219 *Pseudomonas aeruginosa* and Other *Pseudomonas* Species

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SHORT VIEW SUMMARY

Epidemiology

- *Pseudomonas* species are gram-negative bacteria that inhabit diverse environments, including soil, water, plants, insects, and animals.
- *P. aeruginosa* is the most important *Pseudomonas* species affecting humans, often causing serious infections associated with substantial morbidity and mortality.
- Other *Pseudomonas* species, including *P. fluorescens, P. luteola, P. putida,* and *P. stutzeri,* are less virulent but are still implicated in a wide variety of infections, primarily occurring among immunocompromised patients.
- *P. aeruginosa* has many virulence factors, including pili, flagella, enzyme secretion systems, and quorum-sensing molecules.
- *P. aeruginosa* is one of the most frequent pathogens implicated in hospital-acquired infections, including ventilator-associated pneumonia and catheter-associated urinary tract infections. Long-term acute care hospitals have very high rates of infections caused by *P. aeruginosa.*
- Characteristic infections caused by *P. aeruginosa* include ecthyma gangrenosum, malignant otitis externa, hot hand-foot syndrome, and hot tub folliculitis.
- Resistance to single and multiple antimicrobial agents is rising rapidly.

Microbiology

- *P. aeruginosa* is an aerobic gram-negative, rod-shaped bacteria.
- Growth occurs in a variety of culture media, forming smooth round colonies with a characteristic grapelike or "corn-taco" odor and a green-blue coloration.
- Identification is based on colony morphology, coloration, oxidase positivity, and growth at 42°C.

Therapy

- The majority of evidence suggests that empirical treatment with combination therapy is indicated if antimicrobial resistance rates are high.
- Streamlining to a single antimicrobial agent, once antimicrobial susceptibility profiles are available, should then be considered.
- Effective antimicrobials include quinolones, carbapenems, and broad-spectrum cephalosporins ± β-lactamase inhibitors (Table 219.3)

Pseudomonas species are ubiquitous gram-negative bacteria capable of inhabiting a wide variety of diverse environments, including soil, water, plants, insects, and animals. Among all *Pseudomonas* species, *P. aeruginosa* is the most important species affecting humans and is responsible for serious debilitating and life-threatening infections.

P. aeruginosa infections were noted in the literature in the 1800s when physicians began to report a "condition" causing a blue-green discoloration on bandages and associated with a "peculiar" odor. The cause of the discoloration was first characterized by Fordos in 1869, who extracted the blue crystalline pigment called pyocyanin.[1] In 1882, Gessard verified "the parasitic origin of this phenomenon" using Pasteur's cultures and isolated the organism, which was originally called *Bacillus pyocyaneus.* Initially, this pathogen was regarded as "a curiosity without any influence upon human pathology," and "old surgeons looked upon blue pus on their dressings as rather a favorable sign."[1] In 1894, Williams provided one of the first reviews of case reports of *B. pyocyaneus* infections.[1] He described septic patients with "hemorrhagic spots of a port-wine color" and pustules, with recovery of the organism from these skin lesions. Subsequently, more case reports of infections caused by *B. pyocyaneus* appeared in the literature.[1–3] In the 1940s, Haynes provided detailed microbiologic characteristics of *P. aeruginosa* that would distinguish it from *Pseudomonas fluorescens.* During the Vietnam War, *P. aeruginosa* was recorded as one of the three most common wound pathogens.[4,5] By the mid-1990s, *P. aeruginosa* became of great concern as a pathogen associated with burn infections and war-related wounds. *P. aeruginosa* is now considered to be of most concern because it causes a variety of infections associated with considerable morbidity and mortality, usually occurring among immunocompromised hosts. Furthermore, single-drug and multidrug resistance rates are particularly high for this pathogen, which severely limits the therapeutic options available to treat infected patients.

MICROBIOLOGY

The pseudomonads are aerobic gram-negative, motile rods. They are ubiquitous in soil, water, plants, and animals and have numerous important ecologic roles (Fig. 219.1). The German botanist Walter Migula first used the term *Pseudomonas,* which is derived from the Greek *pseudo,* meaning "false", and *monas,* meaning "unit". Although the etymology was never explained, it has been postulated that Migula created this name because the bacteria resembled the cells of nonflagellate *Monas* in size and motility.[6] *P. aeruginosa* is an obligate aerobic rod-shaped bacterium measuring 0.5 to 1.0 μm in width and 1 to 3 μm in length. It grows as a single bacterium, although it can occur in short chains. It grows on many types of culture media, forming smooth round colonies with a characteristic grapelike or "corn-taco" odor and green-blue coloration. The coloration is due to the production of pyocyanin (blue) and pyoverdin (green). This distinct color explains the species name of "*aeruginosa,*" a Latin word meaning "verdigris" or "copper rust." Some strains produce other pigments, including pyorubin (dark red) and pyomelanin (black). Isolates from patients with cystic fibrosis (CF) may have a distinct mucoid appearance. *P. aeruginosa* is oxidase positive and grows at 37°C to 42°C. Growth at 42°C allows differentiation from other *Pseudomonas* species, including *P. fluorescens* and *P. putida.* Identification of *P. aeruginosa* is based on colony morphology, coloration, oxidase positivity, and growth at 42°C.

Strains of *P. aeruginosa* can produce an extracellular polysaccharide, referred to as alginate. Overproduction of this substance leads to the formation of a mucoid colony phenotype, which is usually present among

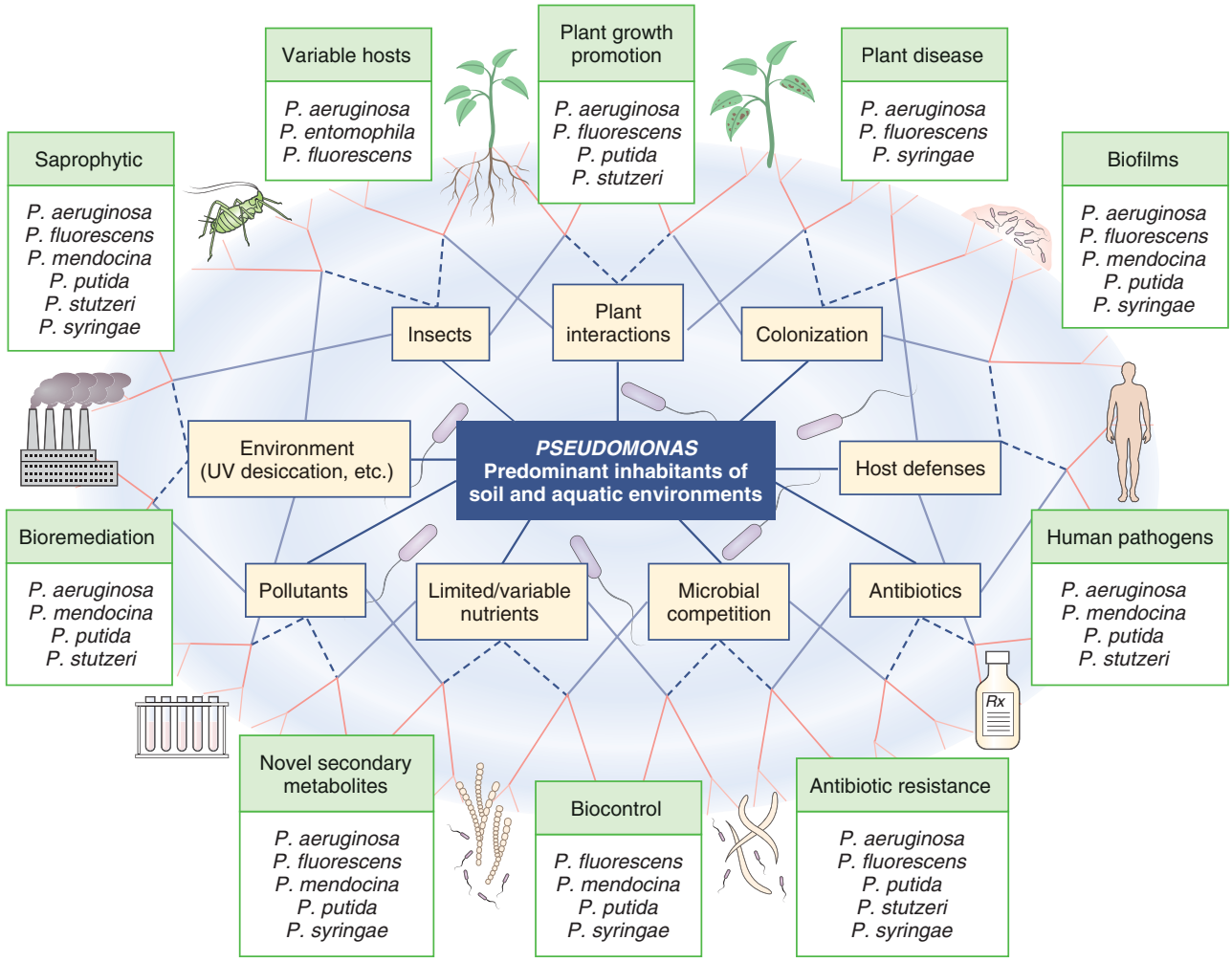

FIG. 219.1 Functional and environmental range of *Pseudomonas* species. The *Pseudomonas'* common ancestor has encountered a wide range of abiotic and biotic environments, which has led to the evolution of a multitude of traits and lifestyles with significant overlap among species. *UV,* Ultraviolet. *(Modified from Silby MW, Winstanley C, Godfrey SA, et al.* Pseudomonas *genomes: diverse and adaptable.* FEMS Microbiol Rev. *2011;35:652–680.)*

isolates recovered from patients with CF and other chronic infections. Isolates recovered from the environment or those causing nosocomial infections are usually nonmucoid.[7–9]

The *Pseudomonas aeruginosa* Genome

The *P. aeruginosa* genome is large (over 6 million base pairs)[10] and complex. In contrast to other large bacterial genomes, the *Pseudomonas* genome does not contain an abundance of gene duplication events but instead contains numerous distinct gene families. This finding explains the great genetic and functional diversity of this pathogen.[11,12]

The genome is composed of a relatively invariable core genome, which contains 90% of the total genome and includes the conserved gene sequences that encode metabolic and pathogenic factors present in the majority of *P. aeruginosa* strains. The accessory genome is highly variable and includes genes found only in certain *P. aeruginosa* strains. The genetic elements in the accessory genome result in distinct *P. aeruginosa* phenotypes, with niche-specific adaption. These genetic elements include virulence factors, resistance genes, and genes encoding specific catabolic pathways that allow persistence in harsh environments (pollutants, pesticides).[11]

Pseudomonas aeruginosa and the Human Microbiota

The Human Microbiome Project, established by the National Institutes of Health, has begun to characterize the human microbial communities colonizing healthy individuals, using 454 FLX Titanium platform pyrosequencing of 16S ribosomal RNA genes. Analysis of the human microbiota among 242 healthy adults from five major body areas (oral cavity and oropharynx, stool, vagina, nares, and skin [inner elbows and behind the ears]) revealed that *P. aeruginosa* was completely absent from both the skin and nares and that *Pseudomonas* species (not identified at the species level) were present in miniscule abundance in the stool and oral cavity, although more abundant in the latter. These data suggest that *P. aeruginosa* is not a common bacterium that inhabits the human microbiota among healthy hosts.[13]

Alterations in the microbiome lead to a decrease in colonization resistance (increasing colonization with antimicrobial-resistant bacteria) and a decrease in resilience (the microbiome's ability to recover). The absence or near absence of *P. aeruginosa* in the healthy human microbiome strongly suggests that for detectable long-term colonization to occur, a perturbation of the microbiome is necessary. Antimicrobial agents, other medications (e.g., anticholinergics), gastrointestinal diseases, and diet may be some of the necessary factors required for *P. aeruginosa* colonization.

VIRULENCE FACTORS

An abundance of virulence factors have been identified among various *P. aeruginosa* strains. These factors are either present on the bacterial cell surfaces or are secreted (Table 219.1). The majority of virulence factors, however, have been identified in cell lines or animal models

TABLE 219.1 Virulence Factors of *Pseudomonas aeruginosa* and Their Role in Pathogenesis

VIRULENCE FACTOR	ROLE IN PATHOGENESIS
Pili and flagella[14]	Attachment to host cells, motility, biofilm formation
Type I secretion system (alkaline protease)[15]	Delivery of toxins to extracellular spaces
Type II secretion system (elastase, exotoxin A, phospholipase A, protease IV)[15]	Cytotoxicity, inflammation, colonization
Type III secretion system (exotoxins S, T, U, and Y)[16,17]	Tissue injury
Endotoxin (lipopolysaccharide)	Resisting host innate defenses
Alginate[21]	Antiphagocytic activity, resists opsonic killing
Pyocyanin[22]	Tissue damage, inhibition of lymphocyte proliferation
Pyoverdin[22]	Binds iron
Quorum-sensing molecules[18,19]	Cell-to-cell communication regulating virulence and biofilm formation

and therefore their role in human disease has not been clearly established. Major virulence factors are discussed in the following sections. Virulence factors associated with CF are discussed in Chapter 71.

Pili

Pili allow the bacteria to adhere to cell surfaces, are involved in biofilm formation, and mediate motility. Five *pilA* alleles have been identified (groups I to V) among *P. aeruginosa* strains. Type IV pili (T4P) has been extensively investigated.[14] This group of pili is unique in that its members can mediate motility independent of flagella. Many *P. aeruginosa* T4P-expressing strains exhibit "twitching motility," a jerky movement with an estimated velocity of approximately 1 mm/h (equivalent to 500 cell lengths per hour, assuming the average length of a *P. aeruginosa* cell is 2 μM).[14] The functions of twitching motility include biofilm formation and exploration of surfaces. Given their role in adherence, T4P are deployed during the early stages of acute infection.[14] Production of pili is frequently lost in chronic infections, such as CF, with selection of strains with other phenotypes better suited for that environmental niche.

P. aeruginosa possesses a single polar flagellum, which plays an important role in motility, colonization, and biofilm formation, similar to pili.

Type I and II Secretion Systems

The type I secretion system (T1SS) secretes toxins in a one-step process into extracellular spaces. The most important toxin studied in the T1SS is alkaline protease, which inhibits fibrin formation and promotes dissemination of *P. aeruginosa*. Secretion of toxins by type II secretion system (T2SS) is a two-step process whereby toxins are synthesized as precursor proteins and then cleaved. Toxins excreted by this system include exotoxin A, phospholipase C, protease IV, and elastase, which mediate cytotoxic effects and inflammatory processes and promote colonization.[15]

Type III Secretion Systems

The type 3 secretion system (T3SS) is a complex secretory system that directly injects exotoxins into the cell cytoplasm. Four proteins have been identified. Exotoxin U (ExoU) is a phospholipase, which induces apoptosis as well as causes necrosis of phagocytes and parenchymal cells. Exotoxin Y (ExoY) is an adenylate cyclase, which may disrupt the barrier function of pulmonary endothelial cells. Exotoxins T and S (ExoT and ExoS) are bifunctional proteins that affect target cell growth by inhibiting DNA synthesis and inducing changes in the cytoskeleton and cellular morphology, thus affecting adherence. Although all strains harbor T3SS genes, only a few are capable of secreting these effector proteins under the conditions tested. The expression of the T3SS in *P. aeruginosa* isolates may confer a worse clinical outcome among humans than nonexpressors.[16,17]

Quorum-Sensing Molecules

Quorum sensing (QS) allows cell-to-cell communication and involves signaling molecules called autoinducers. The usual steps of QS involve the production of autoinducers followed by their active or passive release into the environment. These autoinducers are then recognized by specific receptors, resulting in changes in gene regulation.[18] This complex signaling network allows the "community" of *P. aeruginosa* bacteria to react to different signals and thereby adapt to different niches. There are three QS systems present in *P. aeruginosa* isolates: two are referred to as the LuxI/LuxR-type QS circuits, and the third is referred to as the *Pseudomonas* quinolone signal system.[18,19] These QS systems control the expression of virulence factors, including elastase, exotoxin A, and proteases.

QS also controls biofilm formation (see Chapter 71). Biofilms are a type of growth mode that results in clusters of bacterial colonies, encased in a biopolymer matrix, that attach to surfaces. Biofilms are predominantly formed on implantable devices or during chronic infections, such as osteomyelitis and CF. One of the main functions of biofilms is to reduce the efficacy of antimicrobial agents by impeding the agents' ability to reach the bacteria.[19,20]

Other Virulence Factors

A variety of other virulence factors produced by *P. aeruginosa* have been described. Endotoxin, or lipopolysaccharide, is a virulence factor located on the outer portion of the outer membrane and provides resistance to host defenses. Pyoverdins are siderophores that compete with host proteins for iron chelation. Pyocanin reacts with oxygen to form oxygen radicals, causing tissue damage, and inhibits both lymphocyte proliferation and cilia function. Lastly, alginate is an extracellular polysaccharide, which has antiphagocytic activity and resists killing by opsonization. It is a scavenger of free radicals that are released by macrophages and inhibits neutrophil chemotaxis and complement activation. Its secretion results in a mucoid morphology seen on culture plates.[21,22]

EPIDEMIOLOGY

P. aeruginosa is implicated in both community- and hospital-acquired infections, although it is much more common in the latter. In the United States, *P. aeruginosa* is the 6th most common pathogen implicated in all hospital-acquired infections, as reported in 2016 by the National Healthcare Safety Network (NHSN).[23] It is the second most common pathogen associated with ventilator-associated pneumonia[24] and ranks third among causes of catheter-associated urinary tract infections. *P. aeruginosa* is the 5th most common pathogen causing surgical site infections and 10th most common pathogen causing catheter-related bloodstream infections (BSIs). Patients at high risk for *P. aeruginosa* hospital-acquired infections include those admitted to an intensive care unit (ICU) and those with burns, neutropenia, or CF. These patient populations are discussed in this section and also in Chapter 71.

Rates of *P. aeruginosa* implicated in infections in long-term acute care hospitals (LTACHs) are even higher than rates reported from hospital settings. LTACHs are defined as health care facilities that are accredited as acute care hospitals with an average annual length of stay of at least 25 days for Medicare patients, as per the Centers for Medicare and Medicaid Services. Patients admitted to these LTACHs usually require prolonged care after hospitalization, including hemodialysis, mechanical ventilation, intravenous medication, and wound care. In contrast to the hospital setting, *P. aeruginosa* is the most common cause of catheter-associated urinary tract infections and ventilator-associated pneumonia in LTACHs.[25] Even when rates of *P. aeruginosa* infections in LTACHs are compared with those from ICUs, *P. aeruginosa* is still a more frequent pathogen implicated in LTACH infections. For example, in 2010, 19% of catheter-associated urinary tract infections in patients in LTACHs were caused by *P. aeruginosa* compared with 9% to 12% of those occurring in ICUs. Ventilator-associated pneumonia caused by *P. aeruginosa* was also more frequent in LTACHs (35%) compared with that occurring in ICUs (17%–20%). The higher occurrence of *P. aeruginosa* infections

is likely due to an older, more debilitated patient population with excessive health care exposure.[25]

Transmission Dynamics of *Pseudomonas aeruginosa* and Reservoirs

Acquisition of *P. aeruginosa* can occur both exogenously and endogenously. Exogenous acquisition occurs through contaminated hands of health care workers and environmental surfaces. An in-depth epidemiologic study characterized the exogenous transmission of multidrug-resistant (MDR) *P. aeruginosa* in six ICUs.[26] The investigators obtained cultures from hands, gloves, and gowns of health care workers during routine patient care activities, surveillance cultures from patients, and environmental samples from sinks, bedrails, vital sign monitors, supply carts, door handles, intravenous pumps, ventilators, and floors. Molecular typing, using pulsed-field gel electrophoresis, was performed to determine clonal relatedness among strains. In that study, MDR *Acinetobacter* species were the most common pathogens to contaminate health care workers' gloves and hands, occurring among 33% of interactions between health care workers and patients. *P. aeruginosa* was the second most common MDR pathogen to contaminate health care workers, which occurred during 17.4% of health care worker–patient interactions. Independent risk factors associated with health care worker contamination were presence of environmental contamination, duration in patients' room greater than 5 minutes, performing a physical examination, and contact with the mechanical ventilator. Environmental contamination was also very common: *P. aeruginosa* was recovered from 22% of rooms.[26] This study and many others emphasize that exogenous transmission plays a major role in the nosocomial acquisition of *P. aeruginosa* and that environmental contamination is central to its transmission to patients and health care workers.

Endogenous acquisition of a resistant strain of *P. aeruginosa* is defined as colonization with an antimicrobial-susceptible strain that subsequently becomes resistant primarily through antimicrobial selective pressure within the host. A study of imipenem-resistant *P. aeruginosa* transmission demonstrated that, among events that could be determined, endogenous acquisition accounted for 19% of identified acquisition events and that exogenous acquisition accounted for 31% of events.[27]

As outlined earlier, environmental reservoirs contribute substantially to the spread of *P. aeruginosa.* The most common sites either have high moisture or humidity or are water related (Table 219.2). In the hospital setting, outbreaks of *P. aeruginosa* have been linked predominantly to water sources, including potable water, showerheads, and sinks (see Table 219.2).[28,29] Other sources have included health care workers' artificial or long nails, intraocular lens solution, ultrasound transmission gel during transesophageal echocardiography, retained tissue in surgical instruments,[30] and soap dispensers. The ability of *P. aeruginosa* to form biofilms on surfaces increases its ability to survive on inanimate surfaces and makes it difficult to eradicate. Biofilms are microbial communities held together by structural polysaccharides (slime), which attach strongly to surfaces. Biofilms produced by *P. aeruginosa* lead to antimicrobial tolerance and impede eradication by environmental cleaning agents.[19,28]

TABLE 219.2 Environmental Reservoirs of *Pseudomonas aeruginosa*

Hospital Reservoirs of *P. aeruginosa*
Sinks, taps, showerheads
Potable water
Respiratory therapy equipment
Flower vases, ice makers
Hydrotherapy pools
Cleaning equipment (mops, buckets)
Bronchoscopes, endoscopes
Resuscitators
Water baths
Multidose vials
Community Reservoirs of *P. aeruginosa*
Home humidifiers
Whirlpools, hot tubs, spas
Swimming pools
Water-damaged homes

True community-acquired infections among people without any prior exposure to a health care setting are rare. The rarity of community-acquired infections reflects the fact that *P. aeruginosa* is not part of the healthy human microbiota[13] and that colonization occurs predominantly after hospitalization and antimicrobial exposure. Community-acquired infections, however, have been reported, including outbreaks from contaminated community reservoirs and among intravenous drug users. As with the hospital setting, water-related reservoirs are the main sources of *P. aeruginosa* in the community and include whirlpools, hot tubs, contact lenses, home humidifiers, water-damaged houses, swimming pools, loofah sponges, and even holy water.[31,32] Contaminated recreational water, however, is among the most common sources of *P. aeruginosa* outbreaks.[33,34] A review of outbreaks associated with recreational water, from 1971 to 2000, identified *P. aeruginosa* as the second most frequent causative pathogen, after *Cryptosporidium* species. *P. aeruginosa* was implicated in 36 outbreaks during the study period, with most of the outbreaks associated with whirlpool baths, hot tubs, and swimming pools. The main presentation is that of a superficial folliculitis that is pruritic and maculopapular and progresses to vesiculopustular within hours to days after exposure. It remits spontaneously. Conjunctivitis and otitis externa were also reported.[33] Common nonmedical terms associated with community-acquired *P. aeruginosa* infections include "hot tub rash," "swimmer's ear," and "hot hand-foot syndrome" (see "Skin and Soft Tissue Infections," later).

Food products may also be sources of *P. aeruginosa* in both community and hospital settings, because this pathogen has been isolated in a variety of vegetables, including lettuce, mushrooms, and carrots, and is present in soil.[35–37] A definitive link between the presence of *P. aeruginosa* in vegetables and subsequent colonization or infection, however, has not been clearly established. Nevertheless, it is plausible that ingestion of *P. aeruginosa*–contaminated raw vegetables by high-risk individuals, including neutropenic patients and other immunocompromised hosts and those with decreased gastric acidity or oropharyngeal invasive devices,[38,39] may increase the risk for colonization.

ANTIMICROBIAL RESISTANCE

P. aeruginosa possesses a plethora of different resistance mechanisms. It is therefore not surprising that rates of antimicrobial resistance and multidrug resistance are among the highest in these organisms compared with other common human pathogens. Of even greater concern is the paucity of novel antimicrobial agents being developed to combat *P. aeruginosa* infections. The US Food and Drug Administration (FDA), however, approved ceftolozane-tazobactam in 2014. It has enhanced affinity for *P. aeruginosa* penicillin-binding proteins and appears to be unaffected by loss of porin channels or upregulation of efflux pumps. Over 80% of isolates resistant to ceftazidime or meropenem retain susceptibility to this novel agent. Currently, it is approved for use in urinary tract and intraabdominal infections,[40] and several reports suggest that it may also be useful for treating other severe infections caused by MDR *P. aeruginosa* with confirmed susceptibility to ceftolozane-tazobactam[41,42] (see Chapter 21).

Rates of antimicrobial resistance among *P. aeruginosa* hospital isolates recovered from different types of health care–associated infections in the United States in 2014, as reported by the NHSN, were as follows: aminoglycosides, 7% to 21%; extended-spectrum cephalosporins, 10% to 27%; fluoroquinolones, 12% to 33%; carbapenems, 8% to 28%; and piperacillin ± tazobactam, 7% to 19%. Multidrug resistance, defined as resistance to three or more of these antimicrobial classes, was present among 4% to 20% of isolates.[23] Similarly to previous reports, isolates from ventilator-associated pneumonia had the highest rates, and those from surgical site infections had the lowest rates.

The 2016 Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) reported rates of *P. aeruginosa* resistance to piperacillin ± tazobactam, ceftazidime, fluoroquinolones, aminoglycosides, and carbapenems. Overall, resistance rates to ceftazidime increased from 2013 to 2016. Conversely, the mean percentages of resistance for fluoroquinolones, aminoglycosides, and carbapenems significantly decreased over the same period of time, whereas resistance

to piperacillin ± tazobactam remained stable. In 2016, 33.9% of isolates were resistant to one or more of the five antimicrobial classes, 13.6% were resistant to three or more, and 4.4% were resistant to all five classes.[43] Resistance rates to three or more groups of antimicrobials varied considerably between European countries, with lowest percentages reported from Iceland, Denmark, Luxembourg, the United Kingdom, the Netherlands, and Norway (<3%) and highest percentages from Bulgaria and Romania (36%–49%). Percentages of single-drug resistance among *P. aeruginosa* isolates obtained from Latin America and the Asia-Pacific rim range from 23% to 41%.[44,45]

In the United States in 2010, resistance rates in LTACH units were reported to be even higher than in ICUs. For example, MDR *P. aeruginosa* was more common among patients with catheter-associated urinary tract infections in LTACHs (25%) compared with those occurring in patients in ICUs (12%). Similarly, rates of multidrug resistance in patients with catheter-associated BSI were higher among those in LTACHs (16%) than those in ICUs (2%–9%).[25]

Resistance Mechanisms

P. aeruginosa harbors numerous resistance mechanisms that either decrease penetration to the target site, alter the target site, or inactivate the antimicrobial agent using bacterial enzymes. These mechanisms can be broadly categorized as intrinsic,[46–48] acquired, or adaptive, with overlap between categories.

Intrinsic Resistance

Decreased Permeability of the Outer Membrane

The semipermeable outer membrane of *P. aeruginosa* allows important nutrients to enter the cell through channels present on the cell membranes called porins. Numerous antimicrobial agents, including β-lactams, aminoglycosides, tetracyclines, fluoroquinolones, and carbapenems, enter the bacterial cell through these porins. Several families of porins have been characterized, including OprF, OprD, OprM, and TonB. Although OprF is a major porin in the outer cell membrane, allowing transport of large substrates, its role in antimicrobial resistance has not been definitively proven because loss of OprF porins in mutant strains does not alter antimicrobial penetration. Among the remaining three families, OprD has been the most studied. This channel allows entry of carbapenems but not of other β-lactams. Loss of OprD, however, may not have an equal impact on minimal inhibitory concentration increases for all carbapenems equally. Lastly, some porins in the family of OprM are presumed to be part of efflux systems and are discussed in the next section.

Not all antimicrobial agents use porins to enter the cell but instead decrease cell membrane stability by binding to lipopolysaccharides on the outer cell membrane. Examples of such agents include aminoglycosides and polymyxins.

Efflux Pumps

As the name implies, efflux pumps actively pump antimicrobial agents out of the bacteria. These pumps confer resistance to the great majority of antimicrobial agents (with the exception of polymyxins) and are the predominant systems for multidrug resistance among *P. aeruginosa*. Five superfamilies of efflux pumps have been identified, of which the resistance-nodulation-division (RND) family is among the most common. MexAB-OprM and MexXY-OprM efflux systems of the RND family confer intrinsic multidrug resistance to numerous antimicrobial agents, including fluoroquinolones, aminoglycosides, β-lactams, tetracyclines, tigecycline, and chloramphenicol. MexAB-OprM also confers resistance to meropenem but not imipenem, thus explaining differences in susceptibility patterns among different carbapenems. Similarly, the MexXY-OprM efflux system removes cefepime but not ceftazidime.[49]

Antimicrobial-Modifying Enzymes

The majority of antimicrobial-modifying enzymes are acquired on plasmids and are discussed later in the chapter,[46] with the exception of AmpC, a chromosomally encoded inducible cephalosporinase. AmpC confers resistance to all β-lactams except fourth-generation cephalosporins and carbapenems. When AmpC is overproduced, through mutations, resistance may also be conferred to these antimicrobial classes. Therapeutic failure due to the emergence of resistance during appropriate therapy can occur in over 50% of patients, especially those with serious *P. aeruginosa* infections and those with neutropenia or CF.

Acquired Resistance

Acquired resistance genes predominantly confer resistance to β-lactams and aminoglycosides.[47] Extended-spectrum β-lactamases (ESBLs) are plasmid mediated and confer resistance to penicillins, narrow- and extended-spectrum cephalosporins, aztreonam, and sometimes carbapenems. ESBL-producing *P. aeruginosa* strains have rapidly spread worldwide. ESBL families identified in *P. aeruginosa* include PER, VEB, GES, TEM, SHV, and CTX-M enzymes. GES-type enzymes also extend their activity to carbapenems. These enzymes have been recovered from isolates from China, South Africa, Brazil, and France.[47] Oxacillinase β-lactamases (OXAs) can either be narrow spectrum or broad spectrum and are weakly inhibited by clavulanic acid. Carbapenemase-hydrolyzing oxacillinases, which can be either acquired or naturally occurring, have also been identified in *P. aeruginosa* isolates, although less frequently than in *Acinetobacter* species. Resistance to carbapenems can also occur via metallo-carbapenemases and include the Verona integron-encoded metallo-β-lactamase (VIM), IMP, and New Delhi metallo-β-lactamase (NDM) families. These enzymes are of great concern because they are active against penicillins and cephalosporins as well as carbapenems. VIM-type isolates were first reported in *P. aeruginosa* isolates recovered in Italy in 1997 and subsequently spread into members of the Enterobacteriaceae, especially *Klebsiella pneumoniae*. Isolates with NDM enzymes may also carry aminoglycoside and fluoroquinolone resistance genes and remain susceptible only to colistin and polymyxin B.[50] Another enzyme active against carbapenems, present in *P. aeruginosa* isolates, is the *K. pneumoniae* carbapenemase (KPC) type. KPC-producing strains were first identified in Colombia and have since spread to Puerto Rico, China, and the United States, and most recently Brazil.[51] Carbapenem-resistant isolates, regardless of the mechanism of resistance, result in serious infections. A longitudinal study from 1989 to 2006 demonstrated that rates of imipenem-resistant *P. aeruginosa* isolates increased from 13% to 20% and that infections caused by these resistant pathogens were associated with higher in-hospital mortality. Prior exposure to carbapenems increased the risk for imipenem-resistant *P. aeruginosa* infection by almost eightfold.[52]

Aminoglycoside-Modifying Enzyme

Aminoglycoside-modifying enzymes are carried on multiple different genetic mobile elements, such as plasmids, transposons, and integrons. They confer resistance to all aminoglycosides, although, in general, amikacin may be less susceptible to these enzymes. The most common aminoglycoside-modifying enzymes are aminoglycoside nucleotidyltransferase (2′)-I, which confers resistance to gentamicin and tobramycin, and aminoglycoside acetyltransferase (6′)-II, which also confers resistance to netilmicin.

TREATMENT OF *PSEUDOMONAS AERUGINOSA* INFECTIONS

Treatment of *P. aeruginosa* infections, especially BSIs, centers around the controversy of monotherapy versus combination therapy. A few earlier studies support the use of combination therapy since mortality rates were lower when two antimicrobial agents, instead of a single agent, were used to treat BSI caused by *P. aeruginosa*.[53] The main limitation of these studies is that in many the monotherapy study arm consisted of only an aminoglycoside, which is suboptimal for the treatment of *P. aeruginosa* BSI.[53] In a meta-analysis, which also concluded that combination therapy is superior to monotherapy, four of the five included studies used aminoglycosides in the monotherapy study arm.[54] There are numerous other limitations with older studies that support the use of combination therapy, including lack of double blinding and randomization, different sources of BSI, retrospective lack of adjustment for time to start of appropriate antimicrobial therapy, and duration of follow-up. Confounding by indication, whereby the severely ill patients receive combination therapy, is another limitation of studies addressing this issue. Another reason that is often cited for supporting combination therapy is the potential synergy between the two antimicrobial agents,

usually a β-lactam and an aminoglycoside. Although in vitro and animal studies show benefit of this combined regimen, clinical studies have provided conflicting data.[55,56] Preventing the emergence of antimicrobial resistance is another reason often cited for supporting the use of combination therapy, but there are minimal data to support this statement. Administering the appropriate dose, at the correct frequency and for the optimal duration, is likely more important in preventing the emergence of resistance than combination therapy. Prompt initiation of the appropriate antimicrobial agents is also key to a successful outcome, as is removal of invasive devices if implicated.

Overall, the great majority of more recent studies do not show a survival benefit between combination therapy and monotherapy for definitive therapy.[57–61] However, the main conclusion by most investigators is that large randomized clinical trials are needed to definitively answer the question of efficacy between combination therapy and monotherapy.

Use of combination therapy should be strongly considered in the severely ill patient for the empirical treatment of *P. aeruginosa* BSI, especially in those health care institutions with patients with a high rate of multidrug resistance. Using combination therapy will thus ensure that at least one antimicrobial agent is effective against the infecting *P. aeruginosa* strain. Deescalating to a single antimicrobial agent, once antimicrobial susceptibility profiles are available, should then be considered. Narrowing to a single agent is especially relevant when the combination therapy includes an aminoglycoside, because this regimen is associated with increased nephrotoxicity.[60,61] Other adverse events that are more likely to occur with combination therapy, compared with monotherapy, include an increased risk for *Clostridioides difficile* (formerly *Clostridium difficile*) infection, further alterations in the protective effects of the human microbiota against colonization by other MDR organisms, and fungal infections.

Antimicrobial agents effective against *P. aeruginosa* and appropriate doses are listed in Table 219.3. Polymyxins (colistin, polymyxin B) should be reserved for MDR *P. aeruginosa,* when other alternatives are not available, because this class of agents is inferior to other available antipseudomonal agents.[62] Emergence of resistance during treatment has been documented for *K. pneumoniae* BSI and likely also occurs for *P. aeruginosa* infections.[63] High-dose continuous infusion of β-lactams has also been successfully used in the treatment of BSI caused by MDR *P. aeruginosa.* Moriyama and associates reported three patients infected with MDR *P. aeruginosa* strains who were successfully treated with a continuous infusion of ceftazidime (6.5–16.8 g/day) or aztreonam (8.4 g/day) and tobramycin.[64] The rationale behind this approach is that antibacterial activity of β-lactams depends on the time that the antimicrobial concentration is above the minimal inhibitory concentration of the bacteria. Using continuous infusion ensures that the concentration of the β-lactam will be above the minimal inhibitory concentration for the entire dosing interval, whereas intermittent dosing may cause the concentration to fall below the minimal inhibitory concentration. Future clinical studies, however, are required to further validate this treatment regimen.

Novel antipseudomonal agents are reviewed in detail by Wright and colleagues.[65] Several studies indicate that ceftolozane-tazobactam and ceftazidime-avibactam are effective in the treatment of MDR–*P. aeruginosa* BSI and other infections, although resistance can develop even with short courses of therapy.[41,42,66,67] The combination of ceftazidime and the novel non–β-lactam β-lactamase inhibitor avibactam has been approved for the treatment of complicated urinary tract infections and intraabdominal infections.[65] The addition of avibactam to ceftazidime allows this combination to inhibit Ambler class A β-lactamases (including KPC), AmpC β-lactamases, and OXA-type Ambler class D β-lactamases, making this drug an excellent therapeutic option for infections caused by MDR gram-negative bacteria, including *P. aeruginosa.*[67] The recommended dose for patients with normal renal function is 2 g of ceftazidime and 500 mg of avibactam every 8 hours. Resistance to ceftazidime-avibactam among *P. aeruginosa* has been described, with higher rates among MDR isolates involving efflux mechanisms or metallo-carbapenemases.[68,69]

TABLE 219.3 Intravenous Antimicrobial Agents Effective Against *Pseudomonas aeruginosa*

ANTIMICROBIAL AGENT	INTRAVENOUS DOSE
Penicillins Plus β-Lactamase Inhibitor	
Ticarcillin-clavulanate	3.1 g q4h
Piperacillin-tazobactam	4.5 g q6h or 3.375 g q4h
Broad-Spectrum Cephalosporins ± β-Lactamase Inhibitor	
Ceftazidime	2 g q8h
Cefepime	2 g q8–12h
Ceftolozane-tazobactam	1.5g q8h
Ceftazidime-avibactam	2.5 g q8h
Fluoroquinolones	
Ciprofloxacin	400 mg q8h
Levofloxacin	750 mg q24h
Carbapenems	
Imipenem	500 g q6h
Meropenem	1–2 g q8h
Doripenem	500 mg q8h
Monobactam	
Aztreonam	2 g q8h
Aminoglycosides	
Tobramycin	2 mg/kg loading dose, then 1.7 mg/kg q8h *or* 4–7 mg/kg q24h
Gentamicin	As for tobramycin
Amikacin	7.5 mg/kg q12h or 15 mg/kg q24h

For a review of novel antimicrobials with potential activity, refer to Wright et al.[65]

INFECTIONS CAUSED BY *PSEUDOMONAS AERUGINOSA*

Bloodstream Infections

BSIs are among the most serious infections caused by *P. aeruginosa,* with mortality rates reaching 60%. The nationwide Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE), which included data from 49 US hospitals, reported that from 1995 to 2002 the incidence of *P. aeruginosa* nosocomial BSI was 2.1 per 10,000 hospital admissions. *P. aeruginosa* was the third most common gram-negative bacteria causing nosocomial BSI and accounted for 4.3% of all cases. In the ICUs, *P. aeruginosa* was the fifth most common isolate implicated in BSI, accounting for 4.7% of all cases, and was the seventh most common isolate in non-ICU wards, accounting for 3.8% of cases.[70] Outside the United States, *P. aeruginosa* is implicated in even more cases of nosocomial BSI.[71] In a surveillance study that collected data from 16 Brazilian hospitals from 2007 to 2010 and used the same methodology as the SCOPE study, 8.9% of all nosocomial BSI were caused by *P. aeruginosa.*

Risk factors for *P. aeruginosa* BSI include immunodeficiency, prior hospitalization, previous antimicrobial exposure, advanced age, prior surgery, and invasive devices.[72–74] Many of these risk factors represent an association with BSI, irrespective of the implicated pathogen.

Mortality rates for nosocomial BSI caused by *P. aeruginosa* are among the highest. The great majority of reported crude mortality percentages from large surveillance studies range from 39% to 60%. These percentages are similar to those caused by *Candida* species.[70,71] Some studies, however, report lower mortality rates, ranging from 12% to 30%.[75–77] The large range in mortality rates from different studies reflects the multitude of factors that affect outcomes associated with BSI. For *P. aeruginosa* BSI, advanced age, high Acute Physiology and Chronic Health Evaluation II (APACHE II) score, sepsis, poor functional status, polymicrobial bacteremia, and inappropriate initial antimicrobial therapy have all been associated with an increased risk for mortality.[73,76–79]

Multidrug resistance is also a risk factor for increased mortality. Rates of mortality in infections due to MDR *P. aeruginosa* strains are

twofold to threefold higher compared with non-MDR strains.[75,80] Because inappropriate initial empirical therapy is a major contributor to these higher mortality rates, combination therapy for empirical treatment is warranted when multidrug resistance rates are high (see later).[81]

The predominant distinguishing feature of *P. aeruginosa* BSI is the occurrence of ecthyma gangrenosum. Although not pathognomonic for *P. aeruginosa,* the presence of these characteristic skin lesions should raise high suspicion for this pathogen (see "Skin and Soft Tissue Infections" later).

Infective Endocarditis

P. aeruginosa accounts for 3% of all cases of infective endocarditis (IE).[82] Among non-HACEK pathogens (species other than *Haemophilus* species, *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* or *Kingella* species), *P. aeruginosa* is the second most common gram-negative pathogen causing IE after *Escherichia coli.*[83] There are no unique clinical characteristics of IE caused by *P. aeruginosa,* although the presence of ecthyma gangrenosum should raise suspicion. Complications are common, and mortality rates are high, ranging from 36% to 60%.[83]

Intravenous drug users are the patient population at highest risk for *P. aeruginosa* IE. The great majority have used tripelennamine and pentazocine with contaminated water or paraphernalia. Patients predominantly present with right-sided endocarditis. Complications are frequent and include sepsis, embolization, and congestive heart failure.[84] In this patient population, polymicrobial IE, with both *P. aeruginosa* and *Staphylococcus aureus,* can also occur.[84]

Left-sided IE in patients without intravenous drug use also occurs, although infrequently. It is predominantly a nosocomial infection occurring after invasive procedures, including cardiac or urogenital procedures. Infected intravascular catheters have also been implicated in IE. Of note, valvular disease is not a necessary predisposing risk factor for *P. aeruginosa* left-sided IE.[85] Splenic abscesses, neurologic sequelae, and ring and annular abscesses are frequent complications.[86]

The American Heart Association recommends, as per expert opinion, that medical treatment of *P. aeruginosa* IE should include an extended-spectrum penicillin (ticarcillin, piperacillin) and ceftazidime or cefepime in full doses in combination with high-dose tobramycin (8 mg/kg/day IV or IM in once-daily doses) with peak concentrations of 15 to 20 μg/mL and trough concentrations of less than or equal to 2 μg/mL. This combination should be given for at least 6 weeks. Use of ciprofloxacin in combination with an aminoglycoside should be used with caution because ciprofloxacin resistance can occur during therapy. Other regimens that have been successful in a small number of patients include the combination of imipenem and an aminoglycoside.[87]

Case reports have also shown success with other combinations of antimicrobial agents. Among two renal transplant recipients with no valvular heart disease who developed *P. aeruginosa* nosocomial IE, 6 weeks of therapy with imipenem and ciprofloxacin was successful in the first patient and 2 weeks of imipenem and amikacin followed by 6 weeks of imipenem alone was successful for the second patient (amikacin was stopped early owing to nephrotoxicity). Both patients' conditions were stable at 6 months of follow-up.[88]

The need for surgical intervention differs between right- and left-sided IE. Although medical treatment is usually sufficient for right-sided native valve IE, in refractory cases surgical intervention with partial tricuspid valvectomy or "vegectomy" without valve replacement may be necessary.[87] Left-sided IE and prosthetic valve IE usually require early surgical intervention, owing to the high risk for complications and high failure rates associated with medical therapy alone. Survival rates with medical therapy alone among patients with left-sided IE, for example, are only 14%.[85]

Pneumonia

Pneumonia Associated With Hospital Exposure

Three categories of *P. aeruginosa* pneumonia can occur as a result of hospital exposure: (1) hospital-acquired (nosocomial) pneumonia, defined as a pneumonia that occurs 48 hours or more after hospital admission and that was not incubating at the time of admission; (2) ventilator-associated pneumonia, defined as a hospital-acquired pneumonia that develops more than 48 to 72 hours after endotracheal intubation; and (3) health care–associated pneumonia, defined as a pneumonia that occurs among nonhospitalized patients who (a) have had an acute care hospitalization for 2 or more days within 90 days of the infection, (b) live in a nursing home or long-term care facility, (c) received intravenous antimicrobial therapy, chemotherapy, or wound care in the previous 30 days of the current infection, or (d) attended a hospital or dialysis clinic in the previous 30 days of the current infection.[89] These definitions were developed for the 2005 American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines.[89]

Hospital-Acquired (Nosocomial) Pneumonia

P. aeruginosa is the most common gram-negative bacteria implicated in hospital-acquired pneumonia.[23] The great majority of *P. aeruginosa* hospital-acquired pneumonia cases are late onset, occurring after the fifth day of hospitalization, similar to hospital-acquired pneumonia caused by methicillin-resistant *S. aureus.*[90,91] Factors that predispose hospitalized patients to hospital-acquired pneumonia include older age, duration of mechanical ventilation, prior antimicrobial exposure, transfer from a medical unit or ICU, and admission to a ward with a high prevalence of *P. aeruginosa,* reflecting colonization pressure.[91] Mortality rates are extremely high, ranging from 42% to 87%. As with BSI, the wide range reflects the presence of comorbidities, inadequate initial therapy, severity of illness at presentation, and multidrug resistance. The presence of bacteremia is associated with particularly poor outcomes. Hospital-acquired pneumonia can be associated with mechanical ventilation or not, although the former is much more common.

Hospital-Acquired Pneumonia Among Ventilated Patients

P. aeruginosa is the second most common pathogen implicated in ventilator-associated pneumonia after *S. aureus,* as per the 2011 to 2014 NHSN data, which reported rates of hospital-acquired infections from 4515 hospitals in the United States.[23] Among all gram-negative bacteria, *P. aeruginosa* is the most common cause of ventilator-associated pneumonia.[23,90]

Colonization with *P. aeruginosa* is a prerequisite for developing a *P. aeruginosa* ventilator-associated pneumonia. Once the patient becomes colonized, breaches in integrity of the airway mucosa caused by intubation result in tissue invasion by the bacteria, leading to pneumonia. Sources for *P. aeruginosa* colonization are either endogenous or exogenous. Endogenous sources include *P. aeruginosa* colonizing the oropharynx and stomach with subsequent aspiration.[92] Exogenous sources include health care workers carrying the organism and inanimate surfaces. Contaminated water sources are a particularly common reservoir for exogenous acquisition of *P. aeruginosa* implicated in ventilator-associated pneumonia. Numerous *P. aeruginosa* outbreaks have been traced to contaminated faucets, sinks, and tap water. Contaminated bronchoscopes have also been implicated as a source of *P. aeruginosa* ventilator-associated pneumonia. These cases were linked to inadequate disinfection procedures, contaminated disinfecting machines, and manufacturing defects of bronchoscopes.[93]

Antimicrobial resistance among *P. aeruginosa* strains implicated in ventilator-associated pneumonia is high. Reported percentages from US hospitals in 2014 are as follows: aminoglycosides, 18.2%; cefepime-ceftazidime, 25.7%; ciprofloxacin-levofloxacin, 31.9%; imipenem-meropenem, 28.4%; and piperacillin-tazobactam, 19.4%. Multidrug resistance, defined as resistance to three or more antimicrobial classes, was also frequent, occurring in 19.9% of strains.[23] These high rates support the use of combination therapy as empirical treatment for ventilator-associated pneumonia to ensure that at least one antimicrobial agent is active against *P. aeruginosa.* In a study of 100 consecutive patients with bacteremic *P. aeruginosa* pneumonia, adequate empirical combination therapy was associated with significantly lower 28-day mortality rates.[94]

The ATS/IDSA guidelines recommend empirical antimicrobial therapy for ventilator-associated pneumonia with an antipseudomonal β-lactam plus either an antipseudomonal quinolone or an aminoglycoside. The choice of specific antimicrobial agents should take into account the local antimicrobial susceptibility patterns and avoiding agents to which

the patient was recently exposed. If aminoglycosides are chosen, consideration should be given toward a short (5-day) course, to minimize nephrotoxicity, when used in combination with a β-lactam to treat *P. aeruginosa* pneumonia.[89] Once susceptibility profiles are available, monotherapy also should be considered because data supporting combination therapy are lacking.[89,94] Aerosolized antimicrobial agents (aminoglycosides, polymyxins) can be used as adjunctive therapy to systemic antimicrobial agents in patients with highly resistant *P. aeruginosa* ventilator-associated pneumonia.[95]

Duration of antimicrobial therapy for *P. aeruginosa* ventilator-associated pneumonia should be longer than for other pathogens. A prospective randomized, double-blind study evaluated the efficacy of 8 days versus 15 days of antimicrobial therapy for ventilator-associated pneumonia and showed that, for ventilator-associated pneumonia caused by *P. aeruginosa,* an 8-day course was suboptimal and was associated with higher recurrence rates.[96] A 15-day course is therefore recommended.[89]

Hospital-Acquired Pneumonia Among Nonventilated Patients

P. aeruginosa is also the most common gram-negative bacteria implicated in pneumonia among nonventilated hospitalized patients, accounting for 9% of all cases in this category.[90] These high percentages warrant antipseudomonal antimicrobial agents in the empirical treatment of these types of infections, similar to that used for patients with ventilator-associated pneumonia.[89]

Health Care–Associated Pneumonia

Health care–associated pneumonia develops outside the hospital among patients who have had recent substantial exposure to the health care setting. *P. aeruginosa* is implicated in 2% to 25% of health care–associated pneumonia cases.[97–99] Surveillance studies report that it is the most common or second most common gram-negative pathogen causing health care–associated pneumonia.[98,99] Because *P. aeruginosa* strains implicated in this type of pneumonia are more likely to be resistant to antimicrobial agents because of prior health care exposure, the ATS/IDSA guidelines recommend that treatment regimens should follow those for health care–associated pneumonia, as outlined previously.[89] However, these recommendations may not apply in health care settings and countries with low rates of antimicrobial resistance; therefore treatment regimens recommended for community-acquired pneumonia may be more appropriate in these settings.[97]

A retrospective, observational study compared characteristics of health care–associated and community-acquired pneumonia among patients admitted to a tertiary care hospital in South Korea from 2008 to 2010. Among 31% of patients with pneumonia in whom a pathogen was identified, *P. aeruginosa* was the second most common gram-negative bacteria, after *K. pneumoniae,* and accounted for 20% of health care–associated pneumonia and 11% of community-acquired pneumonia. These percentages were not statistically different. The percent of bacterial species, including *P. aeruginosa,* that were "potentially drug-resistant" was significantly higher among the health care–associated group (32%) than the community-acquired group (15%).[99] The investigators included the following bacteria as "potentially drug-resistant": methicillin-resistant *S. aureus, Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas maltophilia,* and extended-spectrum β-lactamase–producing Enterobacteriaceae. Actual antimicrobial susceptibility profiles, however, were not determined.

Compared with community-acquired pneumonia, patients presenting with health care–associated pneumonia are more likely to be older and have more comorbidities, a higher pneumonia severity index, and a worse functional status at presentation.[97,98] Mortality percentages are subsequently higher for health care–associated pneumonia compared with community-acquired pneumonia and range from 17% to 20%.[98,99]

Community-Acquired Pneumonia

Reported percentages of *P. aeruginosa* implicated in community-acquired pneumonia vary from 0.3% to 17%.[97–100] Although *P. aeruginosa* is not usually considered to be a common cause of community-acquired pneumonia, the high percentages reported by some studies suggest otherwise.[98,99] A surveillance study on the microbiology of pneumonia in 59 US hospitals from 2003 to 2004 found that *P. aeruginosa* was the causative pathogen for 17% of community-acquired pneumonia cases, a percentage similar to those for community-acquired pneumonia caused by *Streptococcus pneumoniae* (16.6%) and *Haemophilus* species (17.1%). In this study, the percentage for pneumonia caused by *P. aeruginosa* was similar for community-acquired pneumonia and health care–associated pneumonia.[98]

Studies have identified numerous risk factors for *P. aeruginosa* community-acquired pneumonia, including chronic obstructive pulmonary disease, bronchiectasis, alcoholism, smoking, and frequent antibiotic therapy.[101,102] An immunocompromised state, due to malignancy, transplantation, or immunosuppressive drugs, is also frequently associated with community-acquired pneumonia.[102,103] Of note, many of these studies were performed before the inclusion of health care–associated pneumonia as a new category of pneumonia, and, therefore, many of these factors likely reflect an increased risk for health care–associated pneumonia and not true community-acquired pneumonia.

The ATS/IDSA guidelines for *P. aeruginosa* community-acquired pneumonia recommend an antipseudomonal β-lactam antimicrobial agent plus either ciprofloxacin, levofloxacin, or an aminoglycoside. An alternative recommended regimen is an aminoglycoside plus either ciprofloxacin or levofloxacin.[102] Tapering to monotherapy once antimicrobial susceptibilities are available should then be considered. Studies defining the optimal duration of antimicrobial therapy are lacking. The ATS/IDSA guidelines state that longer durations of 3 to 7 days are rarely necessary but may be warranted if there are pulmonary cavities or other evidence of tissue necrosis.[102]

Mortality rates associated with *P. aeruginosa* community-acquired pneumonia are higher than those for pneumonia caused by other pathogens. In one study specifically addressing *P. aeruginosa* community-acquired pneumonia, 28% of patients died, compared with 10% who died of community-acquired pneumonia caused by other pathogens.[101]

Cystic Fibrosis

CF and bronchiectasis are two pulmonary diseases that lead to chronic colonization with *P. aeruginosa* and recurrent pneumonia. CF is a genetic disease that affects multiple systems to varying degrees. Mutations in the CF transmembrane conductance regulator (*CFTR*) gene result in abnormal ion transport, leading to inefficient mucociliary clearance and an increased risk of bacterial infections.[104–106] *P. aeruginosa* is one of the main bacterial pathogens associated with CF.[107] Initial events of *P. aeruginosa* infection in CF patients can occur early during childhood. Subsequently, the infection dynamics usually follow a model of recurrent episodes of infections that eventually lead to the establishment of a chronic infection in which *P. aeruginosa* can be continuously cultured from respiratory secretions.[106] The transition from an intermittent to a chronic infection state may occur in up to 80% of adult CF patients, and is frequently associated with the emergence of *P. aeruginosa* isolates with a mucoid phenotype, characterized by overproduction of the polysaccharide alginate.[106,108] Environmental factors, such as oxidative stress and antimicrobial selective pressure, are major drivers of the changes in gene expression that lead to the mucoid-type *P. aeruginosa*. The chronic infection caused by mucoid *P. aeruginosa* isolates is a strong predictor of pulmonary function decline, and represents a significant clinical challenge because it is associated with biofilm formation and multidrug resistance.[109]

Bone and Joint Infections

Bone and joint infections can occur via contiguous spread, direct inoculation, or secondary seeding from bacteremia, and occur frequently among intravenous drug users. Although *P. aeruginosa* is an infrequent pathogen implicated in bone and joint infections, certain specific presentations are more often seen with this pathogen. These entities include sternoclavicular septic arthritis, septic arthritis of the symphysis pubis with osteomyelitis, vertebral osteomyelitis, skull base osteomyelitis, and osteomyelitis associated with nail punctures. *P. aeruginosa* is also implicated in a majority of combat-related osteomyelitis cases.

Osteomyelitis caused by *P. aeruginosa* has a poor prognosis when compared with that caused by other pathogens. A study of 454 patients with osteomyelitis characterized risk factors for poor outcomes. *P.*

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.

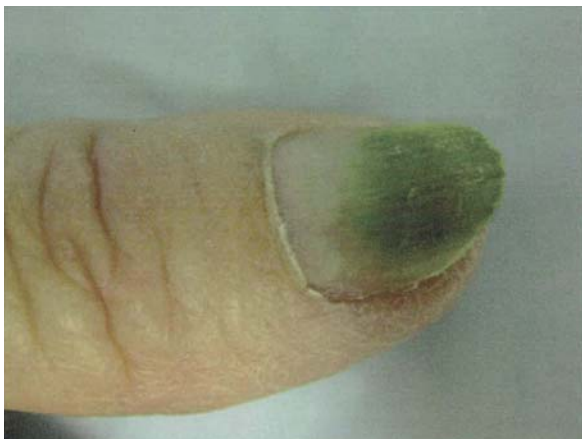

FIG. 219.2 Green nail syndrome caused by *Pseudomonas aeruginosa.* *(Modified from Wu DC, Chan WW, Metelitsa AI, et al.* Pseudomonas *skin infection: clinical features, epidemiology, and management.* Am J Clin Dermatol. *2011;12:157–169.)*

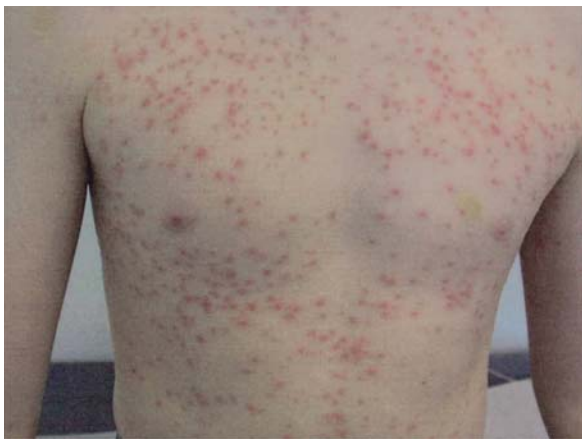

FIG. 219.3 *Pseudomonas aeruginosa* folliculitis of the trunk region. *(Modified from Wu DC, Chan WW, Metelitsa AI, et al.* Pseudomonas *skin infection: clinical features, epidemiology, and management.* Am J Clin Dermatol. *2011;12:157–169.)*

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

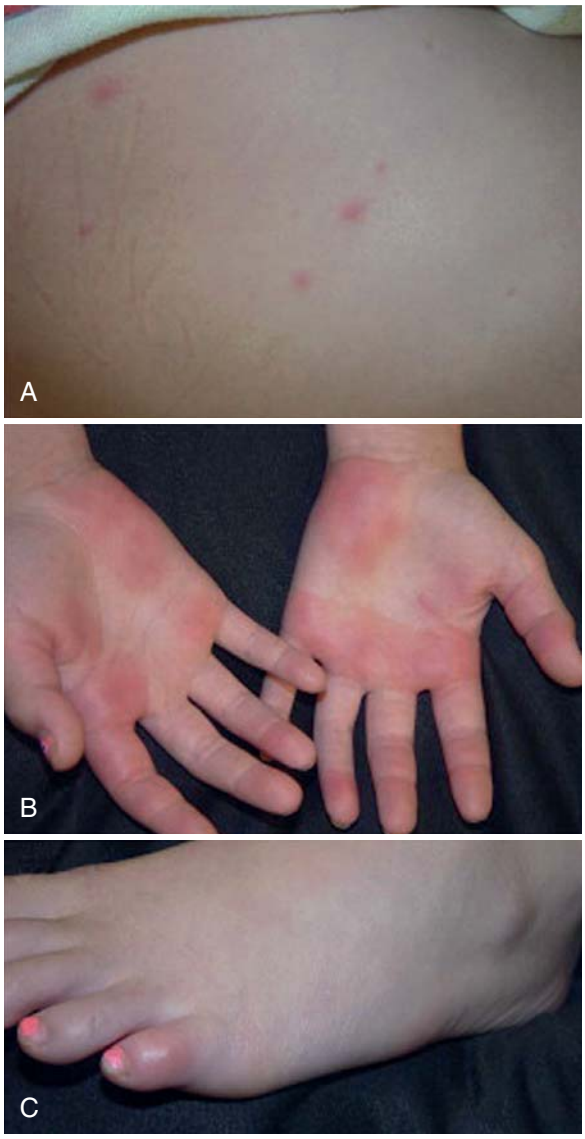

FIG. 219.4 Lesions developing after exposure to a hot tub/pool. (A) Erythematous pustules involving the abdomen. (B) Tender erythematous nodular lesions on the palms. (C) Erythema and swelling over the lateral surface of the toe. *(Modified from Yu Y, Cheng AS, Wang L, et al. Hot tub folliculitis or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

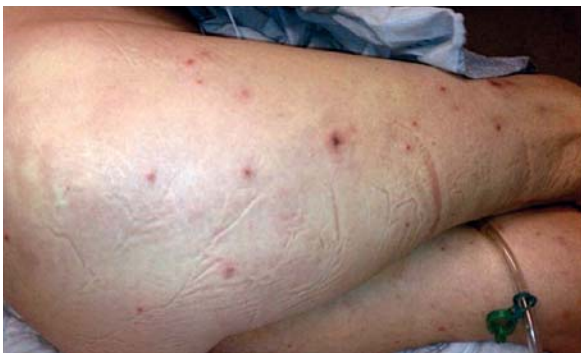

FIG. 219.5 Ecthyma gangrenosum in 67-year-old man with chronic lymphocytic leukemia. *(Modified from Walls AC, Frangos JE, Goralnick E. Ecthyma gangrenosum in a 67-year-old man with chronic lymphocytic leukemia.* J Emerg Med. *2012;43:339–341.)*

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_{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.*

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