

ANTIPSEUDOMONAL ANTIBIOTICS

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ANTIBIOTIC THERAPY

ANTIPSEUDOMONAL ANTIBIOTICS

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***Pseudomonas aeruginosa* is responsible not only for infections associated with considerable morbidity and mortality in the immunocompromised host, but also serious nosocomial infections, particularly in the intubated intensive care unit (ICU) patients. [43] *P. aeruginosa* bacteremia carries a high mortality rate exceeding 50%, indicating the intrinsic virulence of the microorganism. [41] Despite the availability of several antipseudomonal antimicrobials, steadily increasing resistance rates are reported worldwide, rendering the end of antibiotics for *P. aeruginosa* an approaching reality. [5] [8] [23] [24] [25] [39] [43] [44] This article focuses mainly on newer antipseudomonal agents and on more recent information for the older compounds.**

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ANTIPSEUDOMONAL PENICILLINS

In Vitro Activity and Resistance Mechanisms

Two groups of antipseudomonal penicillins have been studied extensively and applied therapeutically over the years: the carboxypenicillins, including carbenicillin and ticarcillin, and the ureidopenicillins, including mezlocillin, azlocillin, and piperacillin. [27] [42] Carbenicillin because of its well-known disadvantages and mezlocillin because of its limited activity against *P. aeruginosa* are not included in this review. Ticarcillin is at least two to four times as active as carbenicillin against *P. aeruginosa*; however, cross-resistance is the rule. Through the years because of the extent of use, resistance rates in ICUs, burn units, and hematology units became extremely high. Azlocillin appears in vitro as superior to ticarcillin, and piperacillin appears twice as active as azlocillin against *P. aeruginosa*. Their superiority over ticarcillin has been disputed, however, because minimal inhibitory concentrations (MICs) are inoculum dependent; they are less bactericidal with poor serum bactericidal activity; and, in contrast to ticarcillin, they are hydrolyzed by the chromosomally mediated pseudomonal β -lactamases. Current susceptibility breakpoints and interpretation of susceptibility results are shown in Table 1. [35]

TABLE 1 -- INTERPRETIVE STANDARDS FOR DISK DIFFUSION AND BREAKPOINTS IN SUSCEPTIBILITY TESTING OF *P. AERUGINOSA*

Antimicrobial Agent	MIC ($\mu\text{g/mL}$)			Zone Diameter (mm)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Ticarcillin	≤ 64	NA	≥ 128	≥ 15	NA	≤ 14
Azlocillin	≤ 64	NA	≥ 128	≥ 18	NA	≤ 17
Piperacillin	≤ 64	NA	≥ 128	≥ 18	NA	≤ 17
Ceftazidime	≤ 8	16	≥ 32	≥ 18	15–17	≤ 14
Cefoperazone	≤ 16	32	≥ 64	≥ 21	16–20	≤ 15
Aztreonam	≤ 8	32	≥ 32	≥ 22	16–21	≤ 15
Imipenem	≤ 4	16	≥ 16	≥ 16	14–15	≤ 13
Meropenem	≤ 4	8	≥ 16	≥ 16	14–15	≤ 13
Ciprofloxacin	≤ 1	8	≥ 4	≥ 21	16–20	≤ 15
Gentamicin	≤ 4	2	≥ 16	≥ 15	13–14	≤ 12
Tobramycin	≤ 4	8	≥ 16	≥ 15	13–14	≤ 12
Netilmicin	≤ 8	8	≥ 32	≥ 15	13–14	≤ 12
Amikacin	≤ 16	16	≥ 64	≥ 17	15–16	≤ 14
Isepamicin	≤ 16	32	≥ 64	≥ 17	15–16	≤ 14

MIC = Minimal inhibitory concentration; NA = not available.

From NCCLS *M*₁₀₀₋₅₉ (M2-A6): Performance Standards for Antimicrobial Susceptibility Testing: Ninth Informational Supplement. Wayne, PA, 1999; with permission. [35]

Virtually all *P. aeruginosa* isolates produce chromosomally mediated β -lactamases, whereas plasmids code for the production of at least 15 different types of β -lactamases. The former do not inactivate carbenicillin and ticarcillin, but the latter hydrolyze all antipseudomonal penicillins. During therapy with piperacillin, intrinsic resistance resulting from changes in penicillin-binding proteins (PBPs) has emerged, particularly in cystic fibrosis patients. *P. aeruginosa* cells, particularly in patients with chronic infections, can develop a biofilm, however, in which bacteria are enmeshed into a mucoid ex-polysaccharide, becoming more resistant to β -lactams and aminoglycosides as well.

Results from several resistance surveillance studies conducted from 1991 until 1997, [5] [12] [23] [25] [46] in which most β -lactam antipseudomonal antibiotics were compared regarding resistance rates and their intrinsic activity, are shown in Tables 2 and 3. Whenever data are derived from ICUs, resistance rates are steeply increased, the obtained high resistance rates to ticarcillin not permitting its empiric use in the seriously infected patient. Whenever ticarcillin or piperacillin is combined with a β -lactamase inhibitor (clavulanic acid or tazobactam), no difference in the obtained MICs is observed. It was reported that clavulanate, by inducing expression of the *P. aeruginosa* Amp C cephalosporinase at physiologically relevant concentrations, antagonizes in vitro the antibacterial activity of ticarcillin, whereas in similar tests with tazobactam, no antagonism of piperacillin's bactericidal activity was observed. [29] Ticarcillin or ureidopenicillins in combination with gentamicin, tobramycin, or amikacin is mostly synergistic in vitro against *P. aeruginosa*. [22] Combination of piperacillin or azlocillin with imipenem should be avoided because the latter is a strong β -lactamase inducer that antagonizes the action of the former. Although the addition of any cephalosporin is unpredictable, the combination with ciprofloxacin can be additive or synergistic.

TABLE 2 -- COMPILED DATA OF SIX RESISTANCE SURVEILLANCE S

Year Performed	Country	Year of Publication	No. Strains Tested	Resistance Rates to the Indicated A					
				Gentamicin	Tobramycin	Amikacin	Ticarcillin	Piperacillin	Ceftazidime
1991	France (39 ICUs)	1996 [25]	634	63	36	NA	47	20	19
1992 (EPIC STUDY)	Europe (17 Western countries, 1417)	1995 [46]	410	46.3	NA	NA	NA	37.4	27.7

1994-95	ICUs) Europe (5 countries, 118 ICUs)	1999 [23]	2153	7-46	NA	4-13 *	NA	5-26 *	2-16 *
1995	Italy (15 centers)	1998 [5]	1005	NA	NA	10.6	22.8	12	13.4
1997	Greece (17 centers)	Personal communication	1704, Ward	32	27	27	30	30	25
1997 (SENTRY STUDY)	United States		ICU 276	66 12	65 5	63 3	64 16	64 9	45 13
	Canada	1999 [12]	83	16	5	5	12	4	12
	Latin America		92	28	22	16	25	20	14

ICUs = Intensive care units; NA = not available.

*Range of resistance rates among countries.

TABLE 3 -- IN VITRO BROTH MICRODILUTION SUSCEPTIBILITY RESULTS FOR *P. AERUGINOSA* CAUSING BLOODSTREAM INFECTIONS IN 48 MEDICAL CENTERS IN THE UNITED STATES, CANADA, AND LATIN AMERICA *

Class	Antimicrobial Agent	Canada (n = 83)		United States (n = 276)		Latin America (n = 92)	
		MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
β-Lactams	Meropenem	0.25	2	0.25	2	0.5	4
	Imipenem	2	>8	2	8	2	>8
	Cefepime	2	8	2	16	4	>16
	Ceftazidime	2	16	2	16	2	>16
	Piperacillin tazobactam	4	64	4	64	8	>64
	Aztreonam	4	16	8	>16	8	>16
	Piperacillin	4	32	4	64	8	>128
	Ticarcillin	32	128	32	128	32	>128
Quinolones	Levofloxacin	≤0.5	>4	≤0.5	4	≤0.5	>4
	Ciprofloxacin	0.12	2	0.12	2	0.25	>2
	Gatifloxacin	1	>4	1	>4	1	>4
	Sparfloxacin	1	>2	1	>2	1	>2
	Trovafloxacin	0.5	4	0.5	4	1	>4
Aminoglycosides	Amikacin	4	16	4	8	4	>32
	Tobramycin	0.5	2	0.5	2	1	>16
	Gentamicin	2	8	2	8	2	>16

MIC = Minimal inhibitory concentration.

From Diekema DJ, Pfaller MA, Jones RN, et al: Survey of bloodstream infections due to gram-negative bacilli: Frequency of

*n = 451.

Pharmacokinetics

Pharmacokinetics are shown in Table 4. Pharmacokinetics are similar except for bile excretion and clearance when renal insufficiency coexists. Serum levels are dose dependent for all; however, for azlocillin and piperacillin, they are more than proportional to increments in the dose because with higher doses saturation of the drug's biotransformation in the liver and biliary excretion are observed. All antipseudomonal penicillins penetrate poorly into bronchial secretions, a fact that should be influential in the decision to treat patients with cystic fibrosis. Penetration into the cerebrospinal fluid is poor in noninflamed status; however, when inflammation is present, 13.3% and 32% of the mean serum levels for azlocillin and piperacillin are detected. Low levels are reached in normal bone, whereas in patients with cirrhosis and ascites, plasma half-life is doubled.

TABLE 4 -- PHARMACOKINETIC PROPERTIES OF SEVERAL ANTIPSEUDOMONAL ANTIBIOTICS

	Ticarcillin	Azlocillin	Piperacillin	Ceftazidime	Cefoperazone	Cefsulodin	Cefepime	Aztreonam	Imipenem	M
Peak serum level (µg/mL)	240 (after 3 g IV over 90–120 min)	410 (after 5 g IV over 30 min)	330 (after 4 g IV bolus)	180 (after 2 g IV over 15 min)	108 (after 2 g IV over 30 min)	60.5 (after 1 g IV over 30 min)	126 (after 2 g IV over 30 min)	255 (after 2 g IV over 30 min)	68 (after 1 g IV over 30 min)	5: I
Half-life (min)	70	60–100	40–60	100	95	95	120	120	60	
Distribution volume (L)	14–18	18–19	16–19	18	8	11	14–20	?	19	
Renal excretion (%)	80	70	50–80	75–90	25	60	88	68	75	
Biliary excretion (%)	3.5	20–30	20–30	<1	70	—	?	<1	—	
Protein binding (%)	45	20–40	20–40	15	90	15	18	30–50	25	

Dosage Schedule Intervals in Renal Insufficiency

Creatinine Clearance

10–15 mL/min (h)	12–24	8	8	12–24	8–12	12–24	12–16	8	8–12	12
<10 mL/min (h)	24–48	12	12	24	12	24	24	12	12	24
Supplement for dialysis	Yes (H)									
	? P	No (P)	No (P)	Yes (P)	? P	Yes (P)				

H = Hemodialysis; P = peritoneal dialysis.

Data from references [27] [36] [42]

Dosage Schedules

In the treatment of serious *P. aeruginosa* infections, ticarcillin and azlocillin should be given intravenously at 200 to 300 mg/kg in 4 to 6 doses over 24 hours (i.e., 3 to 4 g every 4 to 6 hours). Piperacillin should be given intravenously at 4 to 6 g every 6 to 8 hours. In pregnancy higher doses of piperacillin should be administered because peak plasma levels are half that of nonpregnant women.

Whenever antipseudomonal penicillins are coadministered with an aminoglycoside, based on reports of in vitro inactivation of the latter by high levels of penicillins, it is prohibited for the agents to be mixed in the same bottle. This adverse interaction is an in vivo possibility in end-stage renal failure because prolonged blood levels are maintained as a result of their compromised clearance. Tobramycin and gentamicin are the most rapidly inactivated aminoglycosides. Piperacillin because of its increased rate of nonrenal elimination, particularly in patients with renal insufficiency, inactivates aminoglycosides to a lesser extent and less rapidly.

Adverse Effects

The main toxicity manifestations are hypersensitivity reactions, neurotoxicity, and bleeding disorders. Rash, drug fever, and eosinophilia are more common with ureidopenicillin therapy (0.3% to 2.2%) than with ticarcillin. Neurotoxicity, presenting as convulsions or recurrent paralysis, is dose dependent and occurs mostly in patients with renal failure who are given ticarcillin. Bleeding diathesis, attributed to some defect in platelet function, is prominent with ticarcillin whereas clinical bleeding has not been reported with azlocillin, and piperacillin has less of an effect on platelet function. Severity of these hematologic disturbances is dose dependent; they persist for 12 days after therapy is discontinued, indicating that not only circulating platelets, but also megakaryocytes are affected. The clinician should be alert for the possibility of sodium overload (5.2 mEq/g) and hypokalemia mostly with ticarcillin as well as the remote occurrence of interstitial nephritis, cholestatic jaundice with transaminase elevation, neutropenia, and thrombocytopenia.

ANTIPSEUDOMONAL CEPHALOSPORINS

Three groups of antipseudomonal cephalosporins have been developed: (1) ceftazidime, cefoperazone, and cefsulodin, all third generation cephalosporins possessing a quaternary pyridium group at the 3 position to which their antipseudomonal activity is attributed; (2) 7 β -aminothiazolyl-1 or 7 β -aminothiadiazolyl-oxymino, 3-quaternary ammonium cephalosporins; and (3) catecholic cephalosporins. [27] [47]

In Vitro Activity and Resistance Mechanisms

Ceftazidime is intrinsically more active against *P. aeruginosa* than cefoperazone. Ceftazidime resistant strains, however, can arise when difficult infections are treated in humans, as in the case of ICU pneumonia in the intubated and mechanically ventilated patient. Resistance surveillance data are shown in Tables 2 and 3. Although the most frequent mechanism of resistance appears to be the overproduction of chromosomally mediated type I (AmpC) β -lactamase (owing to a chromosomal mutation or commonly by enzyme induction), which slowly inactivates ceftazidime as well as almost all β -lactams with the exception of carbapenems, decreased outer membrane permeability also can be responsible for resistance development. The in vivo emergence of multidrug-resistant *P. aeruginosa* during therapy with antipseudomonal β -lactams being also cross-resistant to quinolones has been described, indicative of the presence of multidrug-resistant active efflux mutants overexpressing the MexA-MexB-OprM system as a result of mutations in the regulatory *mexR* gene. [50] Two newer ESBLs (TEM-42 and PER-1) [10] [33], two metallo- β -lactamases (IMP-I [41] and VMI-I [28]), and six new OXA- β -lactamase derivatives (OXA 11, 13, 14, 15, 16, and 19), [11] [32] all plasmid mediated capable of hydrolyzing antipseudomonal cephalosporins, have been reported from Turkey and France. With the exception of IMP-I and VIM-I, carbapenems are not a suitable substrate for the other newer β -lactamases.

When first introduced in 1980, cefoperazone inhibited 50% of *P. aeruginosa* isolates by 4 μ g/mL and 90% by 32 μ g/mL; however, MICs are increased whenever large inocula are used in the sensitivity tests. In vitro, cefoperazone seems to be comparable to antipseudomonal activity with azlocillin and piperacillin. Mainly because of the induction of chromosomally mediated β -lactamases, resistance strains have emerged.

Cefsulodin is a narrow-spectrum cephalosporin active mainly against *P. aeruginosa*. At 4 μ g/mL, greater than 90% of *Pseudomonas* strains are inhibited. On a weight basis, it is more active in vitro against azlocillin, piperacillin, and cefoperazone; ceftazidime possesses the highest intrinsic activity. In contrast to the other compounds, cefsulodin has a low affinity for chromosomally induced cephalosporinases. All newer plasmid-mediated β -lactamases that are capable of hydrolyzing ceftazidime also inactivate cefsulodin, however. *P. aeruginosa* strains resistant to cefsulodin show a significant reduction in affinity for PBP-3, the main target of its antipseudomonal activity.

The fourth-generation cephalosporins belong in the second group. Cefpirome, cefepime, and cefoselis possess an α -oxymino-aminothiazolyl-group in the 7 β side-chain plus a quaternary ammonium group in the 3 side-chain, whereas cefclidine, ceftazidime, cefepime, cefluprenam, FK-518, and YM-40220 possess an aminothiadiazolyl group replacing the aminothiazolyl group in the 7 β side-chain. All compounds have a wide spectrum of activity against aerobic and anaerobic bacteria, including *P. aeruginosa*. A common

characteristic of fourth-generation cephalosporins is their low affinity for chromosomal cephalosporinases, coupled with high resistance to cephalosporinase hydrolysis. Cefepime is hydrolyzed from the same plasmid-mediated β -lactamases as ceftazidime, while it is reported that ceftazidime penetrates better through the outer cell membrane than ceftazidime, ceftazidime, and cefclidine, and there is no appreciable difference in the affinity for PBP-3 the most sensitive of the essential PBPs. Cefepime also binds to PBP-2 an unusual feature for a cephalosporin.

After comparing the in vitro activity of the newer cephalosporins against a collection of Japanese clinical isolates of *P. aeruginosa*, cefepime antipseudomonal activity is roughly comparable to that of ceftazidime, and ceftazidime is twofold less active, whereas ceftazidime and ceftazidime are twofold more active.^[47] Cefclidine is the most active among the β -lactams, but its activity is reduced by fourfold against ceftazidime-resistant *P. aeruginosa* strains. After relevant experiments in vitro, the activities of ceftazidime, ceftazidime, cefepime, ceftazidime, and ceftazidime were lowered by a factor of 8 to 32 against strains derepressed for cephalosporinase production. Cefclidine activity was reduced only four to eightfold, its MIC remaining in the susceptible range. The antipseudomonal potency order of the described eight newer cephalosporins is as follows: ceftazidime > FK-518 > ceftazidime = ceftazidime > ceftazidime = ceftazidime > ceftazidime > ceftazidime. There is complete cross-resistance between ceftazidime and ceftazidime, whereas both usually are active against aminoglycoside-resistant *P. aeruginosa* strains. All antipseudomonal cephalosporins when combined with aminoglycosides and particularly with amikacin are synergistic in vitro. Even for strains highly resistant to both compounds, an enhanced bactericidal effect with in vivo relevance has been described.^[22]

Pharmacokinetics

The pharmacokinetic characteristics of ceftazidime, ceftazidime, cefepime, and ceftazidime are shown in Table 4. Ceftazidime penetrates successfully in ascitic fluid, peritoneal fluid, and pleural fluid in which levels greater than 10 $\mu\text{g}/\text{mL}$ are found as well as in bone tissue. Regarding bronchial secretions, maximum levels of 5.7 $\mu\text{g}/\text{mL}$ were obtained after a dose of 3 g intravenously. Sputum concentration in cystic fibrosis patients (4.13 $\mu\text{g}/\text{mL}$) exceeded the MICs only for 50% of *P. aeruginosa* isolated from these patients, the MIC for 90% never being reached. In the case of meningitis, after a 2-g intravenous bolus dose of ceftazidime, mean cerebrospinal fluid levels of 22.6 $\mu\text{g}/\text{mL}$ were found. Cefepime penetrates successfully bronchial mucosa, prostatic tissue, and bone as well as inflamed cerebrospinal fluid. Cefoperazone serum half-life because of its high biliary excretion is prolonged to 3.5 to 6 hours in patients with concomitant liver disease. Biliary obstruction eliminates ceftazidime biliary tract excretion, however. After usual therapeutic doses, adequate ceftazidime levels are reached in muscles, sputum, ascitic fluid, and surgical wound drainage. Cefepime after 2-g bolus administration in patients undergoing cardiac surgery creates levels in heart valves, subcutaneous tissues, and muscles greater than the MICs of 90% of *P. aeruginosa* strains.

Compounds of the third group, the so-called catecholic cephalosporins, are incorporated into the bacterial cells by the iron transport systems, and they overcome the poor permeability of the outer membrane of *P. aeruginosa*. For unknown reasons, none of these agents has been brought to clinical use.

Dosage Schedules

In severe *P. aeruginosa* infection, ceftazidime and ceftazidime should be given intravenously at a dose of 2 g every 8 hours or every 6 hours, either intravenous bolus or over 30 minutes. Because in patients with cystic fibrosis the MICs of *P. aeruginosa* usually are 16 $\mu\text{g}/\text{mL}$, to maintain trough levels above the MIC, 2-g every 6 hours is recommended. Cefoperazone dose, depending on the severity of the infection, is 2 to 3 g intravenously every 12 hours. Cefepime dose is 2 to 3 g every 8 hours.

Adverse Effects

Adverse effects are similar to those induced by other cephalosporins (i.e., hypersensitivity reactions, eosinophilia, neutropenia, positive Coombs' test without hemolysis, and mild reversible elevations in liver enzymes). All have some effect on fecal flora with overgrowth of enterococci and yeasts and sometimes of *Clostridium difficile*. Cefoperazone in particular, because it is excreted mainly through the bile into the gut, causes major changes in fecal flora, and diarrhea is more common than after other parenteral cephalosporins. Because ceftazidime has a *N*-methylthiotetrazole side-chain, it may cause hypoprothrombinemia and bleeding as well as disulfiram-like reactions if alcoholic beverages are used during or several days after stopping therapy. Cefepime's toxicity is difficult to determine because a large number of patients have not been treated; in several countries, the drug is not commercially available.

AZTREONAM

In Vitro Activity and Resistance Mechanisms

Aztreonam is the only available monobactam that possesses antipseudomonal activity, but ceftazidime is twice as active.^[27] Compared with ceftazidime, aztreonam is a poor inducer of the chromosomally mediated β -lactamases. The newer plasmid-mediated β -lactamases—PER-1, VIM-I, and OXA-10 derivatives—cause a moderate hydrolysis, whereas IMP-I induced hydrolysis is extraordinarily low. In *P. aeruginosa* isolates from cystic fibrosis patients, greater than 45% exhibited in vitro synergism with tobramycin or gentamicin.

Pharmacokinetics

Pharmacokinetics are described in Table 2. Aztreonam reaches levels in the inflamed cerebrospinal fluid of 3.5 to 6.2 $\mu\text{g/mL}$. In bronchial secretions of intubated patients, concentrations of 4.8 to 18.7 $\mu\text{g/mL}$ have been found after a 2-g intravenous dose, while after the same dose levels in prostatic tissue mounted to 78 $\mu\text{g/g}$.

Dosage Schedules

Aztreonam commonly is dosed at 2 to 3 g every 8 hours intravenously as a bolus or as a 30-minute infusion.

Adverse Events

The advantage of aztreonam over the other β -lactams is its low level of immunologic cross-reactivity with IgG antibodies to penicillin G and cephalothin. Despite the reduced cross-reactivity, however, aztreonam should be administered with caution to patients with known allergies to β -lactams. It does not interfere with coagulation disorders. Because it is absolutely inactive against anaerobes, aztreonam does not disturb colonization resistance of the bowel.

CARBAPENEMS

Carbapenems possess the widest spectrum of antimicrobial activity among the β -lactam antibiotics, including all common bacterial species as well as *P. aeruginosa* strains resistant to aminoglycosides, fluoroquinolones, and newer cephalosporins.^{[13] [15] [18] [21] [27] [28] [40] [44] [48]} Usually there is no cross-resistance between carbapenems and the latter groups of antimicrobials. Imipenem and meropenem, as well as some newer compounds, such as biapenem and panipenem,^[27] are reviewed briefly. In contrast to the other β -lactams, which have PBP-3 as their primary target, imipenem and meropenem bind to PBP-2 and PBP-1 or PBP-2 and PBP-3 resulting in rapid lysis of the bacterial cells. Imipenem does not form filaments, a potential advantage over cephalosporins regarding endotoxin release when bacteria lyse.

In Vitro Activity and Resistance Mechanism

P. aeruginosa normally is sensitive to imipenem, with MICs of greater than 1 to less than 8 $\mu\text{g/mL}$. Resistant strains arise in vivo during therapy, leading to therapeutic failures. Resistance is due to the loss of the specific outer membrane porin protein OprD₂, resulting in decreased penetration of the antibiotic across the outer membrane of *P. aeruginosa* cells.^[36] Because this route of entry into the bacterial cell is not used by other antipseudomonal β -lactams, emergence of resistance to imipenem through this mechanism does not imply cross-resistance to other β -lactams. It was found, however, that the D₂-porin loss is not adequate for resistance development to imipenem.^[30] This mechanism could function only when the chromosomal β -lactamase was also induced, suggesting that the activity of a carbapenem, more β -lactamase stable, should be less affected by the porin loss, and it seems that meropenem approaches this behavior. Imipenem is a potent inducer of the class I (Amp C) chromosomal cephalosporinases, which hydrolyze third-generation cephalosporins, whereas it is slowly hydrolyzed by itself. The Japanese in 1991 described a plasmid-mediated metallo- β -lactamase, which hydrolyzed ceftazidime and imipenem and subsequently all β -lactams with antipseudomonal activity.^[48] Resistance was transferred to *P. aeruginosa* but not to *Escherichia coli*. Since its description, this enzyme, which has not been determined further by molecular techniques, has not been reported from any other country worldwide. Five potential outbreaks of *P. aeruginosa* carrying metallo- β -lactamase genes on large plasmids identical to the β -lactamase *IMP-I* gene were reported in 1995 from hospitals from different geographic areas in Japan.^[40] These strains, with the exception of aztreonam, were simultaneously resistant to all β -lactams with antipseudomonal activity, including carbapenems. A new integron-borne metallo- β -lactamase, bla_{VIM}, was isolated in Italy from a *P. aeruginosa* clinical isolate, resulting in a significant decrease in susceptibility to all antipseudomonal β -lactams, including carbapenems.^[28]

The activity of meropenem against *P. aeruginosa* is comparable to that of imipenem (see Table 2). In cases when D₂ porin synthesis

is suppressed and imipenem resistance emerges, meropenem retains its activity on *P. aeruginosa*, suggesting the existence of another undefined route of meropenem transport through the outer membrane. In contrast, meropenem-resistant *P. aeruginosa* strains with cross-resistance to antipseudomonal cephalosporins and the quinolones (but not to imipenem) have been described. Such strains possess an increase of the outer membrane protein Opr M. In contrast to imipenem, meropenem is a less potent inducer of type 1 (class C) β -lactamases in *P. aeruginosa*. The acquisition of a metallo- β -lactamase gene alone does not necessarily confer elevated resistance to carbapenems, and the secondary changes in regulatory systems of metallo- β -lactamase gene expression, outer membrane permeability active efflux systems, and/or multiplication of structure genes may be implicated in acquisition of high-level carbapenem resistance. [28]

Resistance to carbapenems more commonly is observed in *P. aeruginosa* strains isolated from the respiratory tract, from patients in ICUs and in teaching hospitals. [44] In the United States, among potential risk factors for the selection of imipenem-resistant *P. aeruginosa*, it was found that prior imipenem use ($P < .0001$) and organ transplantation ($P = .008$) were characterized as independent risk factors, the adjusted risk being about 23 times higher in patients who received imipenem than in those who did not. [8] [44] Imipenem was associated with a significantly higher overall risk of emergence of resistance and the strongest association with emergence of resistance to itself. [8] This observation is consistent with the results of several clinical studies from various countries worldwide, in which resistant strains of 14% to 53% have emerged, these rates being significantly higher for imipenem than for ciprofloxacin or piperacillin-tazobactam. [8] An analysis of epidemiology and clinical outcomes of patients with multiresistant *P. aeruginosa* infections (including ciprofloxacin, imipenem, ceftazidime, and piperacillin) revealed that multiresistant strains emerge in a stepwise manner in patients with *difficult-to-treat* and prolonged infections, after lengthy exposure to many classes of antipseudomonal antibiotics and long hospitalization, resulting in adverse outcomes. [44] The fact that not all patients infected with multiresistant strains die is related to decreased virulence, however, because such strains may be less fit than susceptible strains. [24] It has been postulated that decreased virulence is more likely to occur with resistance conferred by the loss of a porin, which may result in a decrease in *Pseudomonas* ability to use nutrients efficiently. Hospital laboratories should be careful when performing imipenem susceptibilities because imipenem degrades easily.

From compiled data of 122 studies, the in vitro activity against 3018 *P. aeruginosa* strains expressed as MIC₉₀ for meropenem, imipenem, ceftazidime, gentamicin, and ciprofloxacin was 4 greater than 8 greater than 16 greater than 64 and 2 μ g/mL; in other studies, MIC₅₀ for meropenem, imipenem, ceftazidime, cefepime, and piperacillin was 0.5 μ g/mL, 2 μ g/mL, 2 μ g/mL, 4 μ g/mL, and 8 μ g/mL. [13] The greater intrinsic activity of meropenem over imipenem may be explained, at least in part, by improved stability against common serine β -lactamases and enhanced penetration of cells through alternative routes. The latter properties of meropenem plus high affinity for the PBPs render carbapenems bactericidal agents. Regarding compatible killing kinetics, meropenem has been found to kill at a slower rate than imipenem. [18] Of *P. aeruginosa* strains, 40% versus 11.1% developed resistance to imipenem and meropenem after 24 hours of exposure to carbapenems. This effect might be attributed to higher stability of meropenem to hydrolysis by the induced class I chromosomal β -lactamases. The combination of imipenem plus ciprofloxacin or amikacin has been reported to be synergistic in 36% and 45% of imipenem-sensitive *P. aeruginosa* strains but only in 10% when strains were resistant to imipenem. [21] Combinations of meropenem with gentamicin, amikacin, or tobramycin have been found synergistic or indifferent. [27]

Pharmacokinetics

Pharmacokinetic properties of imipenem and meropenem are shown in Table 2. Imipenem is subjected to postexcretion renal metabolism by a dehydropeptidase I (DHP-I), a dipeptidase of the brush border of the renal tubular cells that hydrolyzes and breaks the β -lactam's bond of the carbapenem molecule, resulting in great variation of urinary recovery plus nephrotoxicity. A compatible DHP-I inhibitor, cilastatin, has been developed that is used in a 1:1 combination with imipenem. Meropenem is stable to DHP-I, and it is administered without cilastatin. Both undergo metabolism by about 30%, the end products being imipenemoyl and meropenemoyl, which are inactive, but the place of their production is unknown. Imipenem has been detected in adequate concentrations in pleural, peritoneal, pericardial, and synovial fluid; sputum; pus; bone; aqueous humor; and inflamed cerebrospinal fluid, in which levels of 0.5 to 11 μ g/mL have been measured. Imipenem crosses the placenta, and adequate levels are found in amniotic fluid. No differences in serum half-lives and peak serum levels were observed in patients with cystic fibrosis and normal adult volunteers given imipenem. Meropenem attains levels almost equal to serum concentrations in the noninflamed peritoneal fluid, but levels in the noninflamed meninges are minimal. In bacterial meningitis, cerebrospinal fluid concentrations are 0.9 to 6.5 μ g/mL.

Dosage Schedules

For *P. aeruginosa* infections, imipenem should be administered in adults as a 1-g dose every 6 to 8 hours by bolus injection or preferably over a 30-minute infusion dissolved in 100 to 200 mL of saline. Severe renal failure results in a half-life of 4 hours for imipenem and 16 hours for cilastatin; however, both drugs are well cleared by hemodialysis. Meropenem is given at a dose of 1 to 2 g intravenous bolus or over 30 minutes every 8 hours. In case of meningitis, the highest dose should be administered.

Adverse Events

In 3% to 4% of patients given imipenem, nausea and vomiting are observed, but this side effect is lessened with meropenem by slowing the infusion rate. Nausea and vomiting occur less frequently compared with imipenem and because they are dose per time unit related, meropenem also can be given as an intravenous bolus. Grand mal or focal seizures and myoclonus have been observed in 3% to 20% of patients given imipenem, but most of them had renal insufficiency (and the dose was not appropriately decreased) or a background of central nervous system disease. In animal models and in humans, meropenem compared with imipenem is much less epileptogenic after treatment with high doses (2 g every 8 hours). Because of the minimal amount that reaches the intestine, imipenem and meropenem do not influence the normal fecal flora.

Newer Carbapenems

The newer carbapenems include promising broad-spectrum compounds, such as biapenem and panipenem.^[27] They are stable against hydrolysis by kidney DHP-I, and they possess higher in vitro intrinsic activity against *P. aeruginosa* than imipenem and meropenem, including strains resistant to both agents.

CIPROFLOXACIN

In Vitro Activity and Resistance Mechanisms

Among fluoroquinolones available in the market ciprofloxacin is still the most active against *P. aeruginosa*; it also exhibits the highest intrinsic activity, being four to eightfold more potent compared with the other compounds, with MIC₉₀ of 0.12 to 2 µg/mL.^{[12] [27] [49]} Similar to all other quinolones, ciprofloxacin is a bactericidal agent with a postantibiotic effect (PAE) of about 2 hours. *P. aeruginosa* isolates when attached to siliconized latex urinary catheters, and the induced biofilms render ciprofloxacin a static drug with minimal bactericidal concentration 64-fold higher than for the original strains.^[27]

As shown in Table 3, through the years, mainly as a consequence of the ever-increasing use of fluoroquinolones, resistance rates to ciprofloxacin exceeded for some centers, particularly for ICU isolates, 50%. In a report from five European countries (Belgium, France, Germany, Spain, Sweden) between 1995 and 1996, 22% of *P. aeruginosa* isolates derived from patients with respiratory tract infections were found resistant to ciprofloxacin, Sweden having the lowest and France the highest resistance rates.^[23] Chromosomal mutations affecting DNA gyrase A subunit, cell membrane permeability, and hyperactive efflux system have been confirmed as the underlying resistance mechanisms. Resistance resulting from spontaneous single-step chromosomal mutation occurs at a low frequency in vivo. Multiple mechanisms of resistance to ciprofloxacin usually are observed in *P. aeruginosa*. Whenever strains are cross-resistant to β-lactams and aminoglycosides, alteration in outer membrane porins has been incriminated. Enzymatic drug modification or destruction and plasmid-mediated resistance in *P. aeruginosa* have not been described. At the clinical level, resistance has been reported mostly in respiratory isolates, especially associated with cystic fibrosis, from wound infections, and whenever foreign bodies are present. Synergy or an additive effect between ciprofloxacin and azlocillin, amikacin, or the antipseudomonal β-lactams including imipenem has been reported in vitro for less than 50% of the tested *P. aeruginosa* strains.^{[21] [27]}

Pharmacokinetics

Ciprofloxacin generally is 60% to 70% absorbed, but food delays the time to reach serum peak levels. After 750-mg and 1000-mg doses in healthy volunteers, serum peak concentrations of 2.54 and 3.38 µg/mL are achieved. Serum half-life is 4.1 to 6.7 hours after 500-mg to 750- to 1000-mg oral doses suggesting that ciprofloxacin elimination is nonlinear. The volume of distribution is 358 L, whereas the area under curve (AUC) is 5.8 mg.h/L, and protein binding is approximately 30%. High serum levels are obtained in elderly individuals, whereas in cystic fibrosis patients elimination of ciprofloxacin is faster with shorter half-lives, although in some studies no kinetic difference was observed between healthy subjects and patients. Regarding serum kinetics, a 400-mg intravenous dose every 8 hours is considered as equivalent to 750 mg twice daily. After a 1-hour infusion of 400 mg, peak steady-state levels of 4.07 ± 0.88 µg/mL are found. Ciprofloxacin is excreted by the kidneys (50% to 75%), and at least six microbiologically almost inactive metabolites have been identified. About 15% of an intravenous dose and 11% to 30% of an oral dose are found in the feces. Because ciprofloxacin is eliminated poorly from the bile (0.41%), direct transintestinal elimination has been postulated as the explanatory mechanism. Ciprofloxacin possesses advantageous kinetics in the various body tissues. It has excellent penetration, exceeding serum peak levels in endothelial and epithelial cells as well as in the neutrophils and macrophages (14 to 18 fold the serum levels) and in saliva, bronchial secretions, epithelial lining fluid (1.8 to 2.1 times the serum levels), pleural fluid, and lung tissue. In inflamed cerebrospinal fluid, however, only approximately 15% of peak serum levels is achieved. Excellent penetration in peritoneal fluid, pancreatic tissue, prostatic fluid or tissue, biliary tract tissues (four to eightfold serum peak levels), gynecologic tissue, heart valves, and myocardium as well as in bone has been reported. Levels obtained in aqueous humor are inadequate to kill *P. aeruginosa*, however.

Dosage Schedules

For *P. aeruginosa* infections, doses of 400 mg intravenously over 30 to 60 minutes every 8 hours and 750 to 1000 mg orally every 12 hours are required.

Adverse Events and Drug Interactions

Gastrointestinal side effects are reported in 2% to 15% of patients and usually are mild and transient and more common with higher doses. Central nervous system toxicity is reported in 1% to 7.5%, including headache, insomnia, nightmares, somnolence, acute psychosis, paresthesia, transient paresis, and peripheral neuropathy as well as seizures. Hypersensitivity reactions are rare; however, dose dependent photosensitivity, particularly in cystic fibrosis patients, with an incidence of approximately 50% might be a serious problem. Arthralgia, tenosynovitis, joint stiffness, and Achilles tendinitis including rupture have been reported in less than 1%. Acute interstitial nephritis is rare but is the most common serious renal adverse reaction. Increased serum transaminase levels are the most common manifestation of hepatotoxicity, occurring in approximately 2%; in 0.5% to 5.3% of patients, hematologic side effects have been reported.

Antacids containing calcium, aluminum, magnesium, and sucralfate (but not β_2 -blockers) as well as vitamins containing ferrous sulfate and zinc reduce ciprofloxacin bioavailability about 60%. Occasionally, interaction with warfarin results in prothrombin time prolongation. Ciprofloxacin, similar to other quinolones, inhibits cytochrome P-450, reducing the metabolism of some drugs and increasing their serum levels to critical concentrations as happens with theophylline (requiring careful monitoring) and caffeine.

Newer Quinolones

Among newer quinolones (i.e., levofloxacin, lomefloxacin, rufloxacin, grepafloxacin, moxifloxacin, gatifloxacin, sparfloxacin, clinafloxacin, and trovafloxacin), only the last two compounds possess antipseudomonal activity, whereas the remaining have moderate or poor activity (four to eightfold less active than ciprofloxacin).^{[27] [37]} Trovafloxacin and clinafloxacin have MIC₉₀ against *P. aeruginosa* of 1 to 2 $\mu\text{g/mL}$ and 0.5 to 1 $\mu\text{g/mL}$, clinafloxacin activity being similar or marginally less active than ciprofloxacin. Trovafloxacin after a single 100-mg or 300-mg oral dose in healthy volunteers creates peak levels of 1.5 and 4.4 $\mu\text{g/mL}$ that increase linearly with dose. The parenteral form is alatrofloxacin, which is metabolized to trovafloxacin. The half-life of trovafloxacin is 9.9 ± 2.5 hours and is independent of the administered dose. It is 70% protein bound, and only 8% is excreted unchanged from urine; however, the obtained levels are adequate to treat urinary tract infections. Trovafloxacin is given in a 100- to 300-mg dose once daily. Despite its promising in vitro and kinetic profile, 1 year after being introduced on the U.S. market, reports on trovafloxacin hepatotoxicity causing deaths led the Food and Drug Administration to restrict its administration to only special indications of nosocomial infections. Clinafloxacin is given in 100-mg or 200-mg oral doses with peaks of 0.89 and 2.5 $\mu\text{g/mL}$ and a half-life of 6 hours. Side effects include diplopia, confusion, and photosensitivity skin rash, the incidence of the last-mentioned exceeding that of other quinolones. It is not yet in the market anywhere in the world.

AMINOGLYCOSIDES

Despite the advent of newer antipseudomonal compounds such as carbapenems and the fluoroquinolones, aminoglycosides have an important role in the therapy of serious *P. aeruginosa* infections. They continue to be used because of (1) their excellent and fast concentration-dependent bactericidal activity, a determining factor in the prognosis of severe *P. aeruginosa* infections in neutropenic patients or in ICU life-threatening nosocomial infections, particularly during the first 24 hours of treatment; (2) their limited tendency to develop resistance during therapy; (3) the synergistic effect when combined with antipseudomonal penicillins and antipseudomonal cephalosporins in vitro and in vivo; (4) the protective effect toward resistance development in the β -lactams whenever they are given simultaneously in vivo; (5) their lack of inoculum effect; (6) their prolonged and concentration-dependent postantibiotic effect (> 2 hours); (7) their antimicrobial activity at levels below their MICs; and (7) the possibility to be given once daily despite a half-life that demands twice-daily or thrice-daily administration.^[9] The last-mentioned possibility is based on their prolonged PAE and the *first exposure effect* (i.e., the down-regulation of subsequent uptake of the drug after initial exposure of bacteria to it). All aminoglycosides share the same disadvantages, however: (1) nephrotoxic, ototoxic, and neuromuscular blockade potential; (2) poor kinetics in cerebrospinal fluid, eye compartments, prostate, and phagocyte with an intracellular-to-extracellular ratio of less than 1; (3) reduced in vitro activity under modification of environmental factors, such as divalent cation concentration, acidic pH, decreased arterial oxygen tension, and microaerobic or anaerophilic conditions, as happens in abscesses; and (4) in vivo inactivation by high concentration of penicillins and cephalosporins.

Because aminoglycosides have been well-known antibiotics for many decades, the short review that follows focuses on worldwide

resistance surveillance and the newest compound, isepamicin.

Resistance Surveillance

A survey of prevalence of aminoglycoside resistance in 20 European university hospitals from 12 European countries is the SENTRY Antimicrobial Surveillance Programme, conducted from April 1997 through April 1998.^[39] Resistance rates to gentamicin, tobramycin, and amikacin in 584 *P. aeruginosa* strains were 21.2%, 19.2%, and 8.4%. Resistance rates were in general higher in Poland, Italy, Portugal, Spain, Greece, Belgium, and France than in Austria, Germany, the Netherlands, and Switzerland. As shown in Table 2, resistance rates of the SENTRY surveillance in Canada and the United States revealed much lower rates; however, SENTRY surveillance results in Latin America were similar to the European results. It is reasonable to assume that the differences between countries reflect variations in antibiotics policies and efforts and goals in hospital hygiene. Resistance to aminoglycosides is observed at several levels. Low-level resistance, common in *P. aeruginosa*, is attributed to impermeability of the outer cell membrane, whereas high-level resistance is associated with chemical modification (acetylation, phosphorylation, and adenylation) of the aminoglycoside molecule. The Aminoglycoside Resistance Study Group between 1988 and 1993 collected 1996 resistant isolates of *Pseudomonas* from 149 hospitals in 8 regions of the world.^{[1] [2] [31]} A great diversity of resistance mechanisms was detected (11 single and 74 combination mechanisms). Much of the diversity was attributed to the combination of permeability resistance (influencing all aminoglycosides) with a variety of plasmid-mediated aminoglycoside-modifying enzymes, particularly AAC(6')-II (Gm, Tm, and Net) and ANT (2'')-I (Gm and Tm) and less commonly AAC(3)-II (Gm, Tm, and Net), AAC(6')-I (Tm, Net, and AmK), and AAC(3)-I (Gm). The occurrence of permeability resistance in combination with so many other mechanisms suggests a response to changing aminoglycoside selective pressure. The previously existing mechanisms usually caused Gm, Tm, and Net resistance, suggesting that a change in AmK usage was associated with this observation.

Isepamicin

Isepamicin has a similar breadth and level of activity to amikacin, the latter considered as the aminoglycoside with the greatest resistance to inactivating enzymes.^{[3] [4] [7] [26]} Among 1103 *P. aeruginosa* isolates, MIC₉₀ for amikacin and isepamicin was almost identical (7.8 and 8.0 µg/mL) indicating their equal potency. AAC (6')-I is a unique enzyme because it inactivates tobramycin, netilmicin, and amikacin, whereas isepamicin is stable. This feature may enable broader isepamicin use in geographic areas where *P. aeruginosa* has a high prevalence of AAC(6')-I resistance enzymes. The fact that in surveillance studies the difference in resistance rates between amikacin and isepamicin was not as great as it has been expected (41.7% versus 36.8%) has been attributed to the high incidence of coexisting permeability mutants conferring resistance to all aminoglycosides. Isepamicin is similar pharmacokinetically to other aminoglycosides. It is not metabolized, being eliminated completely by the renal route. Kinetics are linear with a concentration maxima (C_{max}) of 7.14 µg/mL, AUC of 177 mg.h/L, half-life of 2.25 hours, and distribution volume of 0.23 to 0.29 L/kg. Clinical experience with isepamicin monotherapy after a 15-mg/kg or 8-mg/kg once-daily dose, depending on the severity of the infection, is promising, with a safety profile and tolerance similar to that of amikacin.

PSEUDOMONAS AERUGINOSA INFECTION: ANTIBIOTIC POLICIES IN THE CHOICE OF THERAPY

All antipseudomonal antibiotics reviewed herein, particularly in their early reports after carefully performed and appropriate clinical studies, have been proved efficacious in vivo in the treatment of *P. aeruginosa* systemic infections.^{[27] [36]} *P. aeruginosa*, however, despite the evolution of newer potent antibacterials, continues to be a cause of challenging and difficult-to-treat infections, carrying mortality rates that exceed 40%. This fact should be attributed to the constantly increasing number of hosts susceptible and prone to *Pseudomonas* infection (i.e., the immunocompromised neutropenic patient, patient carrying foreign bodies, and most notably the mechanically ventilated ICU patient). It is the hospital environment per se that because of broad-spectrum antibiotics' overuse and abuse provides the susceptible host with multiresistant pathogens. Despite the emergence of multiresistant *P. aeruginosa* strains susceptible only to carbapenems or colimycin, at least in ventilator-associated pneumonia, only 50% of therapeutic failures are associated with resistance development. The bacterium itself elaborates a variety of enzymes and toxins, causing lung destruction leading to abscess formation and empyema, with subsequent compromised antibiotic kinetics and emergence of resistant population.^[43] Even in the latter case, questions raised by the clinician are constantly the same: On which criteria should antibiotics be selected? Is combination therapy superior compared with monotherapy? Which risk factors should be taken into consideration?

For *P. aeruginosa* nosocomial pneumonia, a comparative study of ciprofloxacin versus imipenem in 74 ICU patients revealed failure of *Pseudomonas* eradication and resistance development in 67% and 33% versus 59% and 53%, raising the question of monotherapy validity at least in the ICU setting.^[15] Combined studies in the 1980s from the University of California Los Angeles and the Baltimore Cancer Research Center indicated that patient survival was best when *P. aeruginosa* strains were susceptible to aminoglycosides (gentamicin and amikacin) and penicillins (carbenicillin and ticarcillin).^[41] Of patients, 80% survived, whereas 58% survived if the organism was susceptible to one antimicrobial and only 20% if the pathogen was susceptible to neither drug. A recent retrospective

analysis of 123 *P. aeruginosa* bacteremias over a 3-year period showed that incidence, epidemiology, clinical characteristics, and outcome of *Pseudomonas* sepsis did not change significantly over the past 2 decades, whereas appropriate monotherapy was as effective as combination therapy, with attributable mortality of 34% for individuals surviving the first 2 days of infection.^[41] The results of another retrospective analysis of 189 episodes of *Pseudomonas* bacteremia were similar, with survival rates of 82%.^[45] To the authors' knowledge, however, no prospective randomized comparison between monotherapy and combination drug therapy has been done in the literature in a series of patients with *Pseudomonas* bacteremia.

In the febrile neutropenic host, in the case of *P. aeruginosa* infections, for improving success rates the addition of an aminoglycoside to an antipseudomonal penicillin or to ceftazidime is necessary, depending on the depth of neutropenia (<100 mm³) and the severity of the clinical picture.^[14] Imipenem and meropenem are successful as monotherapy regimens, whereas ciprofloxacin, at high doses (400 mg intravenously every 8 hours) for the fear of breakthrough gram-positive coccal bacteremias is better to be combined with a penicillin or a macrolide.^[19] It was reported that oral ciprofloxacin combined with amoxicillin-clavulanate is an effective approach for home therapy in the non-critically ill neutropenic patient.^[16] There is no doubt that in the case of nonlethal *P. aeruginosa* infections, such as chronic osteomyelitis or malignant external otitis, high-dose oral ciprofloxacin has a priority because of advantageous bone kinetics, availability of an oral formula, and lack of significant toxicity.^[17] ^[20] For severe *P. aeruginosa* infections and before selecting antibiotics it is better to tailor the choice of therapy individually according to various factors, such as neutropenia, septic shock, source of infections (community or hospital acquired, particularly ICU derived), site of infection, length of hospitalization, previous antimicrobial therapy, and resistance surveillance data. The carbapenems should be restricted, prescribed empirically only for seriously ill ICU patients and nosocomial septic shock in settings with high resistance prevalence or when they are the only active agents in susceptibility reports.

The French criteria for selecting antibiotics for ventilator-associated pneumonia are based on two risk factors^[43]: (1) administration of broad-spectrum antibiotics in the previous 15 days, and (2) mechanical ventilation for fewer than 7 days or 7 or more days. The latter factors predict the implication of multiresistant nosocomial *P. aeruginosa*, indicating the administration of carbapenems mostly in case of mechanical ventilation 7 or more days plus antibiotics in the prior 15 days.

In the cystic fibrosis patient in whom *P. aeruginosa* is an affiliated colonizer and pathogen, data seem optimistic because repeated home therapy with intravenous meropenem was well tolerated, connected with 98% success rates without emergence of resistance.^[6] From a meta-analysis of nebulized antipseudomonal antibiotic therapy in which the effect of amikacin, tobramycin, colimycin, and ceftazidime is evaluated critically, their beneficial effect was shown.^[34] The emergence of antibiotic resistance in *P. aeruginosa* strains was a fact; however, it often was temporary; resistant strains grew slowly; produced small colonies; and lost the ability to produce important virulence factors, such as elastase. Oral ciprofloxacin as a maintenance 3-month-duration antipseudomonal therapy after intravenous ceftazidime plus amikacin in children and young adults with cystic fibrosis was efficacious, safe, and well tolerated.^[38]

In the treatment of systemic *P. aeruginosa* infection, (1) continuous resistance surveillance is important; (2) effectiveness is not the only consideration when selecting an antibiotic or deciding whether to use combination therapy, and prevention of antibiotic resistance is another important issue for choosing combination therapy or monotherapy; and (3) the host plays a critical role in the decision and process of therapy.

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