Chapter 35
Management of Gram-Positive Bacterial Disease: *Staphylococcus aureus*, Streptococcal, Pneumococcal and Enterococcal Infections

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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

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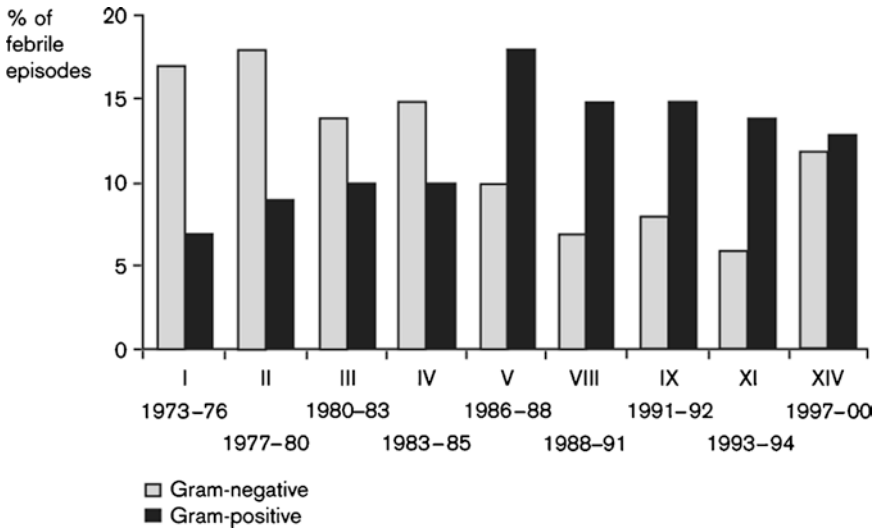

Fig. 35.1 Data demonstrating percent of infection in patients with neutropenia caused by Gram-negative (*gray bars*) and Gram-positive (*black bars*) bacteria. Note the increase in Gram-positive infection beginning in mid-1980s. Data graphs are single organism bacteremias in International Antimicrobial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

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[b]	Low virulence pathogens

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

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

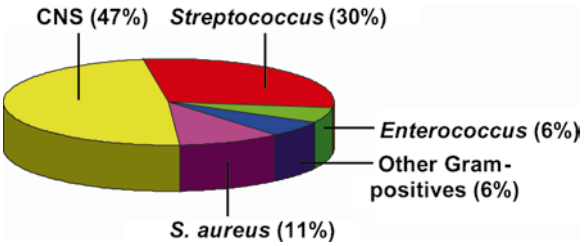

Fig. 35.2 Epidemiology of Gram-positive organisms causing bloodstream infections in patients with neutropenia. Data are from compiled from refs. [4, 6–8]. *CNS* coagulase-negative staphylococci

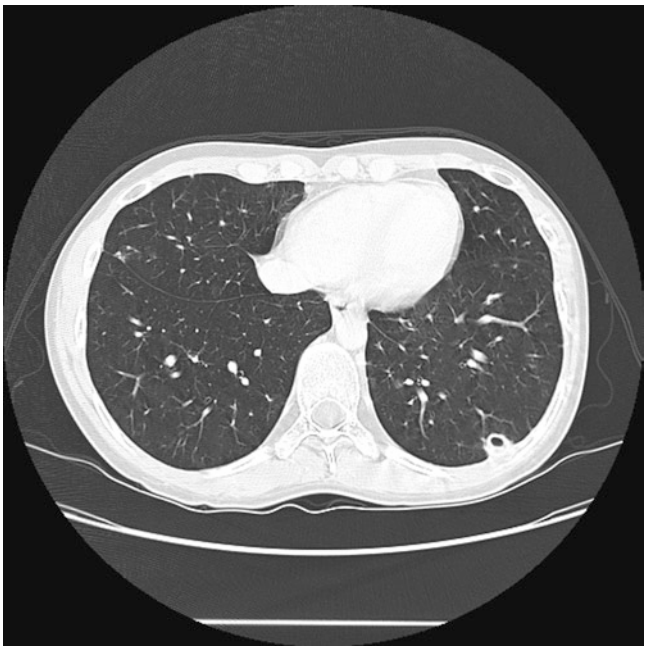

Fig. 35.3 Chest computerized tomography demonstrating cavitary pneumonia due to *S. aureus* that resulted from hematogenous seeding due to an infected Hickman catheter in a 30-year-old man with osteosarcoma

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 fasciitis 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].

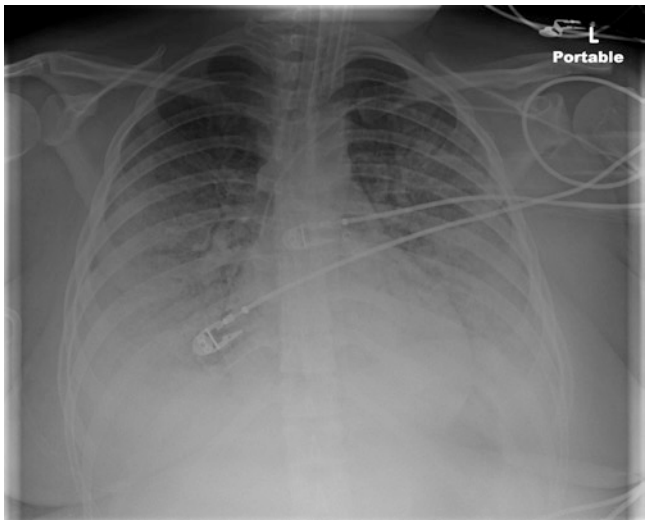

Fig. 35.4 Anterior-posterior chest X-ray demonstrating features consistent with adult respiratory distress syndrome (ARDS) that occurred following viridans group streptococcal bacteremia in a 23-year-old woman being treated for acute lymphoblastic leukemia

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 abscess and cervical lymphadentis, 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.

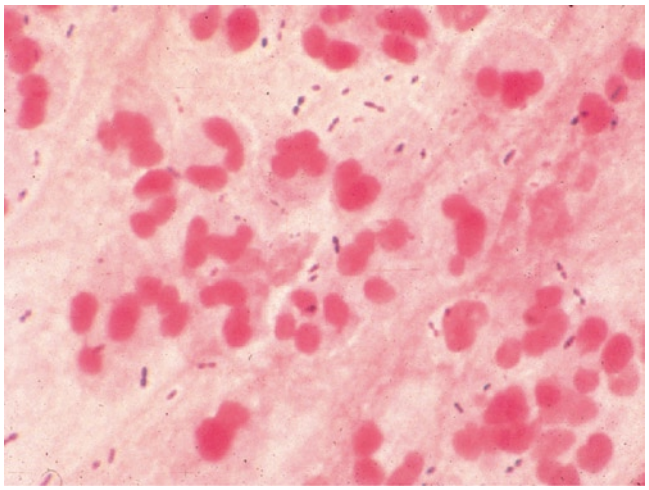

Fig. 35.5 Gram stain of sputum sample from patient with pneumococcal pneumonia. Note diploid organisms surrounded by polymorphonuclear cell infiltrate

Unlike staphylococci or even other streptococci, *S. pneumoniae* can be difficult to identify by sputum culture, and the value of diagnostic cultures is significantly reduced with prior antibiotic administration [136]. When a valid sputum sample can be obtained (this is possible in about two-thirds of pneumonia patients) and the patient has not received prior antibiotics, there is an 85% likelihood of identifying pneumococci in a Gram-stained specimen (Fig. 35.5) and a 90% likelihood of identifying the organism by culture. A subset of patients will have bacteremia along with pneumonia, but blood cultures are positive in only approximately 20% of pneumococcal pneumonia [134]. Serologic studies are not helpful acutely in making a diagnosis of invasive disease due to *S. pneumoniae.* A recently described test (BINAX-NOW) that detects C-polysaccharide in the urine is positive in 75–85% of adult patients with bacteremia pneumococcal pneumonia and a lower proportion of non-bacteremia cases; This test in adults is almost never falsely positive [137]. Patients with pneumococcal meningitis have a leukocytosis with polymorphonuclear predominance, low glucose, and high protein in the CSF. CSF Gram-stain and culture establish the diagnosis in nearly all patients who have not received antibiotics [134].

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 in-dwelling 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].

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