appropriate term.[657,658] Poor glycemic control has been suggested, although not universally accepted, as a KLA risk factor, given impaired neutrophil phagocytosis of K1/K2 capsular serotypes.[659] Strains isolated from patients with invasive syndrome have distinct virulence features compared with less invasive, comparator strains.[660] These factors have genetic similarity with invasive disease isolates despite geographic diversity.[661] Capsular type K1 has emerged as an important factor in KLA and demonstrates a distinct link to a specific clonal complex, CC23, that involves a virulence plasmid; several of the factors discussed later portend higher community acquisition rates, KLA formation, and metastatic spread.[627,661–663]

The K1/2 serotypes demonstrate high rates of hypermucoviscous phenotype,[650] but hyperviscous phenotype is not limited to only the K1/2 serotypes. Presence of *magA* (mucoviscosity-associated gene), ubiquitous in K1 isolates, was initially proposed as a risk factor for both KLA and metastatic infection,[664] but it appears to be associated with K1 capsule and not a driver of virulence.[650,665,666] The regulator of mucoid phenotype *(rmpA)* gene increases mucoid phenotype for most isolates.[634,650,667–670]

K. pneumoniae can produce a variety of fimbrial types, including types 1 and 3 pili, aiding host cell adherence.[671] Aerobactin, a siderophore, increases *K. pneumoniae* virulence,[651,672–674] with increased production in hypervirulent phenotypes supporting its role in invasive disease.[675,676] Much like *E. coli,* KLA isolates may use several iron acquisition systems, of which a majority are regulated by *tonB*.[673]

All strains of *K. pneumoniae* are resistant to ampicillin as a result of the presence of a chromosomal gene encoding a penicillin-specific β-lactamase.[677] Preceding ampicillin use has been shown to increase risk of KLA[633] and postneurosurgical infections.[622] In addition, nosocomial isolates are frequently resistant to numerous other antibiotics as a result of the acquisition of MDR plasmids. For example, *K. pneumoniae* is one of the most common organisms to carry plasmids encoding ESBLs and carbapenemases, and bacteremia with such strains is associated with higher rates of treatment failure and death.[678,679] After the initial description of the novel carbapenemase, KPC-1, in a *Klebsiella* isolate in the United States, *Klebsiella* is an archetype of emerging resistance.[680] Therapeutic options for infections caused by non–MDR strains include first-generation cephalosporins, penicillin/β-lactamase inhibitor combinations, trimethoprim-sulfamethoxazole, fluoroquinolones, and aminoglycosides. For MDR strains, especially those expressing ESBLs, treatment options are often limited to fourth-generation cephalosporins or carbapenems. Carbapenemase-producing strains leave scarce options.[7]

The *K. pneumoniae* subspecies *rhinoscleromatis* is the causative agent of respiratory scleroma, also known as rhinoscleroma, a chronic granulomatous infection of the nasal passages and other parts of the respiratory tract.[627,681] In contrast to *K. pneumoniae*, *K. rhinoscleromatis* is not found outside human hosts.[682] The disease it causes is characterized by chronic inflammation and remains difficult to diagnose because of reliance on biopsy, lack of early symptom specificity, and variation of routine biochemical properties between strains.[683] Often, rhinoscleroma presents in advanced stages with disfigurement and respiratory compromise following a progressive clinical pathway from atrophic through granulomatous to fibrotic stages.[684] The disease is found primarily in impoverished areas of Central and South America, Africa, and Asia or in immigrants from these areas[681,682] and is transmitted by close contact and affected by genetic control of the host immune responses.[682] Respiratory scleroma is characterized by nodules and masses often involving the nasal passages and, less commonly, other areas of the respiratory tract. Occasionally, the infection can erode through bone and invade the CNS. The differential diagnosis includes tuberculosis, leprosy, fungal infections, granulomatosis with polyangiitis, malignancies, and sarcoidosis. Biopsy specimens show granulomatous inflammation with foamy macrophages (Mikulicz cells) containing intracellular organisms (Fig. 218.6).[685] The bacteria can be grown on ordinary laboratory media. Prolonged antibiotic therapy, often for months, and, occasionally, surgical débridement are required for cure, but relapses are common.[682] Traditionally, streptomycin or tetracycline has been used, but more recent reports suggest that trimethoprim-sulfamethoxazole or fluoroquinolones could be alternatives.[682]

The *K. pneumoniae* subspecies *ozaenae* can colonize the nasopharynx of healthy individuals. This subspecies has been associated with chronic atrophic rhinitis (*ozena* means "stench") marked by bone resorption and thick, foul-smelling discharge that often forms crusts, but its etiologic role is controversial. The organism has only rarely been isolated from patients with a variety of infections, including otitis media and mastoiditis, cystitis and pyelonephritis, soft tissue infections, bacteremia associated with neutropenia, pneumonia, and meningitis.[686,687] It is usually susceptible to multiple antibiotics except when isolated from hospitalized patients who have received previous antimicrobial therapy.

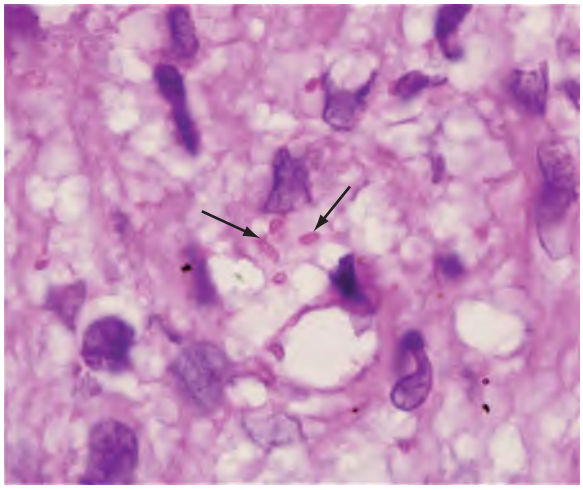

FIG. 218.6 Photomicrograph of Mikulicz cells in a patient with rhinoscleroma. The periodic acid–Schiff–positive structures within the macrophage *(arrows)* are the causative organism, *Klebsiella rhinoscleromatis. (From ID Images. © The Infectious Diseases Society of America. Case presented by Danielle Osterholzer, Tom E. Davis, and Stephen D. Allen.)*

K. oxytoca, like *K. pneumoniae,* can cause a variety of nosocomial infections and is distinguished from *K. pneumoniae* based on its ability to produce indole from tryptophan. *K. oxytoca* is rarely isolated in stool specimens of asymptomatic patients and is not believed to be a constituent of the normal bowel microbiota.[688–690] There is evidence that *K. oxytoca* has increased cytotoxin production not found in other *Klebsiella* species, which may account for its ability to induce antibiotic-associated hemorrhagic colitis with histopathologic findings similar to those of STEC or *Shigella*.[691,692] It may also cause outbreaks and a variety of nosocomial infections and may be resistant to multiple antibiotics.

K. granulomatis (formerly *Calymmatobacterium granulomatis*) is a fastidious member of the genus that causes granuloma inguinale or donovanosis, a chronic genital ulcerative disease (see Chapter 235).

Enterobacter Species, *Pantoea agglomerans,* and *Chronobacter sakazakii*

Enterobacter species have undergone reclassification. *Enterobacter cloacae* is responsible for most *Enterobacter* infections in humans. *Enterobacter aerogenes* was renamed *Klebsiella aerogenes* owing to genetic similarity.[692a,692b] *Enterobacter sakazakii* was reclassified into the genus *Chronobacter,* which includes at least seven distinct species.[693] Several less common *Enterobacter* spp. have been reorganized into the new genera of *Lelliottia*, *Pluralibacter*, and *Kosakonia*.[694] *P. agglomerans* (formerly *Enterobacter agglomerans*) is also a common isolate and is grouped with the *Enterobacter* spp. here. These bacteria ferment lactose, are motile, and form mucoid colonies. *Enterobacter* strains are part of the intestinal microbiota and rose to notoriety with a large nationwide outbreak[695] and continue to be implicated in clonal outbreaks.[696] The normal colonization may become infection, especially in patients who have received antimicrobial therapy or who are admitted to the ICU.[697] *Enterobacter* spp. may cause a wide variety of nosocomial infections,[612,698,699] including pneumonia, UTIs, wound and burn infections, and infections of intravascular and other prosthetic devices. Other than neonates and postneurosurgical patients, *Enterobacter* rarely causes meningitis. There do not seem to be distinguishing characteristics among infections caused by *E. cloacae* and *E. aerogenes*, although *E. cloacae* may have higher

rates of antimicrobial resistance, and *E. aerogenes* may have poorer outcomes.[700]

Given the considerable difficulty in correctly identifying *Chronobacter* spp., not all reports of *E. sakazakii* prior to reclassification in 2007 can be directly attributed to *Chronobacter.*[694] Given those limitations, we know that *Chronobacter* may cause bacteremia, necrotizing enterocolitis, and meningitis, primarily in neonates of low birth weight, and in such infants is associated with consumption of powdered milk formula,[701–705] with mortality rates in excess of 40%.[706,707]

P. agglomerans, a plant pathogen, is often associated with contaminated catheters or penetrating trauma.[708]

Enterobacter, *Pantoea*, and *Chronobacter* use virulence factors typical of other Enterobacteriaceae.[709–712] *Enterobacter* strains associated with illness may deploy a variety of mechanisms, including heavy metal resistance and additional siderophore assembly kits to gain a fitness advantage against other microbes, that facilitate their survival in diverse environments.[711] Efflux pumps are very active in the wide array of antimicrobial resistance in *Enterobacter* but may also help explain *E. cloacae* competitive virulence.[712] *C. sakazakii* can adhere to and invade brain microvascular endothelial cells, similar to NMEC.[713–715] The outer membrane of *C. sakazakii* is encoded by *ompA,* its best-described virulence marker.[716] *C. sakazakii* resists desiccation, which may explain its role in contaminating powdered milk, where it can survive for more than 12 months.[703,717–721] *C. sakazakii* is the only *Chronobacter* species that can metabolize sialic acid, which is found in breast milk, infant formula, the gastrointestinal tract, and the brain, possibly explaining the specific association with these syndromes.[722]

Strains belonging to the genus *Enterobacter* often show antimicrobial resistance, earning them a place in the ESKAPE mnemonic.[723,724] *E. cloacae, E. aerogenes,* and most strains of *Chronobacter* are intrinsically resistant to ampicillin and first- and second-generation cephalosporins as a result of an inducible AmpC chromosomal β-lactamase that is controlled by both positive and negative regulators.[725] Furthermore, mutants that constitutively produce high levels of β-lactamase, conferring resistance to third-generation cephalosporins, arise at frequencies of 10^{-4} to 10^{-7}, often as a result of mutations in the regulatory loci, such that resistant mutants may already be constitutively present before initiation of therapy. As with other members of the Enterobacteriaceae, *Enterobacter* spp. may carry plasmids encoding MDR phenotypes[698,726,727] (see Chapter 18 on antimicrobial resistance). Therapy must therefore be tailored to local resistance patterns and results of individual isolate susceptibility testing. Clinicians must be aware that emergence of stably derepressed resistant mutants may lead to treatment failure when third-generation cephalosporins are used, even if isolates appear susceptible at initial testing.[728] Therefore, fourth-generation cephalosporins and carbapenems may be empirically chosen for severe infections.

Serratia Species

Of the many species in the genus *Serratia, Serratia marcescens* is the one most commonly isolated from human infections, and *Serratia liquefaciens* is occasionally grown. *Serratia* strains are motile, rarely ferment lactose, and produce an extracellular DNase. The organism is widespread in the environment but not a commonly recognized component of the human fecal microbiota; thus most infections appear to be acquired exogenously. Many environmental and some clinical strains of *S. marcescens* produce a red pigment (Fig. 218.7), prodigiosin. Bartolemeo Bizio, an Italian pharmacist, first described the organism in 1819 as the cause of red discoloration of polenta, thereby discrediting the claim that the growth was due to the miraculous appearance of blood.[729] He named the bacterial genus to honor Serafino Serrati, an Italian physicist, and its species name *(marcescens)* for the Latin word for "to decay" because of the tendency of the pigment to change color as the colonies age.[730] The production of prodigiosin and the misconception that the bacterium was harmless led to its frequent use as a biologic marker to study, among other things, the transmission of bacteria through speech and contact, ascending bladder colonization from urinary catheters, and the dissemination of aerosolized bacteria after experimental release into the environment in models of biologic warfare.[731,732] It is now appreciated that *S. marcescens* can cause a wide variety of infections, ranging from UTIs, bacteremia, pneumonia, and CNS infections, to other less common infections, including ocular infections. The most common site of infection is the urinary tract, but the organism is frequently isolated from the respiratory tract and wounds.[732]

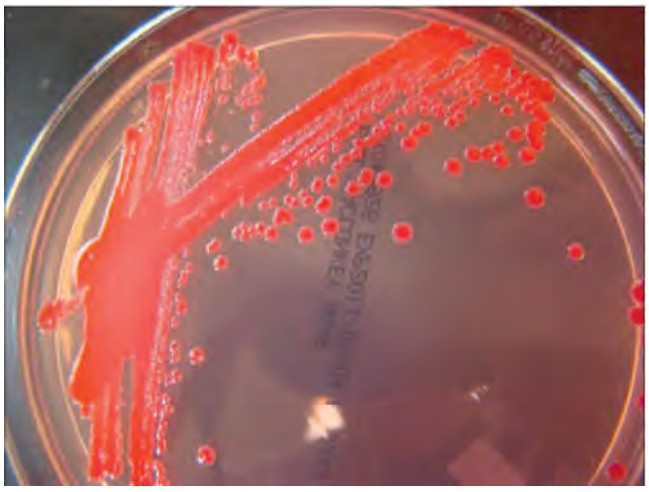

FIG. 218.7 *Serratia marcescens* colonies producing prodigiosin responsible for characteristic red pigmentation. *(From Mahlen SD. Serratia infections: from military experiments to current practice.* Clin Microbiol Rev. *2011;24:755–791.)*

In large epidemiologic surveys, *Serratia* species account for only a small percentage of pneumonia and bacteremia. *Serratia* is typically considered a nosocomial pathogen, but in a population-based study in Australia conducted over 10 years, nearly half of the cases of *Serratia* bacteremia was found to be of community onset.[733] A similar laboratory-based surveillance study from Canada found that nearly two-thirds of incident isolates were of community onset; however, the investigators were unable to distinguish community-acquired from health care–associated isolates.[734] Such data suggest that community infections may play a larger role than previously thought, and that infections may arise from endogenous (microbiota) strains, in addition to being transmitted nosocomially.

There have been more than 200 reported *S. marcescens* outbreaks[732] implicating sources such as compounded drugs,[735] prefilled syringes,[736] contaminated soaps and water,[737–739] medical devices,[740] and total parenteral nutrition.[741,742] *Serratia* outbreaks are of particular concern in pediatric ICUs.[737] *S. liquefaciens* has been noted to be a cause of transfusion-related outbreaks.[743,744]

In addition, *Serratia* species have a historical association with infections in injection drug users who are at particular risk for *S. marcescens* infections, including endocarditis[731,745] and infections at other sites after hematogenous spread.[731] *Serratia* spp. have a predilection for ocular infection, accounting for up to 20% of nosocomial *Serratia* infections, second only to respiratory infections in a retrospective review.[746] *Serratia* can cause keratitis, corneal ulceration, and endophthalmitis, which may follow hematogenous dissemination, and is second only to *Pseudomonas* spp. in the frequency of gram-negative ocular infections and rivals it with regard to infections associated with contact lens wear.[747–749]

Potential virulence factors of *Serratia* have not received as much attention as those of *E. coli* or *Klebsiella,* but *Serratia* likely uses many of the common virulence factors present in other Enterobacteriaceae. The ability to degrade macrophages has been proposed as a possible virulence attribute for *S. liquefaciens.*[750] This process is independent of internalization, but because proximity and contact are required, extracellular toxins or other bacterial effectors may be implicated. More recently, the RssAB-FlhDC-ShlBA pathway has been considered as a complex host invasive pathogenic pathway involving numerous factors, including quorum sensing and swarming.[752,754] Through this pathway, ShlA both exerts cytotoxic properties and contributes to urinary pathogenesis. ShlA, codependent on its activator, ShlB, requires cellular contact consistent with the effects on macrophages noted earlier.[752] RssAB is a regulatory system that decreases ShlA production and thereby swarming.[753] FlhDC is important for quorum sensing and positively regulates

swarming, but negatively affects biofilm formation.[754,755] *Serratia* colonization, invasiveness, and persistence may be aided by biofilm formation[756] and are likely, in part, regulated by quorum sensing.[732,757] However, biofilm formation was not evident in *Serratia* keratitis infections; accordingly, exoenzyme production may be important.[758]

Serratia isolates are resistant to ampicillin and first-generation cephalosporins because of an inducible, chromosomal AmpC β-lactamase similar to that of *Enterobacter.*[759,760] *Serratia* have been associated with nearly all mechanisms of β-lactamase production seen in other gram-negative organisms,[761] including KPC enzymes conferring resistance to carbapenems (see Chapter 18 on antimicrobial resistance). Given the variety of resistance mechanisms found, treatment of infections caused by *S. marcescens* can be difficult, and every effort should be made to identify the sources of outbreaks to control the spread of the organism in susceptible populations.

Citrobacter Species

Members of the genus *Citrobacter* are named for their use of citrate as their sole carbon source. Of the more than 10 recognized species, *Citrobacter freundii* and *Citrobacter koseri* (formerly *Citrobacter diversus*) are the most important human pathogens. They are differentiated by their ability to convert tryptophan to indole, ferment lactose, and use malonate.[762] *C. freundii* produces hydrogen sulfide and therefore can be confused with *Salmonella,* with which it was classified at one time. The urinary tract is the most frequent site from which *Citrobacter* is cultured, often in association with an indwelling catheter, and *Citrobacter* may be a frequent cause of nosocomial UTIs[763] and outbreaks.[764] These bacteria may also be seen in intraabdominal and pulmonary infections.[765,766] Bacteremia from *C. freundii* may have an intraabdominal source more commonly than from the urinary tract, especially in patients with polymicrobial bacteremia and those with underlying malignancy.[765,768] Neonatal meningitis due to *C. koseri* often (approximately 75%) causes multiple brain abscesses associated with high mortality and severe neurologic sequelae in survivors.[769] The predilection for CNS infection has been postulated to be due to a combination of a unique outer membrane in *C. koseri* and infiltration of macrophages infected with *C. koseri* resistant to phagolysosomal effects across the BBB.[769,770] Nosocomial outbreaks have been accompanied by high rates of intestinal colonization by the organism in infants and by carriage of the bacteria on the hands of health care workers.[764,771] A carbapenemase-expressing *C. freundii* outbreak was considered to have a potential foodborne source.[772]

C. freundii strains, like strains of *Enterobacter* and *Serratia,* have inducible *AmpC* genes encoding resistance to ampicillin and first-generation cephalosporins that can be produced constitutively at high levels after mutations selected by prior exposure. Furthermore, isolates of *Citrobacter* may be resistant to multiple other antibiotics as a result of plasmid-encoded resistance genes. The exposure of commensal *Citrobacter* spp. of low virulence to repeated antibiotic courses may select for accumulation of multiple resistance genes, leading to extensive resistance profiles.[773]

Hafnia alvei

H. alvei (formerly *Enterobacter hafniae*) was previously considered to be the sole species in the genus *Hafnia.* Through more recent 16S rRNA gene studies, a novel species, *H. paralvei*, now has been confirmed.[774] There are not clear virulence differences between the species, although *H. alvei* may be more cytotoxic.[775] As with most of the disease-implicated members of the Enterobacteriaceae, *Hafnia* reside in the gastrointestinal tract of humans and many animal species as part of the normal microbiota.[776] *Hafnia* are motile but do not ferment lactose. Although *H. alvei* may be cultured from various sites, it is rarely implicated in monomicrobial infections[777]; this finding suggests that its pathogenicity may be quite low, with the exception of rare case reports of isolated bacteremia. Most infections with *H. alvei* occur in patients with severe underlying illness, including malignancy, trauma, and recent surgery. There have been numerous reports linking diarrhea to the isolation of *H. alvei* from stool specimens and several studies have implicated *H. alvei* in outbreaks, although the evidence is not strong.[776] Furthermore, those strains initially reported to produce A/E lesions similar to EPEC (as described earlier) were reclassified as *E. albertii.*[94] However, in a case-control study the prevalence in stools of *H. alvei* was significantly greater in those with diarrhea than without, consistent with a possible etiologic role.[778] These strains, though, were all negative for the *eae* gene encoding intimin, found in EPEC and *E. albertii.*[94] A majority of *Hafnia* strains tested in vitro produced a cytolytic toxin that has been implicated in gastroenteritis.[775] *H. alvei* are naturally resistant or of intermediate susceptibility to tetracyclines, amoxicillin, amoxicillin-clavulanate, ampicillin-sulbactam, narrow-spectrum cephalosporins, azithromycin, and fosfomycin.[779] Treatment of serious *H. alvei* infections is guided by antimicrobial susceptibility testing. High rates of colistin resistance have been described, given the close phylogenetic relationship with other intrinsically colistin-resistant Enterobacteriaceae.[780] Multiple resistance patterns have been noted.[779,781]

Proteus, Providencia, and *Morganella*

The genera *Proteus, Providencia,* and *Morganella* are related members of the Enterobacteriaceae that are lactose negative and motile and produce phenylalanine deaminase. *Proteus mirabilis* and *Proteus vulgaris* account for most clinical *Proteus* isolates. Both produce urease and hydrogen sulfide, and the latter is indole positive. In contrast to most Enterobacteriaceae, these bacteria may express large numbers of fimbriae and flagella, transforming them into highly elongated rods that translocate rapidly across the surface of agar plates, resulting in a characteristic "swarming" motility. This motility produces a characteristic pattern on growth plates (Fig. 218.8) from sequential rounds of swarm cell differentiation and can overwhelm accompanying organisms. This swarming motility is regulated through a complex network acting on the flagellar transcription regulator, *flhDC.*[782] The name *Proteus* follows from the character in Homer's *Odyssey* who is capable of changing form.

Providencia stuartii is the most common species of its genus isolated from clinical specimens, but *Providencia rettgeri* is occasionally grown. These bacteria can be differentiated from *Proteus* and *Morganella* based on their ability to use citrate and ferment D-mannitol.[783] *Morganella morganii* is, at present, the only member of its genus and is citrate negative.

Proteus spp. are common causes of UTIs, occasionally in normal hosts[784] but more often in those with indwelling catheters or anatomic or functional urinary tract abnormalities.[785,786] *Proteus* are common among the gram-negative bloodstream isolates, with most secondary to UTI and often associated with urinary catheters.[639,787–789]

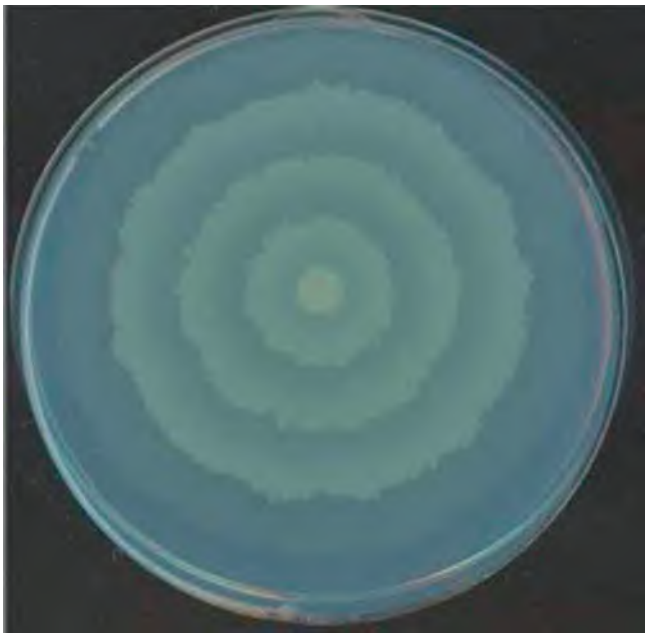

FIG. 218.8 Characteristic bull's eye pattern of sequential rounds of swarming and consolidation frequently seen with *Proteus*. *(From Schaffer JN, Pearson MM. Proteus mirabilis and urinary tract infections.* Microbiol Spectr. *2015;3[5].)*

Community-acquired *Proteus* UTIs in the presence of hydronephrosis or urolithiasis have increased risk of bacteremia.[790] *Proteus* has a remarkable ability to persist in the urinary tract despite antibiotics and catheter exchange, likely due to immune evasion and the protective reservoir that urinary stones provide. Infections not related to the urinary tract or bloodstream have been reported with much less frequency.

The pathogenesis of UTIs caused by *P. mirabilis* has received considerable attention.[782,791] These microorganisms have multiple features devoted to adherence and motility[792] and may produce several types of pili, the most important of which are mannose-resistant *Proteus*-like (MR/P) fimbriae.[793,794] which have been shown to contribute to bladder colonization in a murine model.[795] Ascending UTIs are common, and fimbriae and adhesins are necessary, but not sufficient, to produce infection.[782] Potent urease production contributes to colonization, stone formation, and obstruction,[786,796–798] without which the infectivity of *Proteus* is diminished.[799,800] By hydrolyzing urea to form CO_2 and ammonia, urease leads to the alkalinization of urine, which leads to the precipitation of struvite, formation of calculi, and subsequent urinary catheter obstruction. Urinary pH ≥7 suggests infection with a urease-positive bacterium, most often a *Proteus* species. *P. mirabilis* can cause monomicrobial UTIs but is frequently found in polymicrobial catheter-associated urinary tract infections. In coinfection models with *P. stuartii*, urolithiasis and bacteremia are promoted in a urease-dependent fashion, and the presence of the other uropathogens regardless of their own urease production enhances the urease activity of *Proteus*.[801–803]

Given the increased severity of *Proteus* UTIs and the propensity of this organism to cause bacteremia in community-acquired infections and patients with hydronephrosis or urolithiasis, radiographic studies such as renal sonography or computed tomography should be considered in patients with severe UTIs, especially those complicated by bacteremia.[790] Obstruction due to calculi must be promptly relieved to avert severe clinical outcomes and to avoid persistent sources that can lead to recurrent infection.[785] Most *Proteus* strains are susceptible to commonly used antibiotics, except for nitrofurantoin and tetracycline.[783] Like other members of Enterobacteriaceae, MDR strains exist and are increasing; strains of *P. vulgaris* are generally more resistant.

P. stuartii and *P. rettgeri* are relatively uncommon clinical isolates, except in elderly patients with long-term indwelling urinary catheters,[797,804,805] and are emerging in hospital settings.[806] These infections are sometimes complicated by bacteremia and may cause death.[804,807] *Providencia* uses many of the same virulence factors as *Proteus,* although they are less often studied. Biofilm production, weak urease production, and urease tolerance are proposed virulence mechanisms[797,808] and have been implicated in the organism's ability to disseminate in a hospitalized setting.[809] *P. stuartii* and *P. rettgeri* are often resistant to multiple antibiotics, including gentamicin, first-generation cephalosporins, and ampicillin,[810] although MDR phenotypes have been described.[811–814] Therapy is guided by susceptibility testing.

M. morganii is an infrequent nosocomial isolate, usually isolated from urine or wounds.[783,815] *M. morganii* bacteremia most often is due to a urinary or hepatobiliary port of entry and is often community acquired.[816,817] *Morganella* spp. also may be present in polymicrobial infections and in wounds, which are the next most common source in bacteremic cases.[816] As with other members of this group, *M. morganii* may cause nosocomial outbreaks.[818] *M. morganii* strains possess inducible AmpC β-lactamases and therefore are intrinsically resistant to ampicillin and first-generation cephalosporins; spontaneous derepressed mutants resistant to ESBLs similar to those described previously for *Enterobacter* spp. may arise.[819]

Other Genera

The majority of clinically relevant Enterobacteriaceae are discussed in the previous sections, although as sequencing studies and in-depth biochemical analyses increase, the number of distinct genera within the Enterobacteriaceae continues to expand. Descriptions of clinical disease limited to case-level data include *Averyella*, *Buttiauxella, Cedecea, Kosakonia, Leclercia, Leminorella, Moellerella, Pluralibacter, Rahnella, Tatumella,* and *Yokenella,* in addition to those highlighted here.[694]

Edwardsiella tarda is found in freshwater environments, has been associated with diarrhea, and can cause wound infections, abscesses, and bacteremia, sometimes linked to marine exposure, including in patients "noodling" or hand-fishing of catfish.[820,821] In patients with liver disease and iron overload, the mortality rates from *Edwardsiella* infections are high.[822] Genes related to iron scavenging have shown adaptive evolution, which may facilitate virulence in *Edwardsiella* to a broad range of hosts.[823]

Plesiomonas shigelloides is another organism that is found in water and has been associated with diarrhea and rarely with extraintestinal infections.[824] *P. shigelloides* was previously grouped with vibrios, given their shared oxidase production and polar flagellae, but has been reassigned based on phylogenetic studies based on ribosomal RNA gene sequencing.[825,826] *P. shigelloides* is an infrequent isolate from patients with gastroenteritis. Although the pathogenicity of *P. shigelloides* was questioned initially, it is now an accepted enteric pathogen based on case-control studies and numerous diarrheal illness outbreaks, with strong epidemiologic evidence.[824] *P. shigelloides*–associated diarrhea manifests most commonly with secretory gastroenteritis but can also cause grossly bloody stool or chronic diarrheal illness. Risk factors include recently ingested raw shellfish or travel exposure.[827]

Ewingella americana, named after William Ewing, who made many contributions to our understanding of the microbiology of the Enterobacteriaceae, is a rare cause of nosocomial bacteremia, peritonitis associated with peritoneal dialysis, and conjunctivitis.[828–830] Most isolates are highly sensitive to antibiotics, although multidrug resistance has been reported.[831]

Infections caused by organisms belonging to the genus *Kluyvera,* which closely resembles *E. coli,* are rare. These bacteria have been recovered from urine, sputum, and wounds; and in many cases, the pathologic significance of their presence is unclear. However, pyelonephritis, bacteremia, and abdominal and soft tissue infections caused by *Kluyvera* spp. have occurred, particularly in immunosuppressed patients, with some infections being fatal.[832–834] Chromosomal genes in *Kluyvera* spp. are likely the origin of CTX-M ESBLs, which have become an increasing cause of MDR and have demonstrated global spread.[835–837] Although bacteria belonging to the genus *Photorhabdus* are fascinating bioluminescent nematode symbionts, the nonluminescent species *Photorhabdus asymbiotica* is the only one recovered in humans.[694,838,839]

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The complete reference list is available online at Expert Consult.

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219 *Pseudomonas aeruginosa* and Other *Pseudomonas* Species

Rafael Araos and Erika D'Agata

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

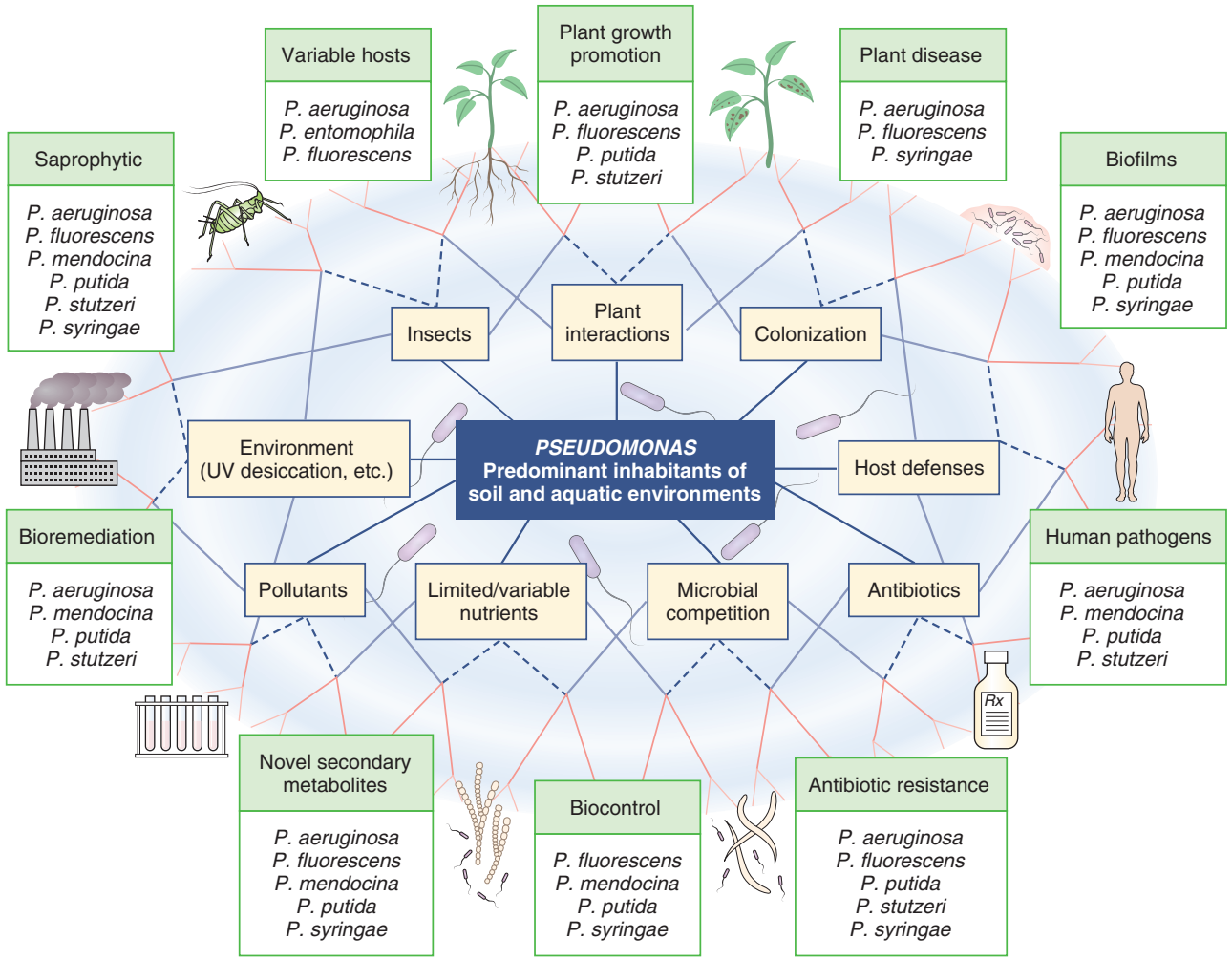

FIG. 219.1 Functional and environmental range of *Pseudomonas* species. The *Pseudomonas'* common ancestor has encountered a wide range of abiotic and biotic environments, which has led to the evolution of a multitude of traits and lifestyles with significant overlap among species. *UV,* Ultraviolet. *(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.*