniae**

**Epidemiology**

Although genetically quite closely related to VGS, *S. pneumoniae* is generally considered distinct because of its prominent role as a major pathogen of both immunocompetent and immunocompromised humans. Pneumococci colonize the nasopharynx of 20–40% of children and 10–20% of healthy adults at any given time [126]. As indicated by its name, *S. pneumoniae* is among the leading causes of community-acquired pneumonia [127]. *S. pneumoniae* is the also the most common etiology of bacterial meningitis [128]. Risk factors for *S. pneumoniae* infection include extremes of age, comorbid illnesses such as chronic obstructive pulmonary disease and chronic kidney disease, and deficiencies in humoral immunity such as in patients with B cell neoplasms like chronic lymphocytic leukemia, non-Hodgkin’s B cell lymphoma or multiple myeloma and following splenectomy or in patients with human immunodeficiency virus infection [129]. Malignancy itself is a risk factor for invasive disease due to *S. pneumoniae* with persons with leukemia or lymphoma, those having undergone a hematopoietic stem cell transplant, and those receiving corticosteroids being at highest risk [130–132]. *S. pneumoniae* causes high rates of invasive disease in children less than 5 years of age so young children with cancer have a particularly increased chance of being infected [133].

**Clinical Presentations/Diagnosis**

*S. pneumoniae* is a major cause of infection in all parts of the respiratory tract and contiguous structures including the middle ear, sinuses, bronchi, and lungs [134]. Community-acquired pneumonia is the most common serious pneumococcal infection among patients with malignancy and generally presents with cough, fatigue, fever, chills, and shortness of breath [135]. Patients with pneumococcal meningitis may or may not have concomitant pneumonia and tend to present with fever, headache, stiff neck, and altered sensorium or obtundation.

**Treatment**

The definition of penicillin susceptibility of *S. pneumoniae* has recently been redefined to include consideration of the site of infection and the route by which antibiotics are being delivered [138]. *S. pneumoniae* causing an infection that does not involve the central nervous system and will be treated with intravenous penicillin is considered susceptible if it is inhibited by ≤2 μg/mL penicillin; in the United States at the present time, about 95% of all pneumococci are susceptible by this definition [138]. In a case of meningitis,
inhibition by <0.06 μg/mL, penicillin defines susceptibility; an MIC of ≥0.12 μg/mL is defined as resistance with about 75% of pneumococcal isolates causing meningitis in the USA being susceptible by these criteria [138]. Pneumococcal isolates are universally susceptible to vancomycin and usually susceptible to quinolones for which there is extensive experience in treating most S. pneumoniae infections, except for meningitis [139]. S. pneumoniae resistance to macrolides, clindamycin, trimethoprim-sulfamethoxazole and tetracyclines ranges from 20 to 40% in the USA, and these drugs should not be used in treating cancer patients who have invasive pneumococcal disease [140] unless susceptibility has been proven by in vitro testing. There are increasing data indicating that linezolid is effective for S. pneumoniae infections whereas daptomycin is not used to treat pneumonia because it is inactivated by pulmonary surfactant [141]. Although mortality for invasive pneumococcal disease remains around 15% for the first 7 days after admission, most infections respond to relatively short course of antimicrobials with longer courses reserved for meningitis, empyema, and complicated bacteremia [134].

Of all the pathogens discussed in this chapter, S. pneumoniae is the only one for which a vaccine is available. A vaccine consisting of capsular polysaccharides from 23 serologic types of pneumococcus is licensed for use in adults [142]. Vaccination is indicated in all adults ≥65 years of age and at any age for patients with malignancy who have an increased risk of pneumococcal disease such as those with lymphoma, multiple myeloma, transplant recipients, and those receiving chronic glucocorticoids [143]. Unfortunately, it is these very adults who are least likely to respond to such vaccination [144]. In the past decade a protein-conjugated vaccine that includes capsular polysaccharides from seven pneumococcal types has been licensed for use in children. Widespread use of this vaccine in infants and toddlers has reduced the incidence of pneumococcal disease in the entire population; however, replacement by other pneumococcal types has eroded vaccine efficacy in the population at large [129].

**Enterococcus**

**Epidemiology**

Similar to CNS and viridans group streptococci, enterococci cause a disproportionate amount of disease in patients with cancer compared to the general population [145]. The two main species causing disease in humans are *Enterococcus faecalis* and *Enterococcus faecium* [146]. As their name implies, enterococci are common colonizers of the gastrointestinal tract. The vast majority of enterococcal infections are nosocomial in origin [146]. The major risk factors for serious enterococcal disease include general debilitation, a prolonged hospital stay, recent surgery, neutropenia, presence of indwelling catheters, and receipt of broad-spectrum antimicrobials [147, 148]. Patients with malignancy appear to have especially high risk for infection with vancomycin resistant enterococci (VRE) perhaps because of broad use of vancomycin and agents with anti-anaerobic activity in this patient population [147].

**Clinical Presentation/Diagnosis**

Enterococci may cause catheter-related urinary tract infection, bacteremia (either catheter-related or from a gastrointestinal source), intra-abdominal infections, wound infections, and meningitis in patients with indwelling CSF catheters [149]. Enterococci are considered to be low virulence pathogens, and enterococcal infections often have a minimal inflammatory component [150]. Fever may or may not be present even in cases of bacteremia [151]. Culture is the mainstay of diagnosis with serologic or antigen tests being of no value. The isolation of enterococci from nonsterile specimens such as urine, sputum, or draining wounds 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 development of antimicrobial resistance and exposing the patient to potentially serious side effects [152]. Even when isolated from sterile sites, such as the abdominal cavity, enterococci are usually present along with one or more other organisms [153], and treatment of more virulent pathogens has been shown to cure such infections even in the absence of targeted enterococcal therapy [151]. This concept is illustrated by the highly effective nature of cephalosporins in treating intra-abdominal infections despite having no anti-enterococcal activity [154].

**Treatment**

Treatment of enterococcal infection is complicated by some unusual antimicrobial resistance. Most *E. faecalis* isolates remain relatively susceptible to penicillins, specifically penicillin, ampicillin, amoxicillin, and piperacillin (not nafcillin) and carbapenems (for example, imipenem), but are intrinsically resistant to cephalosporins [155]. In contrast, penicillin resistance among *E. faecium* isolates exceeds 50% [155]. Enterococci are generally resistant to macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones [156]. Vancomycin has been the drug of choice for treating enterococci resistant to β-lactam agents, but rates of VRE have increased dramatically over the past 20 years [152]. Enterococci are tolerant to β-lactam antibiotics, meaning that they are
inhibited but not killed by them; this becomes clinically meaningful in treating endocarditis and, perhaps, infections in neutropenic patients, as well [152]. A bactericidal effect may be achieved against some isolates by the addition of an aminoglycoside. Because, in this instance, the killing is attributable to the aminoglycosides, no synergy occurs against strains that are highly resistant to aminoglycosides, and such resistance has been increasing [157]. The emergence of VRE has left physicians with relatively few treatment options. Linezolid and quinupristin/dalfopristin are the only drugs approved by the United States Food and Drug Administration for treatment of infections due to VRE, although both drugs have significant limitations such as a lack of efficacy of quinupristin/dalfopristin against *E. faecalis* [158]. In vitro data with daptomycin and tigecycline are encouraging although emergence of resistance and reports of clinical failures are concerning [159]. The lack of clear clinical data regarding VRE treatment has recently led the Infectious Diseases Society of America to declare that determining optimal VRE treatment strategies is an area of paramount importance [160].

**The Effect of the Emergence of Gram-Positive Infections on Empiric Antimicrobial Therapy for Patients with Malignancy**

For many years empiric antimicrobial treatment of cancer patients with possible bacterial infections focused on Gram-negative pathogens, because bacteremic infection with these organisms was associated with a high risk of death [75]. The increased rates of isolation of Gram-positive pathogens has led many physicians to add an anti-Gram-positive antimicrobial, such as vancomycin or linezolid, when treating cancer patients with suspected infection [161], even though the same risk for death has not been documented for Gram-positive compared with Gram-negative bacteremia [66, 162]. In fact, clinical trials demonstrate no clinical benefit for the addition of targeted anti-Gram positive antimicrobials in empiric treatment regimens [94, 163, 164]. Widespread use of vancomycin and other targeted anti-Gram-positive agents is a major factor contributing to the emergence of such multidrug resistant organisms as VRE [165]. Nonetheless, the practice of adding vancomycin or other targeted Gram-positive antimicrobials empirically in neutropenic patients with fever and, by extension, in many other cancer patients who are not neutropenic, remains pervasive [166]. Taken together, these factors have led to specific recommendations against adding empiric anti-Gram-positive treatment in patients with cancer and suspected infection [94]. Institutional attempts to limit additional empiric anti-Gram-positive antimicrobial treatment to patients with specific risk factors have had limited success to date, but provide some hope for minimizing the overuse of antimicrobial agents [4]. Historically, a broad array of Gram-positive pathogens have shown the remarkable ability to overcome any widely prescribed antimicrobial, and thus antimicrobial conservation may play a pivotal role in the long-term control of these prevalent organisms [167].

**References**

1. Klastersky J. Science and pragmatism in the treatment and prevention of neutropenic infection. J Antimicrob Chemother. 1998;41(Suppl D):13–24.
2. Frei III E et al. The nature and control of infections in patients with acute leukemia. Cancer Res. 1965;25(9):1511–5.
3. Viscoli C, Castagnola E. Treatment of febrile neutropenia: what is new? Curr Opin Infect Dis. 2002;15(4):377–82.
4. Cordonnier C 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.
5. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. Clin Infect Dis. 1999;29(3):490–4.
6. Winston DJ et al. Randomized, double-blind, multicenter trial comparing ciprofloxacin with imipenem as empirical monotherapy for febrile granulocytopenic patients. Clin Infect Dis. 2001;32(3):381–90.
7. Feld R et al. Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. J Clin Oncol. 2000;18(21):3690–8.
8. Del Favero A et al. A multicenter, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. Clin Infect Dis. 2001;33(8):1295–301.
9. Rubio M et al. Predominance of Gram-positive microorganisms as a cause of sepsis in patients with hematological malignancies. Infect Control Hosp Epidemiol. 1994;15(2):101–4.
10. Ortega M 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.
11. Koll BS, Brown AE. The changing epidemiology of infections at cancer hospitals. Clin Infect Dis. 1993;17 Suppl 2:S322–8.
12. Safdar A et al. Changing trends in etiology of bacteremia in patients with cancer. Eur J Clin Microbiol Infect Dis. 2006;25(8):522–6.
13. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis. 2004;39 Suppl 1:S25–31.
14. Oppenheim BA. The changing pattern of infection in neutropenic patients. J Antimicrob Chemother. 1998;41(Suppl D):7–11.
15. Viscoli C, Vannier O, Machetti M. Infections in patients with febrile neutropenia: epidemiology, microbiology, and risk stratification. Clin Infect Dis. 2005;40 Suppl 4:S240–5.
16. Rolston KV et al. The spectrum of Gram-positive bloodstream infections in patients with hematologic malignancies, and the in vitro activity of various quinolones against Gram-positive bacteria isolated from cancer patients. Int J Infect Dis. 2006;10(3):223–30.
17. Kanamaru A, Tatsumi Y. Microbiological data for patients with febrile neutropenia. Clin Infect Dis. 2004;39 Suppl 1:S7–10.
18. Wisplinghoff H et al. 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.

19. Puig N et al. A study of incidence and characteristics of infections in 476 patients from a single center undergoing autologous blood stem cell transplantation. Int J Hematol. 2007;86(2):186–92.

20. 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.

21. Moreillon P, Que YA, Glaser 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.

22. Dossi CM, Zepeda FG, Ledermann DW. Nasal carriage of Staphylococcus aureus in a cohort of children with cancer. Rev Chilena Infectol. 2007;24(3):194–8.

23. Kuehnert MJ et al. Prevalence of Staphylococcus aureus nasal colonization in the United States, 2001–2002. J Infect Dis. 2006;193(2):172–9.

24. Klevens RM et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA. 2007;298(15):1763–71.

25. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2008;46 Suppl 5:S34–9.

26. Navarro MB, Hutten 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.

27. Ghanem G et al. The role of molecular methods in the prevention of nosocomial methicillin-resistant Staphylococcus aureus clusters in cancer patients. Am J Infect Control. 2008;36(9):656–60.

28. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis. 2005;40 Suppl 4:S246–52.

29. 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.

30. Mihu CN et al. Risk factors for late Staphylococcus aureus bacteraemia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant. 2008;14(12):1429–33.

31. Wang FD et al. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteraemia. Am J Infect Control. 2008;36(2):118–22.

32. Ghanem GA et al. Catheter-related Staphylococcus aureus bacteremia in cancer patients: high rate of complications with therapeutic implications. Medicine (Baltimore). 2007;86(1):54–60.

33. Raad I et al. Serious complications of vascular catheter-related Staphylococcus aureus bacteraemia in cancer patients. Eur J Clin Microbiol Infect Dis. 1992;11(8):675–82.

34. Rolston KV. The spectrum of pulmonary infections in cancer patients. Curr Opin Oncol. 2008;20(2):1445–53.

35. Miller LG et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med. 2005;352(14):1445–53.

36. Denniston S, Riordan FA. Staphylococcus aureus bacteremia in children and neonates: a 10 year retrospective review. J Infect. 2006;53(6):387–93.

37. Ewig S et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med. 1999;159(1):188–98.

38. Moellering Jr RC. Current treatment options for community-acquired methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis. 2008;46(7):1032–7.

39. Lee MC et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant Staphylococcus aureus. Pediatr Infect Dis J. 2004;23(2):123–7.

40. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339(8):520–32.

41. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351(16):1645–54.

42. Mermel LA et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001;32(9):1249–72.

43. Chang FY et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore). 2003;82(5):333–9.

44. Stryjewski ME et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible Staphylococcus aureus bacteremia. Clin Infect Dis. 2007;44(2):190–6.

45. Ruotsalainen E et al. Methicillin-sensitive Staphylococcus aureus bacteremia and endocarditis among injection drug users and non-addicts: host factors, microbiological and serological characteristics. J Infect. 2008;56(4):249–56.

46. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N Engl J Med. 2007;357(4):380–90.

47. Chang FY et al. A prospective multicenter study of Staphylococcus aureus bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore). 2003;82(5):322–32.

48. Fowler Jr VG et al. Daptomycin versus standard therapy for bacteraemia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006;355(7):653–65.

49. Weigelt J et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2005;49(6):2260–6.

50. Fagon J et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med. 2000;161(3 Pt 1):753–62.

51. Postier RG et al. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. Clin Ther. 2004;26(5):704–14.

52. Kim AJ, 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 passim.

53. Livorsi DJ et al. Outcomes of treatment for hematogenous Staphylococcus aureus vertebral osteomyelitis in the MRSA ERA. J Infect. 2008;57(2):128–31.

54. Murray RJ. Staphylococcus aureus infective endocarditis: diagnosis and management guidelines. Intern Med J. 2005;35 Suppl 2:285–44.

55. Daver NG et al. Oral step-down therapy is comparable to intravenous therapy for Staphylococcus aureus osteomyelitis. J Infect. 2007;54(6):339–44.

56. Kaplan SL. Community-acquired methicillin-resistant Staphylococcus aureus infections in children. Semin Pediatr Infect Dis. 2006;17(3):113–9.

57. Costa SF et al. Colonization and molecular epidemiology of coagulase-negative Staphylococcal bacteremia in cancer patients: a pilot study. Am J Infect Control. 2006;34(1):36–40.

58. Persson L et al. 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.
60. Kirby JT, Fritsche TR, Jones RN. Influence of patient age on the frequency of occurrence and antimicrobial resistance patterns of isolates from hematologic/oncology patients: report from the Chemotherapy Alliance for Neutropenic and the Control of Emerging Resistance Program (North America). Diagn Microbiol Infect Dis. 2006;56(1):75–82.

61. Ashour HM, el-Sharif A. Microbial spectrum and antibiotic susceptibility profile of gram-positive aerobic bacteria isolated from cancer patients. J Clin Oncol. 2007;25(36):5763–9.

62. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infect Dis. 2002;2(11):677–85.

63. Conen A et al. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. Clin Infect Dis. 2008;47(1):73–82.

64. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis. 2007;7(10):645–57.

65. Yusuf SW 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.

66. Klasterky J et al. Bacteremia in febrile neutropenic cancer patients. Int J Antimicrob Agents. 2007;30 Suppl 1:551–9.

67. Wang A et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA. 2007;297(12):1354–61.

68. Chu V et al. Coagulase-negative staphylococcal prosthetic valve endocarditis: a contemporary update based on the International Collaboration on Endocarditis – Prospective Cohort Study. Heart. 2009;95:570–6.

69. 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.

70. Bouza E et al. 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.

71. Raad I et al. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol. 1992;13(4):215–21.

72. 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.

73. Kloor WE, Bannerman TL. Update on clinical significance of coagulase-negative staphylococci. Clin Microbiol Rev. 1994;7(1):117–40.

74. Karchmer AW, Archer GL, Dismukes WE. Rifampin treatment of viridans group streptococci, groups C and G streptococci, and Gemella morbillifontes. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2343–50.

75. 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.

76. Husain E et al. Viridans streptococci bacteremia in children with malignancy: relevance of species identification and penicillin susceptibility. Pediatr Infect Dis J. 2005;24(6):563–6.

77. Johnson CC, Tunkel AR. Viridans group streptococci, groups C and G streptococci, and Gemella morbillifontes. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2434–50.

78. Prabhu RM et al. 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.

79. Marron A et al. Serious complications of bacteremia caused by viridans streptococci in neutropenic patients with cancer. Clin Infect Dis. 2000;30(15):1269–70.

80. Hughes WT et al. Clinical features and complications of viridans streptococci bloodstream infection in pediatric hematopoietic stem cell transplantation patients. Clin Infect Dis. 2001;33(7):947–53.

81. Collin BA et al. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. Clin Infect Dis. 2000;31(5):595–63.

82. Colford Jr JM, 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.

83. Bissol 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.

84. 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.
146. Moellering Jr RC. Enterococcus species, Streptococcus bovis, and Leuconostoc species. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. Philadelphia: Elsevier; 2005. p. 2411–2.

147. Ghanem G et al. 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.

148. Vergis EN et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. Ann Intern Med. 2001;135(7):484–92.

149. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev. 2000;13(4):686–707.

150. Mundy LM, Sahm DF, Gilmore M. Relationships between enterococcal virulence and antimicrobial resistance. Clin Microbiol Rev. 2000;13(4):513–22.

151. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore). 1988;67(4):248–69.

152. Murray BE. Vancomycin-resistant enterococcal infections. N Engl J Med. 2000;342(10):710–21.

153. 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.

154. Fry DE. Third generation cephalosporin antibiotics in surgical practice. Am J Surg. 1986;151(2):306–13.

155. 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.

156. Deshpande LM et al. 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.

157. Chow JW. Aminoglycoside resistance in enterococci. Clin Infect Dis. 2000;31(2):586–9.

158. Boucher HW et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1–12.

159. Jakic B et al. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42(5):597–607.

160. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. Int J Antimicrob Agents. 2008;32 Suppl 1:S30–3.

161. Cometta A et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis. 2003;37(3):382–9.

162. Paul M et al. Additional anti-Gram-positive antibiotic treatment for febrile neutropenic cancer patients. Cochrane Database Syst Rev. 2005;3:CD003914.

163. Camins BC et al. A population-based investigation of invasive vancomycin-resistant Enterococcus infection in metropolitan Atlanta, Georgia, and predictors of mortality. Infect Control Hosp Epidemiol. 2007;28(8):983–91.

164. Kirst HA, Thompson DG, Nicas TL. Historical yearly usage of vancomycin. Antimicrob Agents Chemother. 1998;42(5):1303–4.

165. Irfan S et al. Emergence of carbapenem resistant Gram negative and vancomycin resistant Gram positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study. BMC Infect Dis. 2008;8:80.