Bacterial Pathogens

John W. Wilson

Abstract

Bacterial infections are frequent complications among patients treated for cancer. The type, severity, and treatment of bacterial infections vary and depend upon the specific malignancy, associated chemotherapies, and transplantation. This chapter discusses commonly encountered bacterial pathogens as well as *Nocardia* and mycobacteria in patients with cancer and addresses the clinical syndromes and management. Drug-resistant bacteria are becoming an increasingly recognized problem in patients with cancer. Antimicrobial resistance in select gram-positive and gram-negative bacteria are discussed along with the mechanisms of resistance and recommended therapies.

Keywords

Bacteria · *Nocardia* · Mycobacteria · Resistance

Contents

J. W. Wilson (✉)
Department of Medicine, Division of Infectious Diseases,
Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA
e-mail: wilson.john@mayo.edu

V. Stosor and T. R. Zembower (eds.), *Infectious Complications in Cancer Patients*,
Cancer Treatment and Research 161, DOI: 10.1007/978-3-319-04220-6_3,

1 Introduction

Infectious diseases are among the most frequent complications encountered in cancer management. Optimal patient care necessitates a familiarization with common bacterial pathogens and their treatment. *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and viridans group streptococci are the more common gram-positive bacterial pathogens encountered in patients with cancer. Among the gram-negative bacteria, members of the Enterobacteriaceae family and *Pseudomonas aeruginosa* are the more frequently encountered and virulent pathogens. Many patients with cancer, especially those hospitalized, have prior antimicrobial treatment experience. Antimicrobial resistance is an increasing problem, and understanding the mechanisms of resistance is imperative toward prescribing effective therapy. Drug resistance mechanisms of select gram-positive and gram-negative bacteria as well as treatment options are reviewed.

Nocardia and mycobacteria both stain acid-fast and can produce severe progressive disease in patients with cancer. *Nocardia* may produce pulmonary disease resembling that of mycobacteria, or more distinct forms of extrapulmonary disease. Tuberculosis is less common in the United States, but must be considered in any patient with compatible features. Atypical presentations of tuberculosis are more common in cancer patients. Non-tuberculosis mycobacteria (NTM) encompass a very large group of organisms with diverse manifestations of localized or disseminated clinical disease. An overview of bacterial infections in patients with cancer is provided.

2 Select Gram-Positive Bacteria

2.1 *Staphylococcus* spp.

S. aureus is a virulent pathogen causing significant disease in both immunocompetent and immunocompromised patients. Clinical infections in patients with cancer caused by *S. aureus* are quite diverse and include intravascular catheter infections, skin and soft tissue infections, visceral abscesses, endocarditis, bone and joint infections, and bloodstream infections. Bloodstream infections with

S. aureus are a medical urgency, requiring prompt intervention. Metastatic foci of *S. aureus* infection can develop, requiring prolonged antimicrobial therapy and possible surgery. Intravascular catheters remain one of the most common causes of *S. aureus* nosocomial- and community-acquired bloodstream infections. In the hospital setting, approximately 20 % of bloodstream infections are caused by *S. aureus* [1]. For methicillin- (or oxacillin-) susceptible *S. aureus*, cefazolin or a penicillinase-resistant penicillin is recommended for more serious infections, including bloodstream infections. Vancomycin can be used for B-lactam allergic patients, but is less active. Oral antimicrobials including first-generation cephalosporins, anti-staphylococcal penicillins, trimethoprim–sulfamethoxazole, minocycline, clindamycin, and the newer fluoroquinolones can be used for mild soft tissue infections.

Most *S. aureus* bacteria are resistant to penicillin through plasmid-encoded penicillinase production. Methicillin-resistant *S. aureus* (MRSA) is defined by a minimum inhibitory concentration (MIC) with oxacillin at $\geq$4 mcg/mL. MRSA is becoming an increasing problem in hospitals around the world. Patients who have been treated with an antibiotic within the preceding 3 months (especially B-lactams and fluoroquinolones) are at increased risk for MRSA [2]. In 2003, up to 64 % of hospital-onset *S. aureus* infections in the intensive care units were MRSA [3]. Of the estimated 94,360 MRSA infections that occurred in the USA during 2005, approximately 75 % were bloodstream infections [4]. A surveillance of nine US hospitals in 2005 found the combination of *S. aureus* virulence and the immunosuppression of patients with cancer enables rapid *S. aureus* infection progression and high rates of disease recurrence if not recognized early or treated aggressively [5].

MRSA carries the *mecA* gene that encodes for penicillin-binding protein 2A (PBP2A). PBP2A has very low binding affinity for B-lactam antimicrobials and confers phenotypic bacterial resistance to all B-lactam antimicrobials, including penicillins, cephalosporins (except ceftaroline), and carbapenems. The *mecA* gene is located in a mobile staphylococcal cassette cartridge (SCC), which aids in chromosomal incorporation. There are currently eight SCC *mec* types (I-VIII), that differ in both *mec* and cassette chromosome recombinase gene complexes, along with a number of additional novel SCC subtypes [6, 194]. MRSA is commonly categorized into either health-care-associated (HA) MRSA or community-associated (CA) MRSA. The nomenclature refers to differences in demographic backgrounds, genetic and clonal features, susceptibility patterns, and clinical characteristics of the MRSA strains. About 85 % of all invasive MRSA infections are associated with some type of exposure to health care settings, and approximately 15 % develop within the community. Characteristics and differences between HA-MRSA and CA-MRSA are listed in Table 1.

CA-MRSA typically is more susceptible to non-B-lactam antimicrobials (including fluoroquinolones, macrolides, gentamicin, and clindamycin) and has exotoxin virulence factors [7]. MRSA strains susceptible in vitro to clindamycin but resistant to erythromycin may harbor erythromycin ribosomal methylase (*erm*) genes, conferring an inducible resistance to clindamycin. Clinical failure with

Table 1 Characteristics of HA-MRSA and CA-MRSA

	HA-MRSA	CA-MRSA
Patient risk factors	Prolonged hospitalization, ICU admission, residents of long-term care facilities; comorbidities including diabetes mellitus and hemodialysis	Children, competitive athletes, prisons, soldiers; select ethnic groups (Native Americans, Alaska Natives, Pacific Islanders), intravenous drug users, men who have sex with men
Clinical syndromes	Nosocomial pneumonia, intravenous catheter infections and related bacteremias, urinary catheter-associated urinary tract infections, surgical site infections	Skin and soft tissue infections (furuncles, skin abscesses), necrotizing pneumonia
Antimicrobial resistance	B-lactam class resistance, resistance to other drug classes common	B-lactam class resistance, more susceptible to other drug classes
Predominant SCC types	Types I, II, III	Type IV, V, VII
PVL toxin	Rare	Frequent

(Based on data from Refs. [6] and [192])

clindamycin has been reported in this setting [8]. Inducible clindamycin resistance can be identified in the laboratory with double-disk diffusion testing (D-testing) on erythromycin-resistant, clindamycin-susceptible MRSA strains. USA 300 and USA 400 are the two most commonly encountered CA-MRSA clones. The most common toxin is the Panton–Valentine leukocidin (PVL), a cytotoxin associated with skin and soft tissue infections and necrotizing pneumonia [9]. PVL is characteristically uncommon in HA-MRSA strains.

Treatment options for MRSA depend upon the infection syndrome as well as in vitro drug susceptibility data. Vancomycin, daptomycin, linezolid, ceftaroline, telavancin, teicoplanin and quinupristin-dapfopristin are typically active drugs. Additional options, depending upon drug susceptibility data, may include trimethoprim–sulfamethoxazole, minocycline, doxycycline, tigecycline, clindamycin, and the newer fluoroquinolones. Confirmed vancomycin-intermediate (VISA) or vancomycin-resistant (VRSA) MRSA is fortunately quite rare; however, even 'susceptible' MRSA may be less responsive to vancomycin. Some reports have shown MRSA bacteremia with a vancomycin MIC of $\leq$0.5 ug/mL to have a higher treatment success rate with vancomycin than MRSA with vancomycin MIC 1–2 ug/ml [10, 11].

Coagulase-negative staphylococci (CoNS) comprise a heterogenous group of bacteria that are part of the natural skin microbial flora. Although less virulent compared to *S. aureus*, many CoNS (including *S. epidermidis* and *S. haemolyticus*) are resistant to multiple antibiotics including methicillin. The mechanisms of resistance are similar to those of *S. aureus* and include B-lactamase production and PBP2A production by the *mecA* gene. Both *S. aureus* and CoNS produce a biofilm, enabling attachment to foreign material. CoNS, including *S. epidermidis*, are the

most common cause of intravascular catheter infections [12, 13]. The high usage of short-term and tunneled central venous catheters in patients with cancer (e.g., for chemotherapy and/or blood product infusions) allows for CoNS to be the most common cause of bloodstream infections in this patient group as well as for hospitalized patients in general [1]. Single positive blood cultures with CoNS need to be interpreted with caution as contamination from the skin is common. CoNS are also a common pathogen with other types of foreign body infections including prosthetic valves and other endovascular devices, cerebrospinal fluid shunts, peritoneal dialysis catheters, ocular implants, and prosthetic joints.

S. lugdunensis is a CoNS that deserves special mention. *S. lugdunensis* is more virulent than other CoNS and should never be regarded as a contaminant in blood cultures. Up to 50 % of *S. lugdunensis* community-acquired bloodstream infections in one series were associated with endocarditis, whereas nosocomial *S. lugdunensis* bacteremias were commonly catheter associated [14]. *S. lugdunensis* has also been associated with infections of skin and soft tissues (often with abscess formation), central nervous system (CNS), bone and joint, peritoneum, and oral cavity [15]. Despite its enhanced pathogenicity, *S. lugdunensis* remains susceptible to most B-lactam antimicrobials.

2.2 *Enterococcus* spp. and Viridans Group *Streptococcus*

Enterococcus spp. are a component of the normal gastrointestinal bacterial flora and occasionally may be found in the vagina and oral cavity [16]. Enterococcal infections may develop secondary to a compromise in bowel wall integrity, fecal contamination, genitourinary complications, animal contact, and through nosocomial acquisition. Before the emergence of vancomycin-resistant enterococci (VRE), 85–90 % of clinical enterococcal isolates were *E. faecalis*, 5–10 % were *E. faecium*, and the remaining 3–4 % were other *Enterococcus* spp. [17]. *Enterococcus* spp. have lower intrinsic virulence compared to *S. aureus* and group *A Streptococcus* as well as no exotoxin production.

Although a wide array of clinical infections have been ascribed to *Enterococcus* spp. (including endocarditis, urinary tract infections, and osteomyelitis), enteric and other-related intraabdominal infections as well as bacteremias are especially common in patients with cancer. Any compromise in bowel wall integrity increases the risk for infection with *Enterococcus* spp. Cancers of the gastrointestinal, genitourinary and biliary tracts, antineoplastic chemotherapy, neutropenic colitis (typhlitis), and enteric graft-versus-host disease all enable enterococci and other enteric flora to translocate beyond the bowel lumen and produce clinical disease. Infection in these settings is often polymicrobial and should generally be managed with broadened antibacterial therapy.

Because of lower affinity for the penicillin-binding proteins, *Enterococcus* spp. are less susceptible to B-lactams compared to other gram-positive bacteria. Rarely, enterococci also produce a B-lactamase. The MICs of active penicillins to

Enterococcus spp. are significantly higher compared to most streptococci [16]. Penicillin, ampicillin, amoxicillin, piperacillin, imipenem, meropenem, and doripenem are moderately active against susceptible enterococci, but remain bacteriostatic. The addition of gentamicin or streptomycin may provide additional activity when combined with a B-lactam and is typically recommended in cases of enterococcal endocarditis. The cephalosporins (except ceftaroline against E. faecalis) and clindamycin are not active. Although trimethoprim–sulfamethoxazole (TMP-SMX) may have mild in vitro activity, enterococci can metabolically utilize exogenous folinic acid, dihydrofolate, and tetrahydrofolate to survive, rending this drug clinically ineffective [18]. The fluoroquinolones also have low-level anti-enterococcal activity, but their clinical usefulness is quite limited outside of simple lower urinary tract infections, and rates of quinolone resistance remain high. Enterococci have the ability to exchange genes encoded on plasmids for additional drug resistance. Such acquired drug resistance has rendered most macrolides, tetracyclines, and occasionally vancomycin ineffective.

Peptidoglycan is a crucial component of the bacterial cell wall, and vancomycin exerts it activity through the inhibition of peptidoglycan biosynthesis. Specifically, vancomycin binds to the D-alanyl-D-alanine terminus of the pentapeptide peptidoglycan precursor and inhibits subsequent enzymatic steps in cell wall development [19]. Vancomycin resistance develops through the synthesis of peptidoglycan cell wall precursors that contain an altered terminal dipeptide (e.g., D-alanyl-D-lactate or D-alanyl-D-serine) instead of a D-alanyl-D-alanine terminus. Vancomycin is subsequently not able to bind with the altered enterococcal dipeptide terminus.

VRE were first identified in Europe in 1988 [20, 21] and have subsequently spread worldwide. Vancomycin resistance is much more prevalent in *E. faecium*; however, vancomycin-resistant *E. faecalis* has been isolated, usually as a nosocomial pathogen [22]. The incidence of VRE colonization and infection are increasing. Up to 10 % of hemodialysis patients in one center were reported to be colonized with VRE [23]. Within the USA, a recent multicenter study found 28 % of the enterococci cultured from intensive care unit (ICUs) to be VRE [24]. In a recent national surveillance study of bloodstream infections, 60 % of *E. faecium* and 2 % of *E. faecalis* isolated were VRE [1]. Patients with cancer, especially hematologic malignancies, have a high risk for VRE morbidity and mortality because of extended health care facility and antimicrobial exposures, chemotherapy-associated bowel wall compromise and sustained periods of post-chemotherapy neutropenia [25]. Pretransplant VRE colonization is an independent risk factor for increased mortality in patients receiving allogeneic hematopoietic stem cell transplantations [26]. The increase in mortality in this group correlates with the presence of VRE bacteremia.

There are multiple VRE phenotypes (including A-G and select others) depending upon the altered terminal dipeptide (D-alanyl-D-lactate for VanA, B, and D types; D-alanyl-D-serine for VanC, E, and G types) and elimination of high affinity precursors [27]. VanA is the most common VRE phenotype and demonstrates high-level resistance to both vancomycin and teicoplanin. Transfer of VanA-type resistance via plasmid DNA from enterococci to *S. aureus* has been

identified and poses great concern [28, 29]. VanB is the next most common and exhibits moderate to high resistance to vancomycin but remains susceptible to teicoplanin. The VanC phenotype is characteristic of *E. gallinarum* and *E. casseliflavus/flavescens* and has an intrinsic low-level resistance to vancomycin that is chromosomally encoded [30]. It remains susceptible to teicoplanin. Although *E. gallinarum* and *E. casseliflavus/flavescens* are infrequently encountered, they are more commonly found in patients with immunosuppression, including hematologic malignancies, hematopoietic stem cell, and solid organ transplantation [31]. VanD has been found in *E. faecium* that has moderate levels of resistance to both vancomycin and teicoplanin. VanE and G have been found in *E. faecalis* with a similar terminal D-serine substitution and phenotypic effect as the VanC [30].

Most VRE are resistant to penicillin and ampicillin, but on rare occasions these agents may show in vitro activity. Treatment options for VRE include linezolid, daptomycin, quinupristin/dalfopristin (for *E. faecium* only), and tigecycline. Resistance to each of these agents has been demonstrated. Currently, linezolid is the only oral agent approved by the Food and Drug Administration for the treatment of VRE infection; however, the myelosuppressive effects (including leukopenia and thrombocytopenia) may limit its sustained use in patients with some cancers. Nitrofurantoin may be active for uncomplicated VRE urinary tract [32].

Viridans group streptococci constitute a heterogenous group of bacteria that are found throughout the gastrointestinal and female genital tracts. Contrasting enterococci which predominate more in the lower small bowel and colon, viridans group streptococci are more prevalent in the oral cavity and upper respiratory tract. A breakdown in the mucosal barrier through chemotherapy-associated oral stomatitis and enteritis allows viridans group streptococci to cause infection. *S. mitis* and other viridans group streptococcal infections have been well identified following high-dose cytosine arabinoside therapy for acute leukemia [33]. Other risk factors for the development of viridans group streptococcal infections include profound neutropenia, antimicrobial prophylaxis with TMP-SMX or select fluoroquinolones, and use of stomach acid suppressants [34, 35]. In neutropenic patients, viridans group streptococci can produce a toxic shock-like syndrome, involving multiorgan dysfunction and respiratory failure [35, 36]. Such a syndrome may occur despite early clearance of bacteria from the bloodstream. An unusual outbreak of toxic shock-like syndrome caused by a toxigenic clone of *S. mitis* has also been described in immunocompetent patients [37].

Viridans group streptococci are generally susceptible to most B-lactam antimicrobials. Ceftriaxone is commonly used for its favorable clinical experience and convenient once daily administration. Penicillin historically was the drug of choice, but resistance through altered penicillin-binding proteins is not uncommon and may confer resistance to other beta-lactam antimicrobials. Alternative intravenous agents include vancomycin, daptomycin, quinupristin/dalfopristin, and tigecycline [38, 39], while the newer fluoroquinolones, linezolid, macrolides, and tetracyclines remain oral options. Fluoroquinolone-resistant viridans group streptococci have been increasingly identified in neutropenic patients receiving fluoroquinolone prophylaxis [40, 41].

2.3 Other Gram-Positive Bacteria

Streptococcus bovis is another constituent of normal gastrointestinal tract flora. Similar to other enteric bacteria, *S. bovis* bacteremia can develop when the there is compromise of the bowel wall secondary to either tumor invasion or antineoplastic chemotherapy. Bloodstream infections with *S. bovis* appear to have a higher association than other bacteria with the presence of bowel wall cancers. Patients with otherwise unexplained *S. bovis* bacteremia should undergo appropriate intestinal cancer screening [42]. Many providers also consider enteric evaluation in patients with otherwise unexplained *Clostridium septicum* bloodstream infection [43, 44].

The nutritionally variant streptococci (NVS), *Abiotrophia defectiva*, and *Granulicatella* spp. are fastidious bacteria that may grow as satellite colonies around *S. aureus* and other select bacteria or on pyridoxal- or L-cysteine-supplemented agar. NVS are part of the normal bacterial flora of the upper respiratory, gastrointestinal, and genitourinary tracts. NVS bacteremia can occur in patients with cancers of the gastrointestinal, genitourinary, or upper respiratory tracts and in those receiving antineoplastic chemotherapy. NVS have also been associated with destructive valvular lesions in patients with endocarditis. NVS are less susceptible to penicillin compared to *Streptococcus* spp., and combination therapy with aminopenicillin and aminoglycoside is commonly used for the treatment of endocarditis and refractory infections. Activity of cephalosporins against NVS is variable, but vancomycin and expanded fluoroquinolones remain active [45, 46].

Streptococcus pneumoniae infections are especially problematic in anatomically and functionally asplenic patients. Numerous hematologic indications for splenectomy exist, including hereditary spherocytosis, thalassemia major, myeloproliferative disorders with symptomatic splenomegaly, select cases of non-Hodgkin's disease, and occasionally for immune thrombocytopenia, thrombotic thrombocytopenic purpura, hairy cell leukemia, and as a staging procedure in Hodgkin's disease [47, 48]. *S. pneumoniae* is the most common bacterial infection associated with post-splenectomy severe sepsis. Other pathogens associated with severe disease in asplenic patients include *Neisseria meningitidis*, *Haemophilus influenza* type B, *Capnocytophaga canimorsus*, and *Babesia microti*. Estimates of post-splenectomy infection incidence and mortality vary although two large reviews reported a combined severe infection incidence of 3.2–4.2 % with a mortality of 1.4–2.5 % [49, 50].

Listeria monocytogenes is predominantly seen in neonates, the elderly, pregnant women, and in immunosuppressed patients, primarily those with cell-mediated immunity (CMI) dysfunction. Although an infrequently encountered pathogen, this 'diphtheroid-like' appearing gram-positive bacillus can produce bloodstream infections with a particular tropism for the meninges and brainstem (meningoencephalitis and rhombencephalitis) (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients), as well as food-borne illness and disseminated neonatal disease. A recent review of listeriosis

in patients with cancer at the MD Anderson Cancer Center identified 59 % of patients had a hematologic malignancy (60 % lymphoma and 40 % leukemia or myeloma) and the remaining 41 % had solid tumors [51]. Bloodstream infection was the most common presentation, although 21 % had CNS involvement. *Listeria* bloodstream infection has been associated with CMV reactivation in recipients of allogeneic hematopoietic stem cell transplantation [52, 53].

3 Select Gram-Negative Bacteria

Although the incidence of gram-negative bacterial bloodstream infections in patients with febrile neutropenia is less than that of gram-positive bacteria [54, 55], the mortality of gram-negative bacteremia remains substantially higher [56]. Members of the Enterobacteriaceae family, primarily *E. coli* and *Klebsiella* spp., and *P. aeruginosa* are most commonly encountered [57]. Gram-negative bacteria isolated from a sterile body site should never be discounted as a contaminant.

3.1 The Enterobacteriaceae

The family Enterobacteriaceae contributes to the normal microbial flora of the lower gastrointestinal tract, oropharynx, and vagina and is the most common group of gram-negative bacteria isolated in the laboratory. Enterobacteriaceae produce the vast majority of gram-negative bacterial infections in patients with cancer. They frequently produce bloodstream, urinary tract, peritoneal, hepatobiliary, and nosocomial- and ventilator-associated pulmonary infections. The more commonly encountered members of this family include *E. coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., *Morganella* spp., *Providencia* spp., *Plesiomonas* sp., *Hafnia* sp., *Yersinia* spp., *Salmonella* spp., and *Shigella* spp. Although some of the Enterobacteriaceae including *Salmonella*, *Shigella*, *Aeromonas*, and *E. coli* 0157:H7 can produce distinct infection syndromes, many other species of this large family share similarities in clinical disease.

Gram-negative bacteremia in a neutropenic patient can rapidly turn fatal if effective antimicrobial therapy is not promptly started. *E. coli* is the most common gram-negative bacteria isolated from blood cultures and is also the most common pathogen in urinary tract infections. *E. coli* O157:H7 comprises most of the enterohemorrhagic *E. coli* and can produce shiga-toxin-mediated hemorrhagic colitis in both immunocompromised and immunocompetent patients. *E. coli* O157:H7 often is acquired through the consumption of contaminated ground beef and is the most common cause of hemolytic uremic syndrome (hemolytic anemia with schistocytes, thrombocytopenia, and renal insufficiency). *Klebsiella* spp. are the more commonly encountered Enterobacteriaceae in respiratory tract infections. Although often associated with ‘currant jelly’ sputum and the ‘bulging fissure

sign' on chest X-ray, these findings are not specific to *Klebsiella* spp. *Proteus mirabilis* causes 90 % of *Proteus* infections and is readily identifiable in culture for its 'swarming' tendency on agar. A variety of extended-spectrum penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and TMP-SMX are active against the Enterobacteriaceae; however, drug resistance is not uncommon. Select tetracyclines and macrolides may also be active. Knowledge of both the species and antimicrobial susceptibility data are needed for optimal drug therapy (see gram-negative bacterial drug resistance).

3.2 *Pseudomonas aeruginosa*

P. aeruginosa is one of the most concerning bacteria to produce infection in the immunocompromised patient. Inherent bacterial virulence leading to high mortality and progressive drug resistance through numerous mechanisms have necessitated preemptive treatment in patients suspected of having infection with *P. aeruginosa*. *P. aeruginosa* infections are generally considered to be nosocomially acquired; however, community-acquired primary *Pseudomonas* bloodstream infections occasionally occur [58].

Three sequential studies performed at the University of Texas, MD Anderson Cancer Center, during the 1960s, 1970s, and 1990s on the mortality of *P. aeruginosa* bloodstream infections in patients with underlying malignancies found the overall cure rate of *P. aeruginosa* bacteremia in patients with underlying malignancies to be 21, 62, and 80 %, respectively [59–61]. The favorable trend in outcome may reflect both the additional anti-*Pseudomonas* antimicrobials developed during the past three decades and changes in cancer management, including new chemotherapy regimens and antimicrobial prophylaxis. Despite these medical advances, the morbidity and mortality attributed to *P. aeruginosa* infections remain significant. Compared to immunocompetent patients, both *P. aeruginosa* and Enterobacteriaceae bloodstream infections are more common in patients with neutropenia (absolute neutrophil count $<$500 cells/uL) [62]. *P. aeruginosa* bloodstream infections are also more common in patients with acute leukemia compared to other hematologic or solid organ malignancies [60, 62]. More severe forms of graft-versus-host disease in allogenic hematopoietic stem cell transplantation are another risk factor for *P. aeruginosa* infection [63]. Empiric antibacterial therapy in patients with neutropenia and fever must contain activity against gram-negative bacteria, including *P. aeruginosa*.

P. aeruginosa can also cause serious skin and soft tissues infections in patients receiving antineoplastic chemotherapy. Ecthyma gangrenosum can develop in neutropenic patients with bacteremia. Ecthyma gangrenosum appears as erythematous round skin lesions with developing central necrosis and ulceration. Cutaneous *Pseudomonas* infection in the form of folliculitis may develop after exposure to contaminated hot tubs, whirlpools, or swimming pools. Deep tissue wounds with *P. aeruginosa* may follow puncture wounds to the foot (e.g., nail punctures through tennis shoes). Although not common for patients with cancer, *P. aeruginosa* infections can also produce pulmonary disease, especially in

patients with underlying bronchiectasis or cystic fibrosis; bone and joint disease; CNS infections associated with recent neurosurgery; endocarditis from intravenous drug usage; ear and eye infections, as well as nosocomial urinary tract infections.

Effective antimicrobials against *P. aeruginosa* include cefepime, ceftazidime, meropenem, imipenem, doripenem, piperacillin, piperacillin–tazobactam, aztreonam, ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin, and colistin. Aminoglycoside or colistin therapy alone is not appropriate for the treatment of *P. aeruginosa* bacteremia [64]. *P. aeruginosa* has significant potential for the development of antimicrobial drug resistance. Risk factors for the development of multidrug-resistant *P. aeruginosa* include the use of carbapenems for one or more weeks, a history of *P. aeruginosa* infection or colonization during the preceding year, and a history of chronic obstructive pulmonary disease (COPD) [65].

3.3 Gram-Negative Bacterial Drug Resistance

Antimicrobial drug resistance through B-lactamase production by the Enterobacteriaceae and other gram-negative bacteria pose increasing therapeutic challenges. Over the last two decades, more types of B-lactamase production have been identified, decreasing effective therapeutic drug options. Also concerning is that routine antimicrobial susceptibility testing will not reliably identify some types of B-lactamase production nor predict clinical response to expanded B-lactam therapy. Comparative longitudinal antibiograms show an increasing number of bacterial pathogens with multiple drug resistance mechanisms [66]. Patients with cancer have a high risk for colonization and infection with drug-resistant bacteria. Frequent hospitalizations of this patient group combined with exposures to multiple antibiotics contribute to this risk [67]. Drug-resistant nosocomial infections are most often encountered in the ICU setting, followed by non-ICU hospital wards and outpatient hospital settings [68]. Within the ICU setting, rates of nosocomial drug-resistant bacterial infections are more prevalent in developing countries compared to the United States [69]. Such discrepancies may reflect differences in infection control policies and lack of adequate funding, compliance problems with adequate hand hygiene practices, differences in nurse-to-patient ratios and hospital overcrowding. Efforts to curb the propagation of multidrug-resistant pathogens will require enhanced national and global antimicrobial stewardship as well as appropriate infection control measures.

The first plasmid-mediated B-lactamase identified in gram-negative bacteria was the penicillin hydrolysis enzyme TEM-1 found in *E. coli* during the 1960s. TEM-1 is now the most commonly encountered B-lactamase in gram-negative bacteria, accounting for up to 90 % of the ampicillin resistance in *E. coli* as well as ampicillin and penicillin resistance in strains of *H. influenzae* and *N. gonorrhoeae* [70, 71]. SHV-1 is another common B-lactamase and is found predominantly in *K. pneumoniae* and *E. coli*. The SHV-1 B-lactamase is chromosomally

encoded in the majority of isolates of *K. pneumoniae*, but is usually plasmid mediated in *E. coli* [71].

Continued antimicrobial selective pressure has allowed for the emergence of additional TEM and SHV enzymes that enable select bacteria to hydrolyze an expanded group of B-lactam antimicrobials, including most cephalosporins. Extended-spectrum beta-lactamase (ESBL) enzymes confer resistance to the oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime, and cefepime) and monobactams (aztreonam), but not the cephamycins (cefoxitin, cefotetan) or carbapenems (imipenem, meropenem, ertapenem, and doripenem) [72]. Additionally, ESBL-producing bacteria are resistant to penicillins, but can be inhibited by beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam [73]. Genes encoding for ESBL production are transmissible and problematic in hospitals and long-term care facilities with congregate patient populations [74]. Currently over 150 different ESBL enzymes have been identified.

ESBL production is most commonly found in *K. pneumoniae*, *K. oxytoca*, and *E. coli* [71, 75]. Occasionally, ESBL production has also been seen with *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp., *Salmonella* spp., *Serratia* spp., and other enteric bacteria, as well as in isolates of *Acinetobacter baumannii* and *P. aeruginosa* [66]. Prolonged mechanical ventilation is a significant risk factor for acquiring ESBL-producing bacteria [76] as these patients are usually more debilitated with a higher likelihood of receiving excessive antimicrobial therapy. Other risk factors for ESBL-producing bacterial infection include repetitive and prolonged hospitalizations, use of central venous and urinary catheters, administration of total parenteral nutrition, and exposure to third-generation cephalosporins, aminoglycosides, and TMP-SMX [72, 76]. The use of B-lactam/B-lactamase inhibitor combinations, rather than third-generation cephalosporins, in ventilated patients may help protect against development of ESBL-producing bacterial infections [77].

The Clinical and Laboratory Standards Institute (CLSI) testing platform for ESBL-producing gram-negative bacteria applies only to *E. coli*, *Klebsiella* spp., and *P. mirabilis*. Testing methodologies to identify ESBL production in other bacteria have not yet been validated [72]. In vitro susceptibility testing with ESBL-producing bacteria can be misleading as some antimicrobials may appear falsely active in vitro [66]. Unless proven otherwise, CLSI recommends all phenotypically confirmed ESBL-producing bacteria, irrespective of species, be reported as resistant to all penicillins, cephalosporins (except cefoxitin and cefotetan), and aztreonam in order to avoid therapy with potentially ineffective antimicrobials [72].

ESBL-producing bacteria pose significant therapeutic challenges as resistance genes for other antimicrobials including aminoglycosides, tetracyclines, and TMP-SMX are often present on the same plasmid [76]. Carbapenems should be considered first-line treatment for serious infections with ESBL-producing gram-negative bacteria [72]. Treatment with either imipenem or meropenem produces the most effective bacterial clearance and favorable patient outcomes. Ertapenem is effective as well. Combination therapy with a carbapenem is not superior to carbapenem therapy alone. B-lactam/B-lactamase inhibitor combinations, such as

piperacillin–tazobactam, can be active against bacteria possessing a single plasmid-mediated ESBL. Many bacteria, however, can produce multiple ESBL types, significantly reducing piperacillin–tazobactam activity [78, 79]. Cefepime is less effective than the carbapenems, but may provide some activity when used in higher doses (at least 2 g twice daily) against organisms with a cefepime MIC <2 ug/mL [72]. Cefepime MIC values are generally higher in ESBL-producing strains of *E. cloacae* compared to non-ESBL-producing strains [80]. Cefepime and piperacillin–tazobactam therefore should not be used as first-line treatment against ESBL-producing bacteria and only considered when other more effective antimicrobials are not available. The fluoroquinolones may be effective for some mild-to-moderate ESBL-producing bacterial infections; however, fluoroquinolone resistance rates over 55 % have been reported among ESBL-producing Enterobacteriaceae [81].

Resistance to expanded-spectrum cephalosporins and many broad-spectrum penicillins can also develop with the hyperproduction of the Bush group 1, chromosomal-mediated (AmpC) B-lactamase. The AmpC B-lactamase is inducible and has been most commonly found in *E. cloacae*, *E. aerogenes*, *C. freundii*, and *S. marcescens* [75, 82]. In a surveillance study of nosocomial bloodstream infections in US hospitals, 50 % of *E. aerogenes*, 35 % of *E. cloacae*, and 39 % of *C. freundii* isolates produced AmpC B-lactamase and were resistant to ceftazidime, ceftriaxone, piperacillin, and piperacillin–tazobactam [83]. Less common bacteria that have been found to occasionally harbor chromosomal-mediated AmpC B-lactamases include *Acinetobacter* spp., *Aeromonas* spp., *Chromobacterium violaceum*, *C. freundii*, *Enterobacter* spp., *E. coli*, *H. alvei*, *Morganella morganii*, *Ochrobactrum anthropi*, *P. rettgeri*, *P. stuartii*, *P. aeruginosa*, *S. marcescens*, and *Y. enterocolitica* [75]. In addition, plasmid-mediated AmpC B-lactamases have been found in *K. pneumoniae*, *Salmonella* spp., and *P. mirabilis* [84].

Although *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. may appear susceptible to penicillins and cephalosporins in vitro, select antibiotic pressure (e.g., third-generation cephalosporins) can facilitate production of high levels of AmpC B-lactamase production [85, 86]. Of the third-generation cephalosporins, ceftriaxone appears to be most provocative toward inducing AmpC B-lactamase production in *E. cloacae* [87] and possibly in other bacteria. The higher biliary concentration of ceftriaxone and broad activity against the Enterobacteriaceae may contribute to this effect. Interestingly, the fluoroquinolones may offer a protective effect against AmpC B-lactamase production [87]. In addition to antimicrobial pressure, AmpC B-lactamase production may develop through a spontaneous gene mutation enabling a 'de-repressed' state of B-lactamase hyperproduction [83].

Many AmpC B-lactamase-producing bacteria are resistant to the semisynthetic penicillins (e.g., piperacillin) and combination B-lactam/B-lactamase inhibitors. Antimicrobials that generally remain active include carbapenems, cefepime, aminoglycosides, TMP-SMX, and fluoroquinolones. ESBL- and AmpC-type B-lactamase production can occur together in some *E. cloacae* and *E. aerogenes*. Although cefepime may be clinically useful against AmpC B-lactamase producing gram-negative bacteria, it remains less effective against ESBL-producing bacteria.

Of significant concern has been the propagation of carbapenemase production among select Enterobacteriaceae. Carbapenemase-producing Enterobacteriaceae differ from ESBL- and AmpC B-lactamase-producing bacteria in that no reliably effective antimicrobial treatment options exist. The carbapenemases can hydrolyze all penicillins, cephalosporins, and carbapenems, rendering these drug classes ineffective. Currently, *K. pneumoniae* is the most commonly encountered bacteria with carbapenemase production [88]. Carbapenemase-producing genes have also occasionally been identified in *E. coli* and other genera of the Enterobacteriaceae family, including *Proteus*, *Serratia*, *Salmonella*, and *Citrobacter* [89–92]. Plasmid and chromosomal carbapenemase enzyme production have also been identified in non-Enterobacteriaceae pathogens including *Acinetobacter* sp., *P. aeruginosa*, and *Stenotrophomonas* sp. [74].

Genes encoding seven types of *Klebsiella pneumoniae* carbapenemase (KPC) have been identified on plasmids that can be readily transferred within the same or different species of Enterobacteriaceae [93, 94]. Such drug resistance transmissibility has led to KPC-producing *Enterobacteriaceae* outbreaks in the Northeastern USA and hospitals around the world. From 2000 to 2007, reported cases of carbapenemase-producing *K. pneumoniae* increased from <1 to 8 % of all identified *Klebsiella* spp. [88]. Investigators at Mount Sinai Hospital in New York City found a 26 % prevalence of carbapenemase-producing *K. pneumoniae* among all invasive *K. pneumoniae* isolates identified between 2004 and 2006 [95]. Similarly, one-third of all *K. pneumoniae* isolated in separate surveillance study in New York City were carbapenemase-producing strains [96]. Previously recognized in India and Pakistan, a new carbapenemase called the New Delhi metallo-beta-lactamase (NDM-1), conferring resistance to all beta-lactam agents except aztreonam, was confirmed in *E. coli*, *K. pneumoniae*, and *E. cloacae* within the United States in 2010 [97].

Risk factors for the development of carbapenemase-producing bacteria include solid organ or hematopoietic stem cell transplantation, mechanical ventilation, longer hospital stay, exposure to cephalosporins and carbapenems [95]. Mortality attributed to carbapenemase-producing *Klebsiella* has been estimated at 35–44 % [93]. Currently, there are no CLSI-validated tests for detecting AmpC B-lactamase or carbapenemase production [75]. Treatment options remain quite limited. In addition to broad B-lactam drug resistance, resistance to fluoroquinolones and sulfonamides is common. Aminoglycosides, colistin, tetracycline, and tigecycline have variable activity.

4 Other Bacterial Pathogens

Clostridium difficile is an anaerobic, spore-forming gram-positive bacillus that is the most common cause of antibiotic-associated pseudomembranous colitis. *C. difficile* infection (CDI) is also the most common nosocomial enteric infection in patients with recent antibiotic use or hospitalization. The spectrum of disease

ranges from an asymptomatic carrier state to fulminant toxic megacolon. Antimicrobials that are active against anaerobic bacteria (especially clindamycin, third-generation cephalosporins, and broad-spectrum penicillins) are more likely to provoke *C. difficile* colitis development. The risk is less with linezolid, aminoglycosides, rifampin, and vancomycin. *C. difficile* toxins can be identified in the stool of 15–25 % of patients with antibiotic-associated diarrhea and in more than 95 % of patients with pseudomembranous colitis [98]. Symptoms of CDI are attributed to two exotoxins (A and B), which produce mucosal damage and inflammation to the colon. The BI/NAP1 strain of *C. difficile* has recently been identified to have a higher toxin production and hypersporulation capacity secondary to deletions in the *tcdC* regulatory gene [99]. Both 18- and 39-base pair deletions have been detected in up to 30 % of patients with CDI in one study but without direct correlation to clinical disease severity. Thus, other genetic and/or patient clinical factors likely contribute toward the severity of CDI [100].

The overall incidence of *C. difficile* colitis in hospitalized patients is 1–2 %; however, in patients with a solid organ or hematopoietic stem cell transplant or receiving myeloablative antineoplastic therapy, the incidence is higher. The increased incidence may reflect a higher usage of antimicrobials, underlying disease, and select chemotherapeutic agents (including adriamycin, cyclophosphamide, methotrexate, 5-fluorouracil, and tacrolimus) [101]. Although the incidence of CDI is variable among different patient groups, it has been reported as high as 15–20 % in hematopoietic stem cell recipients in some centers [102, 103].

Initial steps toward CDI management include cessation of any unnecessary antibiotics. Oral metronidazole or oral vancomycin remains first-line treatment options. For more severe disease, a combination of oral vancomycin and intravenous metronidazole can be used [104]. Intravenous immunoglobulins have been used in select cases but with mixed results. *C. difficile* disease can recur, and the risk of disease relapse progressively increases after each episode of *C. difficile* infection. Options for more refractory or relapsing cases of *C. difficile* include high-dose vancomycin (which may also be given as pulse dosing and tapering regimens), rifaximin, nitazoxanide, fidaxomicin and use of probiotics such as *Saccharomyces boulardii* (see Chapter Enteric Infections). Fecal bacteriotherapy / instillation has been used successfully in more treatment refractory cases but not well studied in patients recently receiving antineoplastic chemotherapy.

Many other anaerobic bacteria can produce significant disease when the integrity of gastrointestinal tract is compromised. Myeloablative chemotherapy, especially idarubicin and cytosine arabinoside, used for the treatment of acute myelogenous leukemia, predispose to mucositis, enteritis, and colitis [105]. *Fusobacterium* spp., *Peptostreptococcus* spp., *and Porphyromonas* spp. are commonly encountered in oral and para-pharyngeal infections, whereas *Bacteroides* spp., *Clostridium* spp., *Prevotella* spp., and *Peptostreptococcus* spp. are frequently identified in intra-abdominal infections. Significant pathogen overlap exists, and anaerobic bacterial infections are typically polymicrobial. Novel bacteria include *Fusobacterium necrophorum*, commonly involved with Lemierre's syndrome, and *C. septicum*, commonly involved in neutropenic colitis.

5 Nocardia

The genus *Nocardia* is a ubiquitous group of environmental bacteria containing over 50 species [106]. *Nocardia* is a novel gram-positive branching filamentous aerobic saprophyte, found in soil, decomposing vegetation and other organic matter, and in fresh and salt water. Both *Nocardia* and *Rhodococcus* are members of the family Nocardiaceae, which belongs to a suborder of 'aerobic actinomycetes' that also includes *Mycobacterium*, *Corynebacterium*, *Gordona*, and *Tsukamurella*. *Nocardia* exhibits varying degrees of acid fastness depending upon the mycolic acid composition in the cell wall and type of stain used [106]. The modified Kinyoun acid-fast stain uses a 1 % sulfuric acid as a decolorizer (instead of the more potent hydrochloric acid used in the decoloration step in Ziehl–Neelsen staining procedure), which enhances the ability of *Nocardia* to retain the colored fuchsin [107]. Unlike mycobacteria, *Nocardia* has a 'beaded' acid-fast appearance on microscopy. In contrast to other gram-positive bacteria, *Nocardia* appears as filamentous bacteria with hyphae-like branching. *Nocardia* can resemble *Actinomyces* spp. on gram stain; however, *Actinomyces* spp. are not acid-fast and grow under anaerobic conditions.

The majority of *Nocardia* infections occur in patients with immunosuppressive conditions; however, up to one-third of patients are immunocompetent [108]. Patients with depressed CMI are especially at high risk including those with lymphoma and other hematologic malignancies, patients taking steroids or other CMI-suppressing medications [109]. Patients with allogenic hematopoietic stem cell transplants are at much higher risk for nocardiosis than autologous hematopoietic stem cell transplant recipients [110, 111]. The development of graft-versus-host disease and subsequent additional immunosuppressive treatments may account for much of the increased risk in allogenic hematopoietic stem cell transplant patients. In hematopoietic stem cell transplant patients, nocardiosis can develop at varying time periods, which range from two–three months to one–two years after the transplant [110, 111]. Although the use of cyclosporin has been associated with the development of nocardiosis [112, 113], combination therapy with cyclosporin and prednisone in some patient groups may pose less risk than azathioprine and prednisone or high-dose prednisone alone [114, 115]. Solid tissue cancers with associated chemotherapy represent another novel category for *Nocardia* disease development. Comorbidities including diabetes, chronic lung disease, and alcoholism contribute as well.

Pulmonary nocardiosis is the most common form of *Nocardia* infection. The onset of symptoms may be subacute to more chronic and can include cough which may be productive, shortness of breath, chest pain, hemoptysis, fever, night sweats, weight loss, and progressive fatigue. The chest X-ray may show focal or multifocal disease containing nodular and/or consolidation infiltrate as well as cavitary lesions [116]. Pleural effusions can develop in up to one-third of patients. It can be very difficult clinically and radiographically to differentiate *Nocardia* from filamentous fungal (e.g., aspergillosis, mucormycosis) or mycobacterial

disease. Occasionally, *Nocardia* spp. may be isolated from the respiratory tract in a person without respiratory disease. *Nocardia* found as an 'airway colonizer' is more typical in patients with underlying structural lung disease such as bronchiectasis and cystic fibrosis [106] and should be interpreted cautiously. The isolation of *Nocardia* in an immunocompromised patient should never be ignored, especially if any abnormal clinical or radiologic pulmonary findings are present.

Extrapulmonary nocardiosis is relatively common and can occur through hematogenous dissemination or a contiguous spread of necrotizing pneumonitis into the pleura, pericardium, mediastinum, and vena cava. Abscess formation is characteristic of extrapulmonary nocardiosis and can resemble a pyogenic bacteria process or evolve into a chronic granulomatous or mixed progressive inflammatory mass. The CNS is the most common extrapulmonary location for nocardiosis (up to 44 % in one series) [116] (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients). Patients may have one or more brain abscesses and present with headache, nausea, vomiting, seizures, or alternation in consciousness [106]. Neurologic symptoms typically develop gradually, although an acute presentation with rapid progression may occasionally occur. Cerebral nocardiosis commonly accompanies pulmonary disease, but isolated CNS disease can present. In immunocompetent patients, cerebral nocardiosis is less common and may resemble a brain tumor or vascular infarct [117, 118].

Primary cutaneous and soft tissue nocardiosis can result from traumatic injury to the skin that involves contamination with soil [119]. Unlike other forms of nocardiosis, primary cutaneous disease usually develops in immunocompetent hosts. After skin inoculation, a superficial abscess or localized cellulitis can develop. Cutaneous nocardiosis can resemble soft tissue infections produced by *S. aureus* or streptococci; however, this form of *Nocardia* disease is usually more indolent [116]. The infection can spread to the regional lymph nodes and produce a single or linear chain of nodular lesions. Lymphocutaneous nocardiosis is often called 'sporotrichoid' nocardiosis given the similar presentation of sporotrichosis. In more advanced disease, a mycetoma can develop with sinus tract development. *N. brasiliensis* is the most common *Nocardia* spp. in cutaneous disease (especially progressive and lymphocutaneous disease) although *N. asteroides* and *N. otitidiscaviarum* have also occasionally been isolated [119].

Nocardia bacteremia is less frequently encountered. In one review of *Nocardia* bacteremia, 64 % patients had concurrent pulmonary nocardiosis, 28 % had concurrent cutaneous disease, and 19 % had concurrent CNS disease [120]. *Nocardia* bacteremia associated with central venous catheter infections has been reported [121, 122]. Polymicrobial bloodstream infections with *Nocardia* spp. and gram-negative bacilli have also been identified. Hematogenously disseminated nocardiosis has led to infection in the eyes (keratitis), heart valves, liver, spleen, adrenal glands, thyroid gland, and organ tissues.

General treatment recommendations for nocardiosis are hindered by the lack of prospective controlled trials. Optimal antimicrobial treatment regimens have not been firmly established. *Nocardia* spp. display variable in vitro antimicrobial

susceptibility patterns, and the management of nocardia infections must be individualized [123]. CLSI has published recommendations for antimicrobial susceptibility testing for *Nocardia* spp. and other aerobic actinomycetes [124]. *Nocardia* isolated from clinically significant infections should undergo antimicrobial susceptibility testing to assist in treatment decisions. Drug susceptibility patterns to major *Nocardia* spp. are listed in Table 2.

Sulfonamides, including sulfadiazine and sulfisoxazole, have been the antimicrobials of choice to treat nocardiosis for the past 50 years despite bacteriostatic activity [125]. TMP-SMX is the most commonly used sulfonamide preparation in the USA, although the benefit of the trimethoprim component is unclear. Divided doses of 5–10 mg/kg/d of the trimethoprim component or (25–50 mg/kg/d sulfamethoxazole) are recommended to produce sulfonamide serum concentrations between 100 and 150 mcg/mL. Adverse reactions to high-dose TMP-SMX are frequent and include myelosuppression, hepatoxicity, and renal insufficiency. TMP-SMX is active against the vast majority of *Nocardia* spp.; however, *N. otitidiscaviarum* is typically resistant to TMP-SMX, and *N. nova* and *N. farcinica* are occasionally resistant as well [119, 125].

Alternative antimicrobial agents with activity against *Nocardia* spp. include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin–clavulanic acid. Imipenem is more active than either meropenem or ertapenem against most *Nocardia* spp. [126]. Ertapenem should not be used as a replacement for imipenem or meropenem. Minocycline appears to have the best anti-*Nocardia* activity of the tetracyclines and is an alternative oral agent in patients allergic to sulfonamides. Tigecycline, a glycylcycline, appears to be active in vitro against most *Nocardia* spp. Of the fluoroquinolones, moxifloxacin is fairly active in vitro against *N. asteroides* complex [126, 127]. Linezolid, an oxazolidinone, is quite active against virtually all known pathogenic *Nocardia* spp. and has successfully been used in the treatment of patients with disseminated and CNS nocardiosis [128]. Amoxicillin/clavulanate is moderately active against many strains of *N. asteroides*, *N. farcinica*, and *N. braziliensis*, but inactive against most strains of *N. nova*, *N. otitidiscaviarum*, and *N. transvalensis* [119].

Combination therapy with imipenem–cefotaxime, amikacin–TMP-SMX, imipenem–TMP-SMX, amikacin–cefotaxime, or amikacin–imipenem may provide enhanced activity [129]. In mice models, amikacin and imipenem were more effective in the treatment of cerebral and pulmonary nocardiosis then TMP-SMX alone [130, 131]. For most forms of nocardiosis, initial combination drug therapy is recommended. In patients with CNS disease, therapy should include drugs with favorable CNS penetration (e.g., TMP-SMX plus ceftriaxone). Patients with severe nocardiosis may benefit from the addition of a third agent such as linezolid. Combination therapy should continue until clinical patient improvement, *Nocardia* speciation, and antimicrobial drug susceptibility information can be confirmed. Single drug therapy may suffice thereafter. Duration of treatment is generally prolonged to minimize risk of disease relapse. Immunocompetent patients with pulmonary or multifocal (non-CNS) nocardiosis

Table 2 Major *Nocardia* pathogens and antimicrobial susceptibility patterns

Species	Antimicrobial susceptibility patterns									
	Sulfamethoxazole	Ampicillin	Amoxicillin/ clavulanate	Ceftriaxone	Linezolid	Amikacin	Imipenem	Ciprofloxacin	Clarithromycin	Other
N. abscessus	+	+	+	+	+	+	−	−	−	
N. brevicatena/ paucivorans complex	+	+	+	+	+	+	−	+	−	a
N. nova complex	+	+ or −	−	+	+	+	+		+	b
N. transvalensis complex	+		+	+	+	−	+	+	−	b
N. farcinica	+ or −	−		−	+	+	+	+	−	c
N. asteroides	+	−	−	+	+	+	+	−	−	d

(continued)

Table 2 (continued)

Species	Antimicrobial susceptibility patterns									
	Sulfamethoxazole	Ampicillin	Amoxicillin/ clavulanate	Ceftriaxone	Linezolid	Amikacin	Imipenem	Ciprofloxacin	Clarithromycin	Other
N. brasiliensis	+	−	+		+			−	−	e
N. pseudo–brasiliensis	+	−	−		+			+	+	
N. otitidiscaviarum	+ or −	−	−	−	+	+	−	+		

(+) active
(−) less active/inactive
(+ or −) may be active, but resistance common
(no entry) variable susceptibility results
a Usually resistant to gentamicin, kanamycin MICs low (<1 ug/mL)
b Usually resistant to all aminoglycosides
c Resistant to all aminoglycosides except amikacin
d N. cyriacigeorgica is susceptible to ampicillin; otherwise, the same as the other *N. asteroides* complex
e Susceptible to minocycline
Note Nocardia asteroides complex is a group of bacteria with a heterozygous pattern of antimicrobial drug susceptibilities [193] and responsible for the majority of clinical human *Nocardia* infections. The subsequent taxonomy of *Nocardia asteroides* complex is reorganized into six species based on drug susceptibility patterns: *N. abscessus, N. brevicatena/paucivorans* complex, *N. nova* complex (which includes *N. nova, N. veterana, N. africana, N. keuczakiae*), *N. transvalensis* complex, *N. farcinica*, and *N. asteroides*
(Based on data from Ref. [106])

may be successfully treated with 6–12 months of antimicrobial therapy. Immunosuppressed patients and those with CNS disease should receive at least 12 months antimicrobial therapy with the appropriate clinical monitoring.

TMP-SMX is an effective prophylaxis agent to prevent *Pneumocystis* pneumonia and also can decrease the risk of nocardia infections. Daily TMP-SMX prophylaxis most reliably prevents nocardiosis and may also account for the decreased prevalence of nocardiosis in patients with advanced HIV infection [132]. Intermittent therapy with oral TMP-SMX (two double-strength tablets twice weekly or one single strength tablet thrice weekly) is less protective against nocardiosis [110, 114, 115].

6 Mycobacteria

Mycobacteria are aerobic bacilli that contain long-chain mycolic acid glycolipids in their cell wall and belong to the family Mycobacteriaceae, order Actinomycetales. All mycobacteria are acid-fast bacilli. Using either the Ziehl–Neelsen or Kinyoun stain, mycobacteria do not decolorize with acidified alcohol after staining with carbolfuchsin. The fluorescent stain auramine–rhodamine is more sensitive for mycobacteria identification but generally less specific compared to the Ziehl–Neelsen or Kinyoun stains. Gram staining mycobacteria occasionally reveal gram-positive or gram-variable bacilli; however, mycobacteria may also appear as unstained silhouettes against the background [133].

Compared to other pathogens, mycobacteria are less commonly encountered in patients with cancer; however, mycobacterial infections in patients who have received a solid organ transplant, hematopoietic stem cell transplant, or antineoplastic chemotherapy are becoming increasingly recognized. This may reflect increased environmental exposures, chemotherapy-induced immunosuppression, improved laboratory diagnostic techniques, and international travel for medical care. *Mycobacteria tuberculosis* is more commonly isolated in patients from countries where tuberculosis is endemic, whereas NTM infections predominate in countries with a lower incidence of tuberculosis [134].

The treatment of mycobacteria poses numerous challenges. Mycobacteria are resistant to many ‘conventional’ antimicrobials and require combination drug therapy for prolonged durations. Drug interactions between antimycobacterial treatment regimens and select antineoplastic drugs along with difficulties in drug susceptibility data interpretation for many NTM species create additional complexities. A multidisciplinary management approach between the hematologist–oncologist and the infectious diseases specialist is essential for favorable patient outcomes.

6.1 *Mycobacteria tuberculosis* Complex

Mycobacteria tuberculosis complex in humans and animals includes *M. tuberculosis*, *M. bovis*, and the less commonly encountered *M. africanum, M. microti,*

M. canettii, M. caprae, and *M. pinnipedii* is primarily responsible for tuberculosis in humans. *M. bovis* commonly infects animals (bovine tuberculosis) and occasionally produces disease in humans consuming unpasteurized milk products or though bladder instillation therapies containing the Bacillus Calmette-Guerin strain of *M. bovis*. Approximately one-third of the global population, including more than 11 million persons in the United States, has been infected with *M. tuberculosis*. In 2007, a total of 13,299 tuberculosis cases were reported in the United States with approximated incidence of 4.6 cases per 100,000 persons [135]. The incidence of tuberculosis in foreign-born persons in the United States is nearly 10 times greater than that of US-born persons. It is therefore consistent that the incidence of tuberculosis in patients with cancer is highest in foreign-born patients [136]. Among patients with cancer, *M. tuberculosis* is most commonly seen in those with hematologic malignancies including acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, and those who have undergone allogenic hematopoietic stem cell transplantation comprise [136–139]. Among allogenic hematopoietic stem cell recipients, chronic graft-versus-host disease and total body irradiation augment the risks for tuberculosis development [140, 141]. Rates of tuberculosis in patients with hematologic cancers are approximately 40 times higher than the general US population [137]. With the exception of head and neck cancers, solid tissue cancers do not present as high of a risk for tuberculosis development. Interestingly, there may be an association between pulmonary tuberculosis and the subsequent development of pulmonary adenocarcinoma [142].

Pulmonary tuberculosis can be divided into primary pulmonary tuberculosis and reactivation (post-primary) tuberculosis. Primary tuberculosis develops as an uninterrupted proliferation of *M. tuberculosis* after initial infection and without a period of quiescence [143]. Symptomatic primary pulmonary tuberculosis is typically encountered in young infants and in HIV-infected patients. However, patients with other immunosuppressive conditions, including hematologic malignancies and cell-mediated immune defects, also may present with primary disease (see Chapter Respiratory Infections). Hilar and mediastinal adenopathy are common with primary disease along with confluent infiltrates in the mid and lower lung fields. Reactivation tuberculosis is most commonly encountered in immunocompetent adults and often radiographically presents as upper lobar fibronodular infiltrates, often with thick-walled cavitary disease and volume loss of the lung. Lower lung and other atypical lung findings occur in up to 1/3 of patients. Hilar adenopathy is unusual with reactivation tuberculosis. Among immunosuppressed patients, especially those with advanced HIV infection and hematopoietic stem cell transplantation, pulmonary tuberculosis commonly radiologically presents as multilobar airspace consolidation or nodular disease [144].

In the setting of immunosuppression, extrapulmonary presentations of tuberculosis are common [145, 146]. Lymphadenitis is the most common form of extrapulmonary tuberculosis and historically has been called scrofula when referring to lymphadenitis of the head and neck region. The cervical lymph nodes (about 60 %) and supraclavicular lymph chains are most commonly involved in TB lymphadenitis; however, the submandibular and auricular nodes may be

affected. Other less common lymph nodes affected include the axillary, inguinal, mesenteric, mediastinal, and inframammary nodes. The most common presenting symptom is a gradually enlarging neck mass (98 % in one case series) [147]. Infected lymph nodes can become fluctuant, matted, or suppurative with sinus formation and spontaneous drainage. They can coalesce into an enlarging mass that can eventually compress other structures, including the esophagus and blood vessels [148]. Fine-needle aspirate (FNA) generally should be the first diagnostic step (with multiple needle passes). Excisional biopsy should be performed if the results (histology and staining) of FNA are indeterminate.

Mycobacterial infectious of the CNS are almost always caused by *M. tuberculosis* [149]. Isolated CNS tuberculosis can occur, or present as a component of disseminated disease. Tuberculosis meningitis is the most common presentation of CNS disease, although tuberculomas, parenchymal abscesses, and spinal arachnoiditis (typically in the basilar meninges) can occur. Tuberculosis meningitis is more common in children under 5 years of age but can also occur in adults, especially those with immunosuppressive conditions or HIV infection [150, 151]. The spinal fluid typically has a lymphocyte-predominant pleocytosis with elevated protein and low glucose. An early neutrophil predominance in up to 25 % of HIV-negative patients, although an ensuing shift to lymphocytes usually occurs in the subsequent 24–48 h [152]. Untreated, progressive CNS tuberculosis leads to cognitive decline, seizures, coma, and death.

Abdominal tuberculosis can present in many forms, including infection of the gastrointestinal tract and the peritoneum. Any part of the gastrointestinal tract may be involved; however, ileocecal disease is most common [153]. Peritoneal tuberculosis develops from hematogenous and lymphatic seeding or from contiguous microbial spread from adjacent infected organs. Hepatosplenic lesions of tuberculosis may appear soon after resolution of chemotherapy-induced neutropenia and clinically resemble hepatosplenic candidiasis [154, 155]. Elevations in CA-125 in women, commonly seen in ovarian carcinoma, may be present in patients with abdominal tuberculosis [156]. Other forms of extrapulmonary tuberculosis including bone and joint disease, pericardial and renal disease should also be considered in the appropriate setting among patients with cancer [139, 157].

Treatment guidelines for pulmonary and extrapulmonary tuberculosis have been published and recommend combination anti-tuberculosis drug therapy [158]. First-line drugs include isoniazid, rifampin, pyrazinamide, and ethambutol. Combination drug therapy is generally recommended for 6–12 months depending upon the type of infection, antimicrobial susceptibility data, and combination drug regimen used in treatment. Drug toxicities and interactions with chemotherapeutic agents require monitoring. Rifampin induces the hepatic metabolism and lowers the serum concentration of many drugs (Table 3).

Mycobacteria bovis is a member of *M. tuberculosis* complex and is a component of intramuscular Bacille Calmette–Guérin (BCG) vaccine given to young children throughout much of the world and intravesicular BCG used in men with bladder cancer. The BCG vaccine is one of the most commonly administered vaccines outside of the United States and administered to prevent or reduce miliary

Table 3 Drug interactions with rifampin

Rifampin induces the hepatic cytochrome P450 enzymatic pathway, resulting in increased metabolism and lower serum concentrations of the following drugs[a]:		
Anticonvulsants (e.g., phenytoin)		
Antiarrhythmics (e.g., disopyramide, mexiletine, quinidine, tocainide)		
Azole antifungals (e.g., fluconazole, itraconazole, voriconazole)		
Calcium channel blockers (e.g., diltiazem, nifedipine, verapamil)		
Oral and systemic contraceptive agents[b]		
Oral hypoglycemic agents (sulfonylureas)		
Opiate analgesics including methadone		
Protease inhibitors (atazanivir, indinavir, amprenavir, daurunavir, saquinavir)		
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)		
Select immunosuppressants (corticosteroids, cyclosporine, tacrolimus)		
Select antimicrobials (e.g., macrolides, doxycycline, ciprofloxacin, chloramphenicol)		
Other:		
Benzodiazepines	Beta-blockers	Theophylline
Levothyroxine	Coumadin	Quinine
Dapsone	Barbiturates	Digoxin

[a]It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin

[b]Patients using oral or other systemic hormonal contraceptives should be advised to change to non-hormonal form of birth control (e.g., condoms) during rifampin therapy

and meningeal tuberculosis in children. The protective effects of the BCG vaccine against tuberculosis development in adults remain ill defined [159]. Because both the intramuscular and intravesicular vaccines contain live bacteria, progressive *M. bovis* infection can develop in patients with immunosuppressive conditions. Disseminated infection with marrow and visceral organ involvement has been reported in patients with hematologic malignancies and/or receiving alemtuzumab [160]. *M. bovis* infection can also be acquired through consumption of contaminated unpasteurized milk from cattle with bovine tuberculosis. Contrasting to *M. tuberculosis*, *M. bovis* is universally resistant to pyrazinamide. First-line active drugs include isoniazid, rifampin, and ethambutol.

6.2 Non-tuberculosis Mycobacteria

NTM are ubiquitous environmental organisms found in water, soil, animals, birds, milk, and other foods [161]. There are over 125 species of NTM [162]; however, a relatively small number of species cause the bulk of human disease. The Runyon classification is an older method using bacterial growth rate, colony morphology, and pigment formation to distinguish common NTM pathogens [133]; however,

current laboratory diagnostics incorporate the use of nucleic acid probes and gene sequencing for speciation.

In contrast to *M. tuberculosis*, NTM are generally less pathogenic, acquired through environment exposure, and not transmitted from person to person. NTM infection may develop from direct skin inoculation or trauma, ingestion, and possibly via inhalation of contaminated aerosols. The precise source of infection, however, usually remains inapparent [163]. Phagocytosis by macrophages and subsequent upregulation of interleukin-12 and interferon-gamma are the primary host defense mechanisms against NTM [164]. Suppression of IL-12 and IFN-γ through select cancers, antineoplastic chemotherapy, or genetic deficiency enables progression and dissemination of NTM disease. The incidence of NTM infections ranges from 0.4 to 4.9 % in hematopoietic stem cell transplant patients [134]. Advanced immunosuppression may preclude granuloma formation and lead to mycobacteria-laden histiocytes or macrophages, as seen with Fite or Ziehl–Neelsen stains [133].

Although *Mycobacterium avium* complex (MAC) can be found worldwide, many NTM have a geographic predominance. *M. kansasii* is more commonly isolated from patients living in the central/midwest states and southern/southwestern states as well as in southeast England and Wales [162, 165, 166]. *M. xenopi* is the second most common NTM isolated in Canada and the UK but is rarely encountered in the USA. *M. malmoense* is more commonly seen in Scandinavia. *M. haemophilum* has a wide geographic distribution including Europe, Israel, Australia, Canada, United Kingdom, Africa, Fiji, and the USA. Pulmonary disease with rapidly growing mycobacteria is more prevalent in the warm, humid southern and Gulf coastal regions of the USA [167]. Other forms of rapid growing mycobacterial disease, however, appear to be less geographically restricted.

Pulmonary disease is the most common manifestation of NTM infection, but extrapulmonary and disseminated NTM disease is increasingly common in immunosuppressed patients and those with underlying cancers. MAC is the most common cause of pulmonary NTM disease in the USA [162] and is the most common disseminated opportunistic bacterial infection in patients with advanced HIV infection [168]. Fibronodular MAC pulmonary disease may appear similar to pulmonary tuberculosis with upper lobe predominance, cavitary disease, and a higher organism burden. Nodular bronchiectasis MAC disease tends to present with scattered pulmonary nodular or micro-nodular infiltrates with underlying bronchiectasis. In contrast to immunocompetent patients and those with underlying chronic lung disease, pulmonary MAC disease is less frequently encountered in patients with advanced HIV infection or other forms of significant immunosuppression. *M. kansasii* is the second most common NTM pulmonary pathogen in the USA and a common pathogen encountered in patients with advanced HIV infection and other immunosuppressive conditions [169]. The pulmonary disease produced by *M. kansasii* can resemble tuberculosis with upper lobe disease and cavitary lesions. *M. kansasii* disease often occurs in patients with hematologic and solid organ cancers, occupational lung disease, and COPD [170–172]. Other significant NTM pulmonary pathogens include *M. abscessus*, *M. fortuitum*, and less commonly *M. szulgai*, *M. simiae*, *M. xenopi*, *M. malmoense*, and *M. celatum*. Lung

infections with rapidly growing mycobacteria, including *M. fortuitum* complex and *M. abscessus* complex, are more common with underlying gastrointestinal disorders including GERD and repetitive vomiting.

The isolation of NTM from respiratory specimens without significant clinical or radiologic findings of disease may represent a more indolent infection and not require treatment [164]. The diagnosis NTM pulmonary disease is based on a collective assessment of clinical patient symptoms with radiologic and microbiologic information. Guidelines for the diagnosis of pulmonary NTM disease have been published [162]. Hematologic and solid organ cancers are not common risk factors for the development of NTM pulmonary disease, but the immunomodulatory effects of some cancers and chemotherapy regimens can significantly augment and accelerate disease progression in patients already infected. Multifocal or diffuse pulmonary NTM disease in patients with cancer and immunosuppression may reflect disseminated disease, especially in the presence of unexplained adenopathy, organomegaly, or cytopenias. Hypersensitivity pneumonitis is another form of pulmonary NTM disease that can occur in select patients from exposure to aerosolized droplets of MAC, especially from indoor hot tubs [173, 174]. Cases have also been identified after exposure from swimming pool water and showers.

Disseminated NTM disease is best described in patients with advanced HIV infection, but has also been associated with hematologic malignancies (including acute leukemias, CML, and hairy cell leukemia) and hematopoietic stem cell transplantation [175–177]. Mycobacteria may be identified in blood cultures, bone marrow, lymph nodes, liver, spleen, and other organ tissues. MAC, *M. kansasii*, *M. xenopi*, *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex are the most frequent NTM identified in patients with disseminated disease. Disseminated MAC may result from either previous enteric or respiratory tract infection [178]. Hepatosplenomegaly, diffuse adenopathy, chronic diarrhea, anemia, and leukopenia are common with disseminated disease. Specialized mycobacterial blood cultures provide a good diagnostic measure for disseminated MAC and have a sensitivity above 90 % in HIV-infected patients [179].

Central venous catheter-related infections are the most common NTM disease in hematopoietic stem cell transplant recipients [134]. The rapidly growing mycobacteria (*M. fortuitum* complex, *M. abscessus* complex, *M. chelonae*) are more frequently associated with catheter infections, although *M. haemophilum* and *M. mucogenicum* have occasionally been encountered. Infected venous catheters with mycobacteria should be promptly removed [180].

NTM lymphadenitis may indicate disseminated NTM disease when multiple lymph nodes are involved or localized infection when isolated in the head and neck region of immunocompetent individuals. FNA or excision biopsy is typically used to make the diagnosis and to exclude other infectious causes as well as lymphoma and some soft tissue tumors. Localized MAC and *M. scrofulaceum* infection of the preauricular, submandibular, and cervical lymph notes are common in children. MAC represents over 90 % of mycobacteria causes for pediatric cervical lymphadenitis [181, 182]. Cervical and perihilar lymphadenitis from *M. haemophilum* infection can also develop in immunocompetent children.

Skin and soft tissue NTM disease is well reported in patients with hematologic malignancies [183, 184], although less than 20 % of NTM infections identified in hematopoietic stem cell recipients present with cutaneous disease [134]. The rapidly growing mycobacteria, including *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex, are especially common in cutaneous and soft tissue infections. Localized infections can develop after surgery or penetrating trauma, whereas multifocal and disseminated lesions are more frequent in immunosuppressed patients. *M. fortuitum* complex tends to be more closely associated with recent penetrating trauma or surgery, whereas *M. chelonae* and *M. abscessus* complex occur more commonly in patients with more immunomodulatory conditions [184]. Cutaneous *M. marinum* infection can develop in both immunocompetent and immunosuppressed patients and may present as skin nodules, commonly in the line of lymphatic drainage. This ascending appearance of infection closely resembles that of sporotrichosis and cutaneous nocardiosis. Single or multiple cutaneous lesions, monoarticular or oligoarticular septic arthritis, and osteomyelitis have been frequently reported with *M. haemophilum* [185, 186].

In vitro drug susceptibility testing for NTM species is problematic. There are little data with NTM correlating in vitro antimicrobial susceptibility results and clinical outcomes. Exceptions that correlate susceptibility data with clinical outcomes include clarithromycin for MAC treatment [187–189] and rifampin for *M. kansasii* treatment. Antimicrobial susceptibility testing for MAC should only routinely be performed for clarithromycin. Amikacin susceptibility testing should also be considered when used in combination therapy [195]. Clarithromycin testing results are predictive of susceptibility to azithromycin, and specific testing for azithromycin activity is more difficult to perform. For *M. kansasii,* susceptibility testing should be performed for rifampin, with additional testing performed for other drugs only if rifampin is resistant in vitro (MIC >1 mcg/mL) [162, 190]. *M. kansasii* may be reported as resistant to isoniazid at MIC 0.2–1.0 mcg/mL but clinically remain susceptible at higher concentrations (e.g., MIC ≤5 mcg/mL) [190]. Despite the lack of clear data, antimicrobial susceptibility testing is still recommended for certain NTM species including the rapidly growing mycobacteria [167]. Ciprofloxacin susceptibility testing correlates with susceptibilities to levofloxacin and ofloxacin, but may not predict nor correlate with susceptibilities to moxifloxacin.

6.2.1 Select NTM Species and Treatment Options

MAC is composed of two related species, *M. avium* and *M. intracellulare*. These species generally are considered together as there is no therapeutic or prognostic value in distinguishing between them. The three most common infections caused by MAC include pulmonary disease, lymphadenitis, and disseminated disease. Pulmonary disease is more readily identified in immunocompetent patients, whereas disseminated disease is more commonly seen in advanced HIV infection and other immunosuppressed patients.

The newer macrolides (clarithromycin and azithromycin) remain the cornerstone of MAC treatment. Combination therapy with a newer macrolide is

recommended as monotherapy can lead to the development of drug resistance [189]. Ethambutol is another active drug, and coadministration with clarithromycin has shown to decrease the emergence of macrolide-resistant MAC [191]. Current recommendations for the treatment of pulmonary MAC disease include clarithromycin or azithromycin plus ethambutol and a rifamycin [162]. Daily or intermittent therapy with amikacin or streptomycin can be added for severe disease or in patients with macrolide resistance. Oral fluoroquinolone, especially moxifloxacin, can also be considered for macrolide-resistant MAC.

M. kansasii is one of the most virulent NTMs and a common human pathogen. Tap water is a primary reservoir for *M. kansasii*. *M. kansasii* can appear as a long, banded, or beaded bacillus when stained with Ziehl–Neelsen or Kinyoun stains. The isolation of *M. kansasii* from any site should generally not be disregarded as a contaminant or colonizer; *M. kansasii* usually has a pathogenic role when isolated in culture [165]. In addition to pulmonary disease, *M. kansasii* occasionally can cause lymphadenitis, granulomatous skin lesions, and osteomyelitis. Rifampin is the cornerstone of *M. kansasii* treatment and usually given in combination therapy with isoniazid and ethambutol. Other active drugs include clarithromycin, newer fluoroquinolones, amikacin, streptomycin, and sulfamethoxazole.

The rapidly growing mycobacteria are defined by their faster growth in solid media with mature mycobacterial colonies developing on solid agar within 7 days, compared to other mycobacteria. In addition to *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex, other occasionally encountered rapidly growing mycobacteria include the *M. smegmatis* group (including *M. smegmatis*, *M. wolinsky*, and *M. goodii*) and *M. immunogenicum*. As with other NTM, the rapidly growing mycobacteria group is ubiquitous in the environment and flourishes in warm humid environments such as hot tubs, spas, and hot water pipes. Although this group typically stains positive with the Ziehl–Neelsen stain or Kinyoun method, these organisms can be weakly acid-fast or even occasionally appear negative on acid-fast staining. Clinical disease with rapidly growing mycobacteria usually is more pronounced in patients with immunosuppressive conditions; however, these organisms produce significant disease in immunocompetent patients as well. Infections more commonly seen with rapidly growing mycobacteria include skin and soft tissue infections, intravenous catheter, and other foreign-body-associated infections, laser in site keratomileusis (LASIK) surgery, and pulmonary disease [167].

The treatment of rapidly growing mycobacteria depends upon the species of bacteria. *M. fortuitum* complex is typically susceptible to more antibiotics than other rapid growers and may include the tetracyclines and sulfamethoxazole. *M. chelonae* is resistant to cefoxitin and usually susceptible to tobramycin. The newer macrolides, moxifloxacin, linezolid, imipenem, and tigecycline often remain active. *M. abscessus sensu stricto* is commonly multidrug resistant (including relative resistance to tobramycin) although may be susceptible to cefoxitin and amikacin. Although the newer macrolides are often active against the rapid growing mycobacteria, *M. fortuitum* complex and *M. abscessus sensu stricto* both contain an erythromycin methylase gene (*erm*), which can produce inducible

resistance to the macrolides (including clarithromycin and azithromycin). Thus, macrolide monotherapy is not recommended.

M. marinum is closely associated with exposures to fish tanks, swimming pools, and other water reservoirs. It typically causes a granulomatous cutaneous disease and tenosynovitis. Infection is acquired through skin inoculation or exposure with preferential growth in the cooler areas of the body (commonly the extremities). Antimicrobials that are usually active against *M. marinum* include clarithromycin (or azithromycin), TMP-SMX, minocycline, doxycycline, moxifloxacin, rifampin, and ethambutol. For most cases of cutaneous disease, combination therapy with two active drugs can be used. Clarithromycin and ethambutol have been commonly used with the addition of rifampin in cases of more severe disease [162]. Tenosynovitis and joint disease may require surgical debridement. Transplant recipients and other immunosuppressed patients should wear gloves to clean fish tanks [134].

M. haemophilum infections occur in two general groups: the severely immunocompromised patients (e.g., lymphoma, solid organ and hematopoietic stem cell transplant recipients, and HIV/AIDS patients) and immunocompetent children [185]. *M. haemophilum* infection is more severe in immunosuppressed patients and includes cutaneous lesions, lymphadenitis, septic arthritis, osteomyelitis, and disseminated disease [185, 186]. Disseminated disease in the lung, blood, and lymph nodes may occur. *M. haemophilum* requires hemin- or iron-supplemented culture media and low temperatures for growth. Amikacin, clarithromycin, the fluoroquinolones, and the rifamycins may be active, but treatment should be guided by antimicrobial susceptible data.

References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 39(3):309–317
2. Lyes RD, Weinstein RA, Hota B (2008) Predictors of methicillin resistance in patients with serious *Staphylococcus aureus* infections. In: ICAAC/IDSA Washington, D.C
3. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R (2006) Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. Clin Infect Dis 42(3):389–391
4. Klevens RM, Morrison MA, Nadle J et al (2007) Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 298(15):1763–1771
5. Kaye KS, Anderson DJ, Choi Y, Link K, Thacker P, Sexton DJ (2008) The deadly toll of invasive methicillin-resistant *Staphylococcus aureus* infection in community hospitals. Clin Infect Dis 46(10):1568–1577
6. Deurenberg RH, Stobberingh EE (2008) The evolution of *Staphylococcus aureus*. Infect Genet Evol 8(6):747–763
7. Naimi TS, LeDell KH, Como-Sabetti K et al (2003) Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 290(22):2976–2984
8. Siberry GK, Tekle T, Carroll K, Dick J (2003) Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. Clin Infect Dis 37(9):1257–1260

9. Gillet Y, Issartel B, Vanhems P et al (2002) Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359(9308):753–759
10. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM (2004) Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 42(6):2398–2402
11. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A (2006) High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 166(19):2138–2144
12. Mermel LA, Farr BM, Sherertz RJ et al (2001) Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 32(9):1249–1272
13. Winston DJ, Dudnick DV, Chapin M, Ho WG, Gale RP, Martin WJ (1983) Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 143(1):32–36
14. Zinkernagel AS, Zinkernagel MS, Elzi MV et al (2008) Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. Infection 36(4):314–321
15. Frank KL, Del Pozo JL, Patel R (2008) From clinical microbiology to infection pathogenesis: how daring to be different works for *Staphylococcus lugdunensis*. Clin Microbiol Rev 21(1):111–133
16. Murray BE (1990) The life and times of the *Enterococcus*. Clin Microbiol Rev 3(1):46–65
17. Ruoff KL, de la Maza L, Murtagh MJ, Spargo JD, Ferraro MJ (1990) Species identities of enterococci isolated from clinical specimens. J Clin Microbiol 28(3):435–437
18. Hamilton-Miller JM (1988) Reversal of activity of trimethoprim against gram-positive cocci by thymidine, thymine and 'folates'. J Antimicrob Chemother 22(1):35–39
19. Courvalin P (2006) Vancomycin resistance in gram-positive cocci. Clin Infect Dis 42(Suppl 1):S25–S34
20. Leclercq R, Derlot E, Duval J, Courvalin P (1988) Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. New England J Med 319(3):157–161
21. Uttley AH, Collins CH, Naidoo J, George RC (1988) Vancomycin-resistant enterococci. Lancet 1(8575–6):57–58
22. Oprea SF, Zaidi N, Donabedian SM, Balasubramaniam M, Hershberger E, Zervos MJ (2004) Molecular and clinical epidemiology of vancomycin-resistant *Enterococcus faecalis*. J Antimicrob Chemother 53(4):626–630
23. Burrell LJ, Grabsch EA, Padiglione AA, Grayson ML (2005) Prevalence of colonisation with vancomycin-resistant enterococci (VRE) among haemodialysis outpatients in Victoria: implications for screening. The Medical journal of Australia 182(9):492
24. Streit JM, Jones RN, Sader HS, Fritsche TR (2004) Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents 24(2):111–118
25. DiazGranados CA, Jernigan JA (2005) Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis 191(4):588–595
26. Zirakzadeh A, Gastineau DA, Mandrekar JN, Burke JP, Johnston PB, Patel R (2008) Vancomycin-resistant enterococcal colonization appears associated with increased mortality among allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant 41(4):385–392
27. Courvalin P (2005) Genetics of glycopeptide resistance in gram-positive pathogens. Int J Med Microbiol 294(8):479–486
28. Miller D, Urdaneta V, Weltman A (2002) Vancomycin-resistant *Staphylococcus aureus*–Pennsylvania. Mmwr 51(40):902

29. Sievert DM, Boulton ML, Stoltman G, Johnson D, Stobierski MG et al (2002) *Staphylococcus aureus* resistant to vancomycin–United States. Mmwr 51(26):565–567
30. Reynolds PE, Courvalin P (2005) Vancomycin resistance in enterococci due to synthesis of precursors terminating in D-alanyl-D-serine. Antimicrob Agents Chemother 49(1):21–25
31. Reid KC, Cockerill IF, Patel R (2001) Clinical and epidemiological features of *Enterococcus casseliflavus/flavescens* and *Enterococcus gallinarum* bacteremia: a report of 20 cases. Clin Infect Dis 32(11):1540–1546
32. Zhanel GG, Hoban DJ, Karlowsky JA (2001) Nitrofurantoin is active against vancomycin-resistant enterococci. Antimicrob Agents Chemother 45(1):324–326
33. Engelhard D, Elishoov H, Or R et al (1995) Cytosine arabinoside as a major risk factor for *Streptococcus viridans* septicemia following bone marrow transplantation: a 5-year prospective study. Bone Marrow Transplant 16(4):565–570
34. Tunkel AR, Sepkowitz KA (2002) Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis 34(11):1524–1529
35. Elting LS, Bodey GP, Keefe BH (1992) Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis 14(6):1201–1207
36. Shenep JL (2000) Viridans-group streptococcal infections in immunocompromised hosts. Int J Antimicrob Agents 14(2):129–135
37. Lu HZ, Weng XH, Zhu B et al (2003) Major outbreak of toxic shock-like syndrome caused by *Streptococcus mitis*. J Clin Microbiol 41(7):3051–3055
38. Kennedy HF, Gemmell CG, Bagg J, Gibson BE, Michie JR (2001) Antimicrobial susceptibility of blood culture isolates of viridans streptococci: relationship to a change in empirical antibiotic therapy in febrile neutropenia. J Antimicrob Chemother 47(5):693–696
39. Moet GJ, Dowzicky MJ, Jones RN (2007) Tigecycline (GAR-936) activity against *Streptococcus gallolyticus* (bovis) and viridans group streptococci. Diagn Microbiol Infect Dis 57(3):333–336
40. Prabhu RM, Piper KE, Litzow MR, Steckelberg JM, Patel R (2005) 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 24(12):832–838
41. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R (2002) Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. Clin Infect Dis 34(11):1469–1474
42. Leport C, Bure A, Leport J, Vilde JL (1987) Incidence of colonic lesions in *Streptococcus bovis* and enterococcal endocarditis. Lancet 1(8535):748
43. Bodey GP, Rodriguez S, Fainstein V, Elting LS (1991) Clostridial bacteremia in cancer patients. A 12-year experience. Cancer 67(7):1928–1942
44. Mirza NN, McCloud JM, Cheetham MJ (2009) *Clostridium septicum* sepsis and colorectal cancer—a reminder. World J Surg Oncol 7:73
45. Senn L, Entenza JM, Greub G et al (2006) Bloodstream and endovascular infections due to *Abiotrophia defectiva* and *Granulicatella* species. BMC Infect Dis 6:9
46. Liao CH, Teng LJ, Hsueh PR et al (2004) Nutritionally variant streptococcal infections at a University Hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. Clin Infect Dis 38(3):452–455
47. Katz SC, Pachter HL (2006) Indications for splenectomy. American Surg 72(7):565–580
48. Russell SJ, Richards JD (1989) Medical indications for splenectomy. Br J Hosp Med 42(2):120–123, 5–6, 7
49. Bisharat N, Omari H, Lavi I, Raz R (2001) Risk of infection and death among post-splenectomy patients. J Infect 43(3):182–186
50. Singer DB (1973) Postsplenectomy sepsis. Perspect Pediatr Pathol 1:285–311
51. Rivero GA, Torres HA, Rolston KV, Kontoyiannis DP (2003) Listeria monocytogenes infection in patients with cancer. Diagn Microbiol Infect Dis 47(2):393–398

52. Safdar A, Papadopoulous EB, Armstrong D (2002) Listeriosis in recipients of allogeneic blood and marrow transplantation: thirteen year review of disease characteristics, treatment outcomes and a new association with human cytomegalovirus infection. Bone Marrow Transplant 29(11):913–916
53. Girmenia C, Iori AP, Bernasconi S et al (2000) Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. Eur J Clin Microbiol Infect Dis 19(9):711–714
54. Klastersky J (1998) Science and pragmatism in the treatment and prevention of neutropenic infection. J Antimicrob Chemother 41 Suppl D:13–24
55. Ramphal R (2004) Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 39(Suppl 1):S25–S31
56. Klastersky J, Ameye L, Maertens J et al (2007) Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents 30(Suppl 1):S51–S59
57. Feld R (2008) Bloodstream infections in cancer patients with febrile neutropenia. Int J Antimicrob Agents 32(Suppl 1):S30–S33
58. Cheong HS, Kang CI, Wi YM et al (2008) Clinical significance and predictors of community-onset *Pseudomonas aeruginosa* bacteremia. Am J Med 121(8):709–714
59. Whitecar JP Jr, Luna M, Bodey GP (1970) *Pseudomonas* bacteremia in patients with malignant diseases. Am J Med Sci 60(4):216–223
60. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G (2000) Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch Intern Med 160(4):501–509
61. Bodey GP, Jadeja L, Elting L (1985) *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. Arch Intern Med 145(9):1621–1629
62. Escande MC, Herbrecht R (1998) Prospective study of bacteraemia in cancer patients. Results of a French multicentre study. Support Care Cancer 6(3):273–280
63. Hakki M, Limaye AP, Kim HW, Kirby KA, Corey L, Boeckh M (2007) Invasive *Pseudomonas aeruginosa* infections: high rate of recurrence and mortality after hematopoietic cell transplantation. Bone Marrow Transplant 39(11):687–693
64. Bodey GP (2001) *Pseudomonas aeruginosa* infections in cancer patients: have they gone away? Curr Opin Infect Dis 14(4):403–407
65. Ohmagari N, Hanna H, Graviss L et al (2005) Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. Cancer 104(1):205–212
66. Thomson KS, Smith Moland E (2000) Version 2000: the new beta-lactamases of Gram-negative bacteria at the dawn of the new millennium. Microbes Infect/Institut Pasteur 2(10):1225–1235
67. Nseir S, Di Pompeo C, Cavestri B et al (2006) Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: prevalence, risk factors, and outcome. Crit Care Med 34(12):2959–2966
68. Cardo D, Horan T, Andrus M, Dembinski M, Edwards J, Peavy G et al (2004) National nosocomial infections surveillance (NNIS) system report data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 32(8):470–485
69. Rosenthal VD, Maki DG, Mehta A et al (2008) International nosocomial infection control consortium report, data summary for 2002–2007, issued January 2008. Am J Infect Control 36(9):627–637
70. Livermore DM (1995) beta-Lactamases in laboratory and clinical resistance. Clin Microbiol Rev 8(4):557–584
71. Bradford PA (2001) Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 14(4):933-951, table of contents
72. Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 18(4):657–686

73. Pitout JD (2010) Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs 70(3):313–333
74. Thomson KS (2010) Extended-spectrum-beta-lactamase, AmpC, and Carbapenemase issues. J Clin Microbiol 48(4):1019–1025
75. Jacoby GA, Munoz-Price LS (2005) The new beta-lactamases. N Engl J Med 352(4):380–391
76. Graffunder EM, Preston KE, Evans AM, Venezia RA (2005) Risk factors associated with extended-spectrum beta-lactamase-producing organisms at a tertiary care hospital. J Antimicrob Chemother 56(1):139–145
77. Piroth L, Aube H, Doise JM, Vincent-Martin M (1998) Spread of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: are beta-lactamase inhibitors of therapeutic value? Clin Infect Dis 27(1):76–80
78. Rice LB, Carias LL, Bonomo RA, Shlaes DM (1996) Molecular genetics of resistance to both ceftazidime and beta-lactam-beta-lactamase inhibitor combinations in *Klebsiella pneumoniae* and in vivo response to beta-lactam therapy. J Infect Dis 173(1):151–158
79. Rice L (2001) Evolution and clinical importance of extended-spectrum beta-lactamases. Chest 119(2 Suppl):391S–396S
80. Gottlieb T, Wolfson C (2000) Comparison of the MICs of cefepime for extended-spectrum beta-lactamase-producing and non-extended-spectrum beta-lactamase-producing strains of *Enterobacter cloacae*. J Antimicrob Chemother 46(2):330–331
81. Pitout JD (2008) Multiresistant Enterobacteriaceae: new threat of an old problem. Expert Rev Anti-infect Ther 6(5):657–669
82. Talon D, Bailly P, Bertrand X, Thouverez M, Mulin B (2000) Clinical and molecular epidemiology of chromosome-mediated resistance to third-generation cephalosporins in *Enterobacter* isolates in eastern France. Clin Microbiol Infect 6(7):376–384
83. Pfaller MA, Jones RN, Marshall SA et al (1997) Inducible amp C beta-lactamase producing gram-negative bacilli from blood stream infections: frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE). Diagn Microbiol Infect Dis 28(4):211–219
84. Philippon A, Arlet G, Jacoby GA (2002) Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother 46(1):1–11
85. Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y (2001) Risk factors for emergence of resistance to broad-spectrum cephalosporins among *Enterobacter* spp. Antimicrob Agents Chemother 45(9):2628–2630
86. Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y (2002) Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. Arch Intern Med 162(2):185–190
87. Muller A, Lopez-Lozano JM, Bertrand X, Talon D (2004) Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae*. J Antimicrob Chemother 54(1):173–177
88. Lledo W, Hernandez M, Lopez E, Molinari OL, Soto RQ, Hernandez E et al (2009) Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. Mmwr 58(10):256–260
89. Tibbetts R, Frye JG, Marschall J, Warren D, Dunne W (2008) Detection of KPC-2 in a clinical isolate of *Proteus mirabilis* and first reported description of carbapenemase resistance caused by a KPC beta-lactamase in *P. mirabilis*. J Clin Microbiol 46(9):3080–3083
90. Zhang R, Zhou HW, Cai JC, Chen GX (2007) Plasmid-mediated carbapenem-hydrolysing beta-lactamase KPC-2 in carbapenem-resistant *Serratia marcescens* isolates from Hangzhou, China. J Antimicrob Chemother 59(3):574–576

91. Miriagou V, Tzouvelekis LS, Rossiter S, Tzelepi E, Angulo FJ, Whichard JM (2003) Imipenem resistance in a *Salmonella* clinical strain due to plasmid-mediated class A carbapenemase KPC-2. Antimicrob Agents Chemother 47(4):1297–1300
92. Rasheed JK, Biddle JW, Anderson KF et al (2008) Detection of the *Klebsiella pneumoniae* carbapenemase type 2 Carbapenem-hydrolyzing enzyme in clinical isolates of *Citrobacter freundii* and *K. oxytoca* carrying a common plasmid. J Clin Microbiol 46(6):2066–2069
93. Schwaber MJ, Carmeli Y (2008) Carbapenem-resistant Enterobacteriaceae: a potential threat. JAMA 300(24):2911–2913
94. Nordmann P, Cuzon G, Naas T (2009) The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis 9(4):228–236
95. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP (2008) Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 29(12):1099–1106
96. Bratu S, Mooty M, Nichani S et al (2005) Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. Antimicrob Agents Chemother 49(7):3018–3020
97. (2010) Detection of Enterobacteriaceae isolates carrying metallo-beta-lactamase—United States. Mmwr 59(24):750
98. Bartlett JG (1994) *Clostridium difficile*: history of its role as an enteric pathogen and the current state of knowledge about the organism. Clin Infect Dis 18(Suppl 4):S265–S272
99. Dupuy B, Govind R, Antunes A, Matamouros S (2008) *Clostridium difficile* toxin synthesis is negatively regulated by TcdC. J Med Microbiol 57(Pt 6):685–689
100. Verdoorn BP, Orenstein R, Rosenblatt JE et al (2010) High prevalence of tcdC deletion-carrying *Clostridium difficile* and lack of association with disease severity. Diagn Microbiol Infect Dis 66(1):24–8
101. Schaier M, Wendt C, Zeier M, Ritz E (2004) *Clostridium difficile* diarrhoea in the immunosuppressed patient–update on prevention and management. Nephrol Dial Transplant 19(10):2432–2436
102. Chakrabarti S, Lees A, Jones SG, Milligan DW (2000) *Clostridium difficile* infection in allogeneic stem cell transplant recipients is associated with severe graft-versus-host disease and non-relapse mortality. Bone Marrow Transplant 26(8):871–876
103. Arango JI, Restrepo A, Schneider DL et al (2006) Incidence of *Clostridium difficile*-associated diarrhea before and after autologous peripheral blood stem cell transplantation for lymphoma and multiple myeloma. Bone Marrow Transplant 37(5):517–521
104. Gerding DN, Muto CA, Owens RC Jr (2008) Treatment of *Clostridium difficile* infection. Clin Infect Dis 46(Suppl 1):S32–S42
105. Hogan WJ, Letendre L, Litzow MR et al (2002) Neutropenic colitis after treatment of acute myelogenous leukemia with idarubicin and cytosine arabinoside. Mayo Clin Proc 77(8):760–762
106. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr (2006) Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 19(2):259–282
107. McNeil MM, Brown JM (1994) The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev 7(3):357–417
108. Beaman BL, Burnside J, Edwards B, Causey W (1976) Nocardial infections in the United States, 1972–1974. J Infect Dis 134(3):286–289
109. Rubin R, Young LS (2002) A clinical approach to infection in the compromised host, chapter 7, *Mycobacteria* and nocardial disease in the compromised host, pages 257–61, 4th edn. Kluwer Academic, New York
110. Choucino C, Goodman SA, Greer JP, Stein RS, Wolff SN, Dummer JS (1996) Nocardial infections in bone marrow transplant recipients. Clin Infect Dis 23(5):1012–1019
111. van Burik JA, Hackman RC, Nadeem SQ et al (1997) Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis 24(6):1154–1160

112. Stack WA, Richardson PD, Logan RP, Mahida YR, Hawkey CJ (2001) *Nocardia asteroides* lung abscess in acute ulcerative colitis treated with cyclosporine. Am J Gastroenterol 96(7):2255–2256
113. Tada Y, Fukuoka M, Mitamura M et al (2008) Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci 336(1):77–80
114. Arduino RC, Johnson PC, Miranda AG (1993) Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. Clin Infect Dis 16(4):505–512
115. Roberts SA, Franklin JC, Mijch A, Spelman D (2000) *Nocardia* infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. Clin Infect Dis 31(4):968–972
116. Beaman BL, Beaman L (1994) Nocardia species: host-parasite relationships. Clin Microbiol Rev 7(2):213–264
117. Borm W, Gleixner M (2003) *Nocardia* brain abscess misinterpreted as cerebral infarction. J Clin Neurosci 10(1):130–132
118. Menku A, Kurtsoy A, Tucer B, Yildiz O, Akdemir H (2004) *Nocardia* brain abscess mimicking brain tumour in immunocompetent patients: report of two cases and review of the literature. Acta Neurochirurgica 146(4):411–414, discussion 4
119. Lerner PI (1996) Nocardiosis. Clin Infect Dis 22(6):891–903, quiz 4–5
120. Kontoyiannis DP, Ruoff K, Hooper DC (1998) *Nocardia* bacteremia. Report of 4 cases and review of the literature. Medicine 77(4):255–67
121. Kontoyiannis DP, Jacobson KL, Whimbey EE, Rolston KV, Raad II (2000) Central venous catheter-associated *Nocardia* bacteremia: an unusual manifestation of nocardiosis. Clin Infect Dis 31(2):617–618
122. Lai CH, Chi CY, Chen HP, Lai CJ, Fung CP, Liu CY (2004) Port-A catheter-associated *Nocardia* bacteremia detected by gallium inflammation scan: a case report and literature review. Scand J Infect Dis 36(10):775–777
123. Munoz J, Mirelis B, Aragon LM et al (2007) Clinical and microbiological features of nocardiosis 1997–2003. J Med Microbiol 56(Pt 4):545–550
124. Woods GL, Brown-Elliott BA, Desmond EP, Hall GS, Heifets L, Pfyffer GE et al (2003) Susceptibility testing of mycobacteria, *Nocardiae*, and other aerobic actinomycetes; approved standard. NCCLS document M24-A, vol 23. Clinical and Laboratory Standards Institute (formerly NCCLS), Wayne
125. McNeil MM, Brown JM, Hutwagner LC, Schiff TA (1995) Evaluation of therapy for *Nocardia asteroides* complex infection. CDN/NCID report. Infect Dis Clin Pract 4(4):287–292
126. Cercenado E, Marin M, Sanchez-Martinez M, Cuevas O, Martinez-Alarcon J, Bouza E (2007) In vitro activities of tigecycline and eight other antimicrobials against different *Nocardia* species identified by molecular methods. Antimicrob Agents Chemother 51(3):1102–1104
127. Hoogkamp-Korstanje JA, Roelofs-Willemse J (2000) Comparative in vitro activity of moxifloxacin against Gram-positive clinical isolates. J Antimicrob Chemother 45(1):31–39
128. Moylett EH, Pacheco SE, Brown-Elliott BA et al (2003) Clinical experience with linezolid for the treatment of nocardia infection. Clin Infect Dis 36(3):313–318
129. Gombert ME, Aulicino TM (1983) Synergism of imipenem and amikacin in combination with other antibiotics against *Nocardia asteroides*. Antimicrob Agents Chemother 24(5):810–811
130. Gombert ME, Aulicino TM, duBouchet L, Silverman GE, Sheinbaum WM (1986) Therapy of experimental cerebral nocardiosis with imipenem, amikacin, trimethoprim-sulfamethoxazole, and minocycline. Antimicrob Agents Chemother 30(2):270–273
131. Gombert ME, Berkowitz LB, Aulicino TM, duBouchet L (1990) Therapy of pulmonary nocardiosis in immunocompromised mice. Antimicrob Agents Chemother 34(9):1766–1768
132. Peterson PK, Ferguson R, Fryd DS, Balfour HH Jr, Rynasiewicz J, Simmons RL (1982) Infectious diseases in hospitalized renal transplant recipients: a prospective study of a complex and evolving problem. Medicine 61(6):360–372

133. Jarzembowski JA, Young MB (2008) Nontuberculous mycobacterial infections. Arch Pathol Lab Med 132(8):1333–1341
134. Doucette K, Fishman JA (2004) Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 38(10):1428–1439
135. Pratt R, Robison V, Navin T, Menzies H (2008) Trends in tuberculosis–United States, 2007. Mmwr 57(11):281–285
136. Libshitz HI, Pannu HK, Elting LS, Cooksley CD (1997) Tuberculosis in cancer patients: an update. J Thorac Imaging 12(1):41–46
137. Kamboj M, Sepkowitz KA (2006) The risk of tuberculosis in patients with cancer. Clin Infect Dis 42(11):1592–1595
138. Silva FA, Matos JO, de QMFC, Nucci M (2005) Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignances. Haematologica 90(8):1110–1115
139. De La Rosa GR, Jacobson KL, Rolston KV, Raad II, Kontoyiannis DP, Safdar A (2004) *Mycobacterium tuberculosis* at a comprehensive cancer centre: active disease in patients with underlying malignancy during 1990-2000. Clin Microbiol Infect 10(8):749–752
140. Ip MS, Yuen KY, Woo PC et al (1998) Risk factors for pulmonary tuberculosis in bone marrow transplant recipients. Am J Respir Crit Care Med 158(4):1173–1177
141. Lee J, Lee MH, Kim WS et al (2004) Tuberculosis in hematopoietic stem cell transplant recipients in Korea. Int J Hematol 79(2):185–188
142. Liang HY, Li XL, Yu XS et al (2009) Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. Int J Cancer 125(12):2936–2944
143. Iseman M (2000) A clinician's guide to tuberculosis, chapter 6- pulmonary tuberculosis in adults, page 129. Lippincott Williams & Wilkins
144. Jung JI, Lee DG, Kim YJ, Yoon HK, Kim CC, Park SH (2009) Pulmonary tuberculosis after hematopoietic stem cell transplantation: radiologic findings. J Thorac Imaging 24(1):10–16
145. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF (1993) Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 148(5):1292–1297
146. Khan B, Ahmed P, Ullah K, Hussain CA, Hussain I, Raza S (2005) Frequency of tuberculosis in haematological malignancies and stem cell transplant recipients. J Coll Physicians Surg Pak 15(1):30–33
147. Polesky A, Grove W, Bhatia G (2005) Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. Medicine 84(6):350–362
148. Lazarus AA, Thilagar B (2007) Tuberculous lymphadenitis. Dis Mon 53(1):10–15
149. Garcia-Monco JC (1999) Central nervous system tuberculosis. Neurol Clin 17(4):737–759
150. Yaramis A, Gurkan F, Elevli M et al (1998) Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics 102(5):E49
151. Lesprit P, Zagdanski AM, de La Blanchardiere A et al (1997) Cerebral tuberculosis in patients with the acquired immunodeficiency syndrome (AIDS). Report of 6 cases and review. Medicine 76(6):423–431
152. Verdon R, Chevret S, Laissy JP, Wolff M (1996) Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis 22(6):982–988
153. Sharma MP, Bhatia V (2004) Abdominal tuberculosis. Indian J Med Res 120(4):305–315
154. Chakrabarti S, Varma S, Kochhar R, Gupta S, Gupta SK, Rajwanshi A (1998) Hepatosplenic tuberculosis: a cause of persistent fever during recovery from prolonged neutropenia. Int J Tuberc Lung Dis 2(7):575–579
155. Lee DG, Choi JH, Kim YJ et al (2001) Hepatosplenic tuberculosis mimicking disseminated candidiasis in patients with acute leukemia. Int J Hematol 73(1):119–121
156. Uzunkoy A, Harma M, Harma M (2004) Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature. World J Gastroenterol 10(24):3647–3649
157. Aisenberg GM, Jacobson K, Chemaly RF, Rolston KV, Raad II, Safdar A (2005) Extrapulmonary tuberculosis active infection misdiagnosed as cancer: *Mycobacterium*

tuberculosis disease in patients at a Comprehensive Cancer Center (2001–2005). Cancer 104(12):2882–2887
158. Blumberg HM, Burman WJ, Chaisson RE et al (2003) American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 167(4):603–662
159. Colditz GA, Brewer TF, Berkey CS et al (1994) Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. Jama 271(9):698–702
160. Abad S, Gyan E, Moachon L et al (2003) Tuberculosis due to *Mycobacterium bovis* after alemtuzumab administration. Clin Infect Dis 37(2):e27–e28
161. Wolinsky E (1979) Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 119(1):107–159
162. Griffith DE, Aksamit T, Brown-Elliott BA et al (2007) An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175(4):367–416
163. von Reyn CF, Arbeit RD, Horsburgh CR et al (2002) Sources of disseminated *Mycobacterium avium* infection in AIDS. J Infect 44(3):166–170
164. Johnson MM, Waller EA, Leventhal JP (2008) Nontuberculous mycobacterial pulmonary disease. Curr Opin Pulm Med 14(3):203–210
165. Marras TK, Daley CL (2002) Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 23(3):553–567
166. Griffith DE (2002) Management of disease due to *Mycobacterium kansasii*. Clin Chest Med 23(3):613–621, 6
167. De Groote MA, Huitt G (2006) Infections due to rapidly growing mycobacteria. Clin Infect Dis 42(12):1756–1763
168. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA (1992) Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 165(6):1082–1085
169. Marras TK, Daley CL (2004) A systematic review of the clinical significance of pulmonary *Mycobacterium kansasii* isolates in HIV infection. J Acquir Immune Defic Syndr (1999) 36(4):883–889
170. Jacobson KL, Teira R, Libshitz HI et al (2000) *Mycobacterium kansasii* infections in patients with cancer. Clin Infect Dis 30(6):965–969
171. Bloch KC, Zwerling L, Pletcher MJ et al (1998) Incidence and clinical implications of isolation of *Mycobacterium kansasii*: results of a 5-year, population-based study. Ann Intern Med 129(9):698–704
172. Corbett EL, Churchyard GJ, Hay M et al (1999) The impact of HIV infection on *Mycobacterium kansasii* disease in South African gold miners. Am J Respir Crit Care Med 160(1):10–14
173. Kahana LM, Kay JM, Yakrus MA, Waserman S (1997) *Mycobacterium avium* complex infection in an immunocompetent young adult related to hot tub exposure. Chest 111(1):242–245
174. Embil J, Warren P, Yakrus M et al (1997) Pulmonary illness associated with exposure to Mycobacterium-avium complex in hot tub water. Hypersensitivity pneumonitis or infection? Chest 111(3):813–816
175. Akiyama H, Maruyama T, Uetake T, Kawaguchi K, Sakamaki H, Onozawa Y (1991) Systemic infection due to atypical mycobacteria in patients with chronic myelogenous leukemia. Rev Infect Dis 13(5):815–818
176. Levendoglu-Tugal O, Munoz J, Brudnicki A, Fevzi Ozkaynak M, Sandoval C, Jayabose S (1998) Infections due to nontuberculous mycobacteria in children with leukemia. Clin Infect Dis 27(5):1227–1230
177. Horwitz ME, Uzel G, Linton GF et al (2003) Persistent *Mycobacterium avium* infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency. Blood 102(7):2692–2694

178. Chin DP, Hopewell PC, Yajko DM et al (1994) *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *M. avium* complex bacteremia in patients with human immunodeficiency virus infection. J Infect Dis 169(2):289–295
179. Yagupsky P, Menegus MA (1990) Cumulative positivity rates of multiple blood cultures for *Mycobacterium avium*-intracellulare and *Cryptococcus neoformans* in patients with the acquired immunodeficiency syndrome. Arch Pathol Lab Med 114(9):923–925
180. Mermel LA, Allon M, Bouza E et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 49(1):1–45
181. Maltezou HC, Spyridis P, Kafetzis DA (1999) Nontuberculous mycobacterial lymphadenitis in children. Pediatr Infect Dis J 18(11):968–970
182. Wolinsky E (1995) Mycobacterial lymphadenitis in children: a prospective study of 105 nontuberculous cases with long-term follow-up. Clin Infect Dis 20(4):954–963
183. Ingram CW, Tanner DC, Durack DT, Kernodle GW Jr, Corey GR (1993) Disseminated infection with rapidly growing mycobacteria. Clin Infect Dis 16(4):463–471
184. Uslan DZ, Kowalski TJ, Wengenack NL, Virk A, Wilson JW (2006) Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. Arch Dermatol 142(10):1287–1292
185. Straus WL, Ostroff SM, Jernigan DB et al (1994) Clinical and epidemiologic characteristics of *Mycobacterium haemophilum*, an emerging pathogen in immunocompromised patients. Ann Intern Med 120(2):118–125
186. Dobos KM, Quinn FD, Ashford DA, Horsburgh CR, King CH (1999) Emergence of a unique group of necrotizing mycobacterial diseases. Emerg Infect Dis 5(3):367–378
187. Dautzenberg B, Piperno D, Diot P, Truffot-Pernot C, Chauvin JP (1995) Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Clarithromycin Study Group of France. Chest 107(4):1035–1040
188. Kobashi Y, Yoshida K, Miyashita N, Niki Y, Oka M (2006) Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates. J Infect Chemother 12(4):195–202
189. Chaisson RE, Benson CA, Dube MP et al (1994) Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Ann Intern Med 121(12):905–911
190. Woods GL (2000) Susceptibility testing for mycobacteria. Clin Infect Dis 31(5):1209–1215
191. Bermudez LE, Nash KA, Petrofsky M, Young LS, Inderlied CB (1996) Effect of ethambutol on emergence of clarithromycin-resistant *Mycobacterium avium* complex in the beige mouse model. J Infect Dis 174(6):1218–1222
192. Kowalski TJ, Berbari EF, Osmon DR (2005) Epidemiology, treatment, and prevention of community-acquired methicillin-resistant *Staphylococcus aureus* infections. Mayo Clinic Proc 80(9):1201–1207, quiz 8
193. Wallace RJ Jr, Steele LC, Sumter G, Smith JM (1988) Antimicrobial susceptibility patterns of *Nocardia asteroides*. Antimicrob Agents Chemother 32(12):1776–1779
194. Deurenberg RH, Stobberingh EE (2009) International working group on the classification of staphylococcal cassette chromosome elements. Antimicrob Agents Chemother 53:4961–4967
195. Brown-Elliott, B et al (2013) *In Vitro* activity of amikacin against isolates of *Mycobacterium avium* complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. J Clin Microbiol 51(10):3389–3394