aeruginosa was implicated in 4.4% of all cases. *P. aeruginosa* osteomyelitis was associated with a twofold higher risk for recurrence compared with osteomyelitis caused by *S. aureus,* and amputation was required among 15% of patients compared with 3% to 7% when other pathogens were implicated.[110]

Sternoclavicular Septic Arthritis

P. aeruginosa accounts for approximately 10% of all cases of sternoclavicular septic arthritis. Risk factors include intravenous drug use, diabetes mellitus, trauma, and infected central venous lines. Before 1981, intravenous drug use was the main risk factor for *P. aeruginosa* sternoclavicular septic arthritis and accounted for 82% of all cases in this patient population. During this period, pentazocine with tripelennamine was a popular combination of opiate abuse. The pills required crushing and dissolving with water before injection. This form of injection drug use favored contamination by *P. aeruginosa* owing to the use of nonsterile water for dissolving the pills as well as possible favored growth of *P. aeruginosa* in the tripelennamine component.[111] After 1981, pentazocine was combined with naloxone, a narcotic antagonist when injected parenterally. This reformulation ended the epidemic of pentazocine-tripelennamine abuse and is believed to explain the subsequent decrease in cases of *P. aeruginosa* sternoclavicular septic arthritis.[112] *P. aeruginosa* now accounts for only 14% of cases among intravenous drug users.[112]

Common presenting symptoms include chest and shoulder pain, with fever present among 65% of patients. Over two-thirds have concomitant bacteremia. Complications from sternoclavicular septic arthritis include osteomyelitis, abscess formation, and mediastinitis.

Septic Arthritis of the Symphysis Pubis

Approximately 24% of cases of septic arthritis of the symphysis pubis are caused by *P. aeruginosa.* The great majority of cases are seen among intravenous drug users. As with septic arthritis of the sternoclavicular joint, cases of arthritis of the symphysis pubis caused by *P. aeruginosa* have decreased dramatically after 1981. Other patient populations at high risk are patients who have undergone urologic, pelvic, or gynecologic procedures.[113] Common presenting signs and symptoms include pain on walking or hip motion, fever, and pubic or groin pain. Osteomyelitis is present in the great majority of patients.

Vertebral Osteomyelitis

P. aeruginosa is the most common pathogen implicated in vertebral osteomyelitis among intravenous drug users, accounting for over two-thirds of cases.[114] Patients present after 1 to 3 months of symptoms, which include neck or back pain, with fever present in fewer than half. Any part of the spine can be involved, but lumbar and cervical osteomyelitis are most common, being present among 53% and 27% of patients, respectively. *P. aeruginosa* vertebral osteomyelitis can also occur as a complication of epidural anesthesia.[115]

Skull Base Osteomyelitis

Skull base osteomyelitis occurs predominantly among immunocompromised patients, especially the elderly with diabetes mellitus. *P. aeruginosa* is the most common causative pathogen, implicated in 50% of all cases. Skull base osteomyelitis is a complication of otitis externa and media, as well as infections of the mastoid and sinuses. If due to ear infections, patients will present with severe otalgia and unilateral otorrhea. If there is extension of the local infection, lower cranial nerve palsies ensue, especially involvement of the facial nerve, which is present in 60% of patients. Severe cases can also present as bilateral skull base osteomyelitis and bilateral cranial nerve palsies.[116] Blood cultures are usually negative. Mortality rates approach 15%.[117,118]

Treatment should follow similar principles as for osteomyelitis at other body sites; however, a longer duration of therapy (12 weeks) has also been used.[117]

Osteomyelitis Related to Nail Puncture Wounds

Nail puncture wounds to the plantar surface of the foot caused by *P. aeruginosa* are a result of inoculation of this pathogen through contaminated sneakers (also called tennis shoes). Coinfection with *S. aureus* has been reported. Surgical débridement is usually necessary. Osteomyelitis occurs in 1% to 2% of patients and if present should be treated with ciprofloxacin (750 mg orally twice a day) or levofloxacin (750 mg orally once a day) for a minimum of 6 weeks. Alternative antimicrobial agents include ceftazidime (2 g IV every 8 hours) or cefepime (2 g IV every 12 hours).[119,120] Plain radiographs are necessary to exclude the presence of foreign bodies, and tetanus immunization should be updated.

Combat-Related Osteomyelitis

P. aeruginosa and *Acinetobacter* species are gram-negative bacteria that are frequently recovered from combat-related cases of osteomyelitis. The microbiology of causative pathogens, however, may differ depending on whether the osteomyelitis is a new or recurrent infection. A retrospective study of casualties occurring in Operation Iraqi Freedom and Operation Enduring Freedom identified 110 cases of osteomyelitis occurring from 2003 to 2006. Gram-negative bacteria, including *P. aeruginosa, Acinetobacter* species, and *K. pneumoniae,* were more likely to be recovered during the initial episode of infection as opposed to a recurrence, in which gram-positive bacteria, such as *S. aureus,* was more likely to be recovered.[121–123]

Antimicrobial Therapy for Arthritis and Osteomyelitis

No clinical trial has evaluated whether combination therapy versus monotherapy is the optimal treatment for *P. aeruginosa* arthritis or osteomyelitis. As with other types of infections, a reasonable approach is to begin with combination therapy if *P. aeruginosa* is suspected and there is a high rate of antimicrobial resistance. Streamlining therapy to a single agent to which the pathogen is susceptible, including an antipseudomonal β-lactam antimicrobial agent, ciprofloxacin, or levofloxacin, should then be considered. The IDSA 2013 guidelines for prosthetic joint infections caused by *P. aeruginosa* recommend treatment with cefepime (2 g IV every 12 hours) or meropenem (1 g IV every 8 hours). Alternative antimicrobial agents to consider include ciprofloxacin (750 mg orally twice a day or 400 mg IV every 12 hours) or ceftazidime (2 g IV every 8 hours) for 4 to 6 weeks. These guidelines state that use of aminoglycosides is optional but that use of two active drugs should be considered based on the clinical circumstances of the patient.[124] Until specific guidelines are available for osteomyelitis, it is likely that these recommendations for the treatment of prosthetic joint infections can be extended to the treatment of osteomyelitis.

Skin and Soft Tissue Infections

Pseudomonal infections of the skin are usually the result of excessive local moisture, including swimming, laundry work, or hiking in wet areas, and are often self-limited. More serious skin conditions, such as ecthyma gangrenosum, are usually seen among the immunocompromised population. *P. aeruginosa* has a major impact on burn wound victims, as discussed in Chapter 314.

Paronychia and Green Nail Syndrome

Paronychia presents as erythema, edema, and tenderness at the adjoining nail plate and occurs as a result of inflammation or infection of the nail folds after breaches in the skin integrity between the nail fold and nail plate. Foci of purulence can also develop. Acute paronychia is primarily caused by *Pseudomonas* species, as well as *Staphylococcus* species and *Streptococcus* species. Ongoing exposure to water, as well as repeated trauma, psoriasis, and eczema, leads to chronic paronychia. Green nail syndrome is an extension of chronic paronychia and presents as a classic triad of proximal chronic paronychia, distolateral onycholysis, and bluish-green discoloration of the nail plate. This discoloration is due to the pyocyanin and pyoverdin pigments produced by *Pseudomonas* species (Fig. 219.2). Treatment consists of cessation of water exposure and application of a 2% sodium hypochlorite solution on the nail bed or acetic acid soaks twice a day. Topical antimicrobial agents, including tobramycin otic or ophthalmic drops placed under the nail bed,[125] are also effective in conjunction with the recommendations about water exposure and pH management.

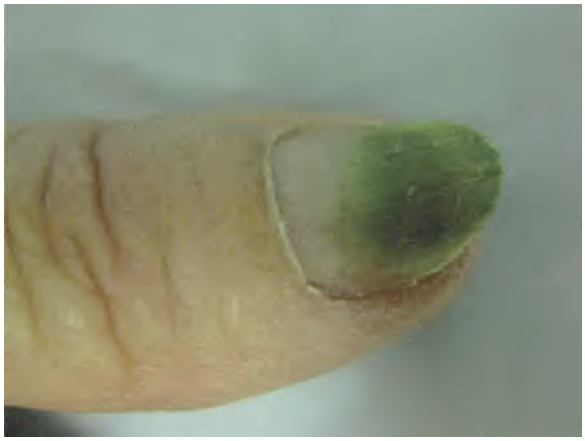

FIG. 219.2 Green nail syndrome caused by *Pseudomonas aeruginosa.* *(Modified from Wu DC, Chan WW, Metelitsa AI, et al.* Pseudomonas *skin infection: clinical features, epidemiology, and management.* Am J Clin Dermatol. *2011;12:157–169.)*

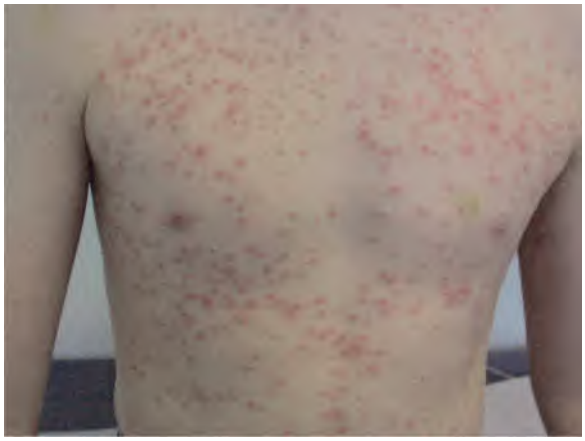

FIG. 219.3 *Pseudomonas aeruginosa* folliculitis of the trunk region. *(Modified from Wu DC, Chan WW, Metelitsa AI, et al.* Pseudomonas *skin infection: clinical features, epidemiology, and management.* Am J Clin Dermatol. *2011;12:157–169.)*

Interdigital Infections

Although foot intertrigo, or toe-web folliculitis, is usually caused by dermatophytes and yeast, superinfection by *Pseudomonas* species can occur. This inflammatory process involves the interdigital spaces and can extend to surrounding areas in severe cases. Lesions are usually erythematous, exudative, and malodorous, with marked maceration. Other gram-negative bacteria have been associated with this skin infection and include *E. coli, Proteus mirabilis,* and *Morganella morganii.*[126]

Hot Tub Folliculitis

Hot tub folliculitis is an infection of the infundibulum (upper segment) of the hair follicle, just beneath the skin surface. It is a recreational skin infection associated with immersion in contaminated swimming pools, hot tubs, and whirlpools. Contaminated bath toys, loofah sponges, creams, and diving suits have also been implicated. The folliculitis is characterized by the sudden onset of painful, pruritic pustules or papules within 24 to 48 hours after exposure to the contaminated water. Affected areas involve those exposed to the water and usually involve the trunk, upper arms, and buttocks. Folliculitis usually resolves spontaneously within 7 to 14 days without any therapy.[125]

The extent of the folliculitis depends on the level of contamination, duration of exposure, and preexisting skin conditions. Serious cases of folliculitis with both skin (hemorrhagic bullae) and systemic progression can occur among immunocompromised hosts and can be life-threatening infections (Fig. 219.3).

Hot Hand-Foot Syndrome

This syndrome is characterized by painful red nodular lesions on the soles of the feet or on the hands. It occurs as a result of abrasions incurred from pool floors in which there are high concentrations of *P. aeruginosa* in the water, and usually develops within 1 to 2 days after the abrasion. It is a benign disorder that is self-limited in previously healthy hosts, with recovery occurring within 7 to 10 days. Hot hand-foot syndrome is a public health hazard. Prevention requires superchlorination of pool water, reducing the abrasiveness of pool floors, and using quaternary ammonium compounds when scrubbing pool floors and water pipes. Ozone treatment is also required to remove biofilms on pool surfaces. Several outbreaks have been described, especially among children using wading pools (Fig. 219.4).[125,127]

Body Piercing

Infection is the most common complication after body piercing, occurring in up to 20% of cases. The most common implicated pathogens are *P. aeruginosa* and *S. aureus.* Transcartilaginous piercing is associated with more serious infections than piercing of the earlobe, owing to decreased vascularity. Complications include hematoma formation, cartilage

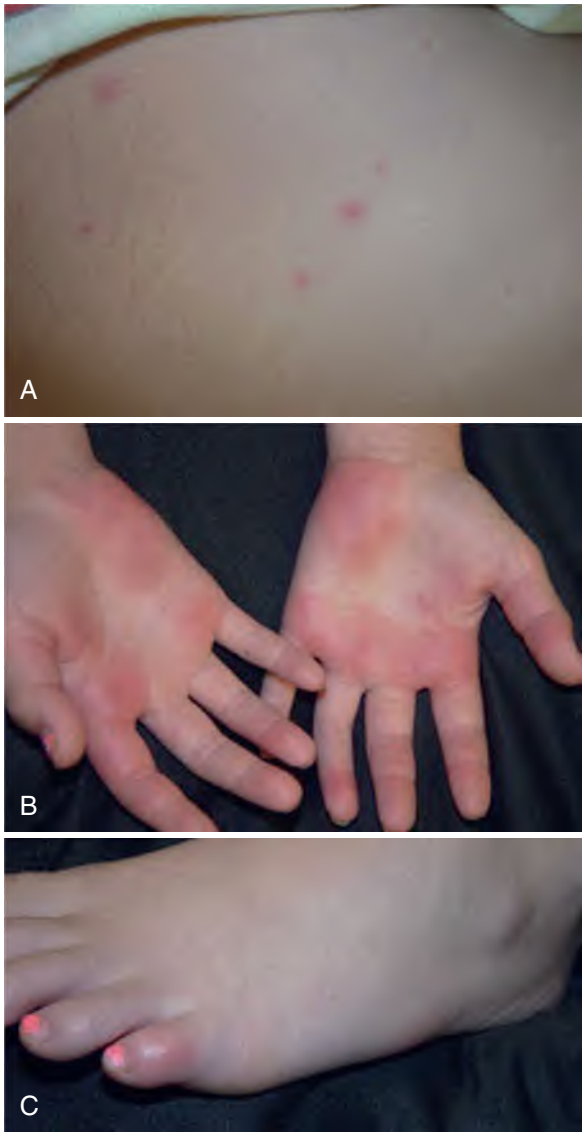

FIG. 219.4 Lesions developing after exposure to a hot tub/pool. (A) Erythematous pustules involving the abdomen. (B) Tender erythematous nodular lesions on the palms. (C) Erythema and swelling over the lateral surface of the toe. *(Modified from Yu Y, Cheng AS, Wang L, et al. Hot tub folliculitis or hot hand-foot syndrome caused by* Pseudomonas aeruginosa. J Am Acad Dermatol. *2007;57:596–600.)*

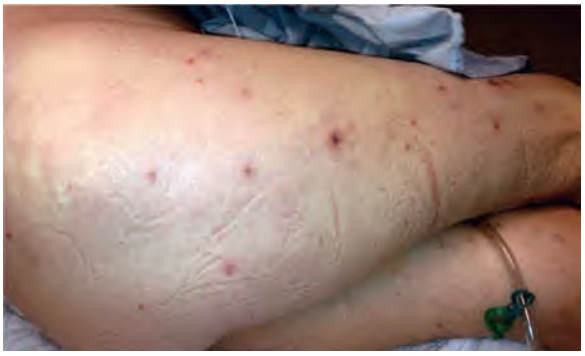

FIG. 219.5 Ecthyma gangrenosum in 67-year-old man with chronic lymphocytic leukemia. *(Modified from Walls AC, Frangos JE, Goralnick E. Ecthyma gangrenosum in a 67-year-old man with chronic lymphocytic leukemia.* J Emerg Med. *2012;43:339–341.)*

ischemia, perichondral auricular abscesses, and deformity, referred to as a "cauliflower ear." Several outbreaks of *P. aeruginosa* infections associated with body piercing have been reported. Sources included repeated use of a single-use disinfectant bottle, use of open-piercing guns, and contaminated aftercare solutions.[128,129]

Ecthyma Gangrenosum

Ecthyma gangrenosum is a characteristic manifestation of *P. aeruginosa* bacteremia among immunocompromised patients, especially those with neutropenia. Ecthyma gangrenosum, however, can also be caused by numerous other gram-negative bacteria, fungi, and viruses and has also been documented to occur among immunocompetent hosts, but with much lower incidence.[130,131]

The characteristic lesions are usually due to hematogenous dissemination, but primary skin lesions, without bacteremia, can also occur. Lesions begin as single or multiple red macules progressing to vesicles and later bullous or pustular lesions. Hemorrhage and necrosis in the central part ensues, followed by the development of a gray-black eschar with surrounding erythema (Fig. 219.5). All body parts can be involved, but ecthyma gangrenosum most commonly affects the perineal and gluteal regions and the extremities. On histology, there is epidermal and upper dermal necrosis with a mixed inflammatory cell infiltrate surrounding the infarcted area along with necrotizing vasculitis and vascular thrombosis. If bacteremia is present, *P. aeruginosa* is isolated from skin biopsy specimens as well as blood. Treatment of the bacteremia and local wound care are indicated.

Ear Infections

Simple Otitis Externa (Swimmer's Ear)

Otitis externa is an inflammation of the external auditory canal that is usually associated with infection. The most common implicated pathogens are *P. aeruginosa* and *S. aureus.* High-risk groups include swimmers, people living in humid environments, and those with narrow ear canals. Other risk factors include trauma, use of hearing devices, and presence of eczema. Patients present with tenderness and pruritus of the external canal, which are exacerbated by movement of the pinna. Erythema, swelling, and purulent discharge may also be visible. Topical antibacterial agents, such as tobramycin otic, ofloxacin, or a combination of ciprofloxacin and dexamethasone otic or aluminum acetate drops, are beneficial.[132]

Malignant Otitis Externa (Necrotizing Otitis Externa)

Malignant otitis externa is an aggressive, life-threatening infection originating in the cartilage of the external auditory canal and progressing to involve the soft tissues and bones of the skull base, resulting in temporal bone osteomyelitis. Palsies of cranial nerves VII to XII can occur with progression. The most common cranial nerve affected is the facial (VII) nerve when the infection extends to the temporal bone. As the infection progresses farther toward the jugular foramen and hypoglossal canal, lower cranial nerve palsies develop. Involvement of blood vessels can lead to septic thromboembolism.[133,134]

The majority of cases are caused by *P. aeruginosa,* followed by *S. aureus.* Other gram-negative bacteria and *Aspergillus* spp. have also been implicated. Elderly patients and those with diabetes mellitus are at highest risk, although malignant otitis externa has been described among patients with a variety of immunocompromised states as well as occasionally among immunocompetent hosts.

Severe prolonged otalgia and otorrhea are the most common presenting symptoms. Aural fullness and hearing loss may also occur. As the infection progresses, headaches, temporomandibular joint pain, trismus, and cranial nerve palsies ensue. Polypoidal granulation tissue arising from the external auditory canal can be present.

Both bacterial and fungal cultures should be obtained from the ear canal, and radiologic imaging should be performed. Antipseudomonal antimicrobial agents are required for at least 6 weeks. Initial therapy with intravenous antimicrobial agents should be considered in severe cases; otherwise, oral ciprofloxacin at high doses (750 mg twice a day) is sufficient, as long as the strain is susceptible. Aggressive débridement of necrotic tissue is also indicated. The use of hyperbaric oxygen therapy has been advocated by some, but its benefit has never been formally tested. If the patient has diabetes, then control of blood glucose concentration is crucial.[133,134]

In a retrospective study of 57 patients with malignant otitis externa treated at a tertiary care hospital from 1990 to 2008, 20% of patients had persistent or aggressive infection (>3 months) despite prolonged appropriate therapy. The risk factors for these patients were facial nerve paralysis, bilateral disease, and extent of disease (temporomandibular joint destruction, infratemporal fossa or nasopharyngeal soft tissue involvement). Outcomes were poor, with a 5-year survival of only 40% to 55%. Patients younger than 70 years had a significantly higher 5-year survival of 75%.[135]

Eye Infections

Keratitis

Keratitis is an inflammation or infection of the cornea usually caused by minor trauma. Contact lenses, especially the extended-wear type, are the main risk factor for *P. aeruginosa* keratitis, likely owing to contamination of lens solution or the use of tap water.[136,137] Patients present with a sensation of "scratchiness" during blinking, pain, and visual blurriness. There is usually excessive tearing and redness. Mild cases can be successfully treated with topical antipseudomonal antimicrobial agents, such as tobramycin ophthalmic (see Chapter 113).

Endophthalmitis

Endophthalmitis is a severe, rapidly progressive infection involving the aqueous and/or vitreous humors of the eye that often results in loss of vision. Patients present with severe eye pain, decreased visual acuity, and a hypopyon (a layering of white blood cells in the anterior chamber). Infections are predominately due to exogenous sources, including penetrating injuries to the eye, or occur as a complication of ocular surgery, especially cataract surgery. Endogenous endophthalmitis from bacteremia is rare, occurring in 2% to 6% of all cases, with other foci of infection usually present. Outcomes of endogenous endophthalmitis are very poor, with 32% of patients having "count fingers" vision, 44% becoming blind, and 25% requiring evisceration or enucleation.[138]

Numerous nosocomial outbreaks after cataract surgeries have been reported. Symptoms usually occur within 1 to 14 days postoperatively. Sources have included contaminated solutions and surgical instruments, breeches in infection control practices, and contamination from conjunctival and lid flora.[139–141]

Endophthalmitis is a medical emergency requiring intravitreal antipseudomonal antimicrobial agents. Vitrectomy is necessary for severe cases and those that do not respond to antimicrobial agents alone in the first 24 to 48 hours. The use of intravenous antipseudomonal antimicrobial agents has not been studied in clinical trials but is recommended by some experts in severe cases of endophthalmitis (see Chapter 114).[142]

Urinary Tract Infections

P. aeruginosa is among the major pathogens implicated in nosocomial urinary tract infections.[143] Mortality rates are high, with up to 17.7% and 33.9% of deaths at 30 and 90 days, respectively.[144] These high rates

likely reflect a host with numerous comorbidities, including chronic liver disease and diabetes mellitus.[144] Community-acquired urinary tract infections caused by *P. aeruginosa* are rare unless there are underlying urologic issues, including prostatitis, urinary tract obstruction, a history of urologic procedures or a neurogenic bladder, and prior treatment. Many of these risk factors suggest that the patients have had health care exposure and, therefore, these infections may not be community acquired but are likely health care associated.

In the NHSN surveillance study from 2011 to 2014, *P. aeruginosa* was the third most common pathogen implicated in catheter-associated urinary tract infections, after *E. coli* and *C. albicans,* accounting for 10.3% of all cases.[23] Surveillance studies from the Asia-Pacific region reported that *P. aeruginosa* was the third most common gram-negative pathogen, causing 7.1% of all nosocomial urinary tract infections in 2009 to 2010.[145] Studies focusing on nosocomial urinary tract infections occurring in the ICU report even higher rates of *P. aeruginosa.* In the national French nosocomial surveillance study, 16% of urinary tract infections were caused by *P. aeruginosa.*[146] Independent risk factors reported in that study were male gender, length of stay and antimicrobial exposure at ICU admission, and transfer from another ICU.[146] Patients in LTACHs also have extremely high rates of urinary tract infections caused by *P. aeruginosa.* In 2010, the NHSN reported rates of catheter-associated urinary tract infections from 104 LTACHs; *P. aeruginosa* was the most common pathogen and accounted for 19% of all of the reported infections.[25] These percentages were higher than those reported in ICU settings, which ranged from 9% to 12%.[25]

Antimicrobial resistance rates are very high among *P. aeruginosa* strains causing nosocomial urinary tract infections.[25,145,147,148] In the surveillance study of the Asia-Pacific region, approximately 40% of isolates were resistant to imipenem, ceftazidime, cefepime, and ciprofloxacin.[145] In the NHSN LTACHs study, 52% of *P. aeruginosa* isolates were resistant to ciprofloxacin, compared with 25% to 37% among ICU isolates. Rates of multidrug resistance were also substantially higher among LTACH isolates compared with ICU isolates (25% vs. 12%–16%, respectively).[25] In countries other than the United States, rates of resistance among ICU isolates are even higher. A large surveillance study of ICU isolates from 422 ICUs from 36 countries throughout Africa, Asia, Latin America, and Europe reported that 51% of strains were resistant to ciprofloxacin, 42% were resistant to piperacillin or piperacillin-tazobactam, 50% were resistant to cefepime, and 37% were resistant to carbapenems.[148] The FDA has approved a novel agent, ceftolozane-tazobactam, for the treatment of complicated urinary tract infections. This antimicrobial has excellent intrinsic activity for *P. aeruginosa,* which remains susceptible (>80 of isolates) to those strains resistant to ceftazidime or meropenem.[40]

Several outbreaks of urinary tract infections caused by *P. aeruginosa* have occurred in health care settings. One outbreak was traced to a transducer used for urodynamic studies that was contaminated with an MDR *P. aeruginosa* strain susceptible only to colistin.[149] A pseudo-outbreak was also reported from contamination of an automated urine analyzer.[150]

Treatment includes removal of the urinary catheter and correction of underlying urologic problems, if present. Avoiding catheter insertion is also the predominant approach to preventing catheter-associated urinary tract infection. Oral ciprofloxacin (500 mg twice a day) for 3 to 5 days for an uncomplicated urinary tract infection is usually sufficient. Prolonging therapy to 2 to 3 weeks is indicated for complications, including urosepsis and pyelonephritis. It is important to note that the presence of pyuria without urinary tract symptoms does not warrant therapy unless the patient is pregnant or is undergoing a transurethral prostate resection or other urologic procedure for which mucosal bleeding is expected.[151]

PSEUDOMONAS SPECIES OTHER THAN *P. AERUGINOSA* OF MAJOR CLINICAL SIGNIFICANCE

The genus *Pseudomonas* includes more than 140 species, which inhabit a variety of niches in soil and water. Genotypic-based analysis has facilitated the identification and phylogenetic assignment of *Pseudomonas* spp.[152] A subset of species other than *P. aeruginosa* cause human infection, usually among immunocompromised hosts, and are discussed in this section. Treatment of these infections should target the site of infection. The great majority of strains are susceptible to third-generation cephalosporins, piperacillin, carbapenems, and ciprofloxacin. However, antimicrobial susceptibility patterns should always guide antimicrobial therapy.

Pseudomonas fluorescens

P. fluorescens belongs to the *fluorescens* group of *Pseudomonas* species, which also includes *P. aeruginosa* and *P. putida.* This pathogen has been implicated in catheter-associated BSI. Because it can grow at 4°C and can therefore survive in blood products, transfusion-related outbreaks due to *P. fluorescens* have occurred. Outbreaks due to contaminated heparin flush solutions, drinking water dispensers in a bone marrow transplant unit, and ice baths used for cardiac output determinations have also been reported. Susceptibility to third-generation cephalosporins, piperacillin, and ciprofloxacin has been reported, but antimicrobial susceptibility profiles are always warranted to guide therapy.[153,154]

Pseudomonas fulva

P. fulva has been recovered from rice seed samples from the Philippines, from rice and petroleum fields and oil brine from Japan, and from the gills of mollusks. *P. fulva* is antagonistic to many bacterial and fungal pathogens of rice, and therefore rice seed can be used as a biologic control agent. *P. fulva* is also used in plant pathogenic fungi elimination in tomato cultures. A VIM-1–producing strain causing meningitis in a 2-year-old girl after placement of a drainage system for a neuroectodermal tumor has been reported.[155] A second case causing human infection was reported in a 56-year-old man with *P. fulva* bacteremia who was hospitalized after trauma incurred at a construction site.[156]

Pseudomonas luteola

P. luteola is another uncommon pseudomonal opportunistic pathogen. It has been previously referred to as *Chryseomonas luteola* and CDC group Ve-1. *P. luteola* is found in water, soil, and damp environments. A survey of 242 cooked ready-to-eat foods from popular roadside cafeterias and retail outlets in South Africa recovered *P. luteola* from 2.4% of food samples (vegetables, rice, beef, and pies). These food areas had no running water, and utensils and hands were washed in one bucket without regular changing of the water.[157] Reported human infections include prosthetic valve endocarditis, bacteremia, peritonitis, meningitis, and osteomyelitis.[158–160] Chronic infection of the index finger after trauma and a cutaneous abscess with bacteremia in a previously healthy man have also been reported.[161,162] Infections can be associated with central venous and peritoneal dialysis catheters.

Pseudomonas mendocina

P. mendocina rarely causes human infection. It was first isolated from soil and water samples from Mendoza, Argentina. Endocarditis, bacteremia, and spondylodiskitis have been reported.[157,158] *P. mendocina* has also been recovered from leg ulcers and urine specimens. Contamination of a reagent used for stem cell assays was responsible for a pseudo-outbreak.[163]

Pseudomonas mosselii

P. mosselii was described as a new species in 2002. Previous strains may have been identified as *P. fluorescens.*[164] Very few cases of *P. mosselii* human infection have been reported. One report concerned a 70-year-old woman with prosthetic valve endocarditis who received intravenous antimicrobial agents but was not a surgical candidate for valve replacement. The patient died of a cardiac arrest several months later, the cause of which was not reported. If *P. mosselii* was misidentified as *P. fluorescens* before recognizing it as a new species, more human infections may have occurred. VIM-producing isolates have been described.[165]

Pseudomonas oryzihabitans

This *Pseudomonas* species was previously referred to as CDC Group Ve-2 or as *Flavimonas oryzihabitans.* It is also an opportunistic pathogen, causing a variety of infections usually associated with foreign devices. Postoperative bacteremias after intraabdominal surgery, coronary artery bypass, and craniotomy have also been reported.[166–168]

P. oryzihabitans causing a cutaneous ulcer after an octopus bite was reported from Germany. A 9-year-old boy was bitten by *Octopus vulgaris* while snorkeling. Two days after the bite, a 2- to 3-cm black ulcerative lesion with a surrounding erythematous area developed. Owing to lack of healing with topical agents over the ensuing months, the lesion was excised, resulting in complete healing without the need for intravenous antimicrobial agents.[169]

Pseudomonas putida

P. putida is an opportunistic pathogen and a member of the *fluorescens* group of *Pseudomonas* species. Catheter-related bacteremia is one of the most common infections. Other infections include cholangitis associated with biliary drainage tubes, cholecystitis, pneumonia, urinary tract infections, and war wounds.[170,171] Infections predominantly occur in immunocompromised hosts, although case reports among healthy individuals have been published.[172] The majority of infections are cured with appropriate antimicrobial therapy and removal of invasive devices. Mortality rates range from 8% to 40%.[170,173]

Outbreaks of *P. putida* due to contaminated fluids or blood have been reported. Pseudo-outbreaks have also occurred as a result of contaminated urine collection kits and an automated spiral platter used to process respiratory specimens.[174]

In recent years, antimicrobial resistance rates have increased among *P. putida* isolates. In one study of nosocomial isolates recovered from 2005 to 2011, up to 20% of isolates were carbapenem resistant.[173] The majority of metallo-β-lactamase–producing *P. putida* cases reported in the literature are due to VIM and IMP enzymes.[173,175–177] KPC-2–producing *P. putida,* resistant to all antimicrobial agents except polymyxin B, has also been reported in a child with bacteremia.[178]

Pseudomonas stutzeri

P. stutzeri is an uncommon opportunistic pathogen found in the environment. Approximately 1% to 3% of *Pseudomonas* species recovered from hospital isolates are identified as *P. stutzeri.* Human infection caused by this *Pseudomonas* species was first reported in 1973 in a person with a tibial infection. Since then, numerous case reports have appeared in the literature documenting a variety of infections that affect most body sites. These infections include osteomyelitis, arthritis, bacteremia, endocarditis, endophthalmitis, pneumonia, empyema, urinary tract infections, and meningitis.[179,180] The majority of patients had underlying disorders, including chronic liver failure, chronic renal disease, or immunosuppression. Infections in otherwise healthy patients have also been reported (i.e., brain abscesses, pneumonia, empyema, and vertebral osteomyelitis). Prior surgery is also a risk factor. Mortality is rare given the low virulence of *P. stutzeri.*

Antimicrobial resistance is not as frequent among *P. stutzeri* isolates compared with *P. aeruginosa* isolates. Many *P. stutzeri* strains are susceptible to quinolones; extended-spectrum penicillins, with and without β-lactamase inhibitors; and carbapenems. However, among those *P. stutzeri* isolates recovered from immunocompromised hosts, resistance rates are higher, likely owing to prior antimicrobial and hospital exposure.[180] A recent case report of a metallo-β-lactamase–producing *P. stutzeri* was reported from a 7-year-old girl from Brazil. This patient had a brain tumor requiring an external ventricular drain. Postoperatively, she developed meningitis, and *P. stutzeri* was recovered from the cerebrospinal fluid. The isolate was resistant to all tested β-lactam antimicrobial agents and only susceptible to amikacin, gentamicin, and polymyxin B. Metallo-β-lactamase production and the class 1 integron carrying $bla_{\text{IMP-16}}$ were later identified.[177]

NOVEL THERAPEUTIC STRATEGIES AGAINST *P. AERUGINOSA* INFECTIONS

The rapid emergence and spread of multidrug resistance among *P. aeruginosa* isolates have led to an intense exploration toward developing therapeutic strategies that do not involve antimicrobial agents.[20,181,182] Numerous innovative approaches have and are being investigated for the treatment or prevention of *P. aeruginosa* infection (Table 219.4). These strategies target key processes involved in colonization, quorum sensing, and related biofilm formation. For example, several strategies, including using natural sources from plant-derived compounds, are being investigated for their antibiofilm properties (Table 219.5).[183] Unfortunately, although many new strategies show in vitro or in vivo promise, developing an effective novel strategy that can be used in humans is unlikely to occur in the near future.

TABLE 219.4 Potential Targets for the Prevention and Management of *Pseudomonas aeruginosa* Colonization and Infection

TARGET	TARGETED EFFECT ON *P. AERUGINOSA*
Biofilms	Decreased resistance to immune defenses and efficacy of antimicrobial agents
Quorum-sensing system	Interference with cell-to-cell communication
Type III secretion system	Prevention of cytotoxin release
Iron chelation	Inhibition of siderophore (pyoverdin) production leading to inhibition of virulence factors and extent of niche occupancy
Bacteriocins (pyocins)	Possible effect on niche establishment
Phage therapy	Infection of *P. aeruginosa* bacteria causing lysis
Immunotherapy	Eradication and prevention of infection
Immunization	Prevention of infection

Data from Fothergill et al.,[20] Carpenter et al.,[171] and Toru et al.[172]

TABLE 219.5 Therapeutic Strategies Against the Quorum-Sensing (QS) System

AGENT	COMMENTS
Macrolides and aminoglycosides	Inhibit QS-regulated factors; inhibit alginate production and biofilm formation Several azithromycin trials in cystic fibrosis patients showed beneficial effects for lung function
Plant-derived products	Inhibit biofilm formation
S-adenosylhomocysteine	Blocks the production of signaling molecules to prevent accumulation of signal, leading to inhibition of virulence genes activation
QS vaccine	Specific antibody to 3-oxo-C12-HSL, which plays a protective role in acute *P. aeruginosa* infection
Degrading enzymes	Degrade QS signals by attacking the lactone ring or the side chains, rendering them ineffective
Synthetic analogues (e.g., furanones)	Inhibit QS-regulated factors and biofilm formation
Plant extracts	Inhibit LasA protease, LasB elastase, and biofilm formation by several different plant extracts
Fungal products (e.g., patulin)	Thought to bind the RhlR protein and inhibit QS

Modified from Fothergill JL, Winstanely C, James CE. Novel therapeutic strategies to counter Pseudomonas aeruginosa *infections.* Expert Rev Anti Infect Ther. *2012:10;219–235.*

Key References

The complete reference list is available online at Expert Consult.

11. Kung VL, Ozer EA, Hauser AR. The accessory genome of *Pseudomonas aeruginosa*. *Microbiol Mol Biol Rev*. 2010;74:621–641.
12. Silby MW, Winstanley C, Godfrey SAC, et al. *Pseudomonas* genomes: diverse and adaptable. *FEMS Microbiol Rev*. 2011;35:652–680.
13. Segata N, Haake S, Mannon P, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol*. 2012;13:R42.
14. Burrows LL. *Pseudomonas aeruginosa* twitching motility: type IV pili in action. *Annu Rev Microbiol*. 2012;66:493–520.
15. Wiener-Kronish JP, Pittet J-F. Therapies against virulence products of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *Semin Respir Crit Care Med*. 2011;32:228–235.
16. El-Solh AA, Hattemer A, Hauser AR, et al. Clinical outcomes of type III *Pseudomonas aeruginosa* bacteremia. *Crit Care Med*. 2012;40:1157–1163.
17. Ledizet M, Murray TS, Puttagunta S, et al. The ability of virulence factor expression by *Pseudomonas aeruginosa* to predict clinical disease in hospitalized patients. *PLoS ONE*. 2012;7.
18. Sifri CD. Healthcare epidemiology: quorum sensing: bacteria talk sense. *Clin Infect Dis*. 2008;47:1070–1076.
19. Rutherford ST, Bassler BL, Hayes CS, et al. Bacterial quorum sensing : its role in virulence and possibilities for its control. *Cold Spring Harb Perspect Med*. 2012;1–26.
20. Fothergill JL, Winstanley C, James CE. Novel therapeutic strategies to counter *Pseudomonas aeruginosa* infections. *Expert Rev Anti Infect Ther*. 2012;10:219–235.
21. Ramsey DM, Baynham PJ, Wozniak DJ. Binding of *Pseudomonas aeruginosa* AlgZ to sites upstream of the algZ promoter leads to repression of transcription. *J Bacteriol*. 2005;187:4430–4443.
23. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
24. Kollef MH, Chastre J, Fagon J-Y, et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Crit Care Med*. 2014;42:2178–2187.
25. Chitnis AS, Edwards JR, Ricks PM, et al. Device-associated infection rates, device utilization, and antimicrobial resistance in long-term acute care hospitals reporting to the National Healthcare Safety Network, 2010. *Infect Control Hosp Epidemiol*. 2012;33:993–1000.
26. Morgan DJ, Rogawski E, Thom KA, et al. Transfer of multidrug-resistant bacteria to healthcare workers' gloves and gowns after patient contact increases with environmental contamination. *Crit Care Med*. 2012;40:1045–1051.
28. Jefferies JMC, Cooper T, Yam T, et al. *Pseudomonas aeruginosa* outbreaks in the neonatal intensive care unit–a systematic review of risk factors and environmental sources. *J Med Microbiol*. 2012;61(Pt 8):1052–1061.
40. Hong M-C, Hsu DI, Bounthavong M. Ceftolozane/tazobactam: a novel antipseudomonal cephalosporin and beta-lactamase-inhibitor combination. *Infect Drug Resist*. 2013;6:215–223.
41. Munita JM, Aitken SL, Miller WR, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2017;65:158–161.
42. Haidar G, Philips NJ, Shields RK, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance. *Clin Infect Dis*. 2017;65:110–120.
43. European Centre for Disease Prevention and Control. Surveillance Report. Surveillance of Antimicrobial Resistance in Europe 2016; 2016.
46. Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev*. 2009;22:582–610.
47. Zavascki AP, Carvalhaes CG, Picao RC, et al. Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: resistance mechanisms and implications for therapy. *Expert Rev Anti Infect Ther*. 2010;8:71–93.
48. Macdougall C. Beyond susceptible and resistant, part I: treatment of infections due to Gram-negative organisms with inducible beta-lactamases. *J Pediatr Pharmacol Ther*. 2011;16:23–30.
53. Bodey GP, Jadeja L, Elting L. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. *Arch Intern Med*. 1985;145:1621–1629.
54. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis*. 2004;4:519–527.
55. Hilf M, Yu VL, Sharp J, et al. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med*. 1989;87:540–546.
56. Chandrasekar PH, Crane LR, Bailey EJ. Comparison of the activity of antibiotic combinations in vitro with clinical outcome and resistance emergence in serious infection by *Pseudomonas aeruginosa* in non-neutropenic patients. *J Antimicrob Chemother*. 1987;19:321–329.
57. Paul M, Silbiger I, Grozinsky S, et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2006;(1):CD003344.
58. Bliziotis IA, Petrosillo N, Michalopoulos A, et al. Impact of definitive therapy with beta-lactam monotherapy or combination with an aminoglycoside or a quinolone for *Pseudomonas aeruginosa* bacteremia. *PLoS ONE*. 2011;6:e26470.
59. Bowers DR, Liew Y-X, Lye DC, et al. Outcomes of appropriate empiric combination versus monotherapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother*. 2013;57:1270–1274.
60. Paul M, Benuri-Silbiger I, Soares-Weiser K, et al. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ*. 2004;328:668.
61. Paul M, Leibovici L. Combination antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia. *Lancet Infect Dis*. 2005;5:192–194.
62. Kvitko CH, Rigatto MH, Moro AL, et al. Polymyxin B versus other antimicrobials for the treatment of *Pseudomonas aeruginosa* bacteraemia. *J Antimicrob Chemother*. 2011;66:175–179.
63. Kanwar A, Marshall SH, Perez F, et al. Emergence of resistance to colistin during the treatment of bloodstream infection caused by Klebsiella pneumoniae carbapenemase–producing Klebsiella pneumoniae. *Open Forum Infect Dis*. 2018;5:ofy054. http://dx.doi.org/10.1093/ofid/ofy054.
64. Moriyama B, Henning SA, Childs R, et al. High-dose continuous infusion beta-lactam antibiotics for the treatment of resistant *Pseudomonas aeruginosa* infections in immunocompromised patients. *Ann Pharmacother*. 2010;44:929–935.
65. Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? *Clin Microbiol Infect*. 2017;23:704–712.
67. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation beta-lactam/beta-lactamase inhibitor combinations. *Clin Infect Dis*. 2016;63:234–241.
68. Sader HS, Castanheira M, Shortridge D, et al. Antimicrobial activity of ceftazidime-avibactam tested against multidrug-resistant enterobacteriaceae and *Pseudomonas aeruginosa* isolates from U.S. Medical Centers, 2013 to 2016. *Antimicrob Agents Chemother*. 2017;61.
72. Vuotto F, Berthon C, Lemaitre N, et al. Risk factors, clinical features, and outcome of *Pseudomonas aeruginosa* bacteremia in patients with hematologic malignancies: a case-control study. *Am J Infect Control*. 2013;41:527–530.
95. Wood GC, Swanson JM. An update on aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia in adults. *Ann Pharmacother*. 2017;51:1112–1121.
99. Jeong B-H, Koh W-J, Yoo H, et al. Performances of prognostic scoring systems in patients with healthcare-associated pneumonia. *Clin Infect Dis*. 2013;56:625–632.
103. Sousa D, Justo I, Dominguez A, et al. Community-acquired pneumonia in immunocompromised older patients: incidence, causative organisms and outcome. *Clin Microbiol Infect*. 2013;19:187–192.
106. Folkesson A, Jelsbak L, Yang L, et al. Adaptation of *Pseudomonas aeruginosa* to the cystic fibrosis airway: an evolutionary perspective. *Nat Rev Microbiol*. 2012;10:841–851.
118. Spielmann PM, Yu R, Neeff M. Skull base osteomyelitis: current microbiology and management. *J Laryngol Otol*. 2013;127(suppl):S8–S12.
124. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.
132. Hajioff D, MacKeith S. Otitis externa. *BMJ Clin Evid*. 2015;2015.
144. Lamas Ferreiro JL, Alvarez Otero J, Gonzalez Gonzalez L, et al. *Pseudomonas aeruginosa* urinary tract infections in hospitalized patients: mortality and prognostic factors. *PLoS ONE*. 2017;12:e0178178.
152. Mulet M, Gomila M, Ramirez A, et al. Uncommonly isolated clinical *Pseudomonas*: identification and phylogenetic assignation. *Eur J Clin Microbiol Infect Dis*. 2017;36:351–359.
176. Juan C, Zamorano L, Mena A, et al. Metallo-beta-lactamase-producing *Pseudomonas* putida as a reservoir of multidrug resistance elements that can be transferred to successful *Pseudomonas aeruginosa* clones. *J Antimicrob Chemother*. 2010;65:474–478.
183. Chung PY. Plant-derived compounds as potential source of novel anti-biofilm agents against *Pseudomonas aeruginosa*. *Curr Drug Targets*. 2017;18:414–420.

References

1. Williams EP, Cameron K. Infection by the *Bacillus pyocyaneus* a cause of infantile mortality. *Public Health Pap Rep*. 1894;20:355–360.
2. Freeman L. Chronic general infection with the *Bacillus pyocyaneus*. *Ann Surg*. 1916;64:195–202.
3. Perkins R. Report of nine cases of infection with *Bacillus pyocyaneus*. *J Med Res*. 1901;6:281–297.
4. Matsumoto T, Wyte SR, Moseley RV, et al. Combat surgery in communication zone. I. War wound and bacteriology (preliminary report). *Mil Med*. 1969;134:655–665.
5. Villavicencio RT. The history of blue pus. *J Am Coll Surg*. 1998;187:212–216.
6. Etymologia: *Pseudomonas*. *J Emerg Infect Dis*. 2012;18:1241.
7. Anastassiou ED, Mintzas AC, Kounavis C, et al. Alginate production by clinical nonmucoid *Pseudomonas aeruginosa* strains. *J Clin Microbiol*. 1987;25:656–659.
8. Theilacker C, Coleman FT, Mueschenborn S, et al. Construction and characterization of a *Pseudomonas aeruginosa* mucoid exopolysaccharide-alginate conjugate vaccine. *Infect Immun*. 2003;71:3875–3884.
9. Pier GB, Desjardins D, Aguilar T, et al. Polysaccharide surface antigens expressed by nonmucoid isolates of *Pseudomonas aeruginosa* from cystic fibrosis patients. *J Clin Microbiol*. 1986;24:189–196.
10. Stover C, Pham X, Erwin A, et al. Complete genome sequence of *Pseudomonas aeruginosa* PAO1, an opportunistic pathogen. *Nature*. 2000;406(August):959–964.
11. Kung VL, Ozer EA, Hauser AR. The accessory genome of *Pseudomonas aeruginosa*. *Microbiol Mol Biol Rev*. 2010;74:621–641.
12. Silby MW, Winstanley C, Godfrey SAC, et al. *Pseudomonas* genomes: diverse and adaptable. *FEMS Microbiol Rev*. 2011;35:652–680.
13. Segata N, Haake S, Mannon P, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol*. 2012;13:R42.
14. Burrows LL. *Pseudomonas aeruginosa* twitching motility: type IV pili in action. *Annu Rev Microbiol*. 2012;66:493–520.
15. Wiener-Kronish JP, Pittet J-F. Therapies against virulence products of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *Semin Respir Crit Care Med*. 2011;32:228–235.
16. El-Solh AA, Hattemer A, Hauser AR, et al. Clinical outcomes of type III *Pseudomonas aeruginosa* bacteremia. *Crit Care Med*. 2012;40:1157–1163.
17. Ledizet M, Murray TS, Puttagunta S, et al. The ability of virulence factor expression by *Pseudomonas aeruginosa* to predict clinical disease in hospitalized patients. *PLoS ONE*. 2012;7.
18. Sifri CD. Healthcare epidemiology: quorum sensing: bacteria talk sense. *Clin Infect Dis*. 2008;47:1070–1076.
19. Rutherford ST, Bassler BL, Hayes CS, et al. Bacterial quorum sensing : its role in virulence and possibilities for its control. *Cold Spring Harb Perspect Med*. 2012;1–26.
20. Fothergill JL, Winstanley C, James CE. Novel therapeutic strategies to counter *Pseudomonas aeruginosa* infections. *Expert Rev Anti Infect Ther*. 2012;10:219–235.
21. Ramsey DM, Baynham PJ, Wozniak DJ. Binding of *Pseudomonas aeruginosa* AlgZ to sites upstream of the algZ promoter leads to repression of transcription. *J Bacteriol*. 2005;187:4430–4443.
22. Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs*. 2012;67:351–368.
23. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
24. Kollef MH, Chastre J, Fagon J-Y, et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Crit Care Med*. 2014;42:2178–2187.
25. Chitnis AS, Edwards JR, Ricks PM, et al. Device-associated infection rates, device utilization, and antimicrobial resistance in long-term acute care hospitals reporting to the National Healthcare Safety Network, 2010. *Infect Control Hosp Epidemiol*. 2012;33:993–1000.
26. Morgan DJ, Rogawski E, Thom KA, et al. Transfer of multidrug-resistant bacteria to healthcare workers' gloves and gowns after patient contact increases with environmental contamination. *Crit Care Med*. 2012;40:1045–1051.
27. Harris AD, Johnson JK, Thom KA, et al. Risk factors for development of intestinal colonization with imipenem-resistant *Pseudomonas aeruginosa* in the intensive care unit setting. *Infect Control Hosp Epidemiol*. 2011;32:719–722.
28. Jefferies JMC, Cooper T, Yam T, et al. *Pseudomonas aeruginosa* outbreaks in the neonatal intensive care unit–a systematic review of risk factors and environmental sources. *J Med Microbiol*. 2012;61(Pt 8):1052–1061.
29. Kerr KG, Snelling AM. *Pseudomonas aeruginosa*: a formidable and ever-present adversary. *J Hosp Infect*. 2009;73:338–344.
30. Tosh PK, Disbot M, Duffy JM, et al. Outbreak of *Pseudomonas aeruginosa* surgical site infections after arthroscopic procedures: Texas, 2009. *Infect Control Hosp Epidemiol*. 2011;32:1179–1186.
31. Kirschner AKT, Atteneder M, Schmidhuber A, et al. Holy springs and holy water: underestimated sources of illness? *J Water Health*. 2012;10:349–357.
32. Thrasher JD, Gray MR, Kilburn KH, et al. A water-damaged home and health of occupants: a case study. *J Environ Public Health*. 2012;2012:312836.
33. Craun GF, Calderon RL, Craun MF. Outbreaks associated with recreational water in the United States. *Int J Environ Health Res*. 2005;15:243–262.
34. Rice SA, van den Akker B, Pomati F, et al. A risk assessment of *Pseudomonas aeruginosa* in swimming pools: a review. *J Water Health*. 2012;10:181–196.
35. Allydice-Francis K, Brown PD. Diversity of antimicrobial resistance and virulence determinants in *Pseudomonas aeruginosa* associated with fresh vegetables. *Int J Microbiol*. 2012;2012:426241.
36. Green SK, Schroth MN, Cho JJ, et al. Agricultural plants and soil as a reservoir for *Pseudomonas aeruginosa*. *Appl Microbiol*. 1974;28:987–991.
37. Curran B, Morgan JAW, Honeybourne D, et al. Commercial mushrooms and bean sprouts are a source of *Pseudomonas aeruginosa*. *J Clin Microbiol*. 2005;43:5830–5831.
38. Mody L, Maheshwari S, Galecki A, et al. Indwelling device use and antibiotic resistance in nursing homes: identifying a high-risk group. *J Am Geriatr Soc*. 2007;55:1921–1926.
39. Leibovitz A, Dan M, Zinger J, et al. *Pseudomonas aeruginosa* and the oropharyngeal ecosystem of tube-fed patients. *Emerg Infect Dis*. 2003;9:956–959.
40. Hong M-C, Hsu DI, Bounthavong M. Ceftolozane/tazobactam: a novel antipseudomonal cephalosporin and beta-lactamase-inhibitor combination. *Infect Drug Resist*. 2013;6:215–223.
41. Munita JM, Aitken SL, Miller WR, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2017;65:158–161.
42. Haidar G, Philips NJ, Shields RK, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance. *Clin Infect Dis*. 2017;65:110–120.
43. European Centre for Disease Prevention and Control. Surveillance Report. Surveillance of Antimicrobial Resistance in Europe 2016; 2016.
44. Bertrand X, Dowzicky MJ. Antimicrobial susceptibility among Gram-negative isolates collected from intensive care units in North America, Europe, the Asia-Pacific Rim, Latin America, the Middle East, and Africa between 2004 and 2009 as part of the Tigecycline Evaluation and Surveillance Trial. *Clin Ther*. 2012;34:124–137.
45. Gales AC, Castanheira M, Jones RN, et al. Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008-2010). *Diagn Microbiol Infect Dis*. 2012;73:354–360.
46. Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev*. 2009;22:582–610.
47. Zavascki AP, Carvalhaes CG, Picao RC, et al. Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: resistance mechanisms and implications for therapy. *Expert Rev Anti Infect Ther*. 2010;8:71–93.
48. Macdougall C. Beyond susceptible and resistant, part I: treatment of infections due to Gram-negative organisms with inducible beta-lactamases. *J Pediatr Pharmacol Ther*. 2011;16:23–30.
49. Li X-Z, Plesiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clin Microbiol Rev*. 2015;28:337–418.
50. Livermore DM. Current epidemiology and growing resistance of gram-negative pathogens. *Korean J Intern Med*. 2012;27:128–142.
51. Jacome PRL, Alves LR, Cabral AB, et al. First report of KPC-producing *Pseudomonas aeruginosa* in Brazil. *Antimicrob Agents Chemother*. 2012;56:4990.
52. Lautenbach E, Synnestvedt M, Weiner MG, et al. Imipenem resistance in *Pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. *Infect Control Hosp Epidemiol*. 2010;31:47–53.
53. Bodey GP, Jadeja L, Elting L. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. *Arch Intern Med*. 1985;145:1621–1629.
54. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis*. 2004;4:519–527.
55. Hilf M, Yu VL, Sharp J, et al. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med*. 1989;87:540–546.
56. Chandrasekar PH, Crane LR, Bailey EJ. Comparison of the activity of antibiotic combinations in vitro with clinical outcome and resistance emergence in serious infection by *Pseudomonas aeruginosa* in non-neutropenic patients. *J Antimicrob Chemother*. 1987;19:321–329.
57. Paul M, Silbiger I, Grozinsky S, et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2006;(1):CD003344.
58. Bliziotis IA, Petrosillo N, Michalopoulos A, et al. Impact of definitive therapy with beta-lactam monotherapy or combination with an aminoglycoside or a quinolone for *Pseudomonas aeruginosa* bacteremia. *PLoS ONE*. 2011;6:e26470.
59. Bowers DR, Liew Y-X, Lye DC, et al. Outcomes of appropriate empiric combination versus monotherapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother*. 2013;57:1270–1274.
60. Paul M, Benuri-Silbiger I, Soares-Weiser K, et al. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ*. 2004;328:668.
61. Paul M, Leibovici L. Combination antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia. *Lancet Infect Dis*. 2005;5:192–194.
62. Kvitko CH, Rigatto MH, Moro AL, et al. Polymyxin B versus other antimicrobials for the treatment of *Pseudomonas aeruginosa* bacteraemia. *J Antimicrob Chemother*. 2011;66:175–179.
63. Kanwar A, Marshall SH, Perez F, et al. Emergence of resistance to colistin during the treatment of bloodstream infection caused by Klebsiella pneumoniae carbapenemase–producing Klebsiella pneumoniae. *Open Forum Infect Dis*. 2018;5:ofy054. http://dx.doi.org/10.1093/ofid/ofy054.
64. Moriyama B, Henning SA, Childs R, et al. High-dose continuous infusion beta-lactam antibiotics for the treatment of resistant *Pseudomonas aeruginosa* infections in immunocompromised patients. *Ann Pharmacother*. 2010;44:929–935.
65. Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? *Clin Microbiol Infect*. 2017;23:704–712.
66. MacVane SH, Pandey R, Steed LL, et al. Emergence of ceftolozane-tazobactam-resistant *Pseudomonas aeruginosa* during treatment is mediated by a single AmpC structural mutation. *Antimicrob Agents Chemother*. 2017;61.
67. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation beta-lactam/beta-lactamase inhibitor combinations. *Clin Infect Dis*. 2016;63:234–241.
68. Sader HS, Castanheira M, Shortridge D, et al. Antimicrobial activity of ceftazidime-avibactam tested against multidrug-resistant enterobacteriaceae and *Pseudomonas aeruginosa* isolates from U.S. Medical Centers, 2013 to 2016. *Antimicrob Agents Chemother*. 2017;61.
69. Livermore DM, Meunier D, Hopkins KL, et al. Activity of ceftazidime/avibactam against problem Enterobacteriaceae and *Pseudomonas aeruginosa* in the UK, 2015-16. *J Antimicrob Chemother*. 2018;73:648–657.
70. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis*. 2004;39:309–317.
71. Marra AR, Camargo LFA, Pignatari ACC, et al. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. *J Clin Microbiol*. 2011;49:1866–1871.
72. Vuotto F, Berthon C, Lemaitre N, et al. Risk factors, clinical features, and outcome of *Pseudomonas aeruginosa* bacteremia in patients with hematologic malignancies: a case-control study. *Am J Infect Control*. 2013;41:527–530.

73. Schechner V, Gottesman T, Schwartz O, et al. *Pseudomonas aeruginosa* bacteremia upon hospital admission: risk factors for mortality and influence of inadequate empirical antimicrobial therapy. *Diagn Microbiol Infect Dis*. 2011;71:38–45.
74. Lee C-C, Lee C-H, Hong M-Y. Risk factors and outcome of *Pseudomonas aeruginosa* bacteremia among adults visiting the ED. *Am J Emerg Med*. 2012;30:852–860.
75. Tam VH, Rogers CA, Chang K-T, et al. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrob Agents Chemother*. 2010;54:3717–3722.
76. Micek ST, Lloyd AE, Ritchie DJ, et al. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother*. 2005;49:1306–1311.
77. Lodise TPJ, Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. *Antimicrob Agents Chemother*. 2007;51:3510–3515.
78. Aliaga L, Mediavilla JD, Llosa J, et al. Clinical significance of polymicrobial versus monomicrobial bacteremia involving *Pseudomonas aeruginosa*. *Eur J Clin Microbiol Infect Dis*. 2000;19:871–874.
79. Hirsch EB, Cottreau JM, Chang K-T, et al. A model to predict mortality following *Pseudomonas aeruginosa* bacteremia. *Diagn Microbiol Infect Dis*. 2012;72:97–102.
80. Morata L, Cobos-Trigueros N, Martinez JA, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother*. 2012;56:4833–4837.
81. Cattaneo C, Antoniazzi F, Casari S, et al. *P. aeruginosa* bloodstream infections among hematological patients: an old or new question? *Ann Hematol*. 2012;91:1299–1304.
82. Selton-Suty C, Celard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis*. 2012;54:1230–1239.
83. Morpeth S, Murdoch D, Cabell CH, et al. Non-HACEK gram-negative bacillus endocarditis. *Ann Intern Med*. 2007;147:829–835.
84. Sousa C, Botelho C, Rodrigues D, et al. Infective endocarditis in intravenous drug abusers: an update. *Eur J Clin Microbiol Infect Dis*. 2012;31:2905–2910.
85. Dawson NL, Brumble LM, Pritt BS, et al. Left-sided *Pseudomonas aeruginosa* endocarditis in patients without injection drug use. *Medicine (Baltimore)*. 2011;90:250–255.
86. Komshian S V, Tablan OC, Palutke W, et al. Characteristics of left-sided endocarditis due to *Pseudomonas aeruginosa* in the Detroit Medical Center. *Rev Infect Dis*. 1990;12:693–702.
87. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. *Circulation*. 2005;111:e394–e434.
88. Nasim A, Baqi S, Akhtar SF. *Pseudomonas aeruginosa* endocarditis in renal transplant recipients. *Transpl Infect Dis*. 2012;14:180–183.
89. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.
90. Weber DJ, Rutala WA, Sickbert-Bennett EE, et al. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. *Infect Control Hosp Epidemiol*. 2007;28:825–831.
91. Venier AG, Gruson D, Lavigne T, et al. Identifying new risk factors for *Pseudomonas aeruginosa* pneumonia in intensive care units: experience of the French national surveillance, REA-RAISIN. *J Hosp Infect*. 2011;79:44–48.
92. Valles J, Mariscal D, Cortes P, et al. Patterns of colonization by *Pseudomonas aeruginosa* in intubated patients: a 3-year prospective study of 1,607 isolates using pulsed-field gel electrophoresis with implications for prevention of ventilator-associated pneumonia. *Intensive Care Med*. 2004;30:1768–1775.
93. Fujitani S, Sun H-Y, Yu VL, et al. Pneumonia due to *Pseudomonas aeruginosa*: part I: epidemiology, clinical diagnosis, and source. *Chest*. 2011;139:909–919.
94. Klibanov OM, Raasch RH, Rublein JC. Single versus combined antibiotic therapy for gram-negative infections. *Ann Pharmacother*. 2004;38:332–337.
95. Wood GC, Swanson JM. An update on aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia in adults. *Ann Pharmacother*. 2017;51:1112–1121.
96. Chastre J, Wolff M, Fagon J-Y, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290:2588–2598.
97. Chalmers JD, Taylor JK, Singanayagam A, et al. Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. *Clin Infect Dis*. 2011;53:107–113.
98. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128:3854–3862.
99. Jeong B-H, Koh W-J, Yoo H, et al. Performances of prognostic scoring systems in patients with healthcare-associated pneumonia. *Clin Infect Dis*. 2013;56:625–632.
100. Falguera M, Sacristan O, Nogues A, et al. Nonsevere community-acquired pneumonia: correlation between cause and severity or comorbidity. *Arch Intern Med*. 2001;161:1866–1872.
101. Arancibia F, Bauer TT, Ewig S, et al. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch Intern Med*. 2002;162:1849–1858.
102. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.
103. Sousa D, Justo I, Dominguez A, et al. Community-acquired pneumonia in immunocompromised older patients: incidence, causative organisms and outcome. *Clin Microbiol Infect*. 2013;19:187–192.
104. Grasemann H. CFTR modulator therapy for cystic fibrosis. *N Engl J Med*. 2017;377:2085–2088.
105. Waters V, Smyth A. Cystic fibrosis microbiology: advances in antimicrobial therapy. *J Cyst Fibros*. 2015;14:551–560.
106. Folkesson A, Jelsbak L, Yang L, et al. Adaptation of *Pseudomonas aeruginosa* to the cystic fibrosis airway: an evolutionary perspective. *Nat Rev Microbiol*. 2012;10:841–851.
107. Crull MR, Somayaji R, Ramos KJ, et al. Changing rates of chronic *Pseudomonas aeruginosa* infections in cystic fibrosis: a population-based cohort study. *Clin Infect Dis*. March 2018.
108. Chotirmall SH, Smith SG, Gunaratnam C, et al. Effect of estrogen on *Pseudomonas* mucoidy and exacerbations in cystic fibrosis. *N Engl J Med*. 2012;366:1978–1986.
109. Troxler RB, Hoover WC, Britton LJ, et al. Clearance of initial mucoid *Pseudomonas aeruginosa* in patients with cystic fibrosis. *Pediatr Pulmonol*. 2012;47:1113–1122.
110. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. *J Antimicrob Chemother*. 2003;51:1261–1268.
111. Botsford KB, Weinstein RA, Nathan CR, et al. Selective survival in pentazocine and tripelennamine of *Pseudomonas aeruginosa* serotype O11 from drug addicts. *J Infect Dis*. 1985;151:209–216.
112. Ross JJ, Shamsuddin H. Sternoclavicular septic arthritis: review of 180 cases. *Medicine (Baltimore)*. 2004;83:139–148.
113. Ross JJ, Hu LT. Septic arthritis of the pubic symphysis: review of 100 cases. *Medicine (Baltimore)*. 2003;82:340–345.
114. Sapico FL, Montgomerie JZ. Vertebral osteomyelitis in intravenous drug abusers: report of three cases and review of the literature. *Rev Infect Dis*. 1980;2:196–206.
115. Kindler CH, Seeberger MD. Infectious complications after epidural anesthesia. *Anesthesiology*. 1996;85:444–445.
116. Rowlands RG, Lekakis GK, Hinton AE. Masked pseudomonal skull base osteomyelitis presenting with a bilateral Xth cranial nerve palsy. *J Laryngol Otol*. 2002;116:556–558.
117. Blyth CC, Gomes L, Sorrell TC, et al. Skull-base osteomyelitis: fungal vs. bacterial infection. *Clin Microbiol Infect*. 2011;17:306–311.
118. Spielmann PM, Yu R, Neeff M. Skull base osteomyelitis: current microbiology and management. *J Laryngol Otol*. 2013;127(suppl):S8–S12.
119. Laughlin RT, Reeve F, Wright DG, et al. Calcaneal osteomyelitis caused by nail puncture wounds. *Foot Ankle Int*. 1997;18:575–577.
120. Gilbert D, Moellering R, Eliopoulos G, et al, eds. *The Sanford Guide to Antimicrobial Therapy 2012*. 42nd ed. 2012.
121. Yun HC, Branstetter JG, Murray CK. Osteomyelitis in military personnel wounded in Iraq and Afghanistan. *J Trauma*. 2008;64(2 suppl):S163–S168, discussion S168.
122. Johnson EN, Burns TC, Hayda RA, et al. Infectious complications of open type III tibial fractures among combat casualties. *Clin Infect Dis*. 2007;45:409–415.
123. Murray CK, Obremskey WT, Hsu JR, et al. Prevention of infections associated with combat-related extremity injuries. *J Trauma*. 2011;71(2 suppl 2):S235–S257.
124. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.
125. Wu DC, Chan WW, Metelitsa AI, et al. *Pseudomonas* skin infection: clinical features, epidemiology, and management. *Am J Clin Dermatol*. 2011;12:157–169.
126. Aste N, Atzori L, Zucca M, et al. Gram-negative bacterial toe web infection: a survey of 123 cases from the district of Cagliari, Italy. *J Am Acad Dermatol*. 2001;45:537–541.
127. Fiorillo L, Zucker M, Sawyer D, et al. The *Pseudomonas* hot-foot syndrome. *N Engl J Med*. 2001;345:335–338.
128. Keene WE, Markum AC, Samadpour M. Outbreak of *Pseudomonas aeruginosa* infections caused by commercial piercing of upper ear cartilage. *JAMA*. 2004;291:981–985.
129. Holbrook J, Minocha J, Laumann A. Body piercing: complications and prevention of health risks. *Am J Clin Dermatol*. 2012;13:1–17.
130. Reich HL, Williams Fadeyi D, Naik NS, et al. Nonpseudomonal ecthyma gangrenosum. *J Am Acad Dermatol*. 2004;50(5 suppl):S114–S117.
131. Walls AC, Frangos JE, Goralnick E. Ecthyma gangrenosum in a 67-year-old man with chronic lymphocytic leukemia. *J Emerg Med*. 2012;43:339–341.
132. Hajioff D, MacKeith S. Otitis externa. *BMJ Clin Evid*. 2015;2015.
133. Karaman E, Yilmaz M, Ibrahimov M, et al. Malignant otitis externa. *J Craniofac Surg*. 2012;23:1748–1751.
134. Hollis S, Evans K. Management of malignant (necrotising) otitis externa. *J Laryngol Otol*. 2011;125:1212–1217.
135. Soudry E, Hamzany Y, Preis M, et al. Malignant external otitis: analysis of severe cases. *Otolaryngol Head Neck Surg*. 2011;144:758–762.
136. Shah A, Sachdev A, Coggon D, et al. Geographic variations in microbial keratitis: an analysis of the peer-reviewed literature. *Br J Ophthalmol*. 2011;95:762–767.
137. Wong VWY, Lai TYY, Chi SCC, et al. Pediatric ocular surface infections: a 5-year review of demographics, clinical features, risk factors, microbiological results, and treatment. *Cornea*. 2011;30:995–1002.
138. Jackson TL, Eykyn SJ, Graham EM, et al. Endogenous bacterial endophthalmitis: a 17-year prospective series and review of 267 reported cases. *Surv Ophthalmol*. 2003;48:403–423.
139. Maltezou HC, Pappa O, Nikolopoulos G, et al. Postcataract surgery endophthalmitis outbreak caused by multidrug-resistant *Pseudomonas aeruginosa*. *Am J Infect Control*. 2012;40:75–77.
140. Pathengay A, Flynn HWJ, Isom RF, et al. Endophthalmitis outbreaks following cataract surgery: causative organisms, etiologies, and visual acuity outcomes. *J Cataract Refract Surg*. 2012;38:1278–1282.
141. Ramappa M, Majji AB, Murthy SI, et al. An outbreak of acute post-cataract surgery *Pseudomonas* sp. endophthalmitis caused by contaminated hydrophilic intraocular lens solution. *Ophthalmology*. 2012;119:564–570.
142. Chen K-J, Sun M-H, Lai C-C, et al. Endophthalmitis caused by *Pseudomonas aeruginosa* in Taiwan. *Retina*. 2011;31:1193–1198.
143. Aguilar-Duran S, Horcajada JP, Sorli L, et al. Community-onset healthcare-related urinary tract infections: comparison with community and hospital-acquired urinary tract infections. *J Infect*. 2012;64:478–483.
144. Lamas Ferreiro JL, Alvarez Otero J, Gonzalez Gonzalez L, et al. *Pseudomonas aeruginosa* urinary tract infections in hospitalized patients: mortality and prognostic factors. *PLoS ONE*. 2017;12:e0178178.
145. Lu P-L, Liu Y-C, Toh H-S, et al. Epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing urinary tract infections in the Asia-Pacific region: 2009-2010 results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents*. 2012;40(suppl):S37–S43.
146. Venier A-G, Lavigne T, Jarno P, et al. Nosocomial urinary tract infection in the intensive care unit: when should *Pseudomonas aeruginosa* be suspected? Experience of the French national surveillance of nosocomial infections in the intensive care unit, Rea-Raisin. *Clin Microbiol Infect*. 2012;18:E13–E15.
147. Karlowsky JA, Lagace-Wiens PRS, Simner PJ, et al. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD surveillance study. *Antimicrob Agents Chemother*. 2011;55:3169–3175.
148. Rosenthal VD, Bijie H, Maki DG, et al. International Nosocomial Infection Control Consortium (INICC)

report, data summary of 36 countries, for 2004-2009. *Am J Infect Control*. 2012;40:396–407.

149. Bilavsky E, Pfeffer I, Tarabeia J, et al. Outbreak of multidrug-resistant *Pseudomonas aeruginosa* infection following urodynamic studies traced to contaminated transducer. *J Hosp Infect*. 2013;83:344–346.
150. Hallin M, Deplano A, Roisin S, et al. Pseudo-outbreak of extremely drug-resistant *Pseudomonas aeruginosa* urinary tract infections due to contamination of an automated urine analyzer. *J Clin Microbiol*. 2012;50: 580–582.
151. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52: e103–e120.
152. Mulet M, Gomila M, Ramirez A, et al. Uncommonly isolated clinical *Pseudomonas*: identification and phylogenetic assignation. *Eur J Clin Microbiol Infect Dis*. 2017;36:351–359.
153. Benito N, Mirelis B, Luz Galvez M, et al. Outbreak of *Pseudomonas fluorescens* bloodstream infection in a coronary care unit. *J Hosp Infect*. 2012;82:286–289.
154. Wong V, Levi K, Baddal B, et al. Spread of *Pseudomonas fluorescens* due to contaminated drinking water in a bone marrow transplant unit. *J Clin Microbiol*. 2011;49:2093–2096.
155. Almuzara MN, Vazquez M, Tanaka N, et al. First case of human infection due to *Pseudomonas fulva,* an environmental bacterium isolated from cerebrospinal fluid. *J Clin Microbiol*. 2010;48:660–664.
156. Seok Y, Shin H, Lee Y, et al. First report of bloodstream infection caused by *Pseudomonas fulva*. *J Clin Microbiol*. 2010;48:2656–2657.
157. Nyenje ME, Odjadjare CE, Tanih NF, et al. Foodborne pathogens recovered from ready-to-eat foods from roadside cafeterias and retail outlets in Alice, Eastern Cape Province, South Africa: public health implications. *Int J Environ Res Public Health*. 2012;9:2608–2619.
158. Chihab W, Alaoui AS, Amar M. *Chryseomonas luteola* identified as the source of serious infections in a Moroccan University Hospital. *J Clin Microbiol*. 2004;42:1837–1839.
159. Casalta J-P, Fournier P-E, Habib G, et al. Prosthetic valve endocarditis caused by *Pseudomonas luteola*. *BMC Infect Dis*. 2005;5:82.
160. Gaschet A, Engrand C, Piau C, et al. Multiple brain abscesses caused by *Pseudomonas luteola*. *Pediatr Infect Dis J*. 2009;28:1144–1146.
161. Dalamaga M, Karmaniolas K, Chavelas C, et al. *Pseudomonas luteola* cutaneous abscess and bacteraemia in a previously healthy man. *Scand J Infect Dis*. 2004;36:495–497.
162. Jayagopal S, Berry MG, Ross G, et al. Hand infection caused by *Chryseomonas luteola*. *Br J Plast Surg*. 2004;57:694–695.
163. Tschudin Sutter S, Halter J, Frei R, et al. Pseudo-outbreak of *Pseudomonas mendocina* in stem cell cultures. *J Hosp Infect*. 2011;77:70–72.
164. McLellan E, Partridge D. Prosthetic valve endocarditis caused by *Pseudomonas mosselii*. *J Med Microbiol*. 2009;58(Pt 1):144–145.
165. Giani T, Marchese A, Coppo E, et al. VIM-1-producing *Pseudomonas mosselii* isolates in Italy, predating known VIM-producing index strains. *Antimicrob Agents Chemother*. 2012;56:2216–2217.
166. Rahav G, Simhon A, Mattan Y, et al. Infections with *Chryseomonas luteola* (CDC group Ve-1) and flavimonas oryzihabitans (CDC group Ve-2). *Medicine (Baltimore)*. 1995;74:83–88.
167. Lin RD, Hsueh PR, Chang JC, et al. *Flavimonas oryzihabitans* bacteremia: clinical features and microbiological characteristics of isolates. *Clin Infect Dis*. 1997;24:867–873.
168. Marin M, Garcia de Viedma D, Martin-Rabadan P, et al. Infection of hickman catheter by *Pseudomonas* (formerly *flavimonas*) *oryzihabitans* traced to a synthetic bath sponge. *J Clin Microbiol*. 2000;38:4577–4579.
169. Aigner BA, Ollert M, Seifert F, et al. *Pseudomonas oryzihabitans* cutaneous ulceration from *Octopus vulgaris* bite: a case report and review of the literature. *Arch Dermatol*. 2011;147:963–966.
170. Yoshino Y, Kitazawa T, Kamimura M, et al. *Pseudomonas putida* bacteremia in adult patients: five case reports and a review of the literature. *J Infect Chemother*. 2011;17:278–282.
171. Carpenter RJ, Hartzell JD, Forsberg JA, et al. *Pseudomonas putida* war wound infection in a US Marine: a case report and review of the literature. *J Infect*. 2008;56:234–240.
172. Toru S, Maruyama T, Hori T, et al. Pseudomonous putida meningitis in a healthy adult. *J Neurol*. 2008;255:1605–1606.
173. Kim SE, Park S-H, Park HB, et al. Nosocomial *Pseudomonas putida* bacteremia: high rates of carbapenem resistance and mortality. *Chonnam Med J*. 2012;48:91–95.
174. Neulier C, Breton N, Pangon B, et al. Pseudo-outbreak of *Pseudomonas putida* respiratory infection caused by laboratory contamination. *Infect Control Hosp Epidemiol*. 2011;32:523–525.
175. Poirel L, Yakupogullari Y, Kizirgil A, et al. VIM-5 metallo-beta-lactamase-producing *Pseudomonas putida* from Turkey. *Int J Antimicrob Agents*. 2009;33:287.
176. Juan C, Zamorano L, Mena A, et al. Metallo-beta-lactamase-producing *Pseudomonas putida* as a reservoir of multidrug resistance elements that can be transferred to successful *Pseudomonas aeruginosa* clones. *J Antimicrob Chemother*. 2010;65:474–478.
177. Carvalho-Assef APD, Gomes MZR, Silva ARA, et al. IMP-16 in *Pseudomonas putida* and *Pseudomonas stutzeri*: potential reservoirs of multidrug resistance. *J Med Microbiol*. 2010;59(Pt 9):1130–1131.
178. Almeida ACS, Vilela MA, Cavalcanti FLS, et al. First description of KPC-2-producing *Pseudomonas putida* in Brazil. *Antimicrob Agents Chemother*. 2012;56: 2205–2206.
179. Grimaldi D, Podglajen I, Aubert A, et al. Case of indolent endocarditis due to *Pseudomonas stutzeri* with genetic evidence of relapse after 4 years. *J Clin Microbiol*. 2009;47:503–504.
180. Lalucat J, Bennasar A, Bosch R, et al. Biology of *Pseudomonas stutzeri*. *Microbiol Mol Biol Rev*. 2006;70:510–547.
181. Jimenez PN, Koch G, Thompson JA, et al. The multiple signaling systems regulating virulence in *Pseudomonas aeruginosa*. *Microbiol Mol Biol Rev*. 2012;76:46–65.
182. Sharma A, Krause A, Worgall S. Recent developments for *Pseudomonas* vaccines. *Hum Vaccin*. 2011;7:999–1011.
183. Chung PY. Plant-derived compounds as potential source of novel anti-biofilm agents against *Pseudomonas aeruginosa*. *Curr Drug Targets*. 2017;18:414–420.

220 *Stenotrophomonas maltophilia* and *Burkholderia cepacia* Complex

David Greenberg

SHORT VIEW SUMMARY

Definition
- *Stenotrophomonas maltophilia* and species of the *Burkholderia cepacia* complex (BCC) are opportunistic gram-negative pathogens that cause a variety of clinical infections in various immunocompromised hosts including individuals with host genetic defects and individuals with weakened immune systems.

Epidemiology
- *S. maltophilia* has had increasing rates of isolation worldwide and has caused nosocomial infections associated with medical equipment and solutions. It also is known to cause invasive infections in patients with cancer and has been increasing in frequency in patients with cystic fibrosis (CF).
- BCC species have caused nosocomial outbreaks associated with contaminated solutions and can cause significant morbidity and mortality in patients with CF and chronic granulomatous disease. *Burkholderia cenocepacia* and *Burkholderia multivorans* are two of the major species that are found to cause disease in patients with CF. Patient-to-patient transmission has been demonstrated in patients with CF.

Microbiology
- *S. maltophilia* and BCC spp. are gram-negative aerobic bacteria that are motile.
- As free-living organisms, they reside in a broad range of environments including aquatic environments.
- They are catalase-positive, they do not ferment glucose, and many BCC members are oxidase-positive.
- BCC spp. comprise a number of phenotypically similar but genotypically distinct species; currently there are at least 20 species in the BCC.
- *S. maltophilia* is found worldwide and has significant genetic diversity among isolates.

Diagnosis
- Accurate diagnosis is critical, as these pathogens have high levels of intrinsic antibiotic resistance. Newer methods have been used for successful identification of both BCC members and *S. maltophilia* including 16S ribosomal RNA sequencing and matrix-assisted desorption/ionization time-of-flight mass spectrometry.

Therapy
- Given that both pathogens have high levels of intrinsic resistance to antibiotics, choice of antibiotics should be driven by antibiotic susceptibility testing.
- Trimethoprim-sulfamethoxazole is the preferred antibiotic for both *S. maltophilia* and BCC, although resistance has been reported and is increasing in certain areas. Combination therapy is frequently used.
- Fluoroquinolones such as moxifloxacin show activity in *S. maltophilia,* but resistance has been reported during single-drug therapy.
- Other drugs that have been shown to have in vitro and in vivo activity in both pathogens include minocycline, ceftazidime, and newer agents such as ceftazidime-avibactam. Carbapenems have activity in BCC, and ticarcillin-clavulanate and ampicillin-sulbactam can retain activity in *S. maltophilia.*

Prevention
- Nosocomial outbreaks require strict infection control measures including isolation measures.
- Surveillance of hospital water supplies is important for preventing iatrogenic infections due to these pathogens.

Stenotrophomonas maltophilia and the *Burkholderia cepacia* complex (BCC) cause infections in a variety of vulnerable patient populations including hospitalized patients such as patients with cancer and patients with specific genetic diseases such as cystic fibrosis (CF) and chronic granulomatous disease (CGD). The high level of inherent and acquired resistance to antibiotics makes treating these infections particularly challenging.

MICROBIOLOGY

Both *S. maltophilia* and BCC species are aerobic gram-negative bacteria. These free-living organisms are present in a variety of aquatic and humid environments.[1] The presence of *S. maltophilia* has been detected in hospital drinking water.[2] These organisms do not ferment glucose and can grow on a variety of enriched bacterial media. Many BCC species are oxidase-positive, whereas *S. maltophilia* is not. Small colony variants can be found on specialized media that may not be appreciated on routine culture.[3–5] These organisms are catalase-positive and motile.[6] Historically, these bacteria were thought to be various *Pseudomonas* spp., and there have been a number of name changes over the years, further separating these out as distinct genera.

Burkholderia cepacia Complex Species

The BCC comprises a number of phenotypically similar but genotypically distinct species. The number of validly determined species has been increasing. There are currently at least 20 different species that are within the BCC.[7,8] Given the phenotypic similarity of many of these species, multiple phenotypic and genetic approaches have been used for identification and typing purposes including sequencing of 16S ribosomal RNA and *recA* genes, multilocus sequence typing, average nucleotide identity, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, and biochemical tests. Despite the ever-increasing number of BCC spp., a limited number cause most human disease. An analysis of 151 isolates from an Italian CF center revealed that greater than 70% of isolates were due to three species: *Burkholderia cenocepacia* (38%), *Burkholderia stabilis* (19%), and *Burkholderia mulitvorans* (14.2%).[9] A large study from the United Kingdom that looked at >1000 *Burkholderia* isolates from both patients with CF and patients without CF showed that 56% of patients had *B. multivorans* and 15% had *B. cenocepacia* IIIA.[10]

Stenotrophomonas Genotypes

S. maltophilia is found worldwide and has been isolated from numerous environmental sources.[6] Given this, there is a large amount of genetic diversity among strains. One study illustrated the genetic diversity of clinical isolates; 80 typeable strains from 18 geographically distinct hospitals showed no predominant sequence type, and genogroup 6 represented about 40% of isolates.[11] A study in a pediatric hospital in Serbia also demonstrated high genetic diversity among both CF and non-CF isolates.[12]

PATHOGENESIS

S. maltophilia and BCC are capable of attaching and invading a number of host cells. Both pathogens have the ability to trigger an inflammatory

response. They also have a number of virulence factors and have the ability to evade host defenses. Given their ability to survive in a variety of environments, these pathogens have a number of factors that allow them to exist in various host tissues or on various abiotic surfaces.

Lipopolysaccharides, Adhesion, and Invasion

Both BCC species and *S. maltophilia* produce lipopolysaccharides (LPSs) that are capable of stimulating cytokine-driven inflammatory responses and allow for resistance to complement-mediated bacterial clearance. *B. cenocepacia* LPSs can activate immune cells through Toll-like receptor 4–mediated signaling.[13] Blood mononuclear cells that have been activated by BCC LPSs release various cytokines including tumor necrosis factor-α, interleukin-6, and interleukin-8.[14] In *S. maltophilia*, lipid A has been shown to stimulate tumor necrosis factor-α in both blood mononuclear cells and alveolar macrophages leading to airway inflammation.[15] In addition, interleukin-8 stimulates recruitment of polymorphonuclear neutrophils to sites of infection, further driving a robust inflammatory response. Divergent Toll-like receptor/MD2 signaling has been shown to occur due to changes in the inner core of BCC LPSs.[16]

B. cepacia has been shown to be able to bind to various epithelial cell receptors such as cytokeratin 13 (CK13) through an adhesin that is expressed on cable pili that helps to anchor bacteria.[17,18] Various epidemiologic studies have provided evidence for the importance of cable pili in establishing colonization as well as allowing for patient-to-patient transmissibility in the CF lung milieu.[19,20] In one study, chronic inflammation enhanced CK13 expression in patients with CF, and in regions that had high CK13 expression this corresponded with an enhanced *B. cenocepacia* burden.[21] BCC species not only can invade respiratory epithelial cells but also have been demonstrated to be able to survive and multiply within epithelial cells.[22–24]

Siderophores and Secreted Enzymes

BCC species have a number of mechanisms for scavenging iron. BCC species possess at least four iron-binding siderophores—pyochelin, ornibactin, cepaciachelin, and cepabactin—for iron chelation and uptake.[25,26] Likewise, *S. maltophilia* uses catechol-type iron-binding siderophores,[27] and these siderophores can be both positively and negatively regulated.[28,29]

S. maltophilia produces a variety of extracellular enzymes including alkaline serine proteases (at least one encoded by *StmPr1*), DNAse, RNase, gelatinase, and lipases that degrade tissue fat.[30–32] Many of these proteases are resistant to inhibitors such as α_1-antitrypsin and α_2-macroglobulin.[32] These exoenzymes allow for tissue necrosis and hemorrhage.[32] Various BCC species produce proteases, lipases, and nonhemolytic phospholipase C.[33,34]

Chronic Infection and Intracellular Survival

BCC species can invade and survive in a number of host cells. Once internalized into respiratory epithelial cells, growth can occur, and microcolonies can be seen (Fig. 220.1).[22] Intracellular survival helps facilitate immune evasion. Although autophagosomes appear to form, BCC species appear to block the full autophagocytic pathway in both epithelial cells and macrophages and use the endoplasmic reticulum for multiplication.[22,35,36] A number of mechanisms are thought to play a role in intracellular survival including blocking enzyme production, degradation of enzymes, and melanin pigment–associated superoxide quenching.[37–41] The BCC type III secretion system assists in delaying the maturation of bacteria-containing phagosomes. The failure of *B. cenocepacia* to fuse with lysosomes allows for prolonged survival in patients with CF.[42,43] Although less is known about the intracellular life cycle of *S. maltophilia,* there are data to support that some strains can survive in human monocyte-derived dendritic cells.[44]

Biofilm and Quorum Sensing

Biofilms normally contain aggregates of bacteria in extrapolymeric substances and can form on numerous foreign objects, on avascular necrotic tissue, and in certain host environments such as the lung affected by CF. Quorum sensing systems and the ability to form biofilm are

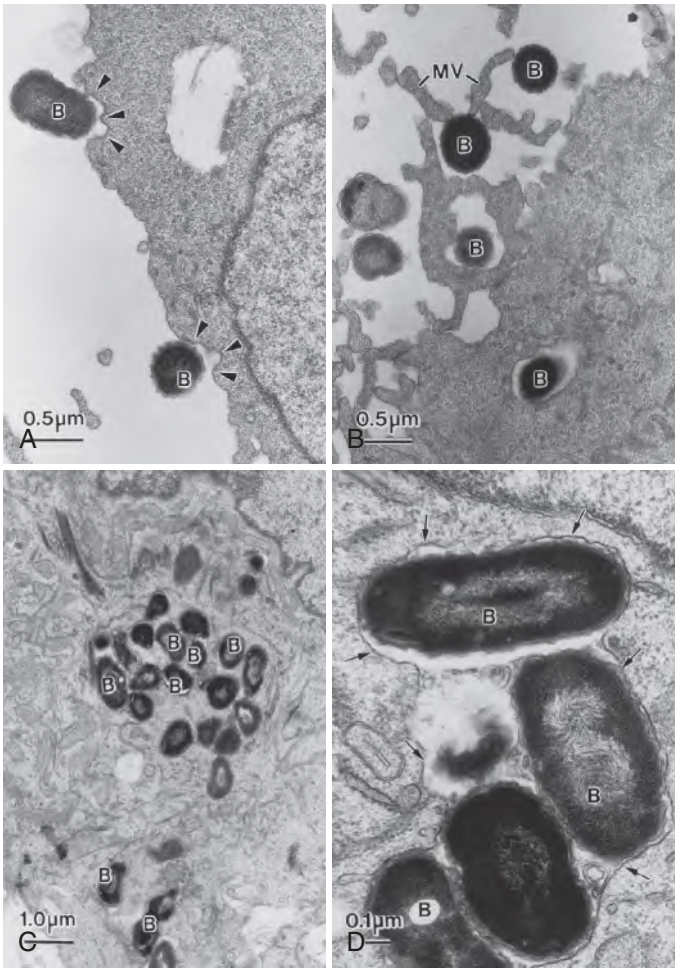

FIG. 220.1 Pathogenesis of *Burkholderia cenocepacia.* Electron micrographs showing invasion of an A549 respiratory epithelial cell monolayer by *B. cepacia* 249-2. All four micrographs show the same epithelial cell monolayer following a 2-hour incubation with the bacteria. (A) Initial contact of bacterial cells *(B)* with the surface of A549 cells. Thickening is seen at the site of contact *(arrowheads)*. (B) Apparent endocytosis of bacteria in contact with microvilli *(MV)* at the cell surface. A single bacterium is present within each membrane-bound vacuole. (C) Lower-power view of bacteria present within the cell cytoplasm. Although apparently ingested singly, organisms appear in clumps within the cytoplasm. (D) Higher-power view of bacteria within the cytoplasm. The organisms are enclosed within membrane-bound vacuoles *(arrows)*. *(Courtesy Dr. A. Griffith. From Burns JL, Jonas M, Chi EY, Clark DK, Berger A, Griffith A. Invasion of respiratory epithelial cells by* Burkholderia (Pseudomonas) cepacia. Infect Immun. *1996;64:4054–4059.)*

traits of both BCC species and *S. maltophilia*.[28,45–47,48,49] The presence of biofilm allows for the ability to withstand both immune cell activity and antibiotic efficacy. In *S. maltophilia,* regulation of biofilm occurs through the production of diffusible signaling factor, and diffusible signaling factor mutants show a number of phenotypes including loss of motility, increased susceptibility to antibiotics, and reduced production of proteases.[50,51] *B. cenocepacia* has been shown to use *N*-acyl homoserine lactones and *cis*-2-dodecenoic acid to regulate biofilm.[52]

EPIDEMIOLOGY AND AT-RISK POPULATIONS

Stenotrophomonas maltophilia

The rate of *S. maltophilia* isolation and infections has increased in multiple regions of the world. There is a broad environmental range where *S. maltophilia* has been isolated, including from animals.[53] It is not clear whether increased numbers of infections in vulnerable patient populations are due to enhanced lifesaving medical advances or an overall increase in incidence. However, there has also been an increase in the isolation

of this pathogen from various medical devices and solutions. One study of gastrointestinal endoscopes found *S. maltophilia* among a group of potential pathogens isolated after routine cleaning of the instruments.[54,55] Outbreaks have been described from other equipment sources including from contaminated bronchoscopy suction valves.[56] Nosocomial infections have been described through contamination of treated hospital water supplies.[57,58]

Health care–associated infections due to *S. maltophilia* have been described in both cancer and noncancer patient populations. Infections at two different hospitals in patients with cancer illustrate this point. At a comprehensive cancer hospital, *S. maltophilia* increased among gram-negative bacterial infections during the period 1986–2002, and at the same hospital there was an increase in moderate-to-severe *S. maltophilia* bacteremias.[59,60] A cluster of bacteremia cases among stem cell transplant patients at a large German hospital illustrated that environmental contamination leading to documented patient transmission was rare, as most patients had prior colonization.[61] Studies from various regions of the world support the increasing prevalence of infections. For the years 2000–06, there was a 93% increase in the annual number of bloodstream isolates in the United Kingdom, and for 1999–2004, there was an 83% increase in a large tertiary hospital in Taiwan.[62,63] *S. maltophilia* has also been increasing in frequency in respiratory specimens from patients with CF, although there is variability of rates based on the specific CF center.[64] In one study, having *S. maltophilia* correlated with more severe lung disease in patients with CF.[65] It remains unclear what the impact of *S. maltophilia* colonization is in both the pretransplant setting and the posttransplant setting. There was no difference in lung function decline in CF patients in the 3 years prior to acquiring *S. maltophilia* and up to 2 years after.[66–68] Although *S. maltophilia* is frequently considered a nosocomial pathogen, the high genetic diversity that has been demonstrated suggests that host colonization is likely a frequent source of the infection.[64]

Factors that have been associated with a high risk of infection include critical illness associated with pulmonary disease, prolonged use of broad-spectrum antibiotics, prolonged assisted ventilation, and prior respiratory tract colonization with *S. maltophilia*.[59,64,69–72] In immunocompromised individuals, such as patients with cancer and transplant recipients, risk factors include prolonged neutropenia, recent or current use of broad-spectrum antibiotics (including carbapenems, third- and fourth-generation cephalosporins, and fluoroquinolones), indwelling medical devices, prolonged hospitalization, hyperalimentation, and the presence of mucositis.[59,64,73,74]

Burkholderia cepacia Complex

BCC species are found widely in the environment, although a limited number of species contribute to the bulk of human disease. Nosocomial outbreaks have involved various contaminated solutions including nebulizers, bronchodilator vials, water, and chlorhexidine-cetrimide solutions.[75–77] However, immunocompromised individuals, such as patients with CF or CGD, are particularly vulnerable to infection. Although not the most frequent pathogen isolated, approximately 3.5% of patients with CF become colonized with BCC by 18 years of age. Not all BCC species cause disease to equal degrees in patients with CF, with some studies showing greater than 90% of isolated strains belonging to *B. cenocepacia* and *B. multivorans*.[78,79,80–83] Epidemiologic studies have demonstrated patient-to-patient transmission of BCC strains.[84,85] Patients with CF can become colonized with BCC and then retain that strain for long periods of time. This does not seem to be the case in patients with CGD, as such patients have been found to have recurrent infections with different strains over time.[86]

CLINICAL MANIFESTATIONS

Stenotrophomonas maltophilia

Bacteremia and Endovascular Infections

Most bloodstream infections seem to be linked to the presence of infected indwelling vascular catheters.[59,74] In transplant patients, catheter-related bacteremia has been described during the nonneutropenic period and often has been associated with catheter manipulations.[59,74,87] In addition, in severely immunocompromised patients, polymicrobial infections have been seen in up to half of cases.[74,87,88] In most cases, removal of the catheter along with a course of antibiotics has resulted in a cure. However, relapses have been described, and the prevention of relapse is related to prompt removal of the catheter (within 72 hours of the diagnosis).[89–91]

Bloodstream infections not associated with catheters can occur and lead to significant morbidity and mortality.[74,87,92,93] Patients who become bacteremic frequently have profound neutropenia that has lasted for greater than 10 days, and hematogenous dissemination usually arises from initial lung or soft tissue infections.[87,94–97] Additional risk factors for bacteremia in a neutropenic patient include hospitalization lasting >3 weeks, antineoplastic therapy, and treatment with broad-spectrum antipseudomonal antibiotics.[94,95] Poor outcomes in patients with cancer and *S. maltophilia* bacteremia include neutropenia, pneumonia, shock, severe thrombocytopenia, and initial discordant therapy.[94–96] Sepsis syndrome due to *S. maltophilia* has also been described in patients who have had mucositis that was prolonged (>3 weeks) or gingival disease.[98,99] Severe oral pain that is unresponsive to narcotics and extensive oral ulceration or bleeding or both should warrant consideration of empirical therapy to cover the possibility of *S. maltophilia*.

Although rare, endocarditis due to *S. maltophilia* has been described, and many affected patients have had septic emboli as a complication.[100–103] Other cardiac-related infections include pacemaker infections that occur late after the time of implantation.[104,105] Prompt removal of the device or prosthetic valve is an important determinant of treatment success; however, mortality remains high (approximately 40%).[100–103] A persistent endovascular focus of infection should be considered in a severely immunosuppressed patient with fever and persistent or recurrent *S. maltophilia* bacteremia.

Pulmonary Infections

The lung is a frequent site of infection, and colonization of the respiratory tract often occurs before overt clinical infection.[106–108] In an immunosuppressed patient, overt clinical signs of active disease may be diminished, and given the tendency of uncontrolled tissue necrosis and bleeding, pulmonary hemorrhage may be a presenting sign of *S. maltophilia* pulmonary disease.[106,109,110] Lobar consolidation and cavitary lesions can be seen on imaging; however, these features can be difficult to distinguish from other pathogens that cause disease in the immunocompromised host. Mortality due to *S. maltophilia* results from disease progression or hemorrhage.[108,109,110,111]

Community-acquired pneumonia has also been described in patients who do not have the traditional risk factors for infection.[112] Certain risk factors such as hematologic malignancy, simultaneous *S. maltophilia* bacteremia, carbapenem exposure, and need for critical care unit stay are less common in these patients compared with patients who acquired *S. maltophilia* from a nosocomial source.[112] Almost one-third of patients with community-acquired *S. maltophilia* pulmonary infections can be treated with oral antibiotics. Being admitted to a critical care unit is considered predictive of a poor outcome.[112] *S. maltophilia* as a pulmonary pathogen in CF is discussed in "*Stenotrophomonas maltophilia*" under "Epidemiology and At-Risk Populations."

Skin and Soft Tissue Infections

Cutaneous infections have been reported including in patients with burn injury who had exposure to nonsterile water.[113] Hematogenous seeding of the skin has been reported in neutropenic patients but is rare.[114] These lesions can manifest as nodular lesions with a violaceous center that ultimately undergoes necrosis and resemble ecthyma gangrenosum. Tissue necrosis can also occur in neutropenic patients at sites of indwelling catheters (Fig. 220.2).[115] Given that these patients are usually immunocompromised, other disseminated infectious causes of similar skin lesions include *Pseudomonas, Fusarium, Candida,* and *Mycobacterium* spp.[116] In individuals who are not immunocompromised, *S. maltophilia* skin infections are usually reported as due to traumatic wounds.[116] Skin biopsy plays an important role in diagnosing skin lesions due to this pathogen.

Head, Neck, and Central Nervous System Infections

Bacterial meningitis due to gram-negative pathogens is a known complication of neurosurgical procedures, and *S. maltophilia* is included in this

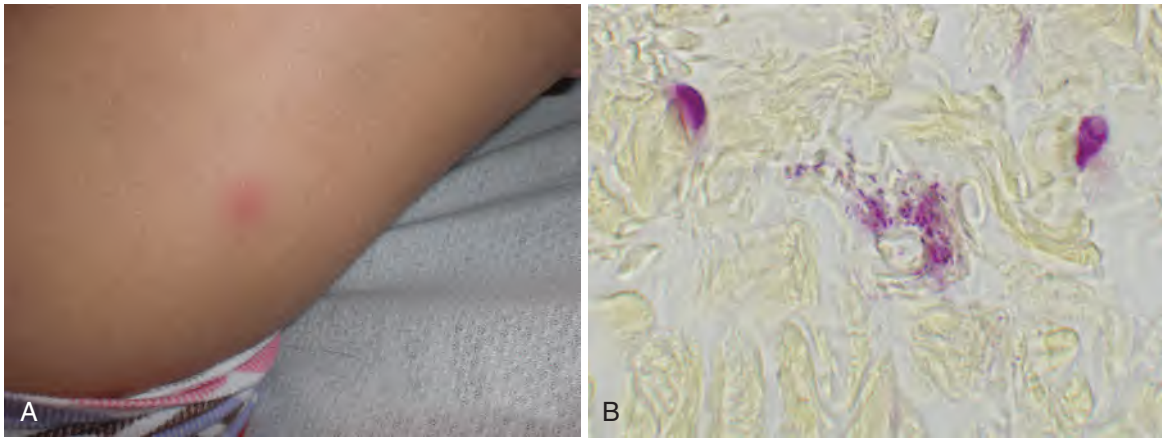

FIG. 220.2 *Stenotrophomonas maltophilia* skin infection. (A) Skin lesion in profoundly neutropenic Vietnamese girl with treatment-refractory aplastic anemia who had undergone related haploidentical stem cell transplantation following cytoxan and fludarabine pretransplant conditioning. (B) Gram-negative bacteria lining the tissue blood vessels (Brown and Hoppes stain of skin biopsy from the right leg lesion, ×1000). *(Courtesy Dr. Fedorko and Dr. John Bennett.)*

list. In addition to neurosurgical procedures, chronic sinusitis and intracranial hemorrhage are also risk factors.[117–119] In patients with infection after a neurosurgical procedure that does not respond to broad-spectrum antibiotics, in addition to other multidrug-resistant pathogens, *S. maltophilia* should be considered as a possible cause.[120] *S. maltophilia* rarely is a cause of chronic sinusitis.[121,122] *S. maltophilia* can cause both corneal infection and endophthalmitis after penetrating eye injury. In addition, it has been found not infrequently in contact lens solutions.[119,123,124]

Genitourinary, Abdominal, and Other Uncommon Infections

Both urinary tract colonization and invasive disease have been described.[125] Peritonitis is also possible and has been seen in patients undergoing peritoneal dialysis in cases where removal of the dialysis catheter is needed when there is no response to antimicrobial therapy.[126–129] Other gastrointestinal infections such as biliary sepsis, necrotizing pancreatitis, and liver abscess have been rarely reported.[130–132] Bone and joint infections are rare but have been described as consequences of trauma, after spinal surgery, and in nonimmunosuppressed patients presenting with community-acquired septic arthritis and bursitis.[133–137]

Burkholderia cepacia Complex

Respiratory Infections in Cystic Fibrosis

Although new species continue to be added to the BCC, *B. cenocepacia* and *B. multivorans* remain the most frequently isolated species from the lungs of patients with CF. Patient-to-patient transmission has been thought to play an important role in colonizing patients with CF.[138] A study from Australia showed that 85% of patients were infected with a unique BCC strain.[139] Compared with *Pseudomonas aeruginosa,* BCC infection can be associated with an accelerated decline in lung function.[140,141,142,143] Another unique feature associated with BCC infections in patients with CF is the development of a severe, rapidly progressive disease with systemic dissemination termed *cepacia syndrome*.[144] This syndrome has been reported with *B. cenocepacia, B. cepacia,* and *B. multivorans* and can occur many years after the initial infection.[140,145–147] A variety of therapeutic approaches have been attempted to treat this syndrome including using appropriate antibiotics and antiinflammatory agents such as corticosteroids and cyclosporine.[148–150]

Lung Transplantation

It has been shown that being colonized with BCC in the pretransplant period is associated with a very high risk of death after posttransplant.[151,152] In one study, there was a 37% absolute difference in long-term survival in patients who were colonized with BCC compared with patients who were not colonized.[153] In transplant recipients in Canada, the hazard ratio for death in the first year after transplant was 6.29 in recipients who had BCC compared with recipients who did not.[154]

Bacteremia and Pneumonia

Although infections of intravascular devices are an uncommon cause of bacteremia due to BCC, nosocomial outbreaks have been described involving contamination of heparin flushes and solutions made in compounding pharmacies.[155–158] Other outbreaks that included bacteremia presentations were related to contaminated liquid docusate sodium and washing gloves.[159,160] When bloodstream infections occur in patients who do not have CF, they are frequently associated with pneumonia.[161,162] Other BCC pneumonias have been reported in susceptible hosts receiving nebulizer-associated therapy.[163] Risk factors for developing nosocomial pneumonia are similar to those for *Stenotrophomonas* and include mechanical ventilation, prolonged intensive care unit stay, and broad-spectrum antibiotics.[77,164]

Other Rare Manifestations

BCC involvement of the skin and joints has been described only in case reports. Infections have been seen in patients in burn units who had exposure to unsterilized skin moisturizers.[165] In patients with cancer or who are immunosuppressed, disseminated skin lesions can resemble ecthyma gangrenosum,[166] and a mixed infection causing necrotizing fasciitis was seen in a nonimmunocompromised individual.[167] Septic arthritis from hematogenous spread is also rare but described.[168] Urinary involvement from colonization of a urinary catheter[169] and infection after renal transplant has been described.[170]

THERAPY

Stenotrophomonas maltophilia

One theme that connects both *S. maltophilia* and the BCC is their inherent resistance to a variety of antibiotics. *S. maltophilia* demonstrates inherent resistance to most β-lactams, aminoglycosides, and various disinfectants.[171,172] *S. maltophilia* also shows resistance to certain heavy metals such as silver.[173] *S. maltophilia* encodes a number of resistance genes including numerous resistance-nodulation-division efflux pumps[172,174] and the efflux pump MfsA.[175] In addition, resistance to quinolones administered for treatment of bacteremia has been described and was linked to a repressor for one of these efflux pumps, SmeDEF.[176] Other studies have shown that approximately 33% of clinical isolates have multidrug resistance to fluoroquinolones, tetracycline, erythromycin, and chloramphenicol through overexpression of SmeDEF.[177,178] Many resistance mechanisms beyond efflux have been found in *S. maltophilia* including β-lactamases, aminoglycoside-modifying enzymes, and reduced permeability of the outer membrane.[179] For many classes of antibiotics, resistance rates have been increasing over time.[180]

Trimethoprim-sulfamethoxazole (TMP-SMZ) has been a mainstay of therapy for *S. maltophilia,* as it has historically had the greatest in vitro potency against clinical isolates.[179,181,182] The vast majority of isolates in early reports showed susceptibility to TMP-SMZ; however, drug resistance has increased worldwide, in part due to the incorporation

of class 1 integrons carrying the *sul1* gene.[179,183] The global spread of this mobile gene has been linked to increased use of TMP-SMZ in patients.[184,185] For systemic infections, treatment frequently involves combination therapy with TMP-SMZ as a backbone. Combination therapy has been suggested for non–catheter-related bacteremia, endovascular infections, bone and joint involvement, central nervous system infection, systemic infection in patients with severe neutropenia or immune defects, and multifocal lung disease.[60,135,186] Some combinations including TMP-SMZ and ticarcillin-clavulanic acid have shown in vitro activity.[187] In one pediatric study, combination of TMP-SMZ with ciprofloxacin or minocycline extended survival.[188]

If resistance arises to TMP-SMZ or it cannot be tolerated, a number of other agents have been shown to have activity. The newer fluoroquinolones such as moxifloxacin demonstrate in vitro activity in *S. maltophilia* even in isolates that are resistant to TMP-SMZ.[189] However, resistance can develop after single-drug therapy, which can be prevented by using various drug combinations with ticarcillin-clavulanic acid or TMP-SMZ or both.[190–192] Although studies are limited, monotherapy with a fluoroquinolone compared with TMP-SMZ has shown similar treatment failure rates and development of resistance during therapy, although the numbers studied have been low.[193,194] In vitro, levofloxacin was shown to have decreased activity in *S. maltophilia* biofilms.[195] Other monotherapy studies included comparing TMP-SMZ with minocycline; although there were no significant differences in the treatment failure rate between the two groups, greater than 30% of the patients in both groups failed single-drug therapy.[58,196] There are no good data to support any unique therapeutic approaches for the treatment of *S. maltophilia* in patients with CF.[197]

A number of other antibiotics have been used to treat *S. maltophilia* infections including some more recently approved agents.[104] Tigecycline was compared with TMP-SMZ over a 3-year period in a Turkish hospital and showed no significant difference in 30-day mortality or clinical response rates between the two groups.[198] Newer agents have shown mixed results with both ceftolozane-tazobactam and meropenem-vaborbactam showing poor activity[199,200] and the siderophore cephalosporin cefiderocol showing good in vitro activity.[201] Ceftazidime-avibactam was shown to clear a very prolonged bacteremia in a patient with end-stage renal disease.[202]

Burkholderia cepacia Complex

BCC species can display significant antibiotic-resistant phenotypes. Mechanisms of resistance include the expression of efflux pumps, antibiotic degrading or modifying enzymes, and altered membrane function.[203] Although the carbapenems, TMP-SMZ, minocycline, and chloramphenicol are frequently active against BCC isolates, the final antibiotic choice is usually driven by results of antimicrobial susceptibility testing.[204] In one large study of 2621 BCC strains from patients with CF, it was found that minocycline (38%), meropenem (26%), and ceftazidime (23%) were the most active.[205] Various antibiotics and antibiotic combinations have had some activity in the setting of biofilm,[46,206] but this was not universal. Tobramycin is frequently used because it has been shown to have activity in biofilms and has been delivered via aerosolization.[207,208]

Given increasing rates of drug resistance, newer therapies or approaches have been tried. Newer cephalosporin combinations show promising results.[209] Ceftazidime combined with the non–β-lactam β-lactamase inhibitor avibactam was active in more than 90% of strains tested (70% of which were multidrug-resistant isolates).[210] A case of persistent BCC bacteremia in an infant was ultimately cleared once ceftazidime-avibactam was started.[211] Ceftolozane-tazobactam has also been shown to have activity in a large percentage of strains.[212] Therapeutic approaches in the discovery stage include narrow-spectrum therapy with bacteriophages and antisense molecules.[213–215] In addition, there has been broad interest in peptide-based therapeutics, as not only can these agents have inherent antimicrobial activity but they can also have antibiofilm activity, which is particularly helpful in patients with CF. The α-helical peptides BMAP-27, BMAP-28, and P19(9/B) were shown to be active in *S. maltophilia*.[216] Frequently active antibiotics and mechanisms of resistance for these pathogens are summarized in Table 220.1.

TABLE 220.1 Antimicrobial Activity and Mechanisms of Resistance in *Stenotrophomonas maltophilia* and *Burkholderia cepacia* Complex

PATHOGEN	ANTIBIOTICS WITH IN VIVO OR IN VITRO ACTIVITY[a]	COMMON MECHANISMS OF RESISTANCE
Stenotrophomonas maltophilia	TMP-SMZ[b] Quinolones (moxifloxacin, ciprofloxacin, levofloxacin) Minocycline or doxycycline Tigecycline Ceftazidime Ceftazidime-avibactam Ceftriaxone Ticarcillin-clavulanate Ampicillin-sulbactam	RND efflux pumps MfsA efflux pump Sme-related efflux pumps *sul* genes (TMP-SMZ resistance) *dfrA* genes (TMP-SMZ resistance) β-Lactamases Aminoglycoside modifying enzymes
Burkholderia cepacia complex	TMP-SMZ[b] Ceftazidime Ceftazidime-avibactam Meropenem or imipenem Minocycline	β-Lactamases (bla_{Pen}-like) RND efflux pumps Polymyxin resistance (altered LPSs) Quinolone resistance (gyrase mutations)

[a]Antimicrobial susceptibility testing should be performed for these pathogens to help guide therapy.
[b]Antibiotic of choice if sensitive.
LPS, Lipopolysaccharide; *RND,* resistance-nodulation-division; *TMP-SMZ,* trimethoprim-sulfamethoxazole.

PREVENTION STRATEGIES, IMMUNIZATION, AND IMMUNOTHERAPY

As with other pathogens, outbreaks of *Stenotrophomonas* and BCC require strict infection-control policies. BCC has been shown to have patient-to-patient transmission in CF populations.[217] Surveillance of the hospital water supply remains an important infection-control issue to prevent hospital-related infections from occurring.

Immunization and Immunotherapy

There are currently no existing vaccines for either *S. maltophilia* or BCC species, although there is interest in developing them.[218] Outer membrane proteins in both *B. cenocepacia* and *B. multivorans* have shown promise as vaccine targets in various animal models.[219,220] Flagellin has been used in *S. maltophilia* as a possible immunization target. In mouse studies, flagellin reduced bacterial colonization and had greater resistance to pulmonary infection.[221] Other strategies have included immunotherapy using antibodies to a broadly conserved surface polysaccharide poly-β-(1-6)-*N*-acetylglucosamine.[222]

Key References

The complete reference list is available online at Expert Consult.

1. Mahenthiralingam E, Urban TA, Goldberg JB. The multifarious, multireplicon *Burkholderia cepacia* complex. *Nat Rev Microbiol.* 2005;3:144–156.
6. Adegoke AA, Stenstrom TA, Okoh AI. *Stenotrophomonas maltophilia* as an emerging ubiquitous pathogen: looking beyond contemporary antibiotic therapy. *Front Microbiol.* 2017;8:2276.
10. Kenna DTD, Lilley D, Coward A, et al. Prevalence of *Burkholderia* species, including members of *Burkholderia cepacia* complex, among UK cystic and non-cystic fibrosis patients. *J Med Microbiol.* 2017;66:490–501.
12. Madi H, Lukic J, Vasiljevic Z, et al. Genotypic and phenotypic characterization of *Stenotrophomonas maltophilia* strains from a pediatric tertiary care hospital in Serbia. *PLoS ONE.* 2016;11:e0165660.
15. Waters VJ, Gomez MI, Soong G, et al. Immunostimulatory properties of the emerging pathogen *Stenotrophomonas maltophilia*. *Infect Immun.* 2007;75:1698–1703.
20. Sun L, Jiang RZ, Steinbach S, et al. The emergence of a highly transmissible lineage of cbl+ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. *Nat Med.* 1995;1:661–666.
22. Sajjan US, Yang JH, Hershenson MB, et al. Intracellular trafficking and replication of *Burkholderia cenocepacia* in human cystic fibrosis airway epithelial cells. *Cell Microbiol.* 2006;8:1456–1466.

28. Lewenza S, Conway B, Greenberg EP, et al. Quorum sensing in *Burkholderia cepacia*: identification of the LuxRI homologs CepRI. *J Bacteriol*. 1999;181:748–756.
35. Al-Khodor S, Marshall-Batty K, Nair V, et al. *Burkholderia cenocepacia* J2315 escapes to the cytosol and actively subverts autophagy in human macrophages. *Cell Microbiol*. 2014;16:378–395.
41. Luciani A, Villella VR, Esposito S, et al. Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat Cell Biol*. 2010;12:863–875.
48. Di Bonaventura G, Spedicato I, D'Antonio D, et al. Biofilm formation by *Stenotrophomonas maltophilia*: modulation by quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. *Antimicrob Agents Chemother*. 2004;48: 151–160.
53. Jayol A, Corlouer C, Haenni M, et al. Are animals a source of *Stenotrophomonas maltophilia* in human infections? Contributions of a nationwide molecular study. *Eur J Clin Microbiol Infect Dis*. 2018;37:1039–1045.
57. Cervia JS, Ortolano GA, Canonica FP. Hospital tap water as a source of *Stenotrophomonas maltophilia* infection. *Clin Infect Dis*. 2008;46:1485–1487.
59. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis*. 2007;45:1602–1609.
64. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis*. 2009;9:312–323.
66. Dalboge CS, Hansen CR, Pressler T, et al. Chronic pulmonary infection with *Stenotrophomonas maltophilia* and lung function in patients with cystic fibrosis. *J Cyst Fibros*. 2011;10:318–325.
68. Raidt L, Idelevich EA, Dubbers A, et al. Increased prevalence and resistance of important pathogens recovered from respiratory specimens of cystic fibrosis patients during a decade. *Pediatr Infect Dis J*. 2015;34:700–705.
73. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev*. 2012;25:2–41.
75. Lipuma JJ. The changing microbial epidemiology in cystic fibrosis. *Clin Microbiol Rev*. 2010;23:299–323.
77. Estivariz CF, Bhatti LI, Pati R, et al. An outbreak of *Burkholderia cepacia* associated with contamination of albuterol and nasal spray. *Chest*. 2006;130:1346–1353.
79. Boussaud V, Guillemain R, Grenet D, et al. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with *Burkholderia cepacia* complex: results from two French centres. *Thorax*. 2008;63:732–737.
86. Greenberg DE, Goldberg JB, Stock F, et al. Recurrent *Burkholderia* infection in patients with chronic granulomatous disease: 11-year experience at a large referral center. *Clin Infect Dis*. 2009;48:1577–1579.
91. Hanna H, Afif C, Alakech B, et al. Central venous catheter-related bacteremia due to gram-negative bacilli: significance of catheter removal in preventing relapse. *Infect Control Hosp Epidemiol*. 2004;25:646–649.
93. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine (Baltimore)*. 2016;95:e4375.
94. Micozzi A, Venditti M, Monaco M, et al. Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. *Clin Infect Dis*. 2000;31:705–711.
99. Apisarnthanarak A, Fraser VJ, Dunne WM, et al. *Stenotrophomonas maltophilia* intestinal colonization in hospitalized oncology patients with diarrhea. *Clin Infect Dis*. 2003;37:1131–1135.
103. Yusuf SW, Ali SS, Swafford J, et al. Culture-positive and culture-negative endocarditis in patients with cancer: a retrospective observational study, 1994-2004. *Medicine (Baltimore)*. 2006;85:86–94.
108. Saugel B, Eschermann K, Hoffmann R, et al. *Stenotrophomonas maltophilia* in the respiratory tract of medical intensive care unit patients. *Eur J Clin Microbiol Infect Dis*. 2012;31:1419–1428.
110. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. *Transpl Infect Dis*. 2012;14:355–363.
113. Azzopardi EA, Azzopardi SM, Boyce DE, et al. Emerging gram-negative infections in burn wounds. *J Burn Care Res*. 2011;32:570–576.
124. Furuhata K, Ishizaki N, Kawakami Y, et al. Bacterial contamination of stock solutions in storage cases for contact lens, and the disinfectant-resistance of isolates. *Biocontrol Sci*. 2010;15:81–85.
138. Biddick R, Spilker T, Martin A, et al. Evidence of transmission of *Burkholderia cepacia, Burkholderia multivorans* and *Burkholderia dolosa* among persons with cystic fibrosis. *FEMS Microbiol Lett*. 2003;228: 57–62.
140. Courtney JM, Dunbar KE, McDowell A, et al. Clinical outcome of *Burkholderia cepacia* complex infection in cystic fibrosis adults. *J Cyst Fibros*. 2004;3:93–98.
142. Ledson MJ, Gallagher MJ, Jackson M, et al. Outcome of *Burkholderia cepacia* colonisation in an adult cystic fibrosis centre. *Thorax*. 2002;57:142–145.
151. Nash EF, Coonar A, Kremer R, et al. Survival of *Burkholderia cepacia* sepsis following lung transplantation in recipients with cystic fibrosis. *Transpl Infect Dis*. 2010;12:551–554.
155. Souza Dias MB, Cavassin LG, Stempliuk V, et al. Multi-institutional outbreak of *Burkholderia cepacia* complex associated with contaminated mannitol solution prepared in compounding pharmacy. *Am J Infect Control*. 2013;41:1038–1042.
160. Glowicz J, Crist M, Gould C, et al. A multistate investigation of health care-associated *Burkholderia cepacia* complex infections related to liquid docusate sodium contamination, January-October 2016. *Am J Infect Control*. 2018;46:649–655.
171. Zhang L, Li XZ, Poole K. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*: involvement of a multidrug efflux system. *Antimicrob Agents Chemother*. 2000;44:287–293.
172. Crossman LC, Gould VC, Dow JM, et al. The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. *Genome Biol*. 2008;9:R74.
179. Nicodemo AC, Paez JI. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. *Eur J Clin Microbiol Infect Dis*. 2007;26:229–237.
183. Toleman MA, Bennett PM, Bennett DM, et al. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of sul genes. *Emerg Infect Dis*. 2007;13:559–565.
186. Muder RR, Harris AP, Muller S, et al. Bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia*: a prospective, multicenter study of 91 episodes. *Clin Infect Dis*. 1996;22:508–512.
192. Ba BB, Feghali H, Arpin C, et al. Activities of ciprofloxacin and moxifloxacin against *Stenotrophomonas maltophilia* and emergence of resistant mutants in an in vitro pharmacokinetic-pharmacodynamic model. *Antimicrob Agents Chemother*. 2004;48:946–953.
193. Wang YL, Scipione MR, Dubrovskaya Y, et al. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother*. 2014;58:176–182.
204. Horsley A, Jones AM, Lord R. Antibiotic treatment for *Burkholderia cepacia* complex in people with cystic fibrosis experiencing a pulmonary exacerbation. *Cochrane Database Syst Rev*. 2016;(1):CD009529.
207. Waters V, Yau Y, Beaudoin T, et al. Pilot trial of tobramycin inhalation powder in cystic fibrosis patients with chronic *Burkholderia cepacia* complex infection. *J Cyst Fibros*. 2017;16:492–495.
209. El Chakhtoura NG, Saade E, Iovleva A, et al. Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward 'molecularly targeted' therapy. *Expert Rev Anti Infect Ther*. 2018;16:89–110.
210. Papp-Wallace KM, Becka SA, Zeiser ET, et al. Overcoming an extremely drug resistant (XDR) pathogen: avibactam restores susceptibility to ceftazidime for Burkholderia cepacia complex isolates from cystic fibrosis patients. *ACS Infect Dis*. 2017;3:502–511.
211. Tamma PD, Fan Y, Bergman Y, et al. Successful treatment of persistent *Burkholderia cepacia* complex bacteremia with ceftazidime-avibactam. *Antimicrob Agents Chemother*. 2018;62.
213. Carmody LA, Gill JJ, Summer EJ, et al. Efficacy of bacteriophage therapy in a model of *Burkholderia cenocepacia* pulmonary infection. *J Infect Dis*. 2010;201:264–271.
215. Greenberg DE, Marshall-Batty KR, Brinster LR, et al. Antisense phosphorodiamidate morpholino oligomers targeted to an essential gene inhibit *Burkholderia cepacia* complex. *J Infect Dis*. 2010;201:1822–1830.
216. Pompilio A, Crocetta V, Scocchi M, et al. Potential novel therapeutic strategies in cystic fibrosis: antimicrobial and anti-biofilm activity of natural and designed alpha-helical peptides against *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Stenotrophomonas maltophilia*. *BMC Microbiol*. 2012;12:145.
217. Saiman L, Siegel J. Infection control in cystic fibrosis. *Clin Microbiol Rev*. 2004;17:57–71.
222. Skurnik D, Davis MR Jr, Benedetti D, et al. Targeting pan-resistant bacteria with antibodies to a broadly conserved surface polysaccharide expressed during infection. *J Infect Dis*. 2012;205:1709–1718.

References

1. Mahenthiralingam E, Urban TA, Goldberg JB. The multifarious, multireplicon *Burkholderia cepacia* complex. *Nat Rev Microbiol*. 2005;3:144–156.
2. Hsu MS, Wu MY, Huang YT, et al. Efficacy of chlorine dioxide disinfection to non-fermentative gram-negative bacilli and non-tuberculous mycobacteria in a hospital water system. *J Hosp Infect*. 2016;93:22–28.
3. Haussler S, Lehmann C, Breselge C, et al. Fatal outcome of lung transplantation in cystic fibrosis patients due to small-colony variants of the *Burkholderia cepacia* complex. *Eur J Clin Microbiol Infect Dis*. 2003;22:249–253.
4. Anderson SW, Stapp JR, Burns JL, et al. Characterization of small-colony-variant *Stenotrophomonas maltophilia* isolated from the sputum specimens of five patients with cystic fibrosis. *J Clin Microbiol*. 2007;45:529–535.
5. Romero-Tabarez M, Jansen R, Sylla M, et al. 7-O-malonyl macrolactin A, a new macrolactin antibiotic from *Bacillus subtilis* active against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and a small-colony variant of *Burkholderia cepacia*. *Antimicrob Agents Chemother*. 2006;50:1701–1709.
6. Adegoke AA, Stenstrom TA, Okoh AI. *Stenotrophomonas maltophilia* as an emerging ubiquitous pathogen: looking beyond contemporary antibiotic therapy. *Front Microbiol*. 2017;8:2276.
7. Martina P, Leguizamon M, Prieto CI, et al. *Burkholderia puraquae* sp. nov., a novel species of the *Burkholderia cepacia* complex isolated from hospital settings and agricultural soils. *Int J Syst Evol Microbiol*. 2018;68:14–20.
8. Ong KS, Aw YK, Lee LH, et al. *Burkholderia paludis* sp. nov., an antibiotic-siderophore producing novel *Burkholderia cepacia* complex species, isolated from Malaysian tropical peat swamp soil. *Front Microbiol*. 2016;7:2046.
9. Teri A, Sottotetti S, Biffi A, et al. Molecular typing of *Burkholderia cepacia* complex isolated from patients attending an Italian Cystic Fibrosis Centre. *New Microbiol*. 2018;41.
10. Kenna DTD, Lilley D, Coward A, et al. Prevalence of *Burkholderia* species, including members of *Burkholderia cepacia* complex, among UK cystic and non-cystic fibrosis patients. *J Med Microbiol*. 2017;66:490–501.
11. Corlouer C, Lamy B, Desroches M, et al, College de Bacteriologie-Virologie-Hygiene des Hopitaux de F. *Stenotrophomonas maltophilia* healthcare-associated infections: identification of two main pathogenic genetic backgrounds. *J Hosp Infect*. 2017;96:183–188.
12. Madi H, Lukic J, Vasiljevic Z, et al. Genotypic and phenotypic characterization of *Stenotrophomonas maltophilia* strains from a pediatric tertiary care hospital in Serbia. *PLoS ONE*. 2016;11:e0165660.
13. Bamford S, Ryley H, Jackson SK. Highly purified lipopolysaccharides from *Burkholderia cepacia* complex clinical isolates induce inflammatory cytokine responses via TLR4-mediated MAPK signalling pathways and activation of NFkappaB. *Cell Microbiol*. 2007;9:532–543.
14. Hutchison ML, Bonell EC, Poxton IR, et al. Endotoxic activity of lipopolysaccharides isolated from emergent potential cystic fibrosis pathogens. *FEMS Immunol Med Microbiol*. 2000;27:73–77.
15. Waters VJ, Gomez MI, Soong G, et al. Immunostimulatory properties of the emerging pathogen *Stenotrophomonas maltophilia*. *Infect Immun*. 2007;75:1698–1703.
16. Ierano T, Silipo A, Sturiale L, et al. The structure and proinflammatory activity of the lipopolysaccharide from *Burkholderia multivorans* and the differences between clonal strains colonizing pre and posttransplanted lungs. *Glycobiology*. 2008;18:871–881.
17. Sajjan US, Sylvester FA, Forstner JF. Cable-piliated *Burkholderia cepacia* binds to cytokeratin 13 of epithelial cells. *Infect Immun*. 2000;68:1787–1795.
18. Sajjan US, Sun L, Goldstein R, et al. Cable (cbl) type II pili of cystic fibrosis-associated *Burkholderia (Pseudomonas) cepacia*: nucleotide sequence of the cblA major subunit pilin gene and novel morphology of the assembled appendage fibers. *J Bacteriol*. 1995;177:1030–1038.
19. Clode FE, Kaufmann ME, Malnick H, et al. Distribution of genes encoding putative transmissibility factors among epidemic and nonepidemic strains of *Burkholderia cepacia* from cystic fibrosis patients in the United Kingdom. *J Clin Microbiol*. 2000;38:1763–1766.
20. Sun L, Jiang RZ, Steinbach S, et al. The emergence of a highly transmissible lineage of cbl+ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. *Nat Med*. 1995;1:661–666.
21. Sajjan U, Wu Y, Kent G, et al. Preferential adherence of cable-piliated *Burkholderia cepacia* to respiratory epithelia of CF knockout mice and human cystic fibrosis lung explants. *J Med Microbiol*. 2000;49:875–885.
22. Sajjan US, Yang JH, Hershenson MB, et al. Intracellular trafficking and replication of *Burkholderia cenocepacia* in human cystic fibrosis airway epithelial cells. *Cell Microbiol*. 2006;8:1456–1466.
23. Martin DW, Mohr CD. Invasion and intracellular survival of *Burkholderia cepacia*. *Infect Immun*. 2000;68:24–29.
24. Tipper JL, Ingham E, Cove JH, et al. Survival and multiplication of *Burkholderia cepacia* within respiratory epithelial cells. *Clin Microbiol Infect*. 1998;4:450–459.
25. Miethke M, Marahiel MA. Siderophore-based iron acquisition and pathogen control. *Microbiol Mol Biol Rev*. 2007;71:413–451.
26. Thomas MS. Iron acquisition mechanisms of the *Burkholderia cepacia* complex. *Biometals*. 2007;20:431–452.
27. Garcia CA, Passerini De Rossi B, Alcaraz E, et al. Siderophores of *Stenotrophomonas maltophilia*: detection and determination of their chemical nature. *Rev Argent Microbiol*. 2012;44:150–154.
28. Lewenza S, Conway B, Greenberg EP, et al. Quorum sensing in *Burkholderia cepacia*: identification of the LuxRI homologs CepRI. *J Bacteriol*. 1999;181:748–756.
29. Riedel K, Hentzer M, Geisenberger O, et al. N-acylhomoserine-lactone-mediated communication between *Pseudomonas aeruginosa* and *Burkholderia cepacia* in mixed biofilms. *Microbiology*. 2001;147(Pt 12):3249–3262.
30. O'Brien M, Davis GH. Enzymatic profile of *Pseudomonas maltophilia*. *J Clin Microbiol*. 1982;16:417–421.
31. Travassos LH, Pinheiro MN, Coelho FS, et al. Phenotypic properties, drug susceptibility and genetic relatedness of *Stenotrophomonas maltophilia* clinical strains from seven hospitals in Rio de Janeiro, Brazil. *J Appl Microbiol*. 2004;96:1143–1150.
32. Windhorst S, Frank E, Georgieva DN, et al. The major extracellular protease of the nosocomial pathogen *Stenotrophomonas maltophilia*: characterization of the protein and molecular cloning of the gene. *J Biol Chem*. 2002;277:11042–11049.
33. Schwager S, Agnoli K, Kothe M, et al. Identification of *Burkholderia cenocepacia* strain H111 virulence factors using nonmammalian infection hosts. *Infect Immun*. 2013;81:143–153.
34. Carvalho AP, Ventura GM, Pereira CB, et al. *Burkholderia cenocepacia, B. multivorans, B. ambifaria* and *B. vietnamiensis* isolates from cystic fibrosis patients have different profiles of exoenzyme production. *APMIS*. 2007;115:311–318.
35. Al-Khodor S, Marshall-Batty K, Nair V, et al. *Burkholderia cenocepacia* J2315 escapes to the cytosol and actively subverts autophagy in human macrophages. *Cell Microbiol*. 2014;16:378–395.
36. Abdulrahman BA, Khweek AA, Akhter A, et al. Autophagy stimulation by rapamycin suppresses lung inflammation and infection by *Burkholderia cenocepacia* in a model of cystic fibrosis. *Autophagy*. 2011;7:1359–1370.
37. Segal BH, Ding L, Holland SM. Phagocyte NADPH oxidase, but not inducible nitric oxide synthase, is essential for early control of *Burkholderia cepacia* and chromobacterium violaceum infection in mice. *Infect Immun*. 2003;71:205–210.
38. Zughaier SM, Ryley HC, Jackson SK. A melanin pigment purified from an epidemic strain of *Burkholderia cepacia* attenuates monocyte respiratory burst activity by scavenging superoxide anion. *Infect Immun*. 1999;67:908–913.
39. Bence NF, Sampat RM, Kopito RR. Impairment of the ubiquitin-proteasome system by protein aggregation. *Science*. 2001;292:1552–1555.
40. Mizumura K, Cloonan SM, Haspel JA, et al. The emerging importance of autophagy in pulmonary diseases. *Chest*. 2012;142:1289–1299.
41. Luciani A, Villella VR, Esposito S, et al. Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat Cell Biol*. 2010;12:863–875.
42. Tomich M, Griffith A, Herfst CA, et al. Attenuated virulence of a *Burkholderia cepacia* type III secretion mutant in a murine model of infection. *Infect Immun*. 2003;71:1405–1415.
43. Lamothe J, Huynh KK, Grinstein S, et al. Intracellular survival of *Burkholderia cenocepacia* in macrophages is associated with a delay in the maturation of bacteria-containing vacuoles. *Cell Microbiol*. 2007;9:40–53.
44. Roscetto E, Vitiello L, Muoio R, et al. In vitro interaction of *Stenotrophomonas maltophilia* with human monocyte-derived dendritic cells. *Front Microbiol*. 2015;6.
45. Traverse CC, Mayo-Smith LM, Poltak SR, et al. Tangled bank of experimentally evolved *Burkholderia* biofilms reflects selection during chronic infections. *Proc Natl Acad Sci U S A*. 2013;110:E250–E259.
46. Dales L, Ferris W, Vandemheen K, et al. Combination antibiotic susceptibility of biofilm-grown *Burkholderia cepacia* and *Pseudomonas aeruginosa* isolated from patients with pulmonary exacerbations of cystic fibrosis. *Eur J Clin Microbiol Infect Dis*. 2009;28:1275–1279.
47. Malott RJ, Baldwin A, Mahenthiralingam E, et al. Characterization of the cciIR quorum-sensing system in *Burkholderia cenocepacia*. *Infect Immun*. 2005;73:4982–4992.
48. Di Bonaventura G, Spedicato I, D'Antonio D, et al. Biofilm formation by *Stenotrophomonas maltophilia*: modulation by quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. *Antimicrob Agents Chemother*. 2004;48:151–160.
49. Huang TP, Somers EB, Wong AC. Differential biofilm formation and motility associated with lipopolysaccharide/exopolysaccharide-coupled biosynthetic genes in *Stenotrophomonas maltophilia*. *J Bacteriol*. 2006;188:3116–3120.
50. Ryan RP, Fouhy Y, Garcia BF, et al. Interspecies signalling via the *Stenotrophomonas maltophilia* diffusible signal factor influences biofilm formation and polymyxin tolerance in *Pseudomonas aeruginosa*. *Mol Microbiol*. 2008;68:75–86.
51. Huedo P, Coves X, Daura X, et al. Quorum sensing signaling and quenching in the multidrug-resistant pathogen *Stenotrophomonas maltophilia*. *Front Cell Infect Microbiol*. 2018;8:122.
52. Schmid N, Pessi G, Deng Y, et al. The AHL- and BDSF-dependent quorum sensing systems control specific and overlapping sets of genes in *Burkholderia cenocepacia* H111. *PLoS ONE*. 2012;7:e49966.
53. Jayol A, Corlouer C, Haenni M, et al. Are animals a source of *Stenotrophomonas maltophilia* in human infections? Contributions of a nationwide molecular study. *Eur J Clin Microbiol Infect Dis*. 2018;37:1039–1045.
54. Saviuc P, Picot-Gueraud R, Shum Cheong Sing J, et al. Evaluation of the quality of reprocessing of gastrointestinal endoscopes. *Infect Control Hosp Epidemiol*. 2015;36:1017–1023.
55. Stigt JA, Wolfhagen MJ, Smulders P, et al. The identification of *Stenotrophomonas maltophilia* contamination in ultrasound endoscopes and reproduction of decontamination failure by deliberate soiling tests. *Respiration*. 2015;89:565–571.
56. Guy M, Vanhems P, Dananche C, et al. Outbreak of pulmonary *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* infections related to contaminated bronchoscope suction valves, Lyon, France, 2014. *Euro Surveill*. 2016;21.
57. Cervia JS, Ortolano GA, Canonica FP. Hospital tap water as a source of *Stenotrophomonas maltophilia* infection. *Clin Infect Dis*. 2008;46:1485–1487.
58. Marzuillo C, De Giusti M, Tufi D, et al. Molecular characterization of *Stenotrophomonas maltophilia* isolates from cystic fibrosis patients and the hospital environment. *Infect Control Hosp Epidemiol*. 2009;30:753–758.
59. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis*. 2007;45:1602–1609.
60. Safdar A, Rodriguez GH, Balakrishnan M, et al. Changing trends in etiology of bacteremia in patients with cancer. *Eur J Clin Microbiol Infect Dis*. 2006;25:522–526.
61. Kampmeier S, Pillukat MH, Pettke A, et al. Evaluation of a *Stenotrophomonas maltophilia* bacteremia cluster in hematopoietic stem cell transplantation recipients using whole genome sequencing. *Antimicrob Resist Infect Control*. 2017;6:115.
62. Tan CK, Liaw SJ, Yu CJ, et al. Extensively drug-resistant *Stenotrophomonas maltophilia* in a tertiary care hospital in Taiwan: microbiologic characteristics, clinical features, and outcomes. *Diagn Microbiol Infect Dis*. 2008;60:205–210.
63. Antimicrobial Resistance in 2000: England and Wales [Internet]. Public Health Laboratory Service. 2000. http://www.hpa.org.uk.
64. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis*. 2009;9:312–323.
65. Berdah L, Taytard J, Leyronnas S, et al. *Stenotrophomonas maltophilia*: a marker of lung disease severity. *Pediatr Pulmonol*. 2018;53:426–430.
66. Dalboge CS, Hansen CR, Pressler T, et al. Chronic pulmonary infection with *Stenotrophomonas maltophilia* and lung function in patients with cystic fibrosis. *J Cyst Fibros*. 2011;10:318–325.
67. Lobo LJ, Tulu Z, Aris RM, et al. Pan-resistant *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* infection in cystic fibrosis does not reduce

survival after lung transplantation. *Transplantation*. 2015;99:2196–2202.

68. Raidt L, Idelevich EA, Dubbers A, et al. Increased prevalence and resistance of important pathogens recovered from respiratory specimens of cystic fibrosis patients during a decade. *Pediatr Infect Dis J*. 2015;34:700–705.
69. Hanes SD, Demirkan K, Tolley E, et al. Risk factors for late-onset nosocomial pneumonia caused by *Stenotrophomonas maltophilia* in critically ill trauma patients. *Clin Infect Dis*. 2002;35:228–235.
70. Nseir S, Di Pompeo C, Soubrier S, et al. Impact of ventilator-associated pneumonia on outcome in patients with COPD. *Chest*. 2005;128:1650–1656.
71. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med*. 1998;157:531–539.
72. Weber DJ, Rutala WA, Sickbert-Bennett EE, et al. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. *Infect Control Hosp Epidemiol*. 2007;28:825–831.
73. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev*. 2012;25:2–41.
74. Boktour M, Hanna H, Ansari S, et al. Central venous catheter and *Stenotrophomonas maltophilia* bacteremia in cancer patients. *Cancer*. 2006;106:1967–1973.
75. Lipuma JJ. The changing microbial epidemiology in cystic fibrosis. *Clin Microbiol Rev*. 2010;23:299–323.
76. Lucero CA, Cohen AL, Trevino I, et al. Outbreak of *Burkholderia cepacia* complex among ventilated pediatric patients linked to hospital sinks. *Am J Infect Control*. 2011;39:775–778.
77. Estivariz CF, Bhatti LI, Pati R, et al. An outbreak of *Burkholderia cepacia* associated with contamination of albuterol and nasal spray. *Chest*. 2006;130:1346–1353.
78. Woods CW, Bressler AM, LiPuma JJ, et al. Virulence associated with outbreak-related strains of *Burkholderia cepacia* complex among a cohort of patients with bacteremia. *Clin Infect Dis*. 2004;38:1243–1250.
79. Boussaud V, Guillemain R, Grenet D, et al. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with *Burkholderia cepacia* complex: results from two French centres. *Thorax*. 2008;63:732–737.
80. Campana S, Taccetti G, Ravenni N, et al. Transmission of *Burkholderia cepacia* complex: evidence for new epidemic clones infecting cystic fibrosis patients in Italy. *J Clin Microbiol*. 2005;43:5136–5142.
81. Jones AM, Dodd ME, Govan JR, et al. *Burkholderia cenocepacia* and *Burkholderia multivorans*: influence on survival in cystic fibrosis. *Thorax*. 2004;59:948–951.
82. McDowell A, Mahenthiralingam E, Dunbar KE, et al. Epidemiology of *Burkholderia cepacia* complex species recovered from cystic fibrosis patients: issues related to patient segregation. *J Med Microbiol*. 2004;53(Pt 7):663–668.
83. Rajan S, Saiman L. Pulmonary infections in patients with cystic fibrosis. *Semin Respir Infect*. 2002;17:47–56.
84. Wainwright CE, France MW, O'Rourke P, et al. Cough-generated aerosols of *Pseudomonas aeruginosa* and other gram-negative bacteria from patients with cystic fibrosis. *Thorax*. 2009;64:926–931.
85. Lipuma JJ. Preventing *Burkholderia cepacia* complex infection in cystic fibrosis: is there a middle ground? *J Pediatr*. 2002;141:467–469.
86. Greenberg DE, Goldberg JB, Stock F, et al. Recurrent *Burkholderia* infection in patients with chronic granulomatous disease: 11-year experience at a large referral center. *Clin Infect Dis*. 2009;48:1577–1579.
87. Yeshurun M, Gafter-Gvili A, Thaler M, et al. Clinical characteristics of *Stenotrophomonas maltophilia* infection in hematopoietic stem cell transplantation recipients: a single center experience. *Infection*. 2010;38:211–215.
88. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. *Clin Infect Dis*. 2007;45:228–233.
89. Huang WT, Chen TY, Su WC, et al. Implantable venous port-related infections in cancer patients. *Support Care Cancer*. 2004;12:197–201.
90. Lai CH, Wong WW, Chin C, et al. Central venous catheter-related *Stenotrophomonas maltophilia* bacteraemia and associated relapsing bacteraemia in haematology and oncology patients. *Clin Microbiol Infect*. 2006;12:986–991.
91. Hanna H, Afif C, Alakech B, et al. Central venous catheter-related bacteremia due to gram-negative bacilli: significance of catheter removal in preventing relapse. *Infect Control Hosp Epidemiol*. 2004;25:646–649.
92. Cherif H, Kronvall G, Bjorkholm M, et al. Bacteraemia in hospitalised patients with malignant blood disorders: a retrospective study of causative agents and their resistance profiles during a 14-year period without antibacterial prophylaxis. *Hematol J*. 2003;4:420–426.
93. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine (Baltimore)*. 2016;95:e4375.
94. Micozzi A, Venditti M, Monaco M, et al. Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. *Clin Infect Dis*. 2000;31:705–711.
95. Lai CH, Chi CY, Chen HP, et al. Clinical characteristics and prognostic factors of patients with *Stenotrophomonas maltophilia* bacteremia. *J Microbiol Immunol Infect*. 2004;37:350–358.
96. Martino R, Gomez L, Pericas R, et al. Bacteraemia caused by non-glucose-fermenting gram-negative bacilli and *Aeromonas* species in patients with haematological malignancies and solid tumours. *Eur J Clin Microbiol Infect Dis*. 2000;19:320–323.
97. Lechner A, Hindler JF, Nelson SF. Biclonal bacteremia due to *Stenotrophomonas maltophilia* in a cancer patient. *Eur J Clin Microbiol Infect Dis*. 2001;20:673–675.
98. Apisarnthanarak A, Mayfield JL, Garison T, et al. Risk factors for *Stenotrophomonas maltophilia* bacteremia in oncology patients: a case-control study. *Infect Control Hosp Epidemiol*. 2003;24:269–274.
99. Apisarnthanarak A, Fraser VJ, Dunne WM, et al. *Stenotrophomonas maltophilia* intestinal colonization in hospitalized oncology patients with diarrhea. *Clin Infect Dis*. 2003;37:1131–1135.
100. Khan IA, Mehta NJ. *Stenotrophomonas maltophilia* endocarditis: a systematic review. *Angiology*. 2002;53:49–55.
101. Mehta NJ, Khan IA, Mehta RN, et al. *Stenotrophomonas maltophilia* endocarditis of prosthetic aortic valve: report of a case and review of literature. *Heart Lung*. 2000;29:351–355.
102. Crum NF, Utz GC, Wallace MR. *Stenotrophomonas maltophilia* endocarditis. *Scand J Infect Dis*. 2002;34:925–927.
103. Yusuf SW, Ali SS, Swafford J, et al. Culture-positive and culture-negative endocarditis in patients with cancer: a retrospective observational study, 1994-2004. *Medicine (Baltimore)*. 2006;85:86–94.
104. Takigawa M, Noda T, Kurita T, et al. Extremely late pacemaker-infective endocarditis due to *Stenotrophomonas maltophilia*. *Cardiology*. 2008;110:226–229.
105. Rostoff P, Paradowski A, Gackowski A, et al. *Stenotrophomonas maltophilia* pacemaker endocarditis in a patient with d-transposition of the great arteries after atrial switch procedure. *Int J Cardiol*. 2010;145:e92–e95.
106. Fujita J, Yamadori I, Xu G, et al. Clinical features of *Stenotrophomonas maltophilia* pneumonia in immunocompromised patients. *Respir Med*. 1996;90:35–38.
107. Vartivarian SE, Anaissie EJ, Kiwan EN, et al. The clinical spectrum of *Stenotrophomonas (Xanthomonas) maltophilia* respiratory infection. *Semin Respir Crit Care Med*. 2000;21:349–355.
108. Saugel B, Eschermann K, Hoffmann R, et al. *Stenotrophomonas maltophilia* in the respiratory tract of medical intensive care unit patients. *Eur J Clin Microbiol Infect Dis*. 2012;31:1419–1428.
109. Tada K, Kurosawa S, Hiramoto N, et al. *Stenotrophomonas maltophilia* infection in hematopoietic SCT recipients: high mortality due to pulmonary hemorrhage. *Bone Marrow Transplant*. 2013;48:74–79.
110. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. *Transpl Infect Dis*. 2012;14:355–363.
111. Rousseau A, Morcos M, Amrouche L, et al. Lethal pulmonary hemorrhage caused by a fulminant *Stenotrophomonas maltophilia* respiratory infection in an acute myeloid leukemia patient. *Leuk Lymphoma*. 2004;45:1293–1296.
112. Aisenberg G, Rolston KV, Dickey BF, et al. *Stenotrophomonas maltophilia* pneumonia in cancer patients without traditional risk factors for infection, 1997-2004. *Eur J Clin Microbiol Infect Dis*. 2007;26:13–20.
113. Azzopardi EA, Azzopardi SM, Boyce DE, et al. Emerging gram-negative infections in burn wounds. *J Burn Care Res*. 2011;32:570–576.
114. Teo WY, Chan MY, Lam CM, et al. Skin manifestation of *Stenotrophomonas maltophilia* infection—a case report and review article. *Ann Acad Med Singapore*. 2006;35:897–900.
115. Sakhnini E, Weissmann A, Oren I. Fulminant *Stenotrophomonas maltophilia* soft tissue infection in immunocompromised patients: an outbreak transmitted via tap water. *Am J Med Sci*. 2002;323:269–272.
116. Moser C, Jonsson V, Thomsen K, et al. Subcutaneous lesions and bacteraemia due to *Stenotrophomonas maltophilia* in three leukaemic patients with neutropenia. *Br J Dermatol*. 1997;136:949–952.
117. Libanore M, Bicocchi R, Pantaleoni M, et al. Community-acquired infection due to *Stenotrophomonas maltophilia*: a rare cause of meningitis. *Int J Infect Dis*. 2004;8:317–319.
118. Yemisen M, Mete B, Tunali Y, et al. A meningitis case due to *Stenotrophomonas maltophilia* and review of the literature. *Int J Infect Dis*. 2008;12:e125–e127.
119. Huang CR, Chen SF, Tsai NW, et al. Clinical characteristics of *Stenotrophomonas maltophilia* meningitis in adults: a high incidence in patients with a postneurosurgical state, long hospital staying and antibiotic use. *Clin Neurol Neurosurg*. 2013;115:1709–1715.
120. Papadakis KA, Vartivarian SE, Vassilaki ME, et al. *Stenotrophomonas maltophilia* meningitis. Report of two cases and review of the literature. *J Neurosurg*. 1997;87:106–108.
121. Grindler D, Thomas C, Hall GS, et al. The role of *Stenotrophomonas maltophilia* in refractory chronic rhinosinusitis. *Am J Rhinol Allergy*. 2010;24:200–204.
122. Manes RP, Batra PS. Bacteriology and antibiotic resistance in chronic rhinosinusitis. *Facial Plast Surg Clin North Am*. 2012;20:87–91.
123. Chaudhry NA, Flynn HW Jr, Smiddy WE, et al. *Xanthomonas maltophilia* endophthalmitis after cataract surgery. *Arch Ophthalmol*. 2000;118:572–575.
124. Furuhata K, Ishizaki N, Kawakami Y, et al. Bacterial contamination of stock solutions in storage cases for contact lens, and the disinfectant-resistance of isolates. *Biocontrol Sci*. 2010;15:81–85.
125. Vartivarian SE, Papadakis KA, Anaissie EJ. *Stenotrophomonas (Xanthomonas) maltophilia* urinary tract infection. A disease that is usually severe and complicated. *Arch Intern Med*. 1996;156:433–435.
126. Azak A, Kocak G, Huddam B, et al. An unusual cause of continuous ambulatory peritoneal dialysis-associated outpatient peritonitis: *Stenotrophomonas maltophilia*. *Am J Infect Control*. 2011;39:618.
127. Machuca E, Ortiz AM, Rabagliati R. *Stenotrophomonas maltophilia* peritonitis in a patient receiving automated peritoneal dialysis. *Adv Perit Dial*. 2005;21:63–65.
128. Tzanetou K, Triantaphillis G, Tsoutsos D, et al. *Stenotrophomonas maltophilia* peritonitis in CAPD patients: susceptibility to antibiotics and treatment outcome: a report of five cases. *Perit Dial Int*. 2004;24:401–404.
129. Lee YK, Kim JK, Oh SE, et al. Successful antibiotic lock therapy in patients with refractory peritonitis. *Clin Nephrol*. 2009;72:488–491.
130. Papadakis KA, Vartivarian SE, Vassilaki ME, et al. *Stenotrophomonas maltophilia*: an unusual cause of biliary sepsis. *Clin Infect Dis*. 1995;21:1032–1034.
131. Monkemuller KE, Morgan DE, Baron TH. *Stenotrophomonas (Xanthomonas) maltophilia* infection in necrotizing pancreatitis. *Int J Pancreatol*. 1999;25:59–63.
132. Calza L, Manfredi R, Marinacci G, et al. Liver abscess caused by *Stenotrophomonas (Xanthomonas) maltophilia* in a patient with AIDS. *AIDS*. 2001;15:2465–2467.
133. Harkness B, Andresen D, Kesson A, et al. Infections following lawnmower and farm machinery-related injuries in children. *J Paediatr Child Health*. 2009;45:525–528.
134. Agger WA, Cogbill TH, Busch H Jr, et al. Wounds caused by corn-harvesting machines: an unusual source of infection due to gram-negative bacilli. *Rev Infect Dis*. 1986;8:927–931.
135. Landrum ML, Conger NG, Forgione MA. Trimethoprim-sulfamethoxazole in the treatment of *Stenotrophomonas maltophilia* osteomyelitis. *Clin Infect Dis*. 2005;40:1551–1552.
136. Aydemir C, Aktas E, Eldes N, et al. Community-acquired infection due to *Stenotrophomonas maltophilia*: a rare cause of septic arthritis. *Turk J Pediatr*. 2008;50:89–90.
137. Papadakis KA, Vartivarian SE, Vassilaki ME, et al. Septic prepatellar bursitis caused by *Stenotrophomonas (Xanthomonas) maltophilia*. *Clin Infect Dis*. 1996;22:388–389.
138. Biddick R, Spilker T, Martin A, et al. Evidence of transmission of *Burkholderia cepacia, Burkholderia multivorans* and *Burkholderia dolosa* among persons with cystic fibrosis. *FEMS Microbiol Lett*. 2003;228:57–62.
139. Ramsay KA, Butler CA, Paynter S, et al. Factors influencing acquisition of *Burkholderia cepacia* complex organisms in patients with cystic fibrosis. *J Clin Microbiol*. 2013;51:3975–3980.
140. Courtney JM, Dunbar KE, McDowell A, et al. Clinical outcome of *Burkholderia cepacia* complex infection in cystic fibrosis adults. *J Cyst Fibros*. 2004;3:93–98.
141. Folescu TW, da Costa CH, Cohen RW, et al. *Burkholderia cepacia* complex: clinical course in cystic fibrosis patients. *BMC Pulm Med*. 2015;15:158.

142. Ledson MJ, Gallagher MJ, Jackson M, et al. Outcome of *Burkholderia cepacia* colonisation in an adult cystic fibrosis centre. *Thorax*. 2002;57:142–145.
143. da Costa Capizzani CP, Cacador NC, Torres L, et al. Clinical and microbiological profile of chronic *Burkholderia cepacia* complex infections in a cystic fibrosis reference hospital in Brazil. *Eur J Clin Microbiol Infect Dis*. 2017;36:2263–2271.
144. Ganesan S, Sajjan US. Host evasion by *Burkholderia cenocepacia*. *Front Cell Infect Microbiol*. 2011;1: 25.
145. Nash EF, Thomas A, Whitmill R, et al. "Cepacia syndrome" associated with *Burkholderia cepacia* (Genomovar I) infection in an adolescent with cystic fibrosis. *Pediatr Pulmonol*. 2011;46:512–514.
146. Shafiq I, Carroll MP, Nightingale JA, et al. Cepacia syndrome in a cystic fibrosis patient colonised with *Burkholderia multivorans*. *BMJ Case Rep*. 2011; 2011.
147. Blackburn L, Brownlee K, Conway S, et al. 'Cepacia syndrome' with *Burkholderia multivorans*, 9 years after initial colonization. *J Cyst Fibros*. 2004;3:133–134.
148. Cunha LG Jr, Assis MC, Machado GB, et al. Potential mechanisms underlying the acute lung dysfunction and bacterial extrapulmonary dissemination during *Burkholderia cenocepacia* respiratory infection. *Respir Res*. 2010;11:4.
149. Grimwood K, Kidd TJ, Tweed M. Successful treatment of cepacia syndrome. *J Cyst Fibros*. 2009;8:291–293.
150. Weidmann A, Webb AK, Dodd ME, et al. Successful treatment of cepacia syndrome with combination nebulised and intravenous antibiotic therapy. *J Cyst Fibros*. 2008;7:409–411.
151. Nash EF, Coonar A, Kremer R, et al. Survival of *Burkholderia cepacia* sepsis following lung transplantation in recipients with cystic fibrosis. *Transpl Infect Dis*. 2010;12:551–554.
152. Meachery G, De Soyza A, Nicholson A, et al. Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. *Thorax*. 2008;63:725–731.
153. de Perrot M, Chaparro C, McRae K, et al. Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. *J Thorac Cardiovasc Surg*. 2004;127:1493–1501.
154. Stephenson AL, Sykes J, Berthiaume Y, et al. Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. *J Heart Lung Transplant*. 2015;34:1139–1145.
155. Souza Dias MB, Cavassin LG, Stempliuk V, et al. Multi-institutional outbreak of *Burkholderia cepacia* complex associated with contaminated mannitol solution prepared in compounding pharmacy. *Am J Infect Control*. 2013;41:1038–1042.
156. Moehring RW, Lewis SS, Isaacs PJ, et al. Outbreak of bacteremia due to *Burkholderia contaminans* linked to intravenous fentanyl from an institutional compounding pharmacy. *JAMA Intern Med*. 2014;174:606–612.
157. Pegues DA, Carson LA, Anderson RL, et al. Outbreak of *Pseudomonas cepacia* bacteremia in oncology patients. *Clin Infect Dis*. 1993;16:407–411.
158. Mann T, Ben-David D, Zlotkin A, et al. An outbreak of *Burkholderia cenocepacia* bacteremia in immunocompromised oncology patients. *Infection*. 2010;38:187–194.
159. Sommerstein R, Fuhrer U, Lo Priore E, et al. *Burkholderia stabilis* outbreak associated with contaminated commercially-available washing gloves, Switzerland, May 2015 to August 2016. *Euro Surveill*. 2017;22.
160. Glowicz J, Crist M, Gould C, et al. A multistate investigation of health care-associated *Burkholderia cepacia* complex infections related to liquid docusate sodium contamination, January-October 2016. *Am J Infect Control*. 2018;46:649–655.
161. Kim KY, Yong D, Lee K, et al. *Burkholderia* sepsis in children as a hospital-acquired infection. *Yonsei Med J*. 2016;57:97–102.
162. Chien YC, Liao CH, Sheng WH, et al. Clinical characteristics of bacteraemia caused by *Burkholderia cepacia* complex species and antimicrobial susceptibility of the isolates in a medical centre in Taiwan. *Int J Antimicrob Agents*. 2018;51:357–364.
163. Yamagishi Y, Fujita J, Takigawa K, et al. Clinical features of *Pseudomonas cepacia* pneumonia in an epidemic among immunocompromised patients. *Chest*. 1993;103:1706–1709.
164. Gruson D, Hilbert G, Vargas F, et al. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities of gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit Care Med*. 2003;31:1908–1914.
165. Irwin AE, Price CS. More than skin deep: moisturizing body milk and *Burkholderia cepacia*. *Crit Care*. 2008;12:115.
166. Aygencel G, Dizbay M, Sahin G. *Burkholderia cepacia* as a cause of ecthyma gangrenosum-like lesion. *Infection*. 2008;36:271–273.
167. Marioni G, Rinaldi R, Ottaviano G, et al. Cervical necrotizing fasciitis: a novel clinical presentation of *Burkholderia cepacia* infection. *J Infect*. 2006;53:e219–e222.
168. Miki RA, Rubin LE, Kirk J, et al. Spontaneous septic arthritis caused by *Burkholderia cepacia*. *Iowa Orthop J*. 2006;26:147–150.
169. Lu DC, Chang SC, Chen YC, et al. *Burkholderia cepacia* bacteremia: a retrospective analysis of 70 episodes. *J Formos Med Assoc*. 1997;96:972–978.
170. Li FK, Chan KW, Chan TM, et al. *Burkholderia* urinary tract infection after renal transplantation. *Transpl Infect Dis*. 2003;5:59–61.
171. Zhang L, Li XZ, Poole K. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*: involvement of a multidrug efflux system. *Antimicrob Agents Chemother*. 2000;44:287–293.
172. Crossman LC, Gould VC, Dow JM, et al. The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. *Genome Biol*. 2008;9:R74.
173. Pages D, Rose J, Conrod S, et al. Heavy metal tolerance in *Stenotrophomonas maltophilia*. *PLoS ONE*. 2008;3: e1539.
174. Gould VC, Okazaki A, Avison MB. Coordinate hyperproduction of SmeZ and SmeJK efflux pumps extends drug resistance in *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother*. 2013;57:655–657.
175. Vattanaviboon P, Dulyayangkul P, Mongkolsuk S, et al. Overexpression of *Stenotrophomonas maltophilia* major facilitator superfamily protein MfsA increases resistance to fluoroquinolone antibiotics. *J Antimicrob Chemother*. 2018;73:1263–1266.
176. Pak TR, Altman DR, Attie O, et al. Whole-genome sequencing identifies emergence of a quinolone resistance mutation in a case of *Stenotrophomonas maltophilia* bacteremia. *Antimicrob Agents Chemother*. 2015;59:7117–7120.
177. Shimizu K, Kikuchi K, Sasaki T, et al. Smqnr, a new chromosome-carried quinolone resistance gene in *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother*. 2008;52:3823–3825.
178. Gould VC, Avison MB. SmeDEF-mediated antimicrobial drug resistance in *Stenotrophomonas maltophilia* clinical isolates having defined phylogenetic relationships. *J Antimicrob Chemother*. 2006;57:1070–1076.
179. Nicodemo AC, Paez JI. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. *Eur J Clin Microbiol Infect Dis*. 2007;26:229–237.
180. Hu LF, Xu XH, Li HR, et al. Surveillance of antimicrobial susceptibility patterns among *Stenotrophomonas maltophilia* isolated in China during the 10-year period of 2005-2014. *J Chemother*. 2018;30:25–30.
181. McGowan JE Jr. Resistance in nonfermenting gram-negative bacteria: multidrug resistance to the maximum. *Am J Med*. 2006;119(6 suppl 1):S29–S36, discussion S62–S70.
182. Friedman ND, Korman TM, Fairley CK, et al. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. *J Infect*. 2002;45:47–53.
183. Toleman MA, Bennett PM, Bennett DM, et al. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of sul genes. *Emerg Infect Dis*. 2007;13:559–565.
184. Toleman MA, Walsh TR. Combinatorial events of insertion sequences and ICE in gram-negative bacteria. *FEMS Microbiol Rev*. 2011;35:912–935.
185. Garrison MW, Anderson DE, Campbell DM, et al. *Stenotrophomonas maltophilia*: emergence of multidrug-resistant strains during therapy and in an in vitro pharmacodynamic chamber model. *Antimicrob Agents Chemother*. 1996;40:2859–2864.
186. Muder RR, Harris AP, Muller S, et al. Bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia*: a prospective, multicenter study of 91 episodes. *Clin Infect Dis*. 1996;22:508–512.
187. Araoka H, Baba M, Okada C, et al. Evaluation of trimethoprim-sulfamethoxazole based combination therapy against *Stenotrophomonas maltophilia*: in vitro effects and clinical efficacy in cancer patients. *Int J Infect Dis*. 2017;58:18–21.
188. Tokatly Latzer I, Paret G, Rubinstein M, et al. Management of *Stenotrophomonas maltophilia* infections in critically ill children. *Pediatr Infect Dis J*. 2018.
189. Giamarellos-Bourboulis EJ, Karnesis L, Galani I, et al. In vitro killing effect of moxifloxacin on clinical isolates of *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole. *Antimicrob Agents Chemother*. 2002;46:3997–3999.
190. Zelenitsky SA, Iacovides H, Ariano RE, et al. Antibiotic combinations significantly more active than monotherapy in an in vitro infection model of *Stenotrophomonas maltophilia*. *Diagn Microbiol Infect Dis*. 2005;51:39–43.
191. Korakianitis I, Mirtsou V, Gougoudi E, et al. Post-antibiotic effect (PAE) of moxifloxacin in multidrug-resistant *Stenotrophomonas maltophilia*. *Int J Antimicrob Agents*. 2010;36:387–389.
192. Ba BB, Feghali H, Arpin C, et al. Activities of ciprofloxacin and moxifloxacin against *Stenotrophomonas maltophilia* and emergence of resistant mutants in an in vitro pharmacokinetic-pharmacodynamic model. *Antimicrob Agents Chemother*. 2004;48:946–953.
193. Wang YL, Scipione MR, Dubrovskaya Y, et al. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother*. 2014;58:176–182.
194. Cho SY, Kang CI, Kim J, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating *Stenotrophomonas maltophilia* bacteremia? *Antimicrob Agents Chemother*. 2014;58:581–583.
195. Pompilio A, Crocetta V, Verginelli F, et al. In vitro activity of levofloxacin against planktonic and biofilm *Stenotrophomonas maltophilia* lifestyles under conditions relevant to pulmonary infection in cystic fibrosis, and relationship with SmeDEF multidrug efflux pump expression. *FEMS Microbiol Lett*. 2016;363.
196. Hand E, Davis H, Kim T, et al. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother*. 2016;71:1071–1075.
197. Amin R, Waters V. Antibiotic treatment for *Stenotrophomonas maltophilia* in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2016;(7):CD009249.
198. Tekce YT, Erbay A, Cabadak H, et al. Tigecycline as a therapeutic option in *Stenotrophomonas maltophilia* infections. *J Chemother*. 2012;24:150–154.
199. Grohs P, Taieb G, Morand P, et al. In vitro activity of ceftolozane-tazobactam against multidrug-resistant nonfermenting gram-negative bacilli isolated from patients with cystic fibrosis. *Antimicrob Agents Chemother*. 2017;61.
200. Castanheira M, Huband MD, Mendes RE, et al. Meropenem-vaborbactam tested against contemporary gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant Enterobacteriaceae. *Antimicrob Agents Chemother*. 2017;61.
201. Hackel MA, Tsuji M, Yamano Y, et al. In vitro activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of gram-negative bacilli collected worldwide in 2014 to 2016. *Antimicrob Agents Chemother*. 2018;62.
202. Mojica MF, Ouellette CP, Leber A, et al. Successful treatment of bloodstream infection due to metallo-beta-lactamase-producing *Stenotrophomonas maltophilia* in a renal transplant patient. *Antimicrob Agents Chemother*. 2016;60:5130–5134.
203. Sass A, Marchbank A, Tullis E, et al. Spontaneous and evolutionary changes in the antibiotic resistance of *Burkholderia cenocepacia* observed by global gene expression analysis. *BMC Genomics*. 2011;12:373.
204. Horsley A, Jones AM, Lord R. Antibiotic treatment for *Burkholderia cepacia* complex in people with cystic fibrosis experiencing a pulmonary exacerbation. *Cochrane Database Syst Rev*. 2016;(1):CD009529.
205. Zhou J, Chen Y, Tabibi S, et al. Antimicrobial susceptibility and synergy studies of *Burkholderia cepacia* complex isolated from patients with cystic fibrosis. *Antimicrob Agents Chemother*. 2007;51:1085–1088.
206. Peeters E, Nelis HJ, Coenye T. In vitro activity of ceftazidime, ciprofloxacin, meropenem, minocycline, tobramycin and trimethoprim/sulfamethoxazole against planktonic and sessile *Burkholderia cepacia* complex bacteria. *J Antimicrob Chemother*. 2009;64:801–809.
207. Waters V, Yau Y, Beaudoin T, et al. Pilot trial of tobramycin inhalation powder in cystic fibrosis patients with chronic *Burkholderia cepacia* complex infection. *J Cyst Fibros*. 2017;16:492–495.
208. Kennedy S, Beaudoin T, Yau YC, et al. Activity of tobramycin against cystic fibrosis isolates of Burkholderia cepacia complex grown as biofilms. *Antimicrob Agents Chemother*. 2016;60:348–355.
209. El Chakhtoura NG, Saade E, Iovleva A, et al. Therapies for multidrug resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward 'molecularly targeted' therapy. *Expert Rev Anti Infect Ther*. 2018;16:89–110.
210. Papp-Wallace KM, Becka SA, Zeiser ET, et al. Overcoming an extremely drug resistant (XDR)

pathogen: avibactam restores susceptibility to ceftazidime for *Burkholderia cepacia* complex isolates from cystic fibrosis patients. *ACS Infect Dis*. 2017;3:502–511.
211. Tamma PD, Fan Y, Bergman Y, et al. Successful treatment of persistent *Burkholderia cepacia* complex bacteremia with ceftazidime-avibactam. *Antimicrob Agents Chemother*. 2018;62.
212. Mazer DM, Young C, Kalikin LM, et al. In vitro activity of ceftolozane-tazobactam and other antimicrobial agents against *Burkholderia cepacia* complex and *Burkholderia gladioli*. *Antimicrob Agents Chemother*. 2017;61.
213. Carmody LA, Gill JJ, Summer EJ, et al. Efficacy of bacteriophage therapy in a model of *Burkholderia cenocepacia* pulmonary infection. *J Infect Dis*. 2010;201:264–271.
214. Daly SM, Sturge CR, Marshall-Batty KR, et al. Antisense inhibitors retain activity in pulmonary models of *Burkholderia* infection. *ACS Infect Dis*. 2018;4:806–814.
215. Greenberg DE, Marshall-Batty KR, Brinster LR, et al. Antisense phosphorodiamidate morpholino oligomers targeted to an essential gene inhibit *Burkholderia cepacia* complex. *J Infect Dis*. 2010;201:1822–1830.
216. Pompilio A, Crocetta V, Scocchi M, et al. Potential novel therapeutic strategies in cystic fibrosis: antimicrobial and anti-biofilm activity of natural and designed alpha-helical peptides against *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Stenotrophomonas maltophilia*. *BMC Microbiol*. 2012;12:145.
217. Saiman L, Siegel J. Infection control in cystic fibrosis. *Clin Microbiol Rev*. 2004;17:57–71.
218. Sousa SA, Seixas AMM, Leitao JH. Postgenomic approaches and bioinformatics tools to advance the development of vaccines against bacteria of the *Burkholderia cepacia* complex. *Vaccines (Basel)*. 2018;6.
219. Makidon PE, Knowlton J, Groom JV 2nd, et al. Induction of immune response to the 17 kDa OMPA *Burkholderia cenocepacia* polypeptide and protection against pulmonary infection in mice after nasal vaccination with an OMP nanoemulsion-based vaccine. *Med Microbiol Immunol*. 2010;199:81–92.
220. Bertot GM, Restelli MA, Galanternik L, et al. Nasal immunization with *Burkholderia multivorans* outer membrane proteins and the mucosal adjuvant adamantylamide dipeptide confers efficient protection against experimental lung infections with *B. multivorans* and *B. cenocepacia*. *Infect Immun*. 2007;75:2740–2752.
221. Zgair AK, Chhibber S. Stenotrophomonas maltophilia flagellin induces a compartmentalized innate immune response in mouse lung. *J Med Microbiol*. 2010;59(Pt 8):913–919.
222. Skurnik D, Davis MR Jr, Benedetti D, et al. Targeting pan-resistant bacteria with antibodies to a broadly conserved surface polysaccharide expressed during infection. *J Infect Dis*. 2012;205:1709–1718.

221 *Burkholderia pseudomallei* and *Burkholderia mallei*: Melioidosis and Glanders

Bart J. Currie

SHORT VIEW SUMMARY

Definition
- Melioidosis is a disease of humans and animals resulting from infection with the soil and water bacterium *Burkholderia pseudomallei.*
- Glanders is a disease primarily of horses resulting from infection with *Burkholderia mallei.*

Epidemiology: Melioidosis
- The major endemic regions for melioidosis are Southeast Asia and northern Australia. Infections in travelers are most commonly in visitors to Southeast Asia, usually Thailand.
- Cases have occurred in other tropical and subtropical locations, such as the Indian subcontinent, China, Africa, the Caribbean, and Central and South America.
- Most cases occur during the rainy season, and clusters can follow severe weather events.
- Exposure occurs through percutaneous inoculation, inhalation, and ingestion (more common with glanders).
- Zoonotic and nosocomial infections are exceedingly rare with melioidosis (more common with glanders).
- Disease and outcomes are tightly linked to risk factors, especially diabetes (see Table 221.1).

Microbiology
- *B. pseudomallei* is a small, gram-negative, oxidase-positive, motile, aerobic bacillus.
- *B. mallei* is a small, gram-negative, oxidase-positive, nonmotile aerobic bacillus.
- *B. mallei* does not persist in the environment outside its equine host; genetic studies suggest that *B. mallei* evolved in animals from the environmental pathogen *B. pseudomallei.*

Diagnosis: Melioidosis
- Most infections with *B. pseudomallei* are asymptomatic.
- Of cases, 85% are acute illnesses after recent infection, and 11% are chronic infections (sick more than 2 months); activation from latency is rare but can occur decades after infection.
- More than half of cases are bacteremic, and up to one-quarter manifest with septic shock with high mortality.
- Presentation is pneumonia in about half of cases, but there are various other presentations (see Table 221.2).
- Culture is required for diagnosis using blood, sputum, urine, or pus, and it is facilitated by inoculating swabs from pus, throat, and rectum directly onto selective medium.
- Identification of *B. pseudomallei* and *B. mallei* by various methods can be problematic.
- Locally developed antigen and DNA detection techniques are available in some locations. Serology has poor specificity because of background positivity in endemic regions.

Therapy
- Ceftazidime or a carbapenem with or without trimethoprim-sulfamethoxazole (TMP-SMZ) is given initially, followed by TMP-SMZ (see Tables 221.3 and 221.4).
- Therapy for glanders is as for melioidosis, although gentamicin, azithromycin, or clarithromycin may have a role.

Prevention
- Melioidosis: Education is needed in endemic areas about minimizing exposure to wet season soils, surface water, and potential aerosols during windy monsoonal rains, especially for diabetics.
- Patients with cystic fibrosis should consider avoiding travel to high-risk areas.
- Glanders: Control of glanders in the equine species and strict precautions to prevent laboratory-acquired infection are crucial.
- Vaccines are under development for both melioidosis and glanders.

The genus *Burkholderia* is currently composed of many species, but only three are notable pathogens for humans or animals: the former *B. cepacia* complex (described in Chapter 220), *B. pseudomallei* (the agent of melioidosis), and *B. mallei* (the agent of equine glanders). All three are aerobic, nonsporulating, straight or slightly curved gram-negative bacilli that were formerly placed in the genus *Pseudomonas.*

MELIOIDOSIS

Melioidosis is a disease of humans and animals; it has enormous clinical diversity, spanning asymptomatic infection, localized skin ulcers or abscesses, chronic pneumonia mimicking tuberculosis, and fulminant septic shock with abscesses in multiple internal organs. Most disease is from recent infection, but latency with subsequent activation is well recognized and can occur decades after exposure. Most cases are reported from Southeast Asia and northern Australia, but melioidosis is increasingly being recognized in other tropical and subtropical locations and in people infected in an endemic region who return or travel to Europe and the United States (Fig. 221.1).[1] More recent modeling suggested that melioidosis is greatly underdiagnosed in most of the 45 countries in which it is known to be endemic and predicted that it may be present in a further 34 countries where it has not yet been reported.[2] The modeling estimated 165,000 infections and 89,000 deaths worldwide annually. Targeted surveillance and support for improved regional microbiology facilities are needed to determine the accuracy of these predictions.[3] The causative bacterium, *B. pseudomallei,* is also considered a potential biological warfare agent.

History

In 1912 Whitmore and Krishnaswami[4] described cases of a newly recognized septicemic disease in morphine addicts in Rangoon, Burma. Fatal cases were characterized by widespread caseous consolidation of the lung and abscesses in liver, spleen, kidney, and subcutaneous tissues. The bacillus isolated from tissues was similar to that causing glanders *(B. mallei)* but was motile. Whitmore and Krishnaswami[4] noted the clinical similarity to glanders, and Stanton and Fletcher[5] subsequently proposed the name *melioidosis,* derived from the Greek *melis* (distemper of asses). Various names were used for the causative bacterium, including *Bacillus whitmori* and, for many years, *Pseudomonas pseudomallei.*[6] In 1992 seven *Pseudomonas* spp. were moved to a new genus, *Burkholderia. B. cepacia* is the type species in the genus, which includes the organisms causing melioidosis *(B. pseudomallei)* and glanders *(B. mallei).*

Etiology

B. pseudomallei is a small, gram-negative, oxidase-positive, motile, aerobic bacillus with occasional polar flagella. On staining, a bipolar

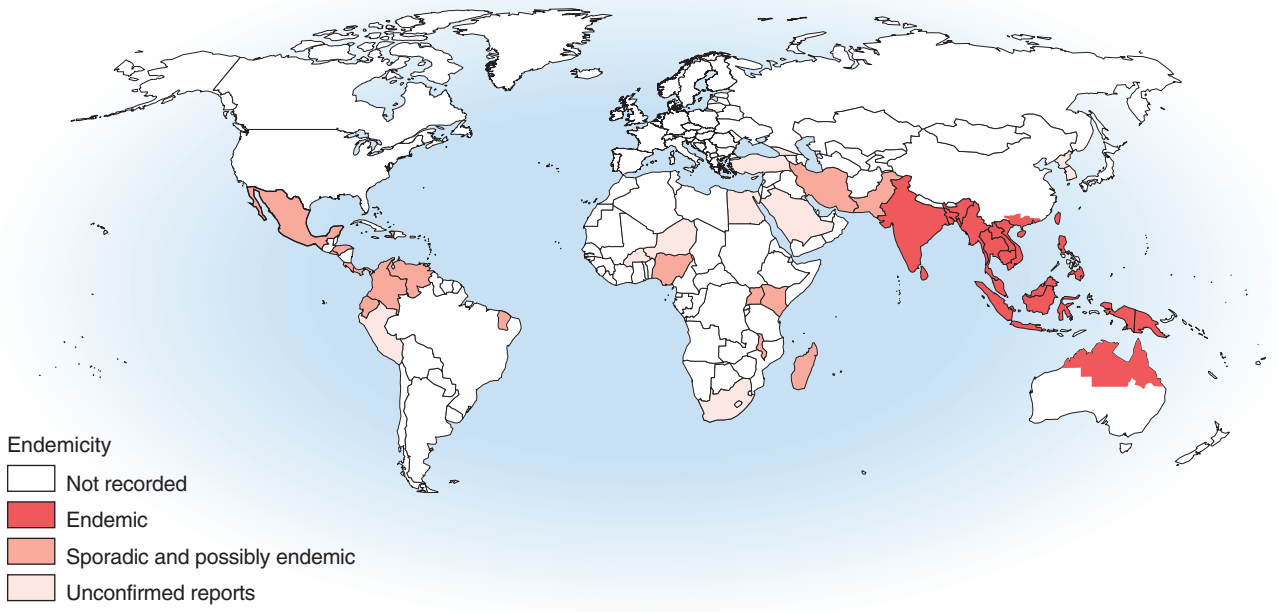

FIG. 221.1 **Known global distribution of melioidosis.**

"safety pin" pattern is seen. The organism is easily recovered on standard culture medium and must be distinguished from the closely related soil saprophytes *B. thailandensis, B. oklahomensis,* and *B. humptydooensis,* as well as from *Pseudomonas stutzeri* and other *Pseudomonas* species.

The organism is present in soil and surface water in endemic regions. Humans and animals are infected by percutaneous inoculation, inhalation, aspiration, or ingestion. Occasional laboratory-acquired infections are described, but person-to-person spread and zoonotic infection are very uncommon.

Epidemiology

After the initial account in Burma, melioidosis was documented in humans and animals in Malaysia and Singapore from 1913, in Vietnam from 1925, and in Indonesia from 1929.[7] Thailand has reported the largest number of cases,[5–8] with an estimated 2000 to 3000 cases of melioidosis each year.[9] Melioidosis is also common in Malaysia[10] and Singapore.[11,12] Other countries in the region where melioidosis is recognized in humans and animals include China (especially Hong Kong), Taiwan, Brunei, Vietnam, Cambodia, and Laos.[13–18,19] Melioidosis is also likely to occur in the Philippines.[9,20] Melioidosis has been increasingly recognized in India, although reports that some of the "plague" scares of 1994 may have been cases of melioidosis have been disproved.[21,22] Cases have been reported from Sri Lanka, Bangladesh, and Pakistan.[20] Despite the early documentation of melioidosis in Burma and Indonesia, more recent cases were not reported from Indonesia until after the 2004 Asian tsunami.[23] Cases of melioidosis have also been documented from Papua New Guinea, Fiji, and New Caledonia,[24] but the extent of endemicity in the Pacific Islands remains to be defined.

Cases of melioidosis are increasingly being documented from outside the classic endemic region of Southeast Asia, Australasia, the Indian subcontinent, and China. These include sporadic human or animal cases or environmental isolates of *B. pseudomallei* from the Middle East, Africa, the Caribbean, and Central and South America. Regional endemicity of the disease in Puerto Rico has been documented.[25] Although some of these reports are from incorrect species diagnosis, others are confirmed, making the endemic limitations of melioidosis very unclear.[20] Sporadic cases and occasional case clusters have recently occurred in Brazil and elsewhere in the Americas.[26,27] Despite more recent cases from Madagascar and Malawi,[28,29] the true extent and magnitude of the presence of *B. pseudomallei* in Africa remain entirely unknown. Global warming may result in expansion of the endemic boundaries of melioidosis.[30,31] A global phylogeny study has supported the origin of *B. pseudomallei* to be Australia, with subsequent spread to Southeast Asia and then to Africa.[32] Spread from Africa to the Americas was calculated to have been much more recent, potentially linked to the times of the slave trade.

The two locations where melioidosis is arguably the most important bacterial pathogen for humans are some northeast provinces in Thailand and the Top End of the Northern Territory of Australia. In northeast Thailand, 20% of community-acquired septicemic cases are caused by melioidosis, which accounts for 39% of fatal septicemias[33] and 36% of fatal community-acquired pneumonias.[34] In the Top End of the Northern Territory, melioidosis has been the most common cause of fatal community-acquired bacteremic pneumonia.[35]

In addition to endemic melioidosis, there are several documented situations where melioidosis became established in nontropical locations. In France in the 1970s cases of melioidosis occurred in animals in a Paris zoo, with spread to other zoos and equestrian clubs.[36] In addition to fatal animal and human cases, there was extensive soil contamination persisting for some years. *B. pseudomallei* is considered likely to have been introduced by importation of infected animals. A cluster of cases occurred over a 25-year period in southwestern Western Australia (31° S) involving animal cases and one human infection in a farmer. Ribotyping of the farm animal and human isolates and one isolate from the soil showed identical patterns.[37] This supported the suggestion of clonal introduction of *B. pseudomallei,* probably via an infected animal, with environmental contamination, local dissemination, and persistence. In 2017, further cases in animals with the same *B. pseudomallei* genotype were again documented in that location following a storm with near record rainfall.[30] This was 26 years after the previous case and demonstrates more than 50 years of persistence of *B. pseudomallei* in this temperate region.

Melioidosis was an important cause of morbidity and mortality in foreign troops fighting in Southeast Asia. Dance[36] noted that at least 100 cases occurred among French forces in Indochina between 1948 and 1954. By 1973, 343 cases had been reported in American troops fighting in Vietnam. Concerns of reactivation of latent infection in soldiers returning from Vietnam, with estimates from serology studies of approximately 225,000 potential cases, resulted in melioidosis being called the "Vietnamese time bomb."[38] However, although occasional cases of reactivation of *B. pseudomallei* still occur in Vietnam veterans, it is rare compared with the numbers of troops exposed.

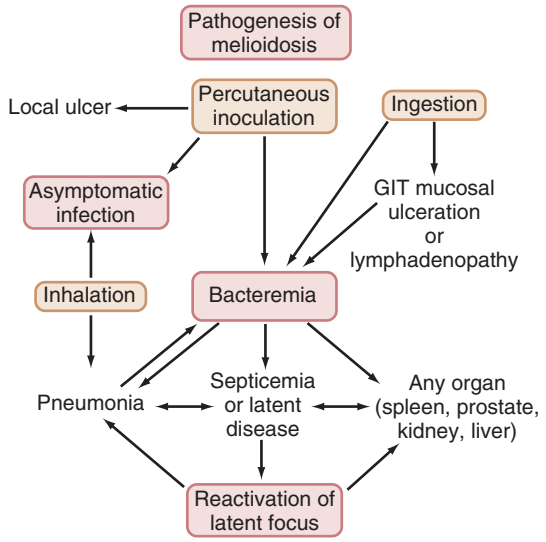

FIG. 221.2 Natural history of infection with *Burkholderia pseudomallei*. *GIT,* Gastrointestinal tract.

Transmission

Fig. 221.2 summarizes the natural history of infection with *B. pseudomallei.* Studies from Malaysia, Thailand,[39] and Australia[40] have found that the organism is more common in cleared, irrigated sites such as rice paddies and farms. It has been suggested that the increase in melioidosis cases in Thailand may be partly due to the increased number of bacteria in such environments and partly due to increased exposure to bacteria resulting from changes in behaviors such as farming techniques.[13] In Australia, *B. pseudomallei* has been found most commonly in clay soils to a depth of 25 to 45 cm, and it has been proposed that the bacteria move to the surface with the rising water table during the wet season.[41] Exposure to mud in an endurance challenge (10-km or 21-km obstacle course including river crossing and mud crawl) has been associated with melioidosis in the Northern Territory of Australia.[42] An alternative explanation for the variable bacterial presence found is that during times of stress such as in prolonged dry seasons, *B. pseudomallei* may persist in soil in a viable but nonculturable state.[43] Differential gene activation may allow such environmental bacteria to respond and adapt to different environmental conditions. This possibility is also relevant to the pathogenicity, latency, and reactivation of infection with *B. pseudomallei* in humans. Melioidosis endemic locations may vary in their specific ecologic niches for *B. pseudomallei.*[44] *B. pseudomallei* colonizes and thrives in the rhizosphere and aerial parts of native and imported grasses in northern Australia, raising implications for global epidemiology and potential dispersal.[45] The role of biofilms in the persistence of *B. pseudomallei* in the environment as well as in animal and human hosts requires further study.[46]

In most endemic regions, there is a close association between melioidosis and rainfall. In northeast Thailand[47] and northern Australia,[7] 75% and 81% of cases, respectively, have occurred in the wet season. In a study of cases in Singapore, increased incidence was associated with humidity and rainfall.[48] Although early animal studies showed infection with *B. pseudomallei* through oral or nasal exposure and from ingestion, more recent reviews have considered that most human cases are from percutaneous inoculation of *B. pseudomallei* after exposure to muddy soils or surface water in endemic locations.[6,20,35] Ingestion and sexual transmission have been suggested as unusual modes of transmission of *B. pseudomallei.* Nevertheless, a more recent study from Thailand raised the possibility that ingestion of water contaminated with *B. pseudomallei* may be a more common infecting event than previously thought, especially in endemic regions with unchlorinated water supplies.[49] Presentations of melioidosis pneumonia after presumptive inoculating skin injuries have been documented in patients with soil-contaminated burns and are common in tropical Australia.[35] This suggests hematogenous spread to the lung rather than inhalation or spread from the upper respiratory tract. However, under certain epidemiologic conditions, the inhalation route may predominate, as suggested for soldiers exposed to dusts raised by helicopter rotor blades in Vietnam.[50] Melioidosis after near drowning is well documented, with the probable infecting event being aspiration.[14] Intensity of rainfall is an independent predictor of melioidosis manifesting as pneumonia and of a fatal outcome,[51] suggesting that heavy monsoonal rainfall and winds may result in a shift toward inhalation as the mode of infection with *B. pseudomallei.* At the present time the overall proportion of melioidosis cases resulting from inhalation rather than percutaneous inoculation remains uncertain.[1,52] Several outbreaks of melioidosis in Australia have been linked to contamination of potable water with *B. pseudomallei.*[53,54] The water supplies involved were unchlorinated, or the chlorination was below standard. The contamination of the water supply has been attributed to soil disturbance during excavations. Drinking water was also identified as a likely source of infections in the more recent study from Thailand.[55]

The incubation period for melioidosis is influenced by inoculating dose, mode of infection, host risk factors, and probably differential virulence of infecting *B. pseudomallei* strains. Onset of melioidosis within 24 hours has been seen in presumed aspiration after near drowning and, in some cases, after severe weather events. In 25 cases of acute melioidosis in which a clear incubation period could be determined between the inoculating injury and the onset of symptoms, the incubation period was 1 to 21 days (mean, 9 days),[56] which is consistent with a series of nosocomial cases from Thailand in which the incubation period was 3 to 16 days (mean, 9.5 days).[57]

In a review of 72 published cases in travelers, 73% acquired the infection in Southeast Asia, most commonly Thailand, and 19% were infected in Central America.[58] In this review and a separate review of 82 published cases, traveling during heavy rains or floods and adventure travel were common.[59] Most patients presented with sepsis, pneumonia, or abscesses. Onset of illness was an average of 23 days after return (range, 1–360 days).[58]

Pathogenesis

Serology studies have shown that most infections with *B. pseudomallei* are asymptomatic.[60,61] In northeast Thailand, most of the rural population is seropositive by indirect hemagglutination (IHA),[47] with most seroconversion occurring between 6 months and 4 years of age.[61] Although melioidosis occurs in all age groups, severe clinical disease, such as septicemic pneumonia, is seen mostly in patients with risk factors such as diabetes, renal disease, and hazardous alcohol use.

In addition to infection by inhalation, bacterial load on exposure (inoculating dose) and virulence of the infecting strain of *B. pseudomallei* are likely to influence the severity of disease. However, it has been noted that despite the large bacterial load in severely ill patients with septicemic pulmonary melioidosis, person-to-person transmission is extremely unusual. This, together with the rarity of fulminant melioidosis in healthy people, supports the primary importance of host risk factors for development of melioidosis. Furthermore, although it is clear from laboratory studies of isolates of *B. pseudomallei* from animals, humans, and the environment that virulence differs among *B. pseudomallei* isolates,[62] the importance of this variation in virulence in determining clinical aspects of melioidosis remains uncertain. Molecular typing that shows clonality of isolates in animal and human clusters has revealed that the same outbreak strain can cause different clinical presentations, with host factors being most important in determining the severity of disease.[54] Whole-genome sequencing and subsequent molecular studies have shown that *B. pseudomallei* has two chromosomes, with a complex accessory genome that includes multiple genomic islands that are variably present in different strains and have a great propensity for horizontal gene transfer.[63,64] Further studies are required to unravel the global phylogeny and evolutionary history of *B. pseudomallei* and related species and to determine which genes or gene clusters may be critical for pathogenesis and disease presentation and outcome.[1,65] Bacterial genome-wide association studies have begun to show presence or absence of specific genes linked to neurologic and cutaneous melioidosis.[66]

B. pseudomallei is a facultative intracellular pathogen that can invade and replicate inside various cells including polymorphonuclear leukocytes

and macrophages and some epithelial cell lines.[67] Resistance to human serum (conferred by lipopolysaccharide [LPS])[68] and the ability of *B. pseudomallei* to survive intracellularly (conferred in part by capsular polysaccharide) appear to be critical in the pathogenesis of melioidosis.[69,70] Type III and type VI secretion systems in *B. pseudomallei* have also been found to be important in cell invasion and intracellular survival.[71,72] Quorum sensing may play an important role in many aspects of virulence of *B. pseudomallei* including cell invasion, cytotoxicity, and antimicrobial resistance.[46,67,73] Other putative virulence factor candidates include flagella; type IV pili and other adhesins; a siderophore; and secreted proteins such as hemolysin, lipases, and proteases.[67] *Burkholderia* lethal factor 1 is similar to *Escherichia coli* cytotoxic necrotizing factor 1 and interferes with initiation of translation, leading to alteration of the actin cytoskeleton and ultimately cell death.[74]

Intracellular survival of *B. pseudomallei* in human and animal hosts is likely to explain the ability for latency. After internalization, *B. pseudomallei* escapes from endocytic vacuoles into the cell cytoplasm, and induction of actin polymerization at one bacterial pole leads to membrane protrusions, with cell-to-cell spread involving these actin tails.[75] An additional survival factor for *B. pseudomallei* is the ability for phenotypic switching with a change in colony morphology resulting in changes in the expression of putative virulence factors such as biofilm and flagella.[76]

A number of studies have shown elevated levels of various endogenous inflammatory mediators and cytokines to be associated with severity and outcomes of melioidosis. Nevertheless, whether these elevated cytokines are a cause or result of severe disease is not established. In Thailand, there was an association of severe melioidosis with tumor necrosis factor-α (TNF-α) gene allele 2, which is linked to higher constitutive and inducible production of TNF-α.[77] However, in a mouse model of melioidosis, neutralization of TNF-α or interleukin-12 increased susceptibility to infection in vivo, and interferon-γ (IFN-γ) was found to be important for survival, with mice treated with monoclonal anti–IFN-γ dying more quickly.[78] A role for Toll-like receptors in the innate immune response in melioidosis has been proposed.[79,80] Therefore there are important host protective mechanisms against *B. pseudomallei* in cytokine responses as well as potentially detrimental ones, with the timing of cytokine release and the balance between proinflammatory and antiinflammatory responses likely to determine the severity of disease and outcome of infection.[67,81] The extent to which host polymorphisms in immune response contribute compared with differences in organism virulence, infecting dose of *B. pseudomallei,* and defined host risk factors such as diabetes remains to be clarified. Nevertheless, the predominant association with fatal melioidosis is the presence of defined patient risk factors.

Although a vigorous cell-mediated immune response may protect against disease progression,[82] there is no definitive evidence for the development of immunity from melioidosis after natural exposure to *B. pseudomallei*. Moreover, reinfection can occur with a different strain of *B. pseudomallei* after successful treatment of melioidosis.[83]

Table 221.1 summarizes the risk factors for melioidosis. The most important risk factors are diabetes, hazardous alcohol use, and renal disease.[6,7,84] In Thailand, the adjusted odds ratios for diabetes and renal disease (chronic renal impairment or renal or ureteric calculi) in cases of melioidosis versus control subjects were 12.9 (95% confidence interval [CI], 5.1–37.2) and 2.9 (95% CI, 1.7–5.0), respectively.[84] Other risk factors for melioidosis include chronic lung disease (including cystic fibrosis), thalassemia[85] (odds ratio in Thailand, 10.2; 95% CI, 3.5–30.8), malignancies, steroid therapy, iron overload, and tuberculosis.[84] Severe disease and fatalities are uncommon in patients without risk factors in whom infection is diagnosed early and early treatment is administered, with only two deaths in 106 patients without risk factors in one study.[7] Risk factors are less common in children than in adults.[86,87] A study from Sabah, Malaysia, demonstrated the importance of iron overload in thalassemia as a risk factor for melioidosis in children, with no cases after introduction of regular iron chelation therapy.[88]

Evidence suggests that the predisposition to melioidosis in patients with diabetes, hazardous alcohol use, or chronic renal disease may reflect impairment of innate immune function, especially neutrophil and other phagocytic cell functions such as mobilization, delivery, adherence, ingestion, and killing.[7,89] Melioidosis has also been described in chronic granulomatous disease.[90]

TABLE 221.1 Risk Factors for Melioidosis

RISK FACTOR[a]	THAILAND (% OF CASES)[b]	AUSTRALIA (% OF CASES)[c]
Diabetes	23–60	37
Alcohol excess	12	39
Renal disease	20–27	10
Chronic lung disease	NR	27
Thalassemia	7	0
No risk factors	24–36	20

[a]Not listed: malignancy, steroid therapy, iron overload, cardiac failure.
[b]Thailand data from Punyagupta S. Melioidosis: review of 686 cases and presentation of a new clinical classification. In: Punyagupta S, Sirisanthana T, Stapatayavong B, eds. *Melioidosis*. Bangkok: Bangkok Medical; 1989:217–229; Chaowagul W, White NJ, Dance DA, et al. Melioidosis: a major cause of community-acquired septicemia in northeastern Thailand. *J Infect Dis*. 1989;159:890–899; Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al. Risk factors for melioidosis and bacteremic melioidosis. *Clin Infect Dis*. 1999;29:408–413; and Limmathurotsakul D, Chaowagul W, Chierakul W, et al. Risk factors for recurrent melioidosis in northeast Thailand. *Clin Infect Dis*. 2006;43:979–986.
[c]Australia data from Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: a 10-year prospective study and review of the literature. *Clin Infect Dis*. 2000;31:981–986.
NR, Not reported.

Clinical Manifestations

The earliest descriptions of melioidosis documented the fulminant end of the clinical spectrum, with abscesses throughout both lungs and in many organs.[4] At the other end of the spectrum are asymptomatic infections and localized skin ulcers or abscesses without systemic illness. Howe and colleagues[50] classified melioidosis as acute, subacute, and chronic. The Infectious Disease Association of Thailand summarized 345 cases in these categories, as follows[6,91]:

1. Multifocal infection with septicemia (45% of cases, 87% mortality)
2. Localized infection with septicemia (12% of cases, 17% mortality)
3. Localized infection (42% of cases, 9% mortality)
4. Transient bacteremia (0.3%)

Bacteremia and overall mortality rates, respectively, have been reported as 60% and 44% in Thailand,[47] 55% and 14% in Australia,[7] and 43% and 39% in Singapore.[20]

Table 221.2 summarizes the clinical manifestations in patients with melioidosis in northern Australia. Pneumonia is the most common clinical manifestation in patients with melioidosis in all studies, accounting for about half of cases. Secondary pneumonia after another primary presentation occurs in about 10% of cases. Acute melioidosis pneumonia has a spectrum from fulminant septic shock (mortality up to 90%) (Figs. 221.3 to 221.6) to mild undifferentiated pneumonia, which can be acute or subacute in nature, with little mortality.[92] Septicemic patients present acutely unwell with high fevers and prostration and often little initial cough or pleuritic pain. On chest radiographs, diffuse nodular infiltrates often develop throughout both lungs, and they coalesce, cavitate, and progress rapidly, consistent with the caseous necrosis and multiple metastatic abscess formation seen at autopsy. Nonsepticemic patients with pneumonia and some patients with septicemic pneumonia have a more predominant cough, with productive sputum and dyspnea, and their chest radiographs show discrete but progressive consolidation in one or more lobes (Fig. 221.7). In endemic regions, acute pneumonia with upper lobe consolidation warrants consideration of melioidosis, although lower lobe infiltrates are also common.

In 11% of cases in northern Australia, patients present with chronic melioidosis, defined as illness with symptoms for longer than 2 months' duration on presentation. Many of these patients have features mimicking tuberculosis, with fevers, weight loss, productive cough (sometimes with hemoptysis), and classic upper lobe infiltrates, with or without cavitation on chest radiographs (Fig. 221.8). In these patients, disease

TABLE 221.2 Clinical Presentations and Outcomes of Melioidosis in Northern Australia

	TOTAL		BACTEREMIC		NONBACTEREMIC	
	Number	Deaths (Mortality)	Number	Deaths (Mortality)	Number	Deaths (Mortality)
Septic shock present	116 (21%)	58 (50%)	103	48 (47%)	13	10 (77%)
Pneumonia	88	43 (49%)	78	35 (45%)	10[a]	8 (80%)
No evident focus	13	8 (62%)	12	7 (58%)	1[b]	1 (100%)
Genitourinary	10	5 (50%)	9	4 (44%)	1[c]	1 (100%)
Osteomyelitis/septic arthritis	4	2 (50%)	4	2 (50%)	0	0 (0%)
Soft tissue abscess	1	0 (0%)	0	0	1	0 (0%)
Not septic shock	424 (79%)	19 (4%)	195	13 (7%)	229	6 (3%)
Pneumonia	190	12 (6%)	89	9 (10%)	101	3 (3%)
Skin infection	68	0 (0%)	1	0 (0%)	67	0 (0%)
Genitourinary	66	2 (3%)	41	2 (5%)	25	0 (0%)
No evident focus	52	2 (4%)	47	2 (4%)	5	0 (0%)
Soft tissue abscess	18	0 (0%)	4	0 (0%)	14	0 (0%)
Osteomyelitis/septic arthritis	16	0 (0%)	10	0 (0%)	6	0 (0%)
Neurologic	14	3 (21%)	3	0 (0%)	11	3 (27%)
Total	540	77 (14%)	298 (55%)	61 (20%)	242 (45%)	16 (7%)

[a]Seven blood cultures not done; three blood cultures negative.
[b]Culture was positive for *Burkholderia pseudomallei* only from rectal swab, although fatal septic shock.
[c]Blood culture not done.
From Currie BJ, Ward L, Cheng AC. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20-year Darwin prospective study. PLoS Negl Trop Dis. *2010;4:e900.*

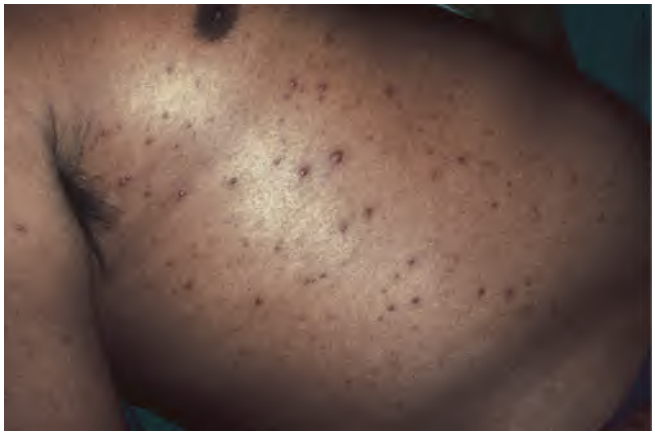

FIG. 221.3 Multiple pustules in a 46-year-old diabetic man with fatal septicemic melioidosis.

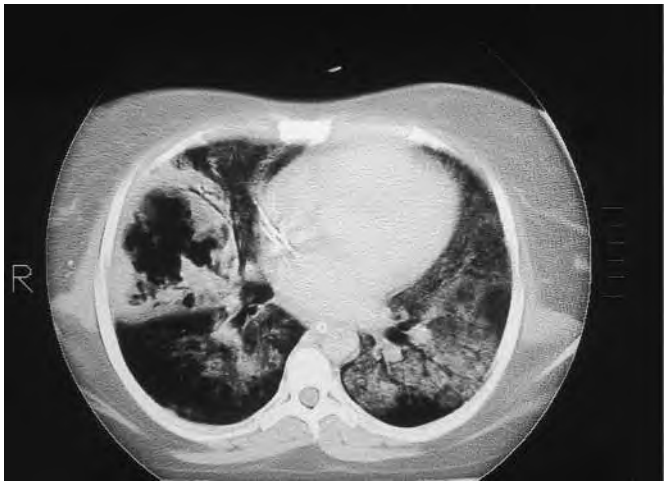

FIG. 221.5 Computed tomography scan of the chest of a 26-year-old woman with fatal melioidosis showing large pulmonary abscess.

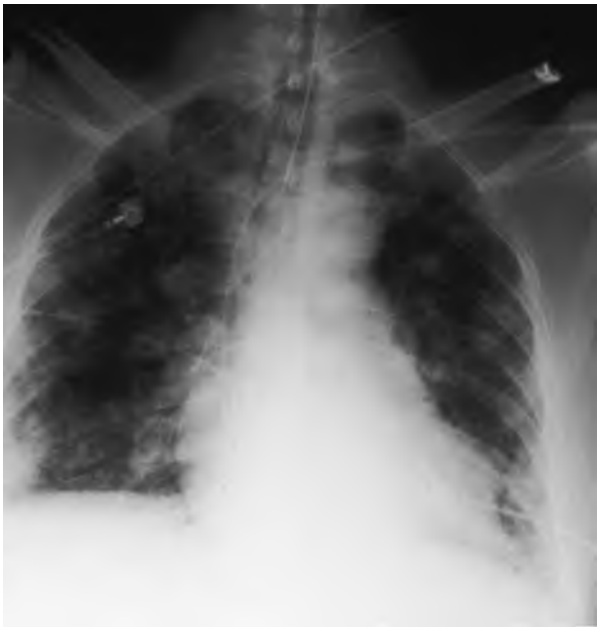

FIG. 221.4 Chest radiograph of patient in Fig. 221.3 showing multiple pulmonary abscesses.

can be remitting and relapsing over many years, sometimes with an initial misdiagnosis of tuberculosis. Although acute deterioration with septicemia may occur, mortality in this group is low.

Previously it was thought that a colonization state did not exist for *B. pseudomallei,* with presence in sputum or the throat always reflecting disease. However, it has more recently become evident that *B. pseudomallei* can both colonize airways and cause disease in patients with cystic fibrosis (CF) and bronchiectasis.[93,94] The similarity to infection with *B. cepacia* complex in CF is concerning, given the association of *B. cepacia* complex with more rapid deterioration in lung function. Furthermore, likely transmission of *B. pseudomallei* between two siblings with CF has been reported.[95] Patients with CF traveling to locations where

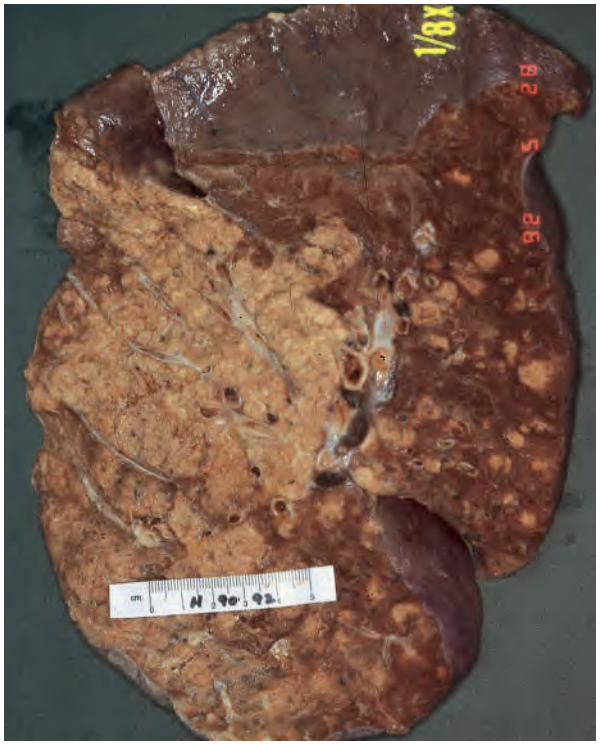

FIG. 221.6 **Multiple lung abscesses seen at autopsy of a patient with acute melioidosis pneumonia.**

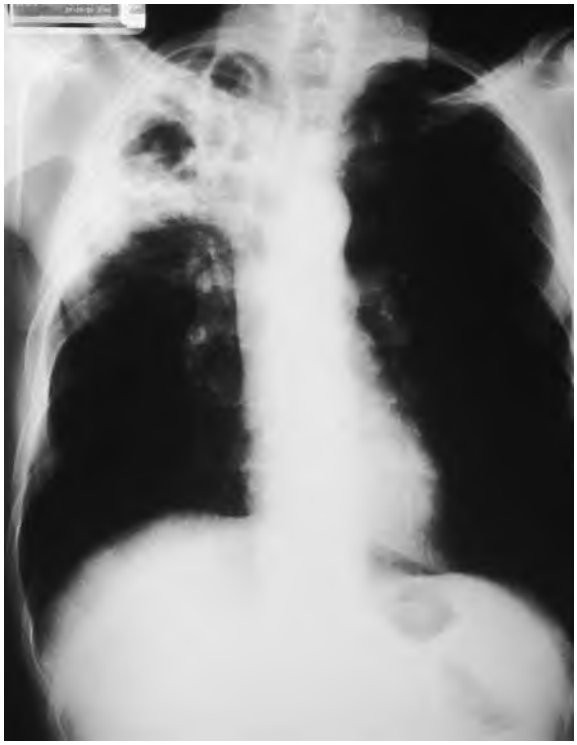

FIG. 221.8 **Radiograph of a 62-year-old man with nonfatal chronic melioidosis showing right upper lobe cavitation.**

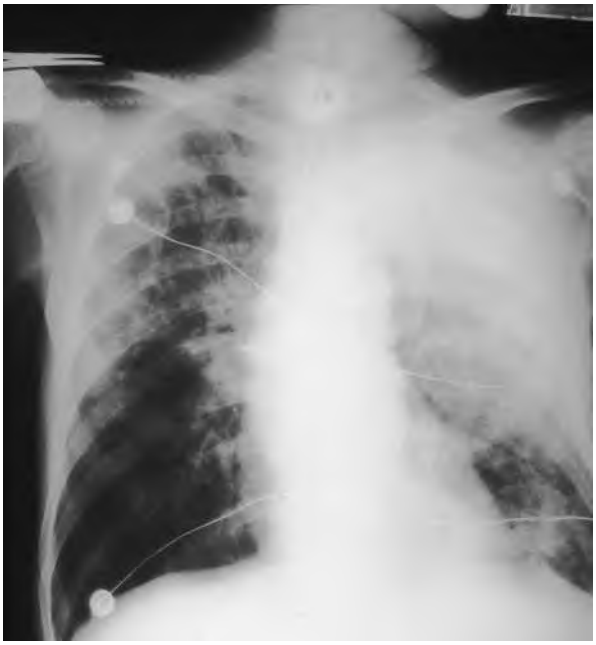

FIG. 221.7 **Extensive left upper lobe consolidation in a 54-year-old man with fatal melioidosis pneumonia.**

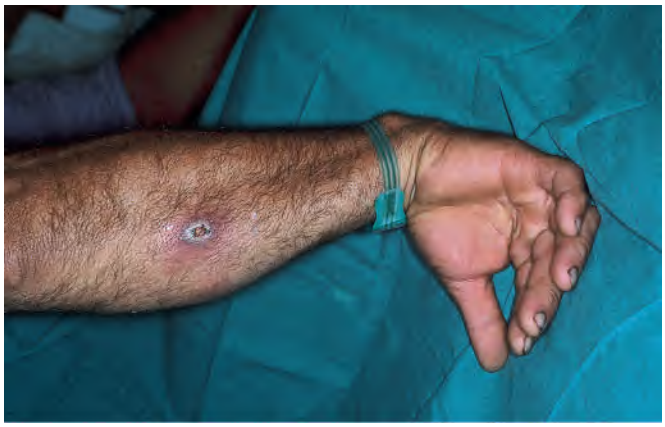

FIG. 221.9 **Cutaneous melioidosis seen on the right forearm of a 50-year-old man.**

melioidosis is endemic should be warned of the risk of melioidosis, which should be considered if they become sick after returning.

It is common for patients to present with skin ulcers or abscesses (Figs. 221.9 and 221.10).[96] Occasionally a patient presents with septic arthritis or osteomyelitis, or one of these conditions can develop after the patient has presented with another primary diagnosis, usually pneumonia (Fig. 221.11). Also well recognized, regardless of the clinical presentation, are abscesses in internal organs, especially spleen, kidney, prostate, and liver (Figs. 221.12 to 221.16). Where available, abdominopelvic computed tomography (CT) scanning is useful in all patients with melioidosis to detect internal abscesses, with ultrasound an alternative for children and women of childbearing age to avoid radiation.

Three differences have been noted between Thailand and tropical Australia. First, suppurative parotitis accounts for 40% of melioidosis in children in Thailand[19,86,97] but is very rare in Australia. Second, prostatic melioidosis is well recognized but uncommon except in Australia, where routine abdominopelvic CT scanning of all patients with melioidosis has shown prostatic abscesses to be present in 18% of all male patients with melioidosis (Fig. 221.17).[98] Some prostatic abscesses were incidental in patients presenting with pneumonia or septicemia, but a primary genitourinary presentation was common with fevers, abdominal discomfort, dysuria, and sometimes diarrhea and urinary retention. Third, neurologic melioidosis accounts for about 4% of cases in northern Australia, with the distinctive clinical features being

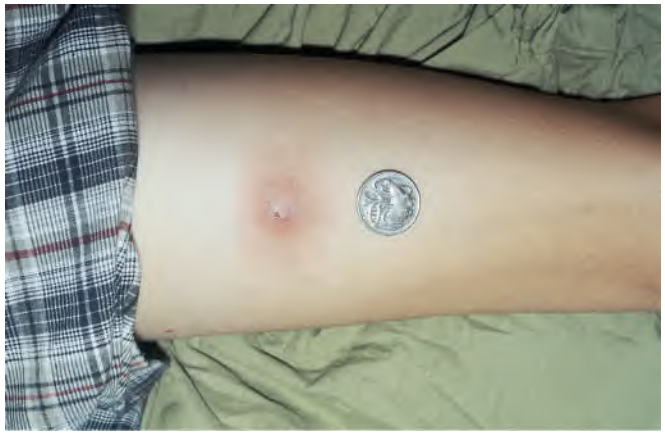

FIG. 221.10 Cutaneous melioidosis of the right thigh in an 11-year-old boy.

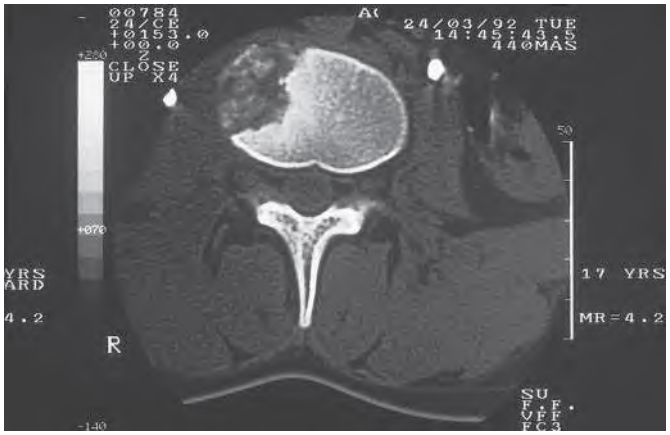

FIG. 221.13 The patient in Fig. 221.12 developed an L3 osteomyelitis 6 weeks later.

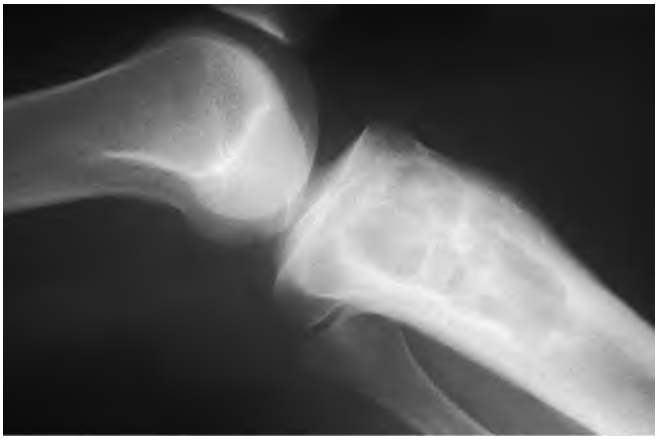

FIG. 221.11 Radiograph of a 43-year-old man showing large lucent areas in proximal tibia.

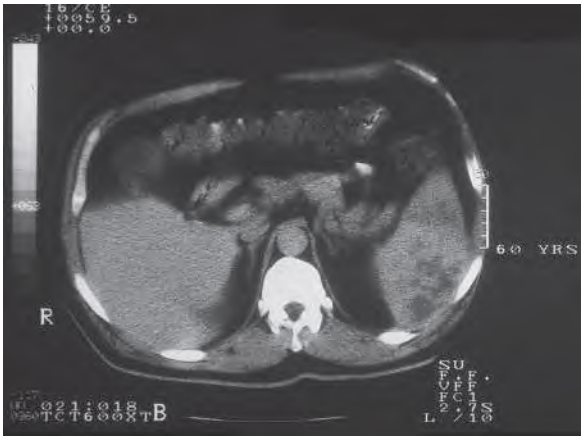

FIG. 221.14 Computed tomography scan of a 60-year-old diabetic patient showing splenic abscesses.

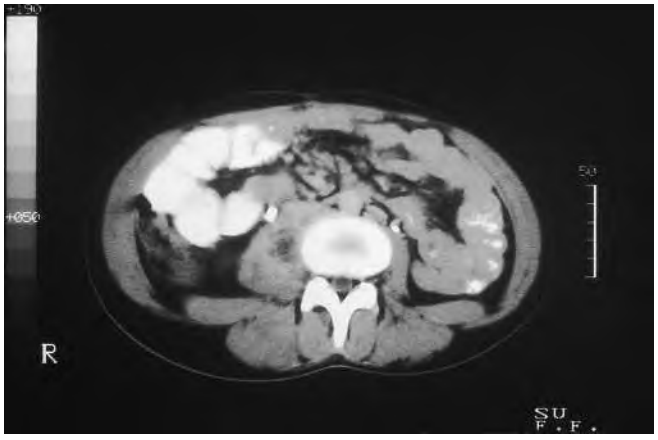

FIG. 221.12 Right psoas abscess in a 17-year-old girl with melioidosis.

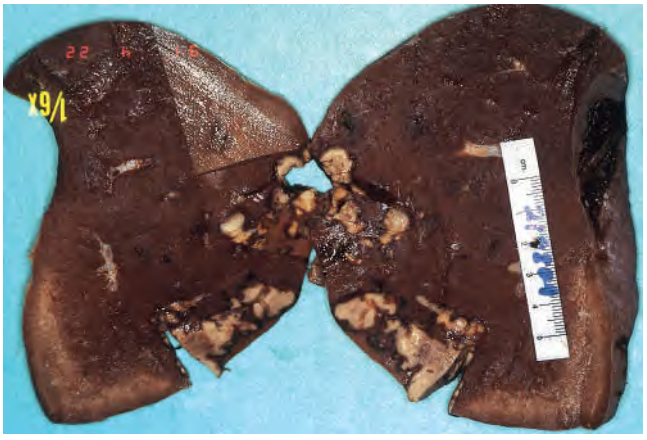

FIG. 221.15 Abscesses seen at splenectomy performed on the patient in Fig. 221.14.

brainstem encephalitis, often with cranial nerve palsies (especially the seventh nerve), together with peripheral motor weakness or occasionally just flaccid paraparesis alone. CT scan is often normal, but dramatic changes are seen on magnetic resonance imaging, most notably a diffusely increased T2-weighted signal in the midbrain, brainstem, and spinal cord (Fig. 221.18).[87,99] Direct bacterial invasion of the brain and spinal cord occurs melioidosis encephalomyelitis.[100,101] Neurologic melioidosis is occasionally seen outside Australia, although mostly as macroscopic brain abscesses.[91,102]

Unusual foci of melioidosis infection described in case reports or case series include mycotic aneurysms, lymphadenitis resembling tuberculosis, mediastinal masses, pericardial collections, and adrenal abscesses.

It has long been recognized that *B. pseudomallei,* similar to tuberculosis, has the potential for reactivation from a latent focus, usually in the lung—hence the concern of the "Vietnamese time bomb" in returned soldiers. The longest latency period from exposure to *B.*