



Pseudomonas aeruginosa

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LEARNING OBJECTIVES

1. Evaluate the microbiology, epidemiology, pathogenesis, mechanisms of resistance, and clinical presentation in patients with a possible *Pseudomonas aeruginosa* infection.
2. Evaluate patient populations at greatest risk of having an infection caused by *P. aeruginosa*, including multidrug-resistant strains.
3. Design a therapeutic regimen for a patient with a suspected or documented *P. aeruginosa* infection.
4. Justify the role of antimicrobial stewardship and the pharmacist in treating patients with *P. aeruginosa* infections.

ABBREVIATIONS IN THIS CHAPTER

AME	Aminoglycoside-modifying enzyme
CDI	<i>Clostridioides difficile</i> infection
ESBL	Extended-spectrum β -lactamase
HABP	Hospital-acquired bacterial pneumonia
HAP	Hospital-acquired pneumonia
MBL	Metallo- β -lactamase
MDR	Multidrug-resistant
PBP	Penicillin binding protein
PDR	Pandrug-resistant
VABP	Ventilator-associated bacterial pneumonia
VAP	Ventilator-associated pneumonia
XDR	Extensively drug-resistant

[*Table of other common abbreviations.*](#)

INTRODUCTION

Pseudomonas aeruginosa is among the more common causes of infections in the hospital setting. These infections are associated with significant morbidity and health care expenditures, especially when receipt of appropriate antibiotic therapy is delayed. Antibiotic selection for patients with *P. aeruginosa* infections is challenging because of the pathogen's intrinsic resistance to many commercially available antibiotics. Multidrug-resistant strains are prevalent, and often require treatment with novel or "last resort" agents. Infectious diseases pharmacists can help provide optimal care for patients with *P. aeruginosa* infections by being familiar with key aspects of its microbiology, epidemiology, pathogenesis, innate and acquired mechanisms of resistance, and clinical presentation. In addition, pharmacists providing care to patients with *P. aeruginosa* infections should be able to proactively identify patient populations at greatest risk of having an infection caused by multidrug-resistant (MDR) strains, detail the available treatment options for its varying clinical presentations, and provide timely evidence-based treatment recommendations, especially for patients with suspected or documented MDR *P. aeruginosa* infections.

MICROBIAL CHARACTERISTICS

Microbiology

P. aeruginosa is a ubiquitous gram-negative aerobe belonging to the family Pseudomonadaceae. *P. aeruginosa* is rod shaped and occurs singly, in pairs, or in short chains. The term *aeruginosa* stems from the green-blue hue within colonies of many clinical isolates. *P. aeruginosa* does not ferment carbohydrates but produces acid from sugars such as glucose, fructose, and xylose but not lactose or sucrose. *P. aeruginosa* can also grow anaerobically if nitrates are available. Almost all

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Common antibiotics with (and without) in vitro activity against *P. aeruginosa*
- Common dosing strategies of antibiotics with in vitro activity against *P. aeruginosa*
- General understanding of susceptibility data and MIC distributions (i.e., knowledge of low vs high MICs for antibiotics with in vitro activity against *P. aeruginosa*)

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Mensa J, Berberan J, Soriano A, et al. [Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: guidelines by the Spanish Society of Chemotherapy](#). Rev Esp Quimioter 2018;31:78-100.
- Moradali MF, Ghods S, Rehm BH. [Pseudomonas aeruginosa lifestyle: a paradigm for adaptation, survival, and persistence](#). Front Cell Infect Microbiol 2017;7:39.
- Livermore DM. [Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare?](#) Clin Infect Dis 2002;34:634-40.
- Pang Z, Raudonis R, Glick BR, et al. [Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and alternative therapeutic strategies](#). Biotechnol Adv 2019;37:177-92.
- Shortridge D, Gales AC, Streit JM, et al. [Geographic and temporal patterns of antimicrobial resistance in *Pseudomonas aeruginosa* over 20 years from the SENTRY Antimicrobial Surveillance Program, 1997-2016](#). Open Forum Infect Dis 2019;6(suppl 1): S63-S68.
- Hawkey PM, Warren RE, Livermore DM, et al. [Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party](#). J Antimicrob Chemother 2018;73(suppl_3):iii2-iii78.
- Kalil AC, Metersky ML, Klompas M, et al. [Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society](#). Clin Infect Dis 2016;63:e61-e111.
- Bassetti M, Vena A, Croxatto A, et al. [How to manage *Pseudomonas aeruginosa* infections](#). Drugs Context 2018;7:212527.

P. aeruginosa strains carry the biosynthetic genes to produce an extracellular polysaccharide known as alginate. Alginate is often called “mucoïd exopolysaccharide” or “glycocalyx,” and overproduction is responsible for the mucoïd colony phenotype. On the molecular level, *P. aeruginosa* has an impressively large genome. Genetic sequencing shows the presence of 6.26 megabase pairs (Mbp), encoding 5567 genes. Around 1500 genes are used in cell growth, division, metabolism, and protein structural integrity. Comparatively, *Escherichia coli* and *Haemophilus influenzae* have 2.81 (2594 genes) and 1.83 Mbp (1714 genes), respectively. This enhanced coding ability of the *P. aeruginosa* genome allows greater metabolic versatility and high adaptability to environmental changes (Pang 2019).

Reservoirs

P. aeruginosa is naturally found in soil, in water, and on plants and animals. Although *P. aeruginosa* is tolerant of a variety of physical conditions, it has a predilection for moist environments. Hospital reservoirs include humid environmental sources such as respiratory equipment, cleaning solutions, sinks, and mops. *P. aeruginosa* is also introduced into the hospital environment by visitors (e.g., bringing plants, fruits, and vegetables) and patients transferred from other facilities. Water-related reservoirs outside hospitals for *P. aeruginosa* include swimming pools, whirlpools, hot tubs, and contact lens solutions.

P. aeruginosa is not a typical member of the human microbiome, and the prevalence of colonization in healthy individuals is relatively low. Up to 5%–10% of healthy humans carry *P. aeruginosa* in the throat, in the nasal mucosa, or on the skin, and stool carriage rates have been reported to be as high as 24% (Berthelot 2001). Human colonization can also occur at moist sites, such as the perineum, axilla, and ear. Hospitalization and other health care facility exposures greatly increase the risk of carriage with *P. aeruginosa*. Carriage is particularly common on the skin of patients with compromised skin integrity, in the lower respiratory tract of patients undergoing mechanical ventilation, and in the GI tract of patients receiving chemotherapy for neoplastic diseases or those with prior antibiotic exposure.

Pathogenesis

P. aeruginosa is an opportunistic pathogen, and most *P. aeruginosa* infections occur in individuals with altered host defense mechanisms. Individuals with compromised immune function are particularly vulnerable to *P. aeruginosa* infections. The original source of the organism and the precise mode of transmission are often unclear in most patients. Health care–associated transmission typically occurs from patient to patient on the hands of hospital personnel, by direct patient contact with contaminated reservoirs, and by the ingestion of contaminated foods and water. In most cases, entry of *P. aeruginosa* into humans occurs by the oral or respiratory route, and colonization often precedes overt infection. Once host entry is

gained, the pathogenesis of *P. aeruginosa* infections is best viewed as occurring in three stages: (1) bacterial attachment and colonization, (2) local invasion, and (3) dissemination and systemic disease. This process often occurs in the setting of disruption of the integrity of natural anatomic barriers to bacterial invasion (e.g., skin, mucous membranes) or by circumvention of them, as with medical devices (e.g., central venous catheters, urinary catheters, endotracheal tubes). *P. aeruginosa* has an array of innate and acquired immune factors that enable it to surmount host defenses and establish infection.

Quorum Sensing and Biofilms

P. aeruginosa expresses several virulence factors that promote the establishment and persistence of infection. Many of these factors are believed to be regulated by cell density–dependent quorum sensing. This process involves single bacteria releasing small molecules called “acylated homoserine lactones” that diffuse to other cells, signaling activation of intracellular transcriptional regulators. This signaling ability is believed to create a substantial advantage for the bacteria against the host, given that coordinated gene regulation can occur within the cellular community. Quorum sensing is believed to contribute to pathogen dissemination within the host and contribute to its virulence (Smith 2003). Quorum sensing contributes to biofilm formation and maturation, which can result in persistent or chronic infection. Biofilms promote microbial persistence given that cells are shielded from antibiotic penetration by an extracellular matrix. Subpopulations within the biofilm can exist as “persister variants,” which are essentially dormant cells with low metabolic function. Persister variants in biofilms may have decreased susceptibility to antibiotics, presumably because of slowed metabolic function and lack of active replication (Grassi 2017). The simultaneous interplay of biofilms, persisters, and quorum sensing among the bacterial population promotes persistent colonization or recurrent infections.

ANTIMICROBIAL RESISTANCE MECHANISMS

The best-characterized mechanisms of antimicrobial resistance in *P. aeruginosa* include outer membrane porins and permeability alterations, efflux pumps, antibiotic-inactivating enzymes, and target binding site mutations. Many resistance mechanisms are often present and expressed simultaneously in a given patient with a *P. aeruginosa* infection. The terms *MDR*, *extensively drug resistant (XDR)*, and *pandrug-resistant (PDR)* are often used to characterize the different patterns of multidrug resistance exhibited by *P. aeruginosa*. An MDR isolate is nonsusceptible to at least one agent in three or more antibiotic classes with intrinsic activity. An XDR isolate is nonsusceptible to at least one agent in all but two or fewer antibiotic classes with intrinsic activity, and a PDR isolate is nonsusceptible to all agents with intrinsic activity. The mechanisms of resistance present and the extent of their expression

determine the degree of resistance (i.e., low or high) to specific agents or classes (e.g., aminoglycoside-modifying enzymes [AMEs]) or an array of agents in unrelated classes (e.g., efflux pumps that can confer resistance to β -lactams, fluoroquinolones, and aminoglycosides) (Table 1).

Resistance mechanisms present in *P. aeruginosa* can be classified as intrinsic, acquired, or adaptive (Figure 1). Intrinsic resistance mechanisms stem from genes that encode the inherent properties of cell structures and composition that provide protection against toxic molecules and antimicrobials. Acquired resistance mechanisms result through mutation of intrinsic genes or horizontal acquisition from other bacteria through transferring plasmids carrying genetic materials encoding for antibiotic resistance. Acquired resistance typically occurs in response to selective antibiotic pressures. These mechanisms are stable and can be transferred vertically (e.g., upon bacterial replication) or horizontally (e.g., resistance genes by plasmids). Adaptive resistance is induced in the presence of specific antibiotics and other environmental stresses and is transient, given that susceptibility is restored upon removal of the stimuli. This type of resistance mainly relies on induced alterations in gene expression, resulting in increased protein production or alterations in antibiotic targets.

Outer Membrane Porins and Permeability Alterations

Intrinsic resistance in *P. aeruginosa* is partly because of the relative impermeability of its outer membrane to many antibiotics. Membrane porins are a means of cellular entry for certain antibiotics such as β -lactams. Mutations including modification of the size or conductance of the porin channel, decrease in the number of porins, and complete porin loss can occur as an important mechanism of resistance. The best-characterized porin mutation for *P. aeruginosa* is loss of OprD, which confers resistance to carbapenems. Imipenem (i.e. imipenem/cilastatin) appears to be most affected, followed by meropenem. Reduced expression of OprF appears to impair the permeability of fluoroquinolones and β -lactams. In isolation, porin changes or loss tends to confer low-level resistance and results in isolates with MIC values slightly above the susceptibility breakpoint.

In addition to porin mutations, other alterations in membrane characteristics can affect antibiotic activity. Unlike the carbapenems, aminoglycosides do not depend on porin channels for cellular entry, given that they can traverse the membranes of porin-deficient *P. aeruginosa* isolates. Instead, aminoglycosides appear to undergo a type of self-promoted uptake across the bacterial membrane secondary to membrane disruption. This may involve interaction with negatively charged lipopolysaccharides, given that aminoglycosides are positively charged molecules. Changes in the polarity or charge of the outer cellular membrane are believed to contribute to aminoglycoside nonsusceptibility. Lipid modifications

Table 1. Mutational Resistance in *P. aeruginosa*

Mechanism	Mutation site	Effect on strain, according to antipseudomonal drug								
		Fq	Carb-Tic	Pip-Azl	Czid-Atm	Cpm-Cpr	Imi	Mero	AgI	Pm
Reduced affinity										
Of topoisomerase II	<i>gyrA</i>	r/R	–	–	–	–	–	–	–	–
Of topoisomerase IV	<i>parC</i>	r/R	–	–	–	–	–	–	–	–
Derepression of AmpC										
Partial	<i>ampD</i>	–	R	R	R	r	–	–	–	–
Total	<i>ampD</i> + other	–	R	R	R	R	–	–	–	–
Up-regulation										
Of MexAB-OprM	<i>nalB</i> at <i>mexR</i> ; <i>nalC</i> at other	R/R	R	r/R	r/R	r/R	–	r	–	–
Of MexCD-OprJ	<i>nfxB</i>	r/R	r/R	r/R	r/R	R	–	r	–	–
Of MexEF-OprN	<i>nfxC</i> at <i>mexT</i>	r/R	r/R	r/R	r/R	r/R	r	r	–	–
Of MexXY-OprM		r/R	r/R	r/R	r/R	r/R	–	r	r/R	–
Reduced aminoglycoside transport										
Loss of OprD	<i>oprD</i> ; <i>nfxC</i> at <i>mexT</i>	–	–	–	–	–	R	r	–	–
Membrane changes										
		–	–	–	–	–	–	–	–	R

AgI = aminoglycosides; Atm = aztreonam; Azl = azlocillin; Carb = carbenicillin; Czid = ceftazidime; Cpm = cefepime; Cpr = ceftipime; FQ = fluoroquinolone; Imi = imipenem; Mero = meropenem; Pip = piperacillin; Pm = polymyxin; r = reduced susceptibility; R = frank resistance, which may vary in its distinction from r according to the breakpoints adopted; Tic = ticarcillin.

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in the bacterial membrane by incorporating positively charged sugars may decrease the affinity for, or even repel, aminoglycosides. This is expected to result in moderate resistance, likely resulting in a susceptibility interpretation of “intermediate.” A similar mechanism of resistance is described for polymyxins. Mutations in the regulatory systems PhoPQ, PmrAB, and ParRS reduce the negative charge of the cell surface, thereby reducing favorable interactions with positively charged polymyxins. Although still largely uncommon, this is the most well-characterized mechanism for polymyxin resistance among *P. aeruginosa*.

Efflux Pump Systems

P. aeruginosa has a robust efflux pump system. The primary purpose of these pumps is to expel toxic environmental compounds or metabolites from the cytoplasm that might otherwise disorganize the cytoplasmic membrane. Substrates of these pump systems include many clinically relevant

antibiotics such as β -lactams, fluoroquinolones, aminoglycosides, macrolides, tetracyclines, sulfonamides, and chloramphenicol, among other compounds. Multidrug-resistant isolates are very likely to have efflux pump system up-regulation.

P. aeruginosa has several multidrug efflux pump systems. Of the five protein efflux system families described to date, most of those expressed in *P. aeruginosa* are members of the same (i.e., resistance-nodulation-cell division) superfamily. These efflux systems usually have three components: a cytoplasmic membrane pump, a cytoplasmic membrane “exit” porin, and a linker protein. The best-described pump system in *P. aeruginosa* is MexAB-OprM, which is expressed in all isolates to varying degrees. Wild-type strains tend to have relatively low expression, but mutations in the *mexR* repressor gene can result in pump overexpression. Overexpression of MexAB-OprM results in high-level resistance (e.g., increases in MIC by 8-fold) to a range of antibiotics. Genetic deletion

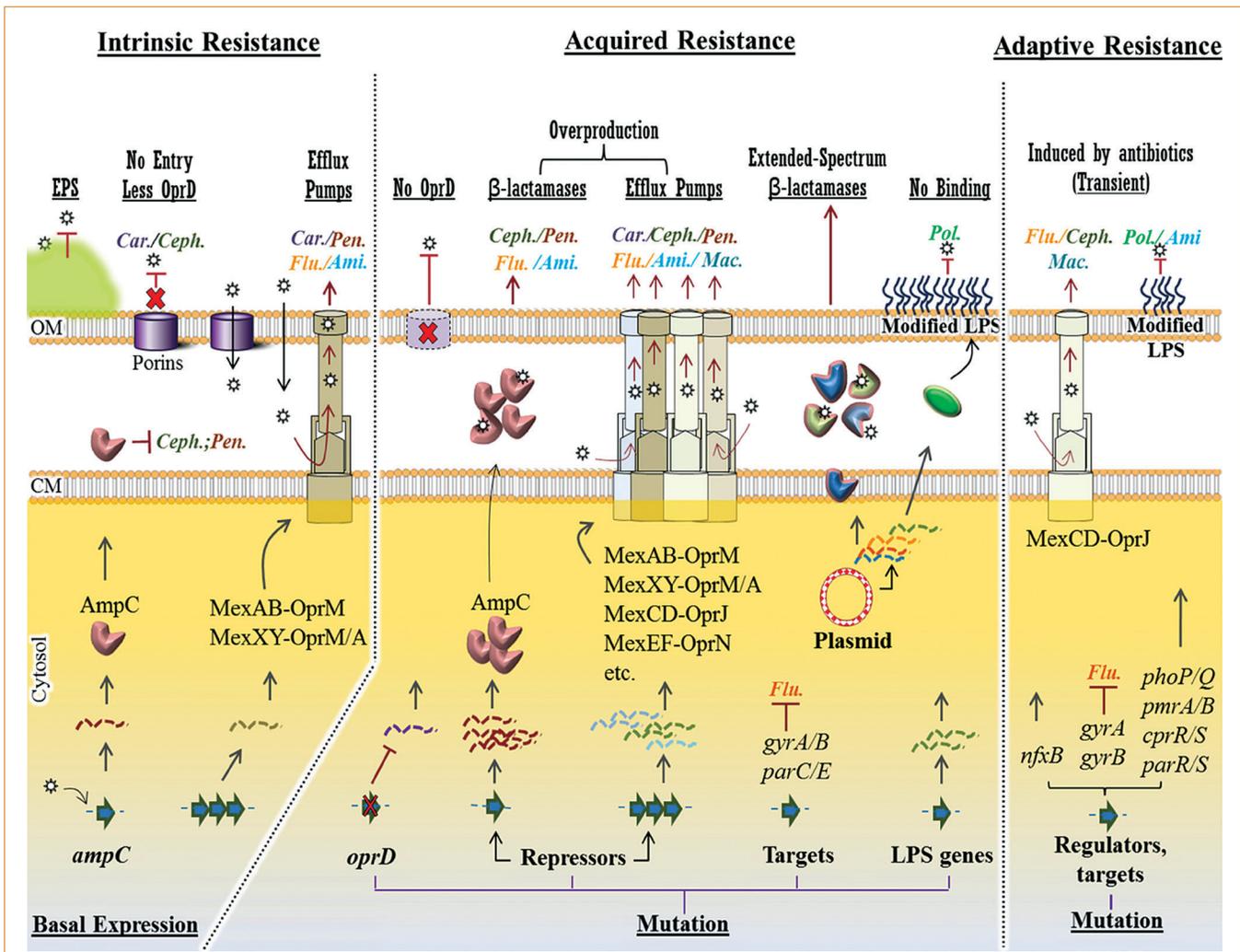


Figure 1. Intrinsic, acquired, and adaptive mechanisms confer antibiotic resistance in *P. aeruginosa*.

Car = carbapenems; Ceph = cephalosporins; Pen = penicillins; Ami = aminoglycosides; Flu = fluoroquinolones; Mac = macrolides and Pol = polymyxins

CM = cytoplasmic membrane; LPS = lipopolysaccharide; OM = outer membrane

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of this pump restores susceptibility to many agents that are not considered clinically active against *P. aeruginosa* such as amoxicillin, cefuroxime, and tetracycline. The antipseudomonal agents perhaps most affected by efflux pumps are β -lactams and aminoglycosides, with fluoroquinolones possibly less affected.

Other pump systems that have been described in *Pseudomonas* include MexCD (or MexXY)-OprJ, MexEF-OprN, MexXY (AmrAB), MexJK-OprM, and MexVW-OprM. These pumps tend to have fewer substrates than MexAB-OprM, and substrate affinity can vary within antibiotic classes. For example, ceftazidime appears to be a poor substrate of MexXY compared with other cephalosporins, whereas meropenem is more prone to efflux than imipenem. Similar to the MexAB-

OprM system, pump expression for these other systems can vary. Several of these systems can be up-regulated in the presence of low concentrations of certain antibiotics, as shown with MexCD-OprJ in the presence of fluoroquinolones and MexXY-OprM in the presence of aminoglycosides. In some cases, pump up-regulation can be associated with increased pump efficiency by enhancing the affinity for specific antibiotic substrates. For example, genetic alterations associated with up-regulation of the MexXY pump system confer increased resistance to aminoglycosides, fluoroquinolones, and cefepime. Antibiotic exposure activates mutant regulatory genes that simultaneously induce up-regulation of efflux pumps (e.g., MexEF-OprN) while down-regulating membrane porins (e.g., OprD). Genetic alterations that encode for

increased pump expression appear to be tightly regulated, and strains having up-regulation of MexAB and MexCD are less virulent than wild-type strains.

Enzyme Mediated

β-Lactamases

Chromosomally Mediated

P. aeruginosa has chromosomally encoded inducible molecular class C AmpC *β*-lactamases (Table 2). This contributes to the inherent nonsusceptibility of *P. aeruginosa* to aminopenicillins and early (i.e., first and second) generation cephalosporins. However, expression tends to be more variable in *P. aeruginosa* than in “classic” AmpC-producing Enterobacteriaceae. In wild-type strains, production levels are low enough to allow for retained activity of antipseudomonal *β*-lactams. However, AmpC *β*-lactamases can be hyperproduced, with or without stable de-repression, often in response to the presence of an antibiotic. Examples of agents that are considered strong and weak inducers of AmpC in *Pseudomonas* include imipenem and cefepime, respectively. AmpC hyperproduction can confer resistance to *β*-lactams that would otherwise be stable against these enzymes, including prototypical antipseudomonal cephalosporins (ceftazidime, cefepime), penicillins (piperacillin), and monobactams (aztreonam). Stable de-repression of AmpC is usually believed to occur through mutations in the regulatory *ampD* or *ampR* genes.

In some cases, the effectiveness of AmpC *β*-lactamase activity can be enhanced in the setting of other concurrent

mechanisms of resistance. Ultimately, decreased intracellular antibiotic concentrations by either porin mutations or efflux can tip the drug-enzyme balance in favor of enzymatic hydrolysis. For example, imipenem is a strong inducer of AmpC enzyme expression but, like other carbapenems, is largely considered stable against these enzymes. However, in the setting of concurrent porin loss (e.g., OprD), lower intracellular concentrations of imipenem can result in decreased stability against hydrolysis because of higher concentrations of AmpC enzyme relative to the drug.

Another notable chromosomally mediated *β*-lactamase expressed in *P. aeruginosa* is the molecular class D enzyme, OXA-50. This is a relatively narrow-spectrum oxacillinase that confers nonsusceptibility to ampicillin and first- and second-generation cephalosporins. However, MIC elevations in aztreonam, ceftazidime, and imipenem, as well as other agents, can be conferred.

Acquired *β*-Lactamases

The most common acquired *β*-lactamases are the PSE (*Pseudomonas*-specific enzyme) penicillinases, which belong to molecular class A (see Table 2). The PSE penicillinases appear to affect the activity of narrow-spectrum *β*-lactams but not extended-spectrum cephalosporins, monobactams, or carbapenems. Other class A *β*-lactamases, such as TEM, SHV, and CTX-M, occur infrequently in *P. aeruginosa*. PER-1, another class A *β*-lactamase, confers high-level resistance to ceftazidime but does not hydrolyze piperacillin or carbapenems.

Table 2. *β*-Lactamase Activity

	Wild Type	Penicillinase			Extended-Spectrum <i>β</i> -Lactamase				Cephalosporinase AmpC	Carbapenemase			
	WT	TEM CARB	PSE	OXA	PER CTX-M	VEB	TEM	SHV	OXA	AmpC	IMP KPC	VIM	NDM
Carboxypenicillins	S	R	R	R					R	R			R
Carboxypenicillins +BLI	S	S/I	I/R	S/I					I/R	R			R
Ureidopenicillins	S	I/R	R	I/R					R	I/R			R
Ureidopenicillins +BLI	S	S/I	I/R	S/I					I/R	I/R			R
Ceftazidime	S	S	S	R					I/R	I/R			R
Cefepime	S	S	I/R	R					I/R	I/R			R
Aztreonam	S	S	S	R					I/R	I/R			S
Imipenem	S	S	S	S					S	S			R

BLI = *β*-lactamase inhibitor; CARBA = carbapenemase; CEPH = cephalosporinase AmpC; ESBL = extended-spectrum *β*-lactamase; I = intermediate resistance; PENI = penicillinase; R = resistance; S = susceptible; WT = wild type.

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The acquired β -lactamases with the broadest spectrum of resistance are the molecular class A and B KPC and metallo- β -lactamases (MBLs), respectively. These enzymes confer significant resistance to carbapenems, antipseudomonal cephalosporins, and antipseudomonal penicillins. These enzymes are not inhibited by clavulanate or tazobactam. However, aztreonam activity is maintained in the setting of MBLs. Unfortunately, these enzymes rarely occur in isolation; therefore, aztreonam would likely be hydrolyzed by another β -lactamase (e.g., AmpC) in the absence of an effective inhibitor. Six types of MBLs have been described for *Pseudomonas*: IMP, VIM, NDM, SPM [Sao Paulo MBL], GIM [Germany imipenemase], and FIM [Florence imipenemase]. These resistance genes are commonly transported on plasmids and integrons. To further complicate clinical treatment, these β -lactamase genes are often transported with AME determinants, conferring concomitant resistance to these agents. There are now widespread reports of MBL-producing, in particular VIM-2-producing, *P. aeruginosa* isolates worldwide.

Acquired molecular class D OXA β -lactamases have been described, though these may be more common outside the United States. Many of these are broad spectrum and confer resistance against antipseudomonal cephalosporins, monobactams, and penicillins, but not carbapenems. Substrate affinity can differ depending on the specific enzyme; for example, OXA-31 is a mutant that confers greater resistance to cefepime than to ceftazidime. Uncommon extended-spectrum β -lactamases (ESBLs) reported to occur in *P. aeruginosa* include VEB, GES, and IBC. These uncommon ESBLs appear to originate from Enterobacteriaceae and are transmitted by genetic mobile elements such as integrons.

Aminoglycoside-Modifying Enzymes

Like with β -lactams, resistance to aminoglycosides in *Pseudomonas* can be enzyme mediated. These AMEs catalyze modification of specific amino or hydroxyl functional groups, which results in suboptimal drug binding to ribosomes. The most well-described AMEs are the *N*-acetyltransferases (AACs), *O*-nucleotidyltransferases, and *O*-phosphotransferases. These enzymes vary in their target sites on the various aminoglycosides, which confers differences in aminoglycoside vulnerability to modification. Although aminoglycoside resistance is usually plasmid mediated, it can also be conferred by transposons, integrons, and other transposable genetic elements. In addition, bifunctional enzymes have been isolated in *P. aeruginosa* (e.g., AAC(6')-30/AAC(6')-Ib) that have more than one mechanism of aminoglycoside modification. If these enzymes are expressed in some form in wild-type strains, their activity against aminoglycosides is believed to be too poor to confer resistance. Increased enzyme expression, to the extent of detectable aminoglycoside resistance, is believed to be stimulated by drug exposure.

Target Site Mutations

Aminoglycosides

Although up-regulated efflux pumps and AME expression are generally considered the best-described mechanisms of resistance against aminoglycosides, target binding site mutations can also occur. The 16S ribosomal RNA methyltransferases, also called RMTases or 16S RNA methylases, can modify the A-site on the 16S RNA, part of the 30S ribosomal subunit, interfering with effective aminoglycoside binding. Although many RMTases exist, the most predominant are RmtB and ArmA. Clinically, the only aminoglycoside that appears to retain activity against RMTases is streptomycin. RMTases are most commonly acquired by plasmid gene transfer. Of note, these enzymes commonly coexist with other genetic elements of resistance, such as β -lactamase-encoding *bla* genes.

Fluoroquinolones

Fluoroquinolone resistance, in addition to being efflux and porin mediated, is conferred by mutational changes in DNA gyrase (*gyrA* and *gyrB*) and/or topoisomerase IV. The primary binding target for fluoroquinolones in *P. aeruginosa* is DNA gyrase. Resistance is conferred by point mutations in the *gyrA* (DNA gyrase) and *parC* (topoisomerase IV) genes. A single-point mutation in *gyrA* can confer elevated MICs to ciprofloxacin and levofloxacin. Two or more point mutations in the same gene (e.g., *gyrA*), or mutations involving multiple genes (e.g., *gyrA* and *parC*), are associated with high-level resistance. Mutational resistance occurs more readily in *P. aeruginosa* than in Enterobacteriaceae because of its poorer inherent susceptibility to these agents by many of the mechanisms discussed previously (i.e., efflux, permeability).

β -Lactams

Although less well described in *P. aeruginosa* than in other pathogens, mutations in penicillin binding proteins (PBPs) may occur and contribute to decreased β -lactam susceptibility. Alterations in PBP5 are believed to contribute to the intrinsic resistance of *P. aeruginosa*. Alterations in PBP4, resulting in lower affinity, may also contribute to imipenem resistance. Penicillin binding protein mutations may also occur related to other resistance mechanisms, such as with the *dacB* mutation, which encodes PBP4 and induces overexpression of AmpC β -lactamase. Alterations in PBP3 have also been described in *P. aeruginosa*.

CLINICAL PRESENTATION AND RISK FACTORS

P. aeruginosa infections can involve any part of the body, including the lungs, urinary tract, skin/skin structure, GI tract, bloodstream, heart valves, and CNS, and are most common in patients with compromised host defenses. *P. aeruginosa* predominantly causes infections in the health care setting (e.g., hospital-acquired bacterial pneumonia [HABP] and

ventilator-associated bacterial pneumonia [VABP]) and infrequently causes community-acquired infections. Patients colonized with *P. aeruginosa* in the lungs and GI tract, especially those with positive pressure ventilation and endotracheal tubes, are at greatest risk of *P. aeruginosa*-associated pneumonia. Pneumonia secondary to *P. aeruginosa* can also result from hematogenous spread to the lungs. Chronic infection of the lower respiratory tract with *P. aeruginosa* is prevalent among patients with cystic fibrosis. Although infrequent, *P. aeruginosa* can infect the GI tract, and the disease spectrum can range from very mild symptoms to severe necrotizing enterocolitis.

P. aeruginosa is a common cause of UTI in hospitalized patients. These infections are often associated with catheterization, instrumentation, and surgery. *P. aeruginosa* is also a major cause of bloodstream infections in hospitalized patients. Bloodstream infections may be acquired through medical devices, whereas colonization of the GI tract may be a source of bacteremia in patients who are immunosuppressed. *P. aeruginosa* may infect native/prosthetic heart valves in individuals who recreation-ally use intravenous drugs; it also can cause meningitis and brain abscesses. Most infections follow an extension from a contiguous parameningeal structure, such as an ear or a mastoid; from para-nasal sinus surgery; or from diagnostic procedures. In some patients, CNS involvement is the result of hematogenous spread of the organism from infective endocarditis, pneumonia, or UTI.

P. aeruginosa can also cause skin and bone and joint infections. The most common sites of involvement are the vertebral column, the pelvis, and the sternoclavicular joint. Infection may be spread hematogenously or contiguously because of penetrating trauma, surgery, or overlying soft tissue infections. Patients at risk of pseudomonal bone and joint infections include those with puncture wounds to the foot, peripheral vascular disease, intravenous drug abuse, and diabetes mellitus.

Skin infections related to the use of hot tubs, whirlpools, swimming pools, and other types of baths are common sources of community-acquired *P. aeruginosa* dermatologic infections. “Hot tub rash” is almost exclusively associated with dermatitis or folliculitis caused by *P. aeruginosa*. Patients can present with pruritic follicular, maculopapular, vesicular, or pustular lesions on any part of the body that was immersed in water. Another type of *P. aeruginosa* skin infection is green nail syndrome. This paronychia infection can develop in individuals whose hands are often submerged in water. Secondary wound infections occur in patients with decubiti, eczema, and tinea pedis. Pseudomonal bacteremia can produce distinctive skin lesions known as ecthyma gangrenosum.

P. aeruginosa infections can also involve the eyes and ears. Otitis externa (swimmer’s ear) is often caused by *P. aeruginosa*. Malignant otitis externa can occur and is a manifestation of invasive infection predominantly in patients with uncontrolled diabetes. Extension of the infection to the

temporal bone can result in osteomyelitis, and further extension can create cranial nerve palsies and possibly CNS infection. *P. aeruginosa* is a common cause of [bacterial keratitis](#), scleral abscess, and [endophthalmitis](#) in adults and ophthalmia neonatorum in children. Predisposing conditions for corneal involvement are trauma, prolonged contact lens use, predisposing ocular conditions, exposure to an ICU environment, and AIDS.

Incidence and Prevalence of *P. aeruginosa*

P. aeruginosa is a common nosocomial pathogen and one of the top three causes of opportunistic human infections. About 8% of all health care-associated infections reported to the CDC’s National Healthcare Safety Network are caused by *P. aeruginosa*, resulting in around 51,000 infections in hospitalized patients each year in the United States. *P. aeruginosa* ranks sixth among all pathogens and third among gram-negative pathogens reported to the national nosocomial infections surveillance system. In hospitalized patients, *P. aeruginosa* is implicated in more than 16% of all ventilator-associated pneumonia (VAP) (second most common pathogen), more than 10% of all catheter-associated UTIs (third most common pathogen) and bloodstream infections (10th) and surgical site infections (fifth). Among patients with surgical site infections, the most common types of surgery associated with *P. aeruginosa* infections are breast (10.9%), cardiac (8.1%), vascular (7.3%), and neck (6.1%) (Weiner 2016; CDC 2013). Knowledge of the incidence and prevalence of *P. aeruginosa* in the community setting is incomplete. Because *P. aeruginosa* is not a reportable disease, its prevalence remains largely unknown in most communities.

Prevalence of Resistance in *P. aeruginosa*

The CDC estimates that 13% of *P. aeruginosa* infections (over 6700) are MDR (CDC 2013). In the National Healthcare Safety Network in the most recent year of reporting, MDR rates for patients with VAP, central line-associated bloodstream infections, catheter-associated UTIs, and surgical site infections were 19.9%, 17.9%, 17.7%, and 4.3%, respectively (2012–2014) (Weiner 2016). Among patients with VAP, central line-associated bloodstream infections, and catheter-associated UTIs, resistance for each antibiotic class varied at 15%–33%. Resistance rates were highest for the fluoroquinolones and carbapenems and lowest for the aminoglycosides and piperacillin/tazobactam (Weiner 2016).

Data analyses on *P. aeruginosa* resistance rates are also available from the SENTRY Antimicrobial Surveillance Program (Shortridge 2019). During 1997–2016, 52,022 clinically significant, consecutive *P. aeruginosa* isolates were collected from over 200 medical centers representing the Asia-Pacific region, Europe, Latin America, and North America. Isolates with the MDR phenotype were most often isolated in Latin America (41.1%), followed by Europe (28.4%), North America (18.9%), and Asia-Pacific (18.8%) (Table 3).

Table 3. *P. aeruginosa* Isolates from SENTRY Program (1997–2016) Stratified by Infection Type and Percentage of Isolates with Resistance Phenotypes

Resistant Phenotype ^a	Bloodstream Infection (n = 14 539)	Pneumonia in Hospitalized Patients (n = 23 227)	Skin and Skin Structure Infection (n = 9952)	Intra-abdominal Infection (n = 648)	Urinary Tract Infection (n = 2838)	Other Infection (n = 818)	Total (n = 52 022)
Multidrug resistant	23.7%	27.7%	21.7%	19.3%	23.0%	19.1%	24.9%
Extensively drug resistant	17.4%	19.0%	15.8%	12.7%	16.5%	12.3%	17.6%
Pan drug resistant	0.1%	0.1%	0.0%	0.5%	0.1%	0.0%	0.1%
Ceftazidime nonsusceptible	22.0%	24.7%	20.1%	19.1%	18.4%	17.2%	22.5%
Meropenem nonsusceptible	22.3%	27.1%	20.6%	21.9%	19.2%	18.1%	23.9%

^aCriteria as published by European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018.

Reprinted with permission from: Shortridge D, Gales AC, Streit JM, et al. Geographic and temporal patterns of antimicrobial resistance in *Pseudomonas aeruginosa* over 20 years from the SENTRY Antimicrobial Surveillance Program, 1997-2016. Open Forum Infect Dis 2019;6(suppl 1):S63-S68.

Risk Factors for Antibiotic-Resistant *P. aeruginosa* Infections

Risk factors for acquiring an antibiotic-resistant *P. aeruginosa* infection are consistent with other those for antibiotic-resistant gram-negative pathogens. Compromised host defenses are a hallmark characteristic of patients with antibiotic-resistant *P. aeruginosa*. In most cases, a combination of risk factors is present, simultaneously augmenting a patient's risk of having an antibiotic-resistant versus a susceptible *P. aeruginosa* infection. Prior antibiotic exposure is an important and well-characterized risk factor. Prior receipt of carbapenems and fluoroquinolones is also a commonly reported risk factor for antibiotic-resistant *P. aeruginosa*. Data analyses also suggest that the cumulative number of prior antibiotics received augments a patient's risk of acquiring an infection caused by an antibiotic-resistant *P. aeruginosa*. Constant and cumulative exposure to antibiotics disturbs the natural bacterial flora, especially in the GI tract, and predisposes patients to colonization by resistant strains. Extensive time in health care facilities (e.g., long-term care stay, prolonged hospitalizations) also predisposes patients to colonization and infection, particularly in areas with endemic rates of antibiotic-resistant *P. aeruginosa*. Residence in the ICU and prolonged courses of mechanical ventilation further contribute to risk. Several studies have tried to characterize the most clinically relevant risk factors for infections caused by resistant *P. aeruginosa*. A systematic review on studies that examined risk factors for infections caused by MDR *P. aeruginosa* has been published (Raman 2018). Overall, the most significant predictors of resistant *P. aeruginosa* infection were prior antibiotic use and

prior hospitalization, including in the ICU. Compared with non-MDR strains, significant risk factors for MDR *P. aeruginosa* infection were prior ICU stay or prior use of fluoroquinolones.

ANTIBIOTIC TREATMENT OF PATIENTS WITH *P. AERUGINOSA* INFECTIONS

Antibiotics are the cornerstone of therapy for patients with serious infections caused by *P. aeruginosa*. Treatment goals for patients with *P. aeruginosa* infections are to cure the patient, minimize the occurrence of the unintended consequences associated with antibiotic use, and prevent transmission. Cure implies both the eradication of *P. aeruginosa* from the infection site(s) and the complete resolution of the signs and symptoms associated with the infection. Unintended consequences associated with antibiotic use include the development of recurrent *P. aeruginosa* infections, subsequent resistant *P. aeruginosa* infections, superinfections, development of *Clostridioides difficile* infection (CDI), and occurrence of adverse events.

P. aeruginosa should be considered a potential pathogen in all "at-risk" patient populations presenting with a clinical syndrome consistent with *P. aeruginosa*. Initial treatment of patients with suspected or documented *P. aeruginosa* infections is largely empiric, given that definitive culture and antibiotic susceptibility results are typically not available until several days after infection onset. Gram stain results and rapid diagnostics can facilitate early identification of patients with *P. aeruginosa* infections. Prompt initiation of

antimicrobial therapy with in vitro activity at infection onset is critically important. Failure to administer early, appropriate therapy substantially increases the morbidity and mortality associated with *P. aeruginosa* infections by 2- to 3-fold. To minimize delays in appropriate therapy among patients with *P. aeruginosa* infections, clinicians need to assess the patient's risk of an MDR, XDR, or PDR *P. aeruginosa* infection when selecting empiric therapy. One of the most predictive risk factors for a highly resistant *P. aeruginosa* infection is prior isolation of a highly resistant *P. aeruginosa*. Prior receipt of several antibiotics, extensive time in health care facilitates, presence of invasive devices, and altered immune function also increase the likelihood of a highly resistant *P. aeruginosa* infection, especially when several risk factors are present in the same patient. Source control is also critically important for achieving a cure. All infected catheters and prosthetic devices should be removed, abscesses should be drained, and obstructions should be relieved, whenever possible.

Selection of agent(s), dose, infusion duration, dosing frequency, and therapy duration for a patient with a suspected or documented *P. aeruginosa* infection greatly depends on the infection site(s), severity of infection, patient-related factors, and likelihood of a resistant *P. aeruginosa* infection. Higher/maximum daily doses are typically required for presumptive or known *P. aeruginosa* infections to achieve the

critical pharmacokinetic/pharmacodynamic (PK/PD) dosing targets associated with maximal response and to prevent the emergence of resistance during therapy. Intensive dosing is particularly important for infection sites where antibiotic concentrations are less than what is in the bloodstream, such as patients with lower respiratory tract infections and CNS infections.

Empiric Therapy for Patients with Suspected or Documented *P. aeruginosa* Infections

Type 2 carbapenems (meropenem, imipenem, or doripenem), piperacillin/tazobactam, or antipseudomonal cephalosporins are recommended as first-line empiric treatment for patients with suspected or documented *P. aeruginosa* infections (Figure 2). Selection of specific antipseudomonal β -lactams for empiric use depends on factors such as the infection site, local resistance rates of *P. aeruginosa*, prior culture data, patient's history of allergies, patient's antibiotic history, and local hospital formulary. The preferred β -lactam for serious *P. aeruginosa* has not been established. Currently, no significant differences have been reported in clinical response or mortality rates between carbapenems, piperacillin/tazobactam, and antipseudomonal cephalosporins except for doripenem, which was associated with worse outcomes than imipenem among patients with VAP (Kollef 2012). One of the meta-analyses conducted as part of the

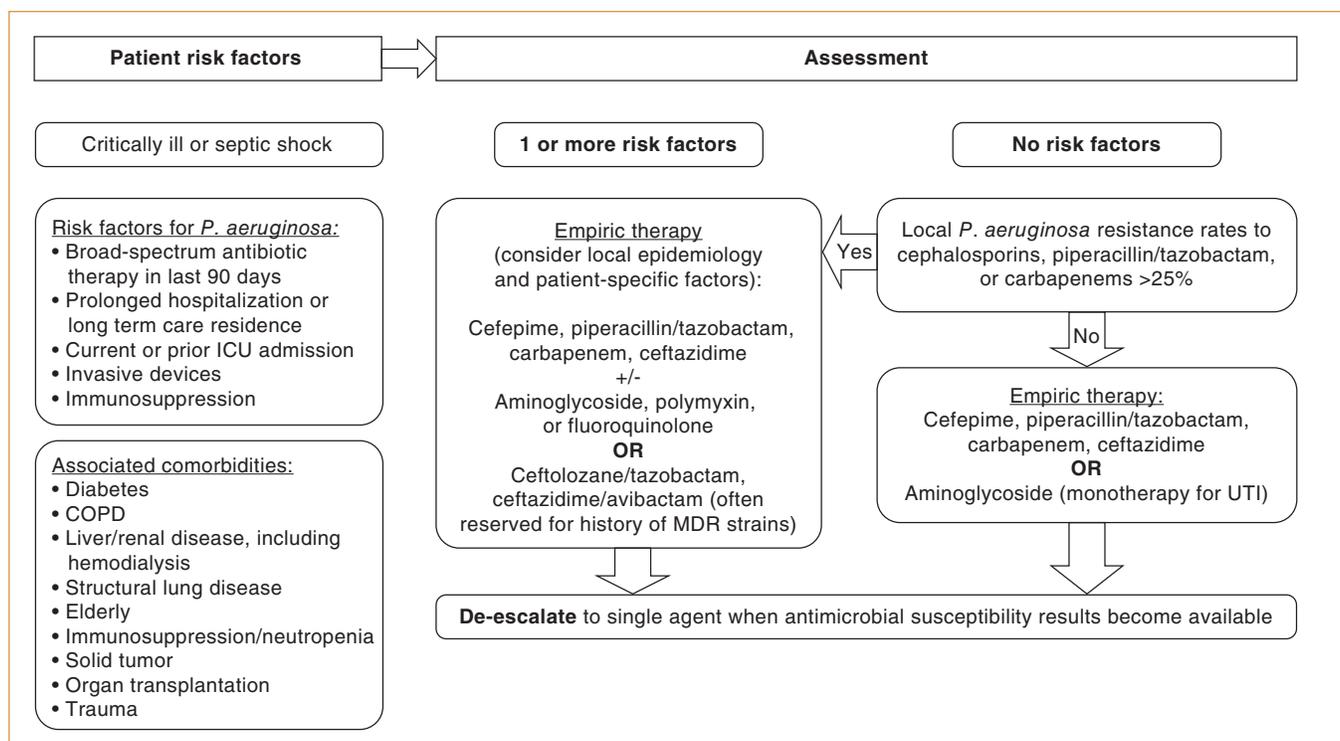


Figure 2. Clinical approach to the patient with *P. aeruginosa* infection.

Information from: Mensa J, Barberan J, Soriano A, et al. Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: guidelines by the Spanish Society of Chemotherapy. Rev Esp Quimioter 2018;31:78-100.

2016 hospital-acquired pneumonia (HAP)/VAP clinical practice guidelines showed that patients with HAP/VAP caused by *P. aeruginosa* and treated with carbapenems alone or in combination with an aminoglycoside had less treatment success, lower eradication rates, and a higher incidence of antibiotic-resistant rates than patients who received an alternative antibiotic (fluoroquinolone or a β -lactam) (Kalil 2016). These findings were mainly a function of studies that included imipenem as the carbapenem comparator, given that no appreciable differences in outcomes occurred in analyses that were restricted to meropenem. A meta-analysis that included five randomized nosocomial pneumonia trials similarly found that patients with *P. aeruginosa* infections treated with imipenem were more likely to have clinical failure and to develop resistance than those treated with piperacillin/tazobactam or cefepime (O'Donnell 2018). Carbapenems, compared with other antipseudomonal β -lactams, have a greater propensity to select for CDI and antibiotic-resistant organisms at both the individual patient level and the hospital level. Conversely, piperacillin/tazobactam is associated with a lower risk of acquiring CDI and a higher loss of CDI colonization than the antipseudomonal cephalosporins (Dubberke 2015). Distinctions in the ability of piperacillin/tazobactam and antipseudomonal cephalosporins to select for other antibiotic-resistant bacteria have not been established.

Other agents with activity against *P. aeruginosa* can be considered empiric treatment in select situations. Aztreonam is a suitable empiric option if a patient has a severe penicillin allergy. However, aztreonam should be avoided in patients with a severe allergy to ceftazidime because of similar side chains. When possible, aztreonam should be reserved because it has lower susceptibility rates than other β -lactams against *P. aeruginosa*. It may be still possible to use a cephalosporin or carbapenem in a penicillin-allergic patient. Cross-reactivity between piperacillin/tazobactam, third/fourth-generation cephalosporins, and type 2 carbapenems is negligible, likely because of their dissimilar side chains. Empiric use of the recently approved β -lactam/ β -lactamase inhibitors with activity against *P. aeruginosa* should be considered in patients with suspected or documented XDR or PDR *P. aeruginosa* infections, or in those with a history of a *P. aeruginosa* infection that was resistant to type 2 carbapenems, piperacillin/tazobactam, and antipseudomonal cephalosporins (see section that follows titled "Strategies for Empiric Treatment of Patients with Suspected or Documented Highly Resistant *P. aeruginosa* Infections").

Aminoglycosides with activity against *P. aeruginosa* include gentamicin, tobramycin, amikacin, and the recently approved plazomicin. Tobramycin is the aminoglycoside with the highest intrinsic activity against *P. aeruginosa*. Tobramycin is twice as active as gentamicin and 3–4 times more active than amikacin. However, susceptibility rates are highest with amikacin because it is hydrolyzed by fewer enzymes. The in vitro

activity of plazomicin against *P. aeruginosa* is similar that of the other aminoglycosides, limiting its potential for use in *P. aeruginosa* infections that are resistant to other aminoglycosides. Despite their in vitro activity, aminoglycosides are not recommended as monotherapy for patients with *P. aeruginosa* infections, except for UTIs and UTI-related bloodstream infections. Use of aminoglycosides should be discouraged in patients with renal insufficiency, patients at risk of aminoglycoside-associated vestibular and auditory ototoxicity, and in those hospitalized in institutions with a high percentage of *P. aeruginosa* isolates resistant to aminoglycosides.

Levofloxacin or ciprofloxacin, are also alternatives to antipseudomonal β -lactams for the empiric treatment of suspected or documented *P. aeruginosa* infections, especially when oral therapy is needed. However, increasing resistance rates and growing safety concerns limit their use as empiric agents. Delafloxacin also exhibits anti-Pseudomonal activity, though clinical data with this agent are lacking compared to other fluoroquinolones.

Combination Therapy

One of the most controversial issues in treating patients with serious infections caused by *P. aeruginosa* involves the use of combination therapy. The rationale for combination therapy is to broaden empiric coverage and increase the likelihood of timely appropriate therapy, achieve synergistic bacterial killing, prevent emergence of resistance, ensure activity against planktonic and sessile organisms, and inhibit toxin production. Combination therapy is typically reserved for empiric treatment of suspected or documented *P. aeruginosa* infections in patients at an increased risk of death or when there is a high risk of resistance to commonly used antipseudomonal agents. Combination therapy should especially be considered in patients for whom inappropriate antibiotic therapy would likely be associated with substantially increased mortality, such as patients with severe sepsis or septic shock, bacteremia, infective endocarditis, and immunosuppression. In vitro PK/PD infection models and animal studies of *P. aeruginosa* clearly show that combination therapy improves bacterial killing compared with monotherapy and is often required for bacterial sterilization and resistance suppression (Drusano 2018).

No randomized clinical trial has conclusively shown that using two active agents compared with one improves outcomes (e.g., survival or treatment success rates) or lessens the emergence of resistance in patients with serious infections caused by *P. aeruginosa*. No significant differences in the development of antibiotic-resistant strains and superinfections were noted between combination and monotherapy across meta-analyses, though few studies assessed these end points. A significantly higher incidence of adverse events, mainly nephrotoxicity with aminoglycosides, was consistently associated with combination therapy. These study findings should be interpreted with caution. Most of the randomized

clinical trials predate 2000 (and therefore are not necessarily reflective of pathogens encountered in clinical practice today), and few evaluated combinations consisting of newer agents. Disease severity was also generally low. Most studies included diverse groups of patients and infection types (febrile neutropenia was the most common). Caution also needs to be used when examining the results of observational studies that included more critically ill patients, given that such patients are highly vulnerable to prescribing and other selection biases.

The best rationale for using combination therapy is to provide empiric broad-spectrum activity when multidrug resistance is a risk. Combination therapy provides a higher probability that one of the agents will be active against the pathogen infecting the patient. Although the benefits of early administration of microbiologically active agents are clear, outcomes do not appear to be improved with receipt of two active agents compared with one (Pena 2013).

If combination empiric therapy is used, two agents from different classes with in vitro activity against *P. aeruginosa* are recommended. In general, a β -lactam is used in combination with an aminoglycoside or a fluoroquinolone. The 2016 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) HAP/VAP guidelines recommend two antipseudomonal antibiotics for empiric treatment of HAP (non-VAP) in patients with a risk factor for antimicrobial resistance (e.g., intravenous antibiotic use during the prior 90 days) or need for ventilator support because of pneumonia and septic shock. For patients with VAP, the guidelines recommend two antipseudomonal antibiotics for empiric treatment in patients with any of the following: a risk factor for antimicrobial resistance (prior intravenous antibiotic use within 90 days, septic shock at time of VAP, acute respiratory distress syndrome preceding VAP, 5 or more days of hospitalization before VAP occurs, or acute renal replacement therapy before VAP onset), patients in units where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available. For patients without any of these additional risk factors for mortality or resistant organisms, empiric treatment with a single antipseudomonal agent is preferred (Kalil 2016). These guidelines also suggest avoiding aminoglycosides when alternative agents with adequate gram-negative activity are available because of aminoglycosides' poor lung penetration, aminoglycosides' increased risk of nephrotoxicity and ototoxicity, and meta-analysis data suggesting they are associated with poorer clinical response rates than other classes. Intravenous polymyxins (colistin or polymyxin B) and intravenous fosfomycin can also be used in combination for empiric treatment of suspected or documented *P. aeruginosa* infections; however, these agents should be reserved for XDR strains and avoided if alternative agents with adequate gram-negative activity are available. In the absence of other options,

aztreonam can also be used as an adjunctive agent with another β -lactam-based agent because it has different targets within the bacterial cell wall.

Strategies for Empiric Treatment of Patients with Suspected or Documented Highly Resistant *P. aeruginosa* Infections

Strategies for treating patients with highly resistant *P. aeruginosa* infections include using alternative dosing strategies, combination drug therapy, and, for HAP/VAP, inhaled antibiotics. However, clinical data analyses supporting these strategies are limited. For infections caused by *P. aeruginosa* resistant to other first-line β -lactams, ceftazidime/avibactam and ceftolozane/tazobactam should be considered. Ceftazidime/avibactam and ceftolozane/tazobactam are two new cephalosporin/ β -lactamase inhibitor combinations. Ceftazidime is a third-generation antipseudomonal cephalosporin with a well-established efficacy and safety profile, and avibactam is a diazabicyclooctane β -lactamase inhibitor. Avibactam has no intrinsic activity alone but expands the spectrum of activity of ceftazidime against *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and certain *P. aeruginosa* strains by inhibiting a broad range of serine β -lactamases, including Ambler class A (ESBL and KPC), class C (AmpC), and some class D (such as OXA-48) enzymes. However, avibactam alone does not appreciably inhibit MBLs such as NDM-1 and VIM-1. Ceftazidime/avibactam is approved for adults with complicated UTIs (including pyelonephritis), complicated intra-abdominal infections (cIAls) (used in combination with metronidazole), HABP/VABP, and other infections caused by aerobic gram-negative organisms in patients with limited treatment options. Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin and a potent PBP3 inhibitor with a higher affinity for PBP1b than other β -lactam agents. Ceftolozane has less affinity for hydrolysis by AmpC cephalosporinases, is a weak substrate for drug efflux systems, and is not affected by OprD loss. Ceftolozane/tazobactam is approved for adults with complicated UTIs (including pyelonephritis), cIAls (used in combination with metronidazole), and HABP/VABP.

Many *P. aeruginosa* isolates resistant by in vitro testing to first-line β -lactams retain susceptibility to ceftazidime/avibactam and/or ceftolozane/tazobactam. Large surveillance studies suggest that ceftazidime/avibactam and ceftolozane/tazobactam retain activity against over 85% of MDR *P. aeruginosa* isolates (Nichols 2016; Torrens 2016). Limited in vitro data analyses suggest that ceftolozane/tazobactam has more microbiologic activity against XDR *P. aeruginosa* isolates than ceftazidime/avibactam. Susceptibility profiles vary between ceftazidime/avibactam and ceftolozane/tazobactam against XDR *P. aeruginosa* isolates, and some MDR isolates that are resistant to ceftazidime/avibactam may be susceptible to ceftolozane/tazobactam and vice versa (Grupper 2017; Humphries 2017). The varying susceptibilities are a function of the particular resistance

mechanisms present in the tested *P. aeruginosa* isolates. These findings highlight the importance of using local susceptibility data to guide decision-making, given that susceptibility rates can vary greatly. Clinicians should treat each patient on an individual basis and conduct susceptibility testing with both ceftazidime/avibactam and ceftolozane/tazobactam when determining optimal treatment for a patient with a suspected or documented *P. aeruginosa* infection that is resistant to other first-line β -lactams. Clinical experience with these agents against MDR, PDR, and XDR *P. aeruginosa* is limited, and no comparator studies have been published to date. Most real-world, non-comparator data against XDR *P. aeruginosa* are with ceftolozane/tazobactam, and results have been mixed; emergence of resistance during therapy to these agents has been reported (Santevecchi 2018; Caston 2017; Haidar 2017; Munita 2017; Xipell 2017).

Meropenem/vaborbactam and imipenem/relebactam are two additional novel β -lactamase inhibitor combinations. Meropenem/vaborbactam was recently approved, but adding vaborbactam does not appreciably increase the activity of meropenem against *P. aeruginosa*. In addition, there is currently no breakpoint for meropenem/vaborbactam against *P. aeruginosa*. Imipenem/relebactam is another treatment option for infections caused by MDR *P. aeruginosa*. Unlike vaborbactam's limited effect of meropenem susceptibility for *P. aeruginosa*, relebactam appears to substantially potentiate imipenem activity against imipenem-resistant isolates. Neither imipenem nor relebactam appear to be substrates for the efflux pumps present in *P. aeruginosa*, and relebactam preserves imipenem activity in the setting of AmpC.

Treatment of infections caused by MBL-producing *P. aeruginosa* is an emerging problem. The aforementioned β -lactam/ β -lactamase inhibitor combinations do not have in vitro activity against these strains, given that no clinically available β -lactamase inhibitors effectively inhibit these enzymes. Adding aztreonam to avibactam has activity in MBL-producing isolates, given that aztreonam is not hydrolyzed by MBLs and avibactam provides protection against Ambler class A, C, and some D enzymes. Although this combination has been established as an option for treating NDM-producing Enterobacteriaceae, few data are available for *P. aeruginosa*. Dual β -lactam therapy may also provide synergy for some MDR or XDR *P. aeruginosa* isolates. Most recently, the combination of ceftolozane/tazobactam and meropenem has shown significant synergy against MDR *P. aeruginosa* (Monogue 2018; Montero 2018). In vitro synergy against *P. aeruginosa* isolates has also been described for other combinations of β -lactams, such as ceftazidime or cefepime plus aztreonam (Rahme 2014).

Polymyxins, aminoglycosides, intravenous fosfomycin (currently under FDA review), and cefiderocol (currently under FDA review) are additional options for patients with XDR *P. aeruginosa* infections and are the only therapeutic options for

some strains of MDR *P. aeruginosa*. Clinical data with these agents against MDR, XDR, and PDR *P. aeruginosa* are limited, and no comparator studies have been published to date. Combination therapy for patients with XDR or PDR *P. aeruginosa* often includes a polymyxin with at least two agents that, individually, have little or no activity against the isolate. Polymyxins are well known to cause nephrotoxicity and neurotoxicity and should be avoided if alternative agents with in vitro activity are available. Polymyxins should also not be used as monotherapy, given the frequent development of resistance and regrowth of bacteria observed by 24 hours in several in vitro studies. Clinically, monotherapy has been associated with increased mortality; however, these data are largely observational and were not limited to patients with *P. aeruginosa* infections. Polymyxins also may be problematic for the treatment of pneumonia. In preclinical models, bactericidal activity (and, in some cases, even bacteriostatic activity) was not achievable even at maximal tolerated doses. Although the exact mechanism for this is unknown, it may be related to poor penetration of these agents into the epithelial lining fluid, as well as the binding of polymyxin molecules by mucin that has been observed ex vivo (Boisson 2014). For colistin, conversion from colistin methanesulfonate to the active drug may be even further limited in the epithelial lining fluid. This has prompted the addition of inhaled colistin, in combination with intravenous colistin, for patients with VAP caused by MDR pathogens.

Amikacin and tobramycin often retain activity against MDR *P. aeruginosa* strains and are treatment options, though these drugs should be used in combination with other agents. For patients with VABP caused by *P. aeruginosa* that is susceptible to only aminoglycosides or polymyxins, the guidelines suggest that both inhaled and systemic antibiotics, rather than systemic antibiotics alone, be used. Intravenous fosfomycin may also play a role in the treatment of highly resistant *P. aeruginosa*. Fosfomycin monotherapy, however, should be avoided, given the frequency of heteroresistance in *P. aeruginosa* and the propensity for developing resistance on therapy (Mensa 2018). Combination therapy may be appropriate for some strains, and synergy has been shown for combinations of fosfomycin and antipseudomonal β -lactams (e.g., meropenem, ceftolozane/tazobactam, and ceftazidime/avibactam). Lastly, cefiderocol, a first-in-class siderophore cephalosporin, may be an additional option against MDR *P. aeruginosa* if approved by the FDA. As a siderophore cephalosporin, cefiderocol binds to ferric iron and is actively transported across the outer membrane and into the periplasmic space of *P. aeruginosa*. This results in high concentrations of cefiderocol in the periplasmic space, where it can then bind to PBPs and inhibit cell wall synthesis. It is also stable to both serine- and MBL-carbapenemases, making it a potential option for XDR *P. aeruginosa* possessing those β -lactamases.

Directed Therapy

Once the results of susceptibility tests are available, definitive therapy can be tailored accordingly. For most infections, definitive therapy with a single active agent is appropriate, given that no convincing clinical data analyses show a mortality benefit to combination therapy. The rare exceptions when continuing the combination regimen may be warranted include neutropenia, bacteremia, and infective endocarditis. Initiating a second antipseudomonal agent may be reasonable in infections that are slow, or that fail, to respond to a single active agent, though few data support this practice. For patients with HAP/VAP who remain in septic shock or at a high risk of death when the results of antibiotic susceptibility testing are known, the ATS/IDSA HAP/VAP guidelines recommend combination therapy using two antibiotics to which the isolate is susceptible, rather than monotherapy (Kalil 2016). Continuation of combination therapy in a patient with an MDR *P. aeruginosa* infection is also reasonable, especially if the patient had delays in receiving appropriate therapy.

Dosing Considerations

β-Lactams

The conventional intermittent β -lactam dosing schemes often used in practice have suboptimal PD profiles against *P. aeruginosa*. Extending the duration of infusion (i.e., increasing the infusion duration to several hours instead of 30–60 minutes) is one way to maximize the PK/PD profiles of β -lactams against *P. aeruginosa*, especially against strains with elevated MIC values. Administering a dose of a β -lactam agent as an infusion longer than the conventional 30- to 60-minute infusion duration has two main effects. First, it produces a lower peak concentration of the drug. Because the bacterial kill rate for these agents is not concentration-dependent, this does not present a major disadvantage. Second, the drug concentrations remain in excess of the MIC for a longer period. Because this is what drives the antibacterial effect for β -lactams, this consequence will yield a more favorable probability of achieving an adequate $fT > MIC$.

Extended infusions may either be prolonged (e.g., over 3–4 hours) or administered as a continuous infusion. Recent meta-analyses show significant improvements in all-cause mortality with extended infusion or continuous infusion compared with intermittent infusion (Rhodes 2018; Vardakas 2018; Falagas 2013). Although the continuous infusion of β -lactams is often perceived to be better than extended infusion, the two infusion methodologies yield almost identical PK/PD profiles. Of note, continuous infusion confers an “all-or-nothing” probability of target result (0% or 100%) at a given MIC value. Because it is only required to be above the MIC for a fraction of the dosing interval to maximize the PK/PD profile of β -lactams, the higher initial concentrations associated with extended infusion compared with continuous infusion (without a loading dose) early in treatment have a better probability of achieving an adequate $fT > MIC$ for infections with higher MICs (Natesan 2017).

Concentration-Dependent Antibiotics

Many agents with clinically relevant activity against *P. aeruginosa* fall into this category, including fluoroquinolones, polymyxins, and fosfomycin. Recent changes in the Clinical & Laboratory Standards Institute (CLSI)-recommended breakpoints for fluoroquinolones reflect the limitations of exposures achieved with maximal recommended dosing regimens for ciprofloxacin (e.g., 400 mg intravenously every 8 hours) and levofloxacin (750 mg intravenously every 24 hours). Probability of target attainment remains low for pathogens with MICs at the new *P. aeruginosa* breakpoints for ciprofloxacin and levofloxacin (0.5 and 1 mg/L, respectively), though these doses are likely adequate for lower MICs (Cojutti 2017; Burgess 2007).

Polymyxins also follow AUC/MIC pharmacodynamics; however, dose escalation is significantly limited by the high nephrotoxicity rates associated with these agents. At maximal recommended exposures (AUC_{0-24hr} = around 50 mg*hour/L), the probability of target attainment is acceptable for organisms with MICs of up to 2 mg/L, the current CLSI and EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints. Of note, optimal exposure targets for pneumonia have not been defined, with preclinical models unable to achieve bacterial killing at maximal tolerable doses. Given the propensity for development of resistance when used as monotherapy, combination therapy is recommended when using polymyxins. It is unknown how adding other agents affects the pharmacodynamic target for these drugs, though the current guidelines recommend static doses regardless of organism MIC or use of other agents.

Intravenous fosfomycin is currently under FDA review for use in adult patients with complicated UTIs in the United States, though it has been clinically available in Europe and Australia for some time. Fosfomycin has some in vitro activity against *P. aeruginosa*; however, formal breakpoints have not been established. Bactericidal activity appears to be most closely linked to the $fAUC/MIC$ ratio, though development of resistance may be linked to a time over threshold index. According to preclinical data using fosfomycin against *P. aeruginosa*, combination therapy may be necessary to prevent the emergence of resistance, despite the use of high simulated doses in these models.

Although the prevailing wisdom has historically been that the fC_{max}/MIC ratio is the critical exposure target for aminoglycosides, an equivalent body of evidence suggests that the $fAUC/MIC$ ratio is the PK/PD driver for bacterial killing and efficacy. Preclinical dose-fractionation studies of animals and in vitro PK/PD infection models have shown no differences in efficacy between once-daily, multiple-daily, and continuous infusion aminoglycoside dosing regimens, indicating that the PK/PD driver for efficacy is better linked to the $fAUC/MIC$ than to the fC_{max}/MIC . The available literature suggests that an $fAUC/MIC$ ratio of 30–50 for aminoglycoside therapy provides optimal outcomes when targeting noncritically ill, immunocompetent patients with low bacterial burden gram-negative infections (e.g., UTIs) or in patients receiving

additional gram-negative therapy with good source control. However, an *fAUC/MIC* ratio target of 80–100 or greater may be more prudent when treating patients with aminoglycoside monotherapy or in critically ill patients with high bacterial burden infections, such as nosocomial pneumonia. Higher doses or combination therapy is needed for infections caused by organisms with reduced susceptibility, which is common in *P. aeruginosa*. Minimizing toxicity is another critical component of optimizing aminoglycoside therapy. Typically, recommendations for minimizing the risk of nephrotoxicity rely on extended interval dosing and attaining low trough concentrations (i.e., 1 mg/L or less for gentamicin and tobramycin; 4–5 mg/L or less for amikacin) before re-dosing.

Inhaled Antibiotics

The ATS/IDSA guidelines for treating VAP recommend inhaled antibiotics, in combination with systemic agents, for infections caused by organisms only susceptible to aminoglycosides or polymyxins. Because both inhaled antibiotics and systemic agents achieve relatively low (and potentially subtherapeutic) exposures in the epithelial lining fluid, direct administration of antibiotic to the infection site improves target attainment. A meta-analysis identified a significantly improved clinical cure rate when inhaled antibiotics were added for treating MDR pathogens, though no differences in mortality or adverse effects were identified (Kalil 2016). A recent randomized trial comparing inhaled amikacin/fosfomycin with placebo identified an improvement in microbiologic eradication, though no difference in clinical outcomes (Kollef 2017).

Patients with Cystic Fibrosis

Cystic fibrosis is associated with pulmonary exacerbations that are often managed with antibiotics targeting pathogens such as *Pseudomonas*. For intermittent infections, the primary goal of antibiotic treatment during an exacerbation is to eradicate the infection to prevent colonization/chronic infection. This is often accomplished with inhaled (e.g., tobramycin, colistin) and systemic antibiotic therapy. Progression to chronic infection is associated with increased patient morbidity and mortality. For chronic infections, prior microbiologic data can help drive agent selection early in exacerbation treatment. For many patients, pulmonary exacerbations are believed to be more likely because of redistribution of existing *P. aeruginosa* or other bacterial colonies, rather than because of infection with new isolates. Therefore, given that these bacteria are most often present at baseline, the treatment goal is not necessarily to sterilize the lungs, but to restore the balance in favor of the immune response. In these patients, assessing historic clinical response to therapy, rather than microbiologic response, appears most helpful when selecting treatment for subsequent exacerbations.

Therapy Duration

The optimal therapy duration for serious infections caused by *P. aeruginosa* is highly debated. A randomized controlled trial of patients with VAP identified an increased risk of

reinfection in patients with VAP infected with *P. aeruginosa* associated with short (8 days) therapy compared with longer therapy (15 days) (Chastre 2003). However, a meta-analysis conducted as part of the new HAP/VAP guidelines identified no increased risk of all-cause mortality or pneumonia recurrence in patients with *P. aeruginosa* between short (7–8 days) and longer (more than 14 days) treatment courses (Kalil 2016). Recent data analyses also have suggested that 7-day treatment courses have clinical outcomes similar to longer (e.g., at least 14 days) treatment courses for uncomplicated bacteremia (Sousa 2019; Yahav 2019; Chotiprasitsakul 2018). These data are primarily from patients with Enterobacteriaceae bacteremia; however, no signal for an increased risk of failure with shorter courses in patients infected with *P. aeruginosa* has been identified. Suggested treatment for complicated UTIs caused by MDR *P. aeruginosa* is 7–14 days.

ROLE OF ANTIMICROBIAL STEWARDSHIP AND THE PHARMACIST

Antimicrobial Stewardship Programs

Antimicrobial stewardship programs promote appropriate antibiotic use using a range of methods, including prescriptive audit and feedback, prior authorization, and implementation of institutional clinical pathways. Many efforts are aimed at optimizing antimicrobial therapy by ensuring early, appropriate broad-spectrum empiric therapy in patients at risk of *P. aeruginosa* infections and minimizing use of broad-spectrum agents (often with antipseudomonal activity) in patients without associated risk factors for resistant gram-negative infections.

Antimicrobial stewardship programs minimize overall antibiotic use to reduce the spread of resistant pathogens, including *P. aeruginosa*, secondary to antibiotic selective pressures. Initiatives aimed at reducing antibiotic use have been shown to reduce resistance, especially in institutions with endemic rates of resistance. One non-U.S. program assessed the incidence rates of XDR and MDR *Pseudomonas* among 2241 isolates in 2012–2017 after structured efforts to decrease antibiotic use and increase use of alcohol-based hand sanitizer. The number of defined daily doses of antimicrobials significantly decreased over the study period, and the use of hand sanitizer increased significantly. The incidence of MDR and XDR *P. aeruginosa* isolates showed a sustained decrease from 2013 to 2017 (from 22% to 15% and from 4% to 1%, respectively) (Liu 2018).

Antimicrobial stewardship programs also may examine how manipulating the use of specific agents affects *P. aeruginosa* susceptibility rates. Several studies have looked specifically at carbapenem and fluoroquinolone use, given that these classes confer a greater risk of resistant *P. aeruginosa*. For example, studies have examined whether ertapenem use affects antipseudomonal carbapenem susceptibilities. Although findings vary, one review of 10 clinical studies suggested that ertapenem use did not improve *P. aeruginosa* susceptibility rates to antipseudomonal carbapenems (Nicolau 2012). Therefore,

stewardship-based efforts to promote the use of ertapenem over meropenem for non-pseudomonal infections may not preserve class susceptibility. Other studies have focused on fluoroquinolone use and whether use of specific fluoroquinolones may affect susceptibility trends. One retrospective study at a medical center in Taiwan found, unsurprisingly, that increased fluoroquinolone (i.e., ciprofloxacin, levofloxacin) use was associated with decreased fluoroquinolone susceptibility at the institutional level. However, when evaluating each drug independently, levofloxacin (both parenterally and orally) was associated with increased fluoroquinolone resistance rates among *P. aeruginosa*, whereas ciprofloxacin was not (Lee 2010).

Role of the Pharmacist

Pharmacists can play a substantial role in treating patients with *P. aeruginosa* infections. Having knowledge of patient risk factors for *Pseudomonas* infection and understanding PK/PD principles, resistance mechanisms, dosing strategies, and clinical outcomes data place pharmacists in a unique role to help select optimal therapy. To minimize the receipt of inappropriate therapy, pharmacists need to assess a patient's risk of having an MDR, XDR, or PDR *P. aeruginosa* infection when making empiric treatment recommendations. Pharmacists also need to consider whether combination empiric therapy is needed, especially among patients at an increased risk of death or when patients have a high risk of resistance to commonly used antipseudomonal agents. Combination therapy should especially be considered in patients for whom inappropriate antibiotic therapy would likely be associated with substantially increased mortality. This includes patients with severe sepsis or septic shock, bacteremia, infective endocarditis, and immunosuppression.

For empiric treatment of suspected or documented *P. aeruginosa* infections, pharmacists can also ensure that patients are receiving appropriate doses of antipseudomonal agents. Many patients with *P. aeruginosa* present with renal impairment. A patient's renal impairment should be characterized as chronic or acute by assessing observed SCr concentrations in relation to prior baseline values. Large changes in SCr from baseline in shorter time intervals are most associated with severe dysfunction and sepsis. For these patients, the risk-benefit of using a "loading" dose and selecting dosing regimens on the basis of baseline renal function relative to their acutely estimated renal function should be considered, especially if patients are critically ill. Consideration for this aggressive approach is based on the need to optimize the PK/PD profile in the first 24 hours of infection onset to ensure the highest probability of a successful outcome. This consideration is also based on the finding that most nonimmunologic exposure-dependent drug adverse events occur after several days of therapy, and the risk of toxicity, even in the presence of high exposures, is typically low during the first 1–2 days of therapy (Bidell 2018).

For definitive treatment, pharmacists can provide additional therapeutic recommendations related to MIC data and susceptibility patterns. With elevated MICs, a working

knowledge of PK/PD principles and both in vitro and clinical data can support efforts to optimize therapy, such as recommending prolonged infusions of β -lactam therapy. Furthermore, a general understanding of common resistance patterns can help in recommending for or against additional susceptibility testing. For example, if MICs to meropenem and other β -lactams are elevated, susceptibility testing for ceftolozane/tazobactam and ceftazidime/avibactam should be considered. Limiting therapy to the shortest effective duration also provides significant benefits. Excessive antibiotic use can lead to the development of resistance, and decreasing therapy durations by one-half (e.g., from 14 to 7 days) can substantially decrease unnecessary exposure without compromising positive patient outcomes.

CONCLUSION

P. aeruginosa is an opportunistic pathogen that most commonly colonizes and infects patients in health care settings with compromised host defense mechanisms. In health care settings, *P. aeruginosa* is a common cause of pneumonia, UTIs, bloodstream infections, and surgical site infections. *P. aeruginosa* is intrinsically resistant to many commercially available antibiotics and has a remarkable ability to develop resistance to commonly used antibiotics like carbapenems, aminoglycosides, and fluoroquinolones through various acquired and adaptive resistance mechanisms that are often expressed simultaneously. Prevalence of resistance to commonly used first-line antibiotics among patients with *P. aeruginosa* infections now exceeds 20% in most hospitals, and MDR, XDR, and PDR strains are increasing.

Pharmacists play a critical role in treating patients with *P. aeruginosa* infections. To minimize the receipt of inappropriate therapy, pharmacists need to assess a patient's risk of having an MDR, XDR, or PDR *P. aeruginosa* infection when recommending empiric therapy. Selection of empiric agent(s), dose, infusion duration, and dosing frequency for a patient with a suspected *P. aeruginosa* infection should be based on the infection site(s), infection severity, patient-related factors, likelihood of a resistant *P. aeruginosa* infection, and local resistance patterns. Combination therapy with antibiotics from two different classes should be advocated in patients at an increased mortality risk (e.g., septic shock) or when there is a high risk of resistance to commonly used antipseudomonal agents. Higher or maximum daily doses are typically required for presumptive or known *P. aeruginosa* infections to optimize PK/PD target attainment and chances of clinical success. Pharmacists should reevaluate therapy as culture and susceptibility data become available and offer therapeutic and dosing recommendations to prescribers to further optimize and potentially streamline therapy. As part of definitive therapy recommendations, pharmacists should look to limiting therapy to the shortest effective duration because excessive antibiotic use perpetuates the development of resistance.

Practice Points

Clinical pharmacists face many challenges when optimizing pharmacotherapy for patients with suspected or documented *P. aeruginosa* infections. Pharmacists can benefit from the ability to recognize patient-specific risk factors associated with these infections, including those associated with MDR strains. Knowledge of common mechanisms of resistance, including among MDR strains, together with knowledge of clinical data, guideline recommendations, and newer therapies empower pharmacists to effectively provide optimal care for their patients.

- *P. aeruginosa* is a highly adaptive opportunistic pathogen that commonly affects those with compromised immune systems or anatomic barriers (e.g., large surface area burns, mechanical ventilation), as well as those with health care or antibiotic exposure.
- Common sites of *P. aeruginosa* infections include the urinary tract, respiratory tract, bloodstream, and skin/soft tissue.
- *P. aeruginosa* has several mechanisms of intrinsic, adaptive, and acquired antibiotic resistance. Multidrug resistance on a culture susceptibility report often suggests involvement of efflux pumps, β -lactamases, and/or other mechanisms of resistance.

- *P. aeruginosa* should be considered a potential pathogen in all “at-risk” patient populations presenting with a clinical syndrome consistent with *P. aeruginosa*. Prompt initiation of antimicrobial therapy with in vitro activity at infection onset is critically important because data analyses show that failure to administer early, appropriate therapy substantially increases morbidity and mortality.
- Combination therapy with antibiotics from two different classes should be advocated in patients at an increased mortality risk (e.g., septic shock) or when there is a high risk of resistance to commonly used antipseudomonal agents.
- Higher doses are generally most appropriate for treating serious infections caused by *P. aeruginosa* in order to optimize the PK/PD indices associated with clinical treatment success and resistance prevention.
- Newer therapies that may play a role in treating MDR *P. aeruginosa* include ceftolozane/tazobactam, ceftazidime/avibactam, and imipenem/relebactam, and several agents in late clinical stage development may be future options for treating infections caused by MDR pathogens.

REFERENCES

- Berthelot P, Grattard F, Mahul P, et al. [Prospective study of nosocomial colonization and infection due to *Pseudomonas aeruginosa* in mechanically ventilated patients](#). *Intensive Care Med* 2001;27:503-12.
- Bidell MR, Lodise TP. [Suboptimal clinical response rates with newer antibiotics among patients with moderate renal impairment: review of the literature and potential pharmacokinetic and pharmacodynamic considerations for observed findings](#). *Pharmacotherapy* 2018;38:1205-15.
- Boisson M, Jacobs M, Gregoire N, et al. [Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate \(CMS\) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients](#). *Antimicrob Agents Chemother* 2014;58:7331-9.
- Burgess DS, Hall RG. [Simulated comparison of the pharmacodynamics of ciprofloxacin and levofloxacin against *Pseudomonas aeruginosa* using pharmacokinetic data from healthy volunteers and 2002 minimum inhibitory concentration data](#). *Clin Ther* 2007;29:1421-7.
- Caston JJ, De la Torre A, Ruiz-Camps I, et al. [Salvage therapy with ceftolozane-tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections](#). *Antimicrob Agents Chemother* 2017;61(3).
- Centers for Disease Control and Prevention (CDC). [Antibiotic Resistance Threats in the United States, 2013](#).
- Chastre J, Wolff M, Fagon JY, et al. [Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial](#). *JAMA* 2003;290:2588-98.
- Chotiprasitsakul D, Han JH, Cosgrove SE, et al. [Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort](#). *Clin Infect Dis* 2018;66:172-7.
- Cojutti PG, Ramos-Martin V, Schiavon I, et al. [Population pharmacokinetics and pharmacodynamics of levofloxacin in acutely hospitalized older patients with various degrees of renal function](#). *Antimicrob Agents Chemother* 2017;61(3).
- Drusano GL, Neely MN, Yamada WM, et al. [The combination of fosfomycin plus meropenem is synergistic for *Pseudomonas aeruginosa* PAO1 in a hollow-fiber infection model](#). *Antimicrob Agents Chemother* 2018;62(12).
- Falagas ME, Tansarli GS, Ikawa K, et al. [Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis](#). *Clin Infect Dis* 2013;56:272-82.
- Grassi L, Di Luca M, Maisetta G, et al. [R. Generation of persister cells of *Pseudomonas aeruginosa* and *Staphylococcus aureus* by chemical treatment and evaluation of their susceptibility to membrane-targeting agents](#). *Front Microbiol* 2017;8:1917.
- Grupper M, Sutherland C, Nicolau DP. [Multicenter evaluation of ceftazidime-avibactam and ceftolozane-tazobactam inhibitory activity against meropenem-nonsusceptible *Pseudomonas aeruginosa* from blood, respiratory tract, and wounds](#). *Antimicrob Agents Chemother* 2017;61(10).
- Haidar G, Philips NJ, Shields RK, et al. [Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance](#). *Clin Infect Dis* 2017;65:110-20.

- Humphries RM, Hindler JA, Wong-Beringer A, et al. [Activity of ceftolozane-tazobactam and ceftazidime-avibactam against beta-lactam-resistant *Pseudomonas aeruginosa* isolates](#). *Antimicrob Agents Chemother* 2017;61(12).
- Kalil AC, Metersky ML, Klompas M, et al. [Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society](#). *Clin Infect Dis* 2016;63:e61-e111.
- Kollef MH, Chastre J, Clavel M, et al. [A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia](#). *Crit Care* 2012;16:R218.
- Lee YJ, Liu HY, Lin YC, et al. [Fluoroquinolone resistance of *Pseudomonas aeruginosa* isolates causing nosocomial infection is correlated with levofloxacin but not ciprofloxacin use](#). *Int J Antimicrob Agents* 2010;35:261-4.
- Liu L, Liu B, Li Y, et al. [Successful control of resistance in *Pseudomonas aeruginosa* using antibiotic stewardship and infection control programs at a Chinese university hospital: a 6-year prospective study](#). *Infect Drug Resist* 2018;11:637-46.
- Mensa J, Barberan J, Soriano A, et al. [Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: guidelines by the Spanish Society of Chemotherapy](#). *Rev Esp Quimioter* 2018;31:78-100.
- Monogue ML, Nicolau DP. [Antibacterial activity of ceftolozane/tazobactam alone and in combination with other antimicrobial agents against MDR *Pseudomonas aeruginosa*](#). *J Antimicrob Chemother* 2018;73:942-52.
- Montero M, VanScoy BD, Lopez-Causape C, et al. [Evaluation of ceftolozane-tazobactam in combination with meropenem against *Pseudomonas aeruginosa* sequence type 175 in a hollow-fiber infection model](#). *Antimicrob Agents Chemother* 2018;62(5).
- Munita JM, Aitken SL, Miller WR, et al. [Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*](#). *Clin Infect Dis* 2017;65:158-61.
- Natesan S, Pai MP, Lodise TP. [Determination of alternative ceftolozane/tazobactam dosing regimens for patients with infections due to *Pseudomonas aeruginosa* with MIC values between 4 and 32 mg/L](#). *J Antimicrob Chemother* 2017;72:2813-6.
- Nichols WW, de Jonge BL, Kazmierczak KM, et al. [In vitro susceptibility of global surveillance isolates of *Pseudomonas aeruginosa* to ceftazidime-avibactam \(INFORM 2012 to 2014\)](#). *Antimicrob Agents Chemother* 2016;60:4743-9.
- O'Donnell JN, Rhodes NJ, Lopez J, et al. [Carbapenems vs. alternative beta-lactams for the treatment of nosocomial pneumonia: a systematic review and meta-analysis](#). *Int J Antimicrob Agents* 2018;52:451-8.
- Pang Z, Raudonis R, Glick BR, et al. [Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and alternative therapeutic strategies](#). *Biotechnol Adv* 2019;37:177-92.
- Pena C, Suarez C, Ocampo-Sosa A, et al. [Effect of adequate single-drug vs combination antimicrobial therapy on mortality in *Pseudomonas aeruginosa* bloodstream infections: a post hoc analysis of a prospective cohort](#). *Clin Infect Dis* 2013;57:208-16.
- Rahme C, Butterfield JM, Nicasio AM, et al. [Dual beta-lactam therapy for serious gram-negative infections: is it time to revisit?](#) *Diagn Microbiol Infect Dis* 2014;80:239-59.
- Raman G, Avendano EE, Chan J, et al. [Risk factors for hospitalized patients with resistant or multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis](#). *Antimicrob Resist Infect Control* 2018;7:79.
- Rhodes NJ, Liu J, O'Donnell JN, et al. [Prolonged infusion piperacillin-tazobactam decreases mortality and improves outcomes in severely ill patients: results of a systematic review and meta-analysis](#). *Crit Care Med* 2018;46:236-43.
- Santevecchi BA, Smith TT, MacVane SH. [Clinical experience with ceftazidime/avibactam for treatment of antibiotic-resistant organisms other than *Klebsiella pneumoniae*](#). *Int J Antimicrob Agents* 2018;51:629-35.
- Shortridge D, Gales AC, Streit JM, et al. [Geographic and temporal patterns of antimicrobial resistance in *Pseudomonas aeruginosa* over 20 years from the SENTRY Antimicrobial Surveillance Program, 1997-2016](#). *Open Forum Infect Dis* 2019;6(suppl 1):S63-S68.
- Smith RS, Iglewski BH. [P. aeruginosa quorum-sensing systems and virulence](#). *Curr Opin Microbiol* 2013;6:56-60.
- Sousa A, Perez-Rodriguez MT, Suarez M, et al. [Short- versus long-course therapy in gram-negative bacilli bloodstream infections](#). *Eur J Clin Microbiol Infect Dis* 2019;38:851-7.
- Torrens G, Cabot G, Ocampo-Sosa AA, et al. [Activity of ceftazidime-avibactam against clinical and isogenic laboratory *Pseudomonas aeruginosa* isolates expressing combinations of most relevant beta-lactam resistance mechanisms](#). *Antimicrob Agents Chemother* 2016;60:6407-10.
- Vardakas KZ, Voulgaris GL, Maliaros A, et al. [Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials](#). *Lancet Infect Dis* 2018;18:108-20.
- Weiner LM, Webb AK, Limbago B, et al. [Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014](#). *Infect Control Hosp Epidemiol* 2016;37:1288-301.
- Xipell M, Bodro M, Marco F, et al. [Clinical experience with ceftazidime/avibactam in patients with severe infections, including meningitis and lung abscesses, caused by extensively drug-resistant *Pseudomonas aeruginosa*](#). *Int J Antimicrob Agents* 2017;49:266-8.
- Yahav D, Franceschini E, Koppel F, et al. [Seven versus fourteen days of antibiotic therapy for uncomplicated gram-negative bacteremia: a non-inferiority randomized controlled trial](#). *Clin Infect Dis* 2019;69:1091-8.

Self-Assessment Questions

Questions 1–4 pertain to the following case.

N.S., a 19-year-old man with a medical history of allergic rhinitis, presents to the ED febrile and in septic shock believed to be caused by a viral illness. He is initiated on high-dose vasopressor therapy and quickly progresses to respiratory failure requiring intubation. A flu swab is positive for influenza A. N.S. receives treatment for influenza and has some response with improving fever curve but remains intubated. On day 6 of intubation, he requires increasing ventilatory settings and has a temperature of 101.3°F. A sputum sample grows the following *P. aeruginosa*:

Antibiotic	MIC Value	Interpretation
Piperacillin/tazobactam	32	Intermediate
Ceftazidime	8	Susceptible
Cefepime	16	Intermediate
Imipenem	≥16	Resistant
Meropenem	≥16	Resistant
Tobramycin	≤1	Susceptible
Ciprofloxacin	1	Susceptible
Levofloxacin	4	Intermediate

- Which one of the following places N.S. at greatest risk of a *P. aeruginosa* infection?
 - Age
 - Influenza
 - Allergic rhinitis
 - Mechanical ventilation
- Which one of the following treatments is best to recommend for N.S.?
 - Tobramycin, high-dose extended interval
 - Cefepime, prolonged infusion
 - Ceftazidime, prolonged infusion
 - Piperacillin/tazobactam, prolonged infusion
- Given the susceptibility patterns of N.S.'s isolate, which one of the following agents would be best to recommend for susceptibility testing?
 - Ceftolozane/tazobactam
 - Amikacin
 - Meropenem/vaborbactam
 - Aztreonam
- According to the most recent (2016) ATS/IDSA hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) guidelines, which would be the best treatment duration (assuming appropriate clinical response) to recommend for N.S.?

- 5 days
- 7 days
- 10 days
- 14 days

Questions 5 and 6 pertain to the following case.

J.S. is a 54-year-old woman with a medical history of multiple sclerosis (complicated by neurogenic bladder and suprapubic catheter/nephrostomy tube) and recurrent UTIs with extended-spectrum β-lactamase (ESBL)-producing organisms, admitted 3 days ago with fevers, suprapubic pain, leukocytosis, and nausea/vomiting. Her urine culture is positive for the following *P. aeruginosa*:

Isolate 1

Antibiotic	MIC Value	Interpretation
Piperacillin/tazobactam	≤4	Susceptible
Ceftazidime	≤1	Susceptible
Cefepime	≤1	Susceptible
Imipenem	2	Susceptible
Meropenem	≤0.25	Susceptible
Amikacin	≤2	Susceptible
Tobramycin	≤1	Susceptible
Ciprofloxacin	≤0.25	Susceptible
Levofloxacin	0.5	Susceptible

- Which one of the following most likely caused the elevated imipenem MIC in this isolate (isolate 1) from J.S.?
 - Porin mutation
 - Efflux pump
 - Carbapenemase
 - AmpC production
- J.S. is treated for her UTI. She is admitted 6 months later with another UTI, again caused by *P. aeruginosa*:

Isolate 2

Antibiotic	MIC Value	Interpretation
Ceftazidime	8	Susceptible
Cefepime	≥64	Resistant
Imipenem	2	Susceptible
Meropenem	1	Susceptible
Amikacin	≥64	Resistant
Tobramycin	4	Susceptible
Ciprofloxacin	≥4	Resistant
Levofloxacin	≥8	Resistant

Which one of the following mechanisms of resistance best explains the multidrug-resistant (MDR) profile in this isolate (isolate 2) from J.S.?

- A. Efflux pump up-regulation
 - B. ESBL
 - C. AmpC hyperproduction
 - D. Carbapenemase
7. Which one of the following patients would most likely benefit from dual antipseudomonal empiric therapy?
- A. 67-year-old woman presenting from a nursing home with suspicion of pneumonia; history of chronic obstructive pulmonary disease (COPD)
 - B. 74-year-old man presenting from skilled nursing facility with complicated diabetic foot infection; history of dry gangrene
 - C. 80-year-old man presenting from home with confusion and septic shock; history of *Pseudomonas* UTI
 - D. 78-year-old woman presenting from assisted living facility with suspicion of osteomyelitis; history of ESBL-producing organisms
8. A 28-year-old man with a history of cystic fibrosis after a bilateral lung transplant 3 years ago presents with a splenic infarct in the setting of a new diagnosis of antiphospholipid syndrome. He is known to be colonized with *Pseudomonas* and has a history of exacerbations; these were successfully treated with cefepime and piperacillin/tazobactam in the past year. The patient is currently stable from a respiratory process, and is receiving inhaled tobramycin and piperacillin/tazobactam. Sputum cultures were obtained, despite relative clinical stability, and grow the following mucoid *Pseudomonas* strains:

Antibiotic	Strain 1	Strain 2
	Interpretation	Interpretation
Piperacillin/tazobactam	Susceptible	Resistant
Ceftazidime	Resistant	Resistant
Cefepime	Resistant	Resistant
Imipenem	Resistant	Resistant
Meropenem	Susceptible	Resistant
Amikacin	Intermediate	Resistant
Tobramycin	Susceptible	Resistant
Ciprofloxacin	Intermediate	Resistant
Levofloxacin	Susceptible	Resistant
Aztreonam	Susceptible	Resistant

Additional testing is done on both mucoid strains obtained from D.S. Ceftolozane/tazobactam results at

an MIC of 4 for both isolates, which is susceptible. If clinical decompensation occurs while on his current regimen, which one of the following regimens is best to recommend for this patient?

- A. Change piperacillin/tazobactam to extended infusion.
 - B. Change to ceftolozane/tazobactam intermittent infusion.
 - C. Change to ceftolozane/tazobactam extended infusion.
 - D. Change to cefepime extended infusion.
9. Each of the following patients is thought to have a *P. aeruginosa* infection, as well as acute moderate renal impairment. Assuming you are assessing these patients on admission, which one of the following would be most likely to benefit from high-dose (i.e., 2 g intravenously every 8 hours) meropenem?
- A. 25-year-old man with a ventriculoperitoneal shunt infection
 - B. 88-year-old man with a COPD exacerbation
 - C. 73-year-old woman with a diabetic foot infection
 - D. 32-year-old woman with a UTI
10. In a patient with biofilm-implanted device infection caused by *P. aeruginosa*, which one of the following microbiologic abilities most contributes to the persisters variants in biofilms?
- A. Quorum sensing and biofilm production
 - B. Endotoxin production
 - C. Coagulase production
 - D. Catalase production
11. The antimicrobial stewardship program wants to preserve antibiotic susceptibilities against *P. aeruginosa* at your institution. According to the available literature, which one of the following initiatives would be best for the program to prioritize?
- A. Minimize broad-spectrum antibiotic use overall.
 - B. Change from meropenem to ertapenem depending on definitive culture and susceptibility data (e.g., for ESBL Enterobacteriaceae)
 - C. Promote fluoroquinolone use.
 - D. Use extended infusions of β -lactams in all ICUs.
12. Which one of the following patients is at highest risk of infection caused by an MDR strain of *P. aeruginosa*?
- A. 65-year-old man with respiratory failure who has been mechanically ventilated for 48 hours
 - B. 65-year-old man with indwelling central intravenous catheter for total parenteral nutrition
 - C. 65-year-old with prior receipt of two courses of fluoroquinolones for UTIs
 - D. 65-year-old with inflammatory bowel disease on chronic prednisone

13. A patient has ventilator-associated bacterial pneumonia (VABP) caused by an extensively drug-resistant (XDR) *P. aeruginosa* strain that was only susceptible to amikacin and colistin on the initial susceptibility report. Susceptibility data to ceftolozane/tazobactam and ceftazidime/avibactam are pending. Together with inhaled amikacin, which one of the following therapy regimens is best to recommend for this patient while awaiting the susceptibility data?
- A. Ceftolozane/tazobactam with intravenous amikacin
 - B. Ceftolozane/tazobactam and intravenous colistin
 - C. Ceftazidime/avibactam and intravenous colistin
 - D. Ceftazidime/avibactam and intravenous amikacin
14. Assuming similar medical histories, which one of the following patients is most at risk of becoming colonized with *P. aeruginosa*?
- A. 45-year-old man who frequents whirlpools and hot tubs
 - B. 45-year-old woman who eats vegetables and fruits from the hospital cafeteria she works in
 - C. 45-year-old man who cleans sinks in the common bathroom at hospitals
 - D. 45-year-old woman who is hospitalized for more than 72 hours
15. From the perspective of the clinical pharmacist and antibiotic stewardship program, which one of the following patients would be best to prioritize to increase the likelihood of a positive clinical outcome?
- A. Clinically stable 70-year-old woman who is on day 14 of hospital-acquired bacterial pneumonia (HABP) treatment for *P. aeruginosa*
 - B. Clinically unstable 65-year-old woman presenting with sepsis and a history of MDR *P. aeruginosa* infection
 - C. Clinically unstable 70-year-old man receiving meropenem with a pan-susceptible *P. aeruginosa* infection
 - D. Clinically stable 65-year-old man with suspected VABP receiving intravenous polymyxin B plus an antipseudomonal β -lactam for *P. aeruginosa* that is only susceptible to polymyxins