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Pneumonia Due to *Pseudomonas aeruginosa*

Part II: Antimicrobial Resistance, Pharmacodynamic Concepts, and Antibiotic Therapy

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Pseudomonas aeruginosa **carries a notably higher mortality rate than other pneumonia pathogens. Because of its multiple mechanisms of antibiotic resistance, therapy has always been challenging. This problem has been magnified in recent years with the emergence of multidrug-resistant (MDR) pathogens often unharmed by almost all classes of antimicrobials. The objective of this article is to assess optimal antimicrobial therapy based on in vitro activity, animal studies, and pharmacokinetic/pharmacodynamic (PK/PD) observations so that evidence-based recommendations can be developed to maximize favorable clinical outcomes. Mechanisms of antimicrobial resistance of** ***P aeruginosa*** **are reviewed. A selective literature review of laboratory studies, PK/PD concepts, and controlled clinical trials of antibiotic therapy directed at** ***P aeruginosa*** **pneumonia was performed.** ***P aeruginosa*** **possesses multiple mechanisms for inducing antibiotic resistance to antimicrobial agents. Continuous infusion of antipseudomonal β-lactam antibiotics enhances bacterial killing. Although the advantages of combination therapy remain contentious, in vitro and animal model studies plus selected meta-analyses of clinical trials support its use, especially in the era of MDR. Colistin use and the role of antibiotic aerosolization are reviewed. An evidence-based algorithmic approach based on severity of illness, Clinical Pulmonary Infection Score, and combination antibiotic therapy is presented; clinical outcomes may be improved, and the emergence of MDR pathogens should be minimized with this approach.** ***CHEST 2011; 139(5):1172–1185***

Abbreviations: ESBL = extended-spectrum β-lactamase; HAP = hospital-acquired pneumonia; MDR = multidrug resistant; MIC = minimal inhibitory concentration; OprD = outer membrane protein; PDR = pan-drug resistant; PK/PD = pharmacokinetic/pharmacodynamic; VAP = ventilator-associated pneumonia

Pseudomonas aeruginosa is notorious for its ability to acquire antibiotic resistance, and the mechanisms for resistance are many. Mortality is high for pneumonia due to *P aeruginosa*, so therapy is particularly challenging. We review the epidemiology of antibiotic resistance, the multiple mechanisms of resistance found in *P aeruginosa*, the antibacterial agents most active against *P aeruginosa*, and the pharmacokinetic/pharmacodynamics (PK/PD) of antipseudomonal β-lactam agents. We also review the issue of advantages of combination antibiotic therapy as well as indications for use of colistin and aerosolized antibiotics.

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Antimicrobial Therapy

In national surveillance studies, those antibiotics that exhibited activity of ≥ 70% against *P aeruginosa* included aminoglycosides, antipseudomonal penicillins, antipseudomonal cephalosporins, and carbapenems (Table 1). Aztreonam, a monobactam, has activity

similar to the antipseudomonal cephalosporins, but it has not been a favored choice mainly because of relative lack of activity against gram-positive bacteria and anaerobes, organisms that are often isolated with *P aeruginosa*. The two quinolones considered as antipseudomonal agents are ciprofloxacin and levofloxacin (Table 1). Although ciprofloxacin has a lower minimal inhibitory concentration (MIC) (0.5 μg/mL) compared with levofloxacin (1.0 μg/mL) against *P aeruginosa*, the superiority of the slightly lower MIC of ciprofloxacin is offset by its lower serum and tissue concentrations as compared with levofloxacin, resulting in similar potency of these two antibiotics against *P aeruginosa*.

Epidemiology of Resistance

Emergence of antimicrobial resistance in *P aeruginosa* is growing (Table 2).[1-8] Three large-scale US surveillance databases[5-7] have demonstrated increasing resistance rates for *P aeruginosa* for fluoroquinolones (from 15% to 40%), third-generation cephalosporins (from 15% to 32%), and carbapenems (from 13% to 23%) in the past 9 to 13 years. *P aeruginosa* isolated from the respiratory tract contributed 57% to 67% of the isolates.[5,6]

Intubated patients in the ICU can acquire multidrug-resistant (MDR) *P aeruginosa* within 10 days after initiation of antipseudomonal antibiotics.[9,10] Cross-resistance is common. For example, piperacillin-resistant and ciprofloxacin-resistant *P aeruginosa* exhibited higher prevalence of resistance to other antibiotic classes compared with piperacillin-susceptible and ciprofloxacin-susceptible *P aeruginosa*, respectively[11,12]

Antimicrobial Resistance

P aeruginosa has emerged as the epitome of MDR gram-negative bacilli causing hospital-acquired pneumonia (HAP).[13-15] It possesses at least five distinct mechanisms for inducing antibiotic resistance (innate resistance). Moreover, it has the capability of acquiring genes encoding antibiotic resistance (acquired resistance). Three mechanisms of resistance predominate: production of β-lactamases, loss of outer membrane proteins, and upregulation of efflux pumps (Table 2). Mutational gyrases and inactivating enzymes are specific for quinolones and aminoglycosides, respectively. These mechanisms can be present simultaneously, thereby conferring MDR.[16]

Numerous β-lactamases are elaborated by *P aeruginosa* leading to widespread and unpredictable resistance patterns. The AmpC gene produces a β-lactamase that is the most common β-lactamase found in *P aeruginosa*. This β-lactamase has the characteristic of being "inducible" by various antipseudomonal antibiotics, thus accelerating appearance of resistance. Repression of the AmpC β-lactamase is controlled within the organism itself. Mutants produce excessive amounts of the AmpC β-lactamase when exposed to some antibiotics. Third-generation cephalosporins and ticarcillin-clavulanate select for these "derepressed" mutants. Extended-spectrum β-lactamases (ESBLs) hydrolyze third-generation cephalosporins, in addition to antipseudomonal penicillins and the first- and second-generation cephalosporins (Table 1). The genetic mechanisms for acquisition of ESBLs are related to insertion sequences, transposons, and integrons.[17]

Carbapenems are the drugs of choice for *P aeruginosa* that produce ESBLs, because carbapenems are not inactivated by most ESBLs. Transferable β-lactamases, including the metalloenzymes, require zinc ions for activity (also called class B β-lactamases). They are not affected by β-lactamase inhibitors, such as clavulanate and sulbactam. They can also hydrolyze cephalosporins and carbapenems.[18] With the appearance of these metalloenzymes, the proportion of *P aeruginosa* that is resistant to carbapenems is increasing; VIM-2 is the dominant carbapenemase in *P aeruginosa*.[19] Some endogenous cephalosporinases of *P aeruginosa* may also confer resistance to imipenem.[20] The abbreviations of these β-lactamases are not in any standard or logical format, rendering nomenclature interpretable only to researchers in the field.

Efflux pump mechanisms actually remove the antibiotic before it can attach to its target site (Table 2).[16] The most relevant pump is Mex AB-OprM, which conveys resistance to quinolones, antipseudomonal penicillins, and third-generation cephalosporins.[21]

Aminoglycoside resistance in *P aeruginosa* is often due to aminoglycoside-modifying enzymes, the most common of which is acetyltransferase.[22] Enzymatic modification of the aminoglycoside structure results in decreased ability of the aminoglycoside to bind to the ribosome of the *P aeruginosa*. Amikacin is the least vulnerable to such mechanisms, because multiple enzymes are necessary for inactivation. Reduced uptake of the aminoglycoside mediates resistance to all aminoglycosides, including amikacin. Novel aminoglycoside resistance gene cassettes are being elucidated—in the worst case scenario, these are being discovered within integrons that also encode metalloenzymes.[23]

Bacterial DNA gyrases maintain the bacterial chromosome in a supercoiled state and repair breaks in DNA that occur during replication. The quinolones act by inhibiting the activity of DNA gyrase enzymes; this leads to interference with DNA replication and cell death. Quinolone resistance is attributable to mutations in the DNA gyrases. The relative in vitro

Table 1—*Drugs of Choice for* Pseudomonas aeruginosa

Aminoglycosides (amikacin, tobramycin, gentamicin)
β-Lactam congeners
Cephalosporins, third-generation (cefoperazone, cefsulodin, ceftazidime)
Cephalosporins, fourth-generation (cefepime, cefpirome, cefclidin)
Monobactam (aztreonam)
Extended-spectrum penicillins (ticarcillin and/or ticarcillin-clavulanate, piperacillin and/or piperacillin–tazobactam, azlocillin)
Carbapenems (imipenem, meropenem, doripenem)
Fluoroquinolones (ciprofloxacin, levofloxacin)
Colistin/polymyxin B

activity of antipseudomonal quinolones, ciprofloxacin and levofloxacin, is lower than that of β-lactam agents.[24] *P aeruginosa* requires greater time of exposure to quinolones[25] as compared with *Streptococcus pneumoniae*, which is rapidly killed by quinolones.

Outer membrane impermeability is a mechanism of resistance for several different classes of antibiotics (Table 2). The most common mechanism by which *P aeruginosa* becomes carbapenem resistant is via mutational loss of outer membrane protein (OprD). Mutational loss of OprD is a frequent occurrence during imipenem therapy; imipenem resistance has emerged during treatment of *P aeruginosa* infections treated with the drug.[21,26] Fortunately, loss of OprD does not confer resistance to β-lactams other than the carbapenems.

Resistance of *P aeruginosa* to colistin is rare and occurs most commonly in patients with cystic fibrosis who have received aerosolized colistin therapy.[27] Structural modifications of the outer membrane protein are responsible for high-level resistance of *P aeruginosa* to colistin.[28] Within the ICU, MDR *P aeruginosa* is often isolated from patients with pneumonia; these isolates are susceptible in vitro only to colistin. Pan-drug-resistant (PDR) *P aeruginosa* are resistant to all commercially available antibiotics, including colistin. Acquisition of resistance in pathogenic bacteria usually leads to decreased virulence (the fitness hypothesis). However, laboratory studies of MDR *P aeruginosa* have shown evidence for both decreased virulence[29-31] and maintenance of virulence.[32]

Table 2—*Mechanisms of Antibiotic Resistance to* P aeruginosa

Mechanism	Resistance for
β-Lactamase	
AmpC	Penicillins, cephalosporins
ESBLs	Penicillins, cephalosporins
Metallo-β-lactamases	Penicillins, cephalosporins, carbapenems
Efflux pumps	Cephalosporins, ureidopenicillins, carbapenems, aminoglycosides, quinolones
Mutational gyrases	Quinolones
Inactivating enzymes	Aminoglycosides
Outer membrane impermeability	Carbapenems, aminoglycosides, quinolones

ESBL = Extended-spectrum β-lactamases.

PK/PD Considerations

Aminoglycosides are concentration-dependent antibiotics. Such antibiotics effectively eradicate the target bacteria when concentrations are ≥ 10 times above their MIC. In animal models of infection, animals are more likely to survive a potentially lethal challenge of bacteria if the aminoglycoside is given as a single daily dose rather than when given in divided doses every 8 h. In contrast, β-lactam agents are classified as time-dependent antibiotics; for these agents, constant infusion maximizes the pharmacodynamic concept of time above the MIC. Pharmacy preparation costs are decreased for once-daily dosing and constant infusion administration.[33,34]

At least seven studies have compared the clinical efficacy of continuous and intermittent β-lactam administration (Table 3).[34-40] In five studies, patients with *P aeruginosa* pneumonia were included, ranging from 13% (4/31) to 53.1% (103/194) of the study population.[34,36,37,39,40] These five studies used piperacillin/tazobactam, imipenem/cilastatin, meropenem, and ceftazidime for treatment. Clinical efficacy was assessed by mortality and treatment outcome (cure, improved, failure). Two studies demonstrated the superior efficacy of continuous infusion,[36,39] and the other three found no difference in the two infusion strategies.[34,37,40] The remaining two studies did not explicitly name the causative pathogen or infection site of the study population, but continuous infusion produced improved outcome.[35,38] Constant infusion has been shown to be superior to intermittent administration in achieving pharmacodynamic targets.[41,42] Thus, strong consideration should be given for the use of constant infusion of antipseudomonal β-lactam antibiotics for *P aeruginosa* pneumonia.

Merely slowing the rate of IV infusion from 1 to 4 h has also been applied for antipseudomonal antibiotics, particularly meropenem and doripenem. This increases the target time above the MIC during any one dosing interval, allowing for treatment of pathogens requiring higher MICs for their eradication. Doripenem is the most active carbapenem in vitro against *P aeruginosa*.[43,44] In a prospective randomized trial of doripenem vs imipenem in 531 patients with ventilator-associated pneumonia (VAP), the clinical and microbiologic cure rate in patients with *P aeruginosa* pneumonia was higher in patients receiving doripenem compared with those receiving imipenem, although the results were not statistically significant.[45]

Table 3—*Comparison Between Patients Receiving Continuous Infusion and Intermittent Infusion for Pneumonia*

Study/Year	Patient No.	% of *P aeruginosa* Pneumonia	Antibiotics	Evaluation Parameter	Continuous Infusion, %	Intermittent Infusion, %	*P* Value
Lorente et al[35]/2007	121	NA	Ceftazidime	Cure rate[a]	89.3	52.3	< 0.001
Lodise et al[36]/2007	194	53.1	Piperacillin/tazobactam	Mortality[b]	12.2	31.6	0.04
Sakka et al[37]/2007	20	20.0	Imipenem/cilastatin	Mortality	10.0	20.0	NS
Rafati et al[38]/2006	40	NA	Piperacillin	Change in APACHE II scores[c]	5.2 ± 2.6	2.8 ± 4.3	0.04
Lorent et al[39]/2006	89	31.0	Meropenem	Cure rate[a]	84.6	40	0.02
Nicolau et al[34]/2001	35	26.0	Ceftazidime	Cure rate[a]	33	41	NS
Hanes et al[40]/2000	31	13.0	Ceftazidime	Successful rate[d]	56	71	NS

APACHE = Acute Physiology and Chronic Health Evaluation; NA = not available; NS = not significant.
[a]Cure, defined as complete resolution of all clinical signs and symptoms of pneumonia.
[b]Mortality, 14-d mortality.
[c]Change in APACHE II scores from baseline to the end of the fourth day (mean ± SD).
[d]Successful, cure and improvement.

The polymyxins also exhibit concentration-dependent antibacterial activity, with area under the concentration-vs-time curve as the best predictor of their activity in nonclinical models of infection.[41] A rapid bacterial kill in a concentration-dependent fashion was observed using time-kill methods with a substantial inoculum effect. Polymyxin exhibits an unusual phenomenon of a negative postantibiotic effect, which means that the growth of *P aeruginosa* markedly increases within 2 to 6 h once polymyxin concentrations drop below the MIC for *P aeruginosa*.[46] Heteroresistance may account for the rapid regrowth as susceptible strains are replaced by resistant subpopulations. Greatest suppression of resistance was seen for a tid dosing regimen of colistin in a pharmacodynamic model.[47] Thus, colistin dosing every 6 to 8 h may be ideal.

Antibiotic Therapy

Initiation of appropriate empiric antibiotic treatment in a timely manner may decrease mortality in hospitalized patients with pneumonia. We reviewed 17 studies (Table 4)[48-64]: 14 studies conducted in ICUs in patients with VAP,[48-53,55-57,59-62,64] one study in patients with generalized infection,[58] and two studies in patients with bacteremia.[54,63] In the latter three studies, pneumonia contributed to 16.0% to 62.7% of the study population.[54,58,63] The proportion of *P aeruginosa* as causative pathogen for pneumonia ranged from

Table 4—*Comparison of Mortality in Patients Receiving Empirical Appropriate and Inappropriate Therapy for Pneumonia*

Study/Year	Patient No.	% of *P aeruginosa*[a]	Mortality (%)		*P* Value
			Appropriate Therapy[b]	Inappropriate Therapy[b]	
Garnacho-Montero et al[48]/2007	183	100.0	33.6	72.5	< .001
Kollef et al[49]/2006	396	14.4	22.7	30.9	NS (.092)
Mueller et al[50]/2005	82	67.1	3.6	22.2	.048
Clec'h et al[51]/2004	142	38.0	36.5	45.6	NS
Dupont et al[52]/2003	322	17.4	17.0	22.8	NS (.18)
Leroy et al[53]/2003	132	43.2	39.6	61.5	.04
Chamot et al[54]/2003[c]	115	100	13.3	17.6	NS
Iregui et al[55]/2002	107	36.4	10.8	39.4	.001
Dupont et al[56]/2001	111	35.1	38.2	48.2	NS
Bercault and Boulain[57]/2001	135	NA	40.2	52.9	NS
Kollef et al[58]/1999[d]	655	16.8	17.7	42.0	< .001
Kollef and Ward[59]/1998	60	33.3	NA	NA	< .05
Sanchez-Nieto et al[60]/1998	38	42.1	25.0	42.9	NS
Luna et al[61]/1997	65	38.5	37.5	81.6	< .01
Rello et al[62]/1997	100	55.0	15.4	37.0	< .05
Leibovici et al[63]/1997[c]	2165	16.0	18.4	34.0	< .001
Alvarez-Lerma et al[64]/1996	430	40.5	16.2	24.7	.034

See Table 3 legend for expansion of abbreviations.
[a]Percentage of *Pseudomonas aeruginosa* is the number of isolates divided by number of the patients.
[b]Appropriate therapy was defined as the regimen containing at least one antibiotic agent to which isolated isolate(s) was (were) susceptible.
[c]Study population was patients with bacteremia; the proportion of pneumonia was 16.0% and 20.9% in Leibovici et al[63] and Chamot et al.[54]
[d]Study population was infected patients requiring ICU admission; the proportion of pneumonia was 62.7%.

14.4% to 100% in these studies (Table 4). Ten studies found that initiation of appropriate empirical antibiotic treatment in a timely manner significantly decreased mortality in hospitalized patients with pneumonia, whereas seven studies did not.

In one study of *P aeruginosa* bacteremia[54] and two studies of VAP,[51,57] the authors noted that the infection could be so severe that death was imminent despite initiation of appropriate empirical antimicrobial agent therapy. In the remaining studies, three attributed the insignificant results to the insufficient statistical power and one provided no explanation.[49,52,56,60]

Nevertheless, mortality was 3.6% to 40.2% in patients with appropriate empirical therapy and increased to 17.6% to 81.6% in those receiving inappropriate empirical antibiotic therapy. Furthermore, modification of initial inappropriate treatment after a delay of 48 to 72 h failed to improve mortality.[36,55,61] Isolated pathogens resistant to the empirically prescribed antimicrobial agents were a common reason for initial treatment classified as inappropriate, with contributions of 18% to 75.0%.[55,58,59,62] *P aeruginosa* was the most common drug-resistant gram-negative bacterium.[55,62,64]

Combination Antibiotic Therapy vs Monotherapy

In Vitro Studies: For combination therapy, the greatest likelihood of synergy is an aminoglycoside with an antipseudomonal penicillin (~90%), and then, in decreasing order, with a cephalosporin (~80%) or a carbapenem (~50%). The interaction of fluoroquinolones combined with β-lactams or aminoglycosides was usually autonomous (additive) or indifferent.[65,66] For quinolone combinations plus antipseudomonal β-lactams, the β-lactam drug accomplished most of the bacterial killing.[65,66] In a pharmacodynamic model, levofloxacin combined with meropenem were synergistic (3-log cell kill) and had higher resistance suppression.[67] Monotherapy with any quinolone for the management of confirmed *P aeruginosa* pneumonia is not recommended, given the high likelihood of the development of bacterial resistance (38%) and the failure to achieve bacteriologic eradication during therapy (67%).[68] This is not surprising owing to the low likelihood for either levofloxacin or ciprofloxacin to attain the target 24-h area under the concentration-vs-time curve ratio of > 100.[69]

Combination Antibiotics in Animal Models

Several animal studies have assessed the impact of combination therapy for *P aeruginosa* pneumonia.[70-76] Guinea pigs were used in four studies and mice in two studies.[70,75] In two studies, neutropenia was induced by cyclophosphamide.[72,74] Mucoid *P aeruginosa* was used in three of the studies.[70,74,75] Pneumonia was induced by inoculation of *P aeruginosa* via the intranasal route in four studies[70,72,74,75] or the intratracheal route in two studies.[71,73,74] The end points were mortality in five studies.[70-73,75] In addition, clearance of *P aeruginosa* from lung was addressed in three studies.[71,73,74] Combination therapy led to significantly lower mortality in two studies[71,75] and a favorable trend in two other studies.[70,73] Ceftazidime plus clarithromycin was superior to both ceftazidime monotherapy and clarithromycin monotherapy.[75] The combination of cefsulodin plus tobramycin led to lower mortality as compared with β-lactam agent monotherapy[71] but not to tobramycin monotherapy. The combination of ceftazidime plus tobramycin was superior to monotherapy of either drug in one study, but statistical significance was not attained.[73] In the Rusnak et al[72] study, in vitro synergy was present for four combinations (ticarcillin plus tobramycin, ceftazidime plus tobramycin, azlocillin plus tobramycin, ceftazidime plus methicillin); however, none of these combinations significantly improved mortality compared with the monotherapy regimens (azlocillin, ceftazidime, tobramycin, methicillin). Clearance of bacteria from lung tissue was also evaluated in three studies.[71,73,74] No significant improvement was seen in one study using cefsulodin plus tobramycin.[71] Increased clearance was seen for ceftazidime plus tobramycin.[73] Increased clearance was seen for mezlocillin plus tobramycin in neutropenic animals but not in nonneutropenic animals.

Combination vs Monotherapy for P aeruginosa *Pneumonia in Patients*

Combination therapy can broaden the antimicrobial spectrum, provide synergistic interaction, decrease emergence of antimicrobial resistance, and minimize superinfection. However, demonstrated improvement in outcome for combination therapy has been elusive. Early studies that documented decreased mortality in patients receiving combination therapy used antibiotics that are no longer used in the current era.[77,78] Moreover, most of the earlier studies involved neutropenic patients with bacteremia. With the advent of broad-spectrum and bactericidal antibiotics, such as third- or fourth-generation cephalosporins or carbapenems, it has been suggested that an additional aminoglycoside antibiotic might be unnecessary.[79]

In a prospective study of *P aeruginosa* bacteremia,[80] combination therapy was assessed in vitro in 123 patients. Checkerboard assays and time-kill curve studies were performed using the antibiotics that the patients received. No improvement in mortality was seen for administration of synergistic combinations assessed by checkerboard methodology. However, improvements in mortality were seen for administration of synergistic combinations as defined by results

from time-kill curves: 46% (56/123) survived who received a synergistic combination as compared with 28% (34/123) who received a nonsynergistic (indifferent or autonomous) combination. Although a clear-cut trend was observed, statistical significance was not attained, (Fisher exact test, two-tailed, $P = .10$).

Several meta-analyses have concluded that combination therapy did not offer a survival benefit in patients with febrile neutropenia, gram-negative bacteremia, and sepsis; it is important to note that these meta-analyses were not directed specifically at *P aeruginosa*.[81-84] Somewhat surprisingly, prevention of antimicrobial resistance and superinfection also was not seen with combination therapy,[81,85] although nephrotoxicity occurred in patients receiving combination therapy.[81] In one meta-analysis of five studies in which *P aeruginosa* was specifically evaluated, mortality decreased significantly in patients receiving combination therapy.[82] However, in four of the five studies in this meta-analysis, a single aminoglycoside was used as monotherapy, which might be considered inadequate treatment of *P aeruginosa* bacteremia.[83,86]

Because few studies compared the efficacy of monotherapy with that of combination therapy in patients with *P aeruginosa* pneumonia,[48] studies regarding comparison of the two treatment strategies for pneumonia were pooled for this discussion. In nine pneumonia studies, *P aeruginosa* was the causative pathogen in 6.0% to 100%; two of these studies showed significantly improved survival by combination therapy.[80,87] In addition, one review[88] combined and summarized the results of treatment of pneumonia from two other reviews.[79,81] The first review included six studies in patients with HAP and one study in patients with HAP or severe community-acquired pneumonia.[79] The second review comprised at least 1,200 patients with HAP.[81] Success rates were similar in studies with monotherapy and in those with combination therapy except for two studies[89,90] in which monotherapy was significantly better. A meta-analysis for 11 trials with 1,805 patients compared the efficacy of monotherapy with that of combination therapy for suspected VAP.[91] A total of 85.1% of the study patients underwent mechanical ventilation and *P aeruginosa* was the causative pathogen in 13.8% of the patients. The rates of mortality and treatment failure for monotherapy were similar to those for combination therapy. In a prospective study of 84 patients in a trauma ICU with *P aeruginosa* VAP diagnosed by quantitative BAL, all patients received empiric monotherapy.[92] A total of 94.1% achieved microbiological resolution; however, 5.9% required combination antibiotic therapy consisting of cefepime and aminoglycoside to achieve resolution.[92] In two studies of VAP, combination therapy did not improve mortality.[48,93] However, the proportion of patients receiving initial appropriate antibiotics was significantly higher in those receiving combination therapy than in those receiving monotherapy[48,93]; microbiologic eradication of *P aeruginosa* was also significantly higher.[93] In a prospective study of 28 ICUs in patients with VAP due to *Pseudomonas* and *Acinetobacter* species, no significant differences were found for combination antibiotic therapy vs monotherapy. However, the appropriateness of antibiotic therapy as defined by in vitro susceptibility and microbiologic eradication was significantly higher for those patients receiving combination therapy.[93]

In a meta-analytic/meta-regression study of randomized and observational studies of serious bacterial infection, combination antibiotic therapy was found to improve outcome for those patients who were severely ill as defined by sepsis and septic shock.[94] This meta-analysis included studies of *P aeruginosa* bacteremia and two studies of *P aeruginosa* VAP.

In their Cochrane review, Paul et al[84] concluded that no clinical benefit is accrued, whereas nephrotoxicity with an aminoglycoside was a disadvantage for combination therapy. We point out that duration of aminoglycoside use correlates with nephrotoxicity. Duration in the early studies of neutropenic patients was >10 to 14 days. In a study of 21 patients with AIDS with *P aeruginosa* bacteremia,[95] the median duration was 12 days (maximum 32 days). (In this study, mortality was significantly lower for those who received combination antibiotic therapy with an aminoglycoside.) In another study of 604 patients with febrile neutropenia, amikacin or tobramycin were given for 16.6 days (range 15.5-122 days).[96] Aminoglycoside toxicity would thus be minimal if duration was limited to 5 days or fewer.[97] Chamot et al[54] found that empirical combination therapy significantly increased survival even if the aminoglycoside was given only for 3 to 5 days, followed by monotherapy.

The emergence of MDR makes monotherapy a tenuous strategy in severely ill patients with the likelihood of *P aeruginosa* pneumonia. Because initial appropriate antimicrobial treatment is critical to decreasing mortality rate in patients with pneumonia, prescription of combination therapy for patients with *P aeruginosa* pneumonia would increase the probability of therapy that is active in vitro. Toxicity of the aminoglycoside component can be mitigated by shortening the duration of aminoglycoside therapy or substituting a quinolone for the aminoglycoside. We would thus recommend combination therapy for patients suspected of having *P aeruginosa* pneumonia, especially in a hospital with endemic MDR *P aeruginosa*. Although randomized controlled trials are ideal, logistic considerations for such a study are almost insurmountable. The obstacles include the large number of patients required to attain statistical

power and the difficulty in establishing a definitive diagnosis of *P aeruginosa* pneumonia.

We recommend an antipseudomonal β-lactam as the primary antibiotic for presumed *P aeruginosa* pneumonia (Table 1) (Keep in mind our caveats on colonization in non-severely ill patients as discussed in the "Diagnosis" section of our previously published article[98] in this two-part series.) Given the possibility of autonomous (additive) or even synergistic interaction in this era of MDR, we would add an aminoglycoside for 3 to 5 days.[99] Once culture of respiratory secretions has confirmed the presence of *P aeruginosa*, treatment could be adjusted based on in vitro susceptibility and the aminoglycoside could be discontinued. Antibiotic therapy could also be simplified if respiratory tract cultures failed to yield *P aeruginosa*.

Although no randomized studies have compared the efficacy of a quinolone vs an aminoglycoside as the second component of combination therapy, many ICU physicians have elected to use quinolones in combination with an antipseudomonal β-lactam agent to avoid the nephrotoxicity of the aminoglycoside. In a retrospective study of bacteremias caused by gram-negative bacilli, including *P aeruginosa*, mortality was lower for non-critically ill patients who received combination therapy with β-lactam agents plus quinolones as compared with β-lactam monotherapy.[100]

We do not recommend combinations of two β-lactam agents. Double β-lactam therapy has proven inferior to the β-lactam-aminoglycoside combination in animal models.[101] Emergence of resistance occurred in 40% (2/5) of patients with *P aeruginosa* infection treated with double β-lactams.[102]

Rifampin has been shown to be synergistic in vitro with antipseudomonal penicillin and aminoglycosides against *P aeruginosa*[103,104] and to improve survival in a neutropenic mouse model of *Pseudomonas* bacteremia.[104,105] This combination has also been used as successful therapy in a limited number of patients with *P aeruginosa* infections refractory to standard combination therapy.[106] A prospective randomized trial of an antipseudomonal β-lactam plus an aminoglycoside with or without rifampin was conducted in 121 patients with *P aeruginosa* bacteremia.[107] Although bacteriologic cure was demonstrated significantly more frequently in patients randomized to the rifampin-containing regimen, survival was not significantly different. Fosomycin was used successfully in combination with a carbapenem for six out of eight patients with MDR *P aeruginosa* pneumoniae.[108]

Algorithm for ICU Pneumonia

An evidence-based algorithm for *P aeruginosa* pneumonia in the ICU is provided for the reader's consideration (Figs 1, 2).[109,110] It is derived, in part, from the approaches described by Singh et al[110] and Torres.[111] It should be noted that as many as 50% to 70% of patients with pulmonary infiltrates who are treated for ICU pneumonia do not actually have an infection but have other conditions, including ARDS, congestive heart failure, atelectasis, and so forth. Thus, establishing that the patient has a true respiratory infection is important, because increased mortality occurs if antibiotics are given indiscriminately to ICU patients who are not infected[110,112,113] or not severely ill.[94] Severity of illness should be assessed (Fig 1): The various Acute Physiology and Chronic Health Evaluation (APACHE) scores or the Pitt Bacteremia Score[109] are useful quantitative scores. If the patient is severely ill, then empirical therapy is a necessity. Factors consistently predisposing to multidrug resistance include evidence of prior colonization or infection by MDR *P aeruginosa* as well as receipt of prior antibiotics during the ICU stay.[114-116] An antipseudomonal β-lactam that is not a carbapenem is generally preferred (Fig 1, Table 1). Local susceptibility patterns should guide initial empiric antibiotic therapy. If an antipseudomonal β-lactam has already been administered within the past 30 days, selecting another antipseudomonal antibiotic of a different class is indicated. If an aminoglycoside is selected as the second component of the combination, the aminoglycoside component might be limited to 3 to 5 days if a clinical or a bacteriological response is seen.

The CPIS score is used as a screening tool to identify patients who can receive short-course monotherapy safely (Fig 1). Given that colonization is a distinct possibility in a stable patient, as discussed previously, the use of CPIS score will minimize the possibility of overtreatment of *P aeruginosa* found in an innocent bystander. At the end of 3 days, the patient should be clinically re-evaluated (Fig 2). Respiratory tract culture results should be available (Fig 2). For patients who were not critically ill at outset and received monotherapy, the antibiotic can be discontinued if the CPIS remains low following 3 days of monotherapy.[110] Vigilant monitoring for subsequent signs of infection is then indicated.

Colistin Therapy

Given the emergence of MDR *P aeruginosa*, colistin has been resurrected (Fig 2). Its efficacy has been reported in several uncontrolled series of ICU pneumonia.[117-124] In a case control study of VAP caused by MDR *P aeruginosa* or *Acinetobacter*, a favorable clinical response was seen in 75% of those treated with IV colistin vs 72% treated with imipenem.[125] As mentioned previously, PK/PD studies suggest that divided doses every 6 to 8 h may be preferred over every 12 h dosing.

In vitro and animal model studies show synergy between colistin plus rifampin and colistin plus carbapenems against *P aeruginosa*,[126,127] although clinical

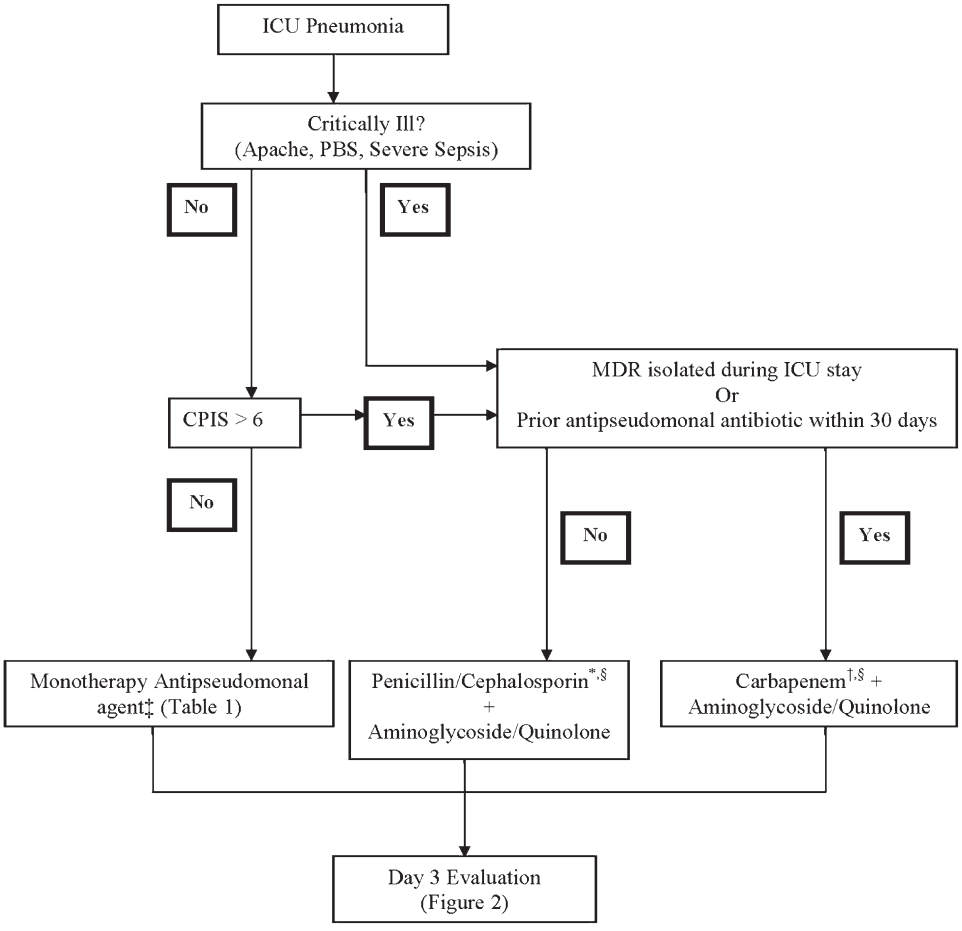

FIGURE 1. Approach to antipseudomonal antibiotic therapy for ICU pneumonia: empirical therapy. *Extended spectrum penicillin or antipseudomonal cephalosporins (Table 1); †antipseudomonal carbapenems are imipenem, meropenem, doripenem; §local antibiotic susceptibility patterns should be considered; ‡monotherapy should not be an aminoglycoside. CPIS = Clinical Pulmonary Infection Score[110]; MDR = Multidrug resistant (resistant to antipseudomonal penicillins, cephalosporins, carbapenems, quinolones); PBS = Pitt Bacteremia Score[109]; Severe Sepsis = sepsis with organ dysfunction (hypotension, hypoperfusion).

studies in humans have not supported the use of colistin-containing combinations. PDR *P aeruginosa*, resistant in vitro to all commercially available antibiotics, including colistin, has been implicated in VAP; the primary risk factor was combined use of colistin plus carbapenems for > 13 days.[128]

Colistin has been reported to cause both reversible nephrotoxicity and reversible neurotoxicity[129-131]; however, these adverse effects are difficult to discern in critically ill patients given the multiplicity of confounding factors. Colistin nephrotoxicity has been shown to be a manageable problem.[121,122,125,132,133] Interestingly, colistin is one of the few nephrotoxic drugs that has no ototoxicity.

Duration of Antibiotic Therapy

A prospective, randomized, double-blind trial in 51 ICU patients with VAP assessed optimal duration of antibiotic therapy: 8 days vs 15 days.[134] Forty-two patients were infected by *P aeruginosa* as defined by quantitative bronchoscopy cultures.[134] The recurrence rate was significantly higher in those who received 8 days vs 15 days of antibiotic therapy (40.6% vs 25.4%), although length of ICU stay and mortality were similar. In contrast, emergence of MDR pathogens was significantly higher in those who received 15 days of therapy, an important finding that has been overlooked by many. The risk of recurrence must therefore be balanced against the emergence of an MDR or PDR *P aeruginosa* within that same patient. Thus, we propose to use 8 days of therapy if the diagnosis of *P aeruginosa* is presumptive and clinical stability has been achieved within 3 days. On the other hand, if the *P aeruginosa* being treated is resistant to the empirical antibiotic initiated or if the ICU course has been complicated, then 15 days may be preferred (Fig 2).

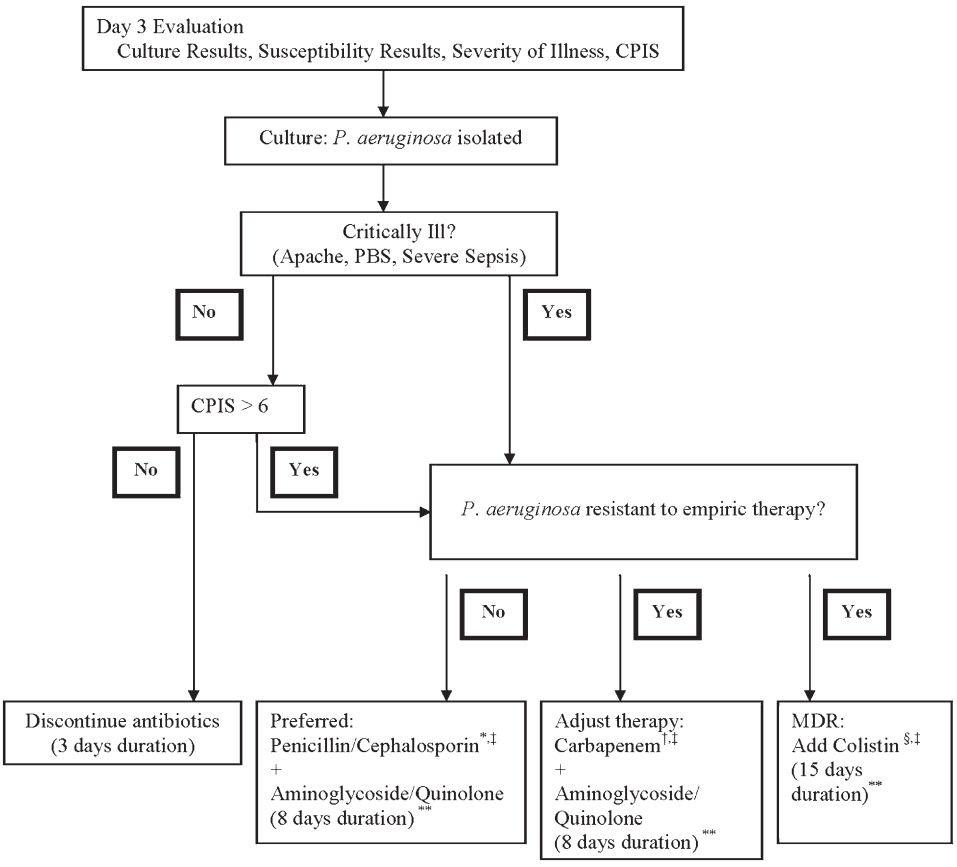

FIGURE 2. Day 3 evaluation for antipseudomonal antibiotic therapy for ICU pneumonia. *Extended spectrum penicillin or antipseudomonal cephalosporin (Table 1); †antipseudomonal carbapenems are imipenem, meropenem, doripenem; §add colistin as inhalation or parenteral therapy to the most active combination therapy; ‡local antibiotic susceptibility patterns within that institution should be considered; **duration of β-lactam therapy should be 8-15 days. The aminoglycoside/quinolone can be discontinued at 3-5 days based on results from in vitro susceptibility testing and clinical response. Note: The three antibiotic regimens displayed are intended for confirmed *P aeruginosa* pneumonia in patients who have a CPIS > 6 and are critically ill. Deescalation is recommended if these conditions are not fulfilled. See Figure 1 legend for expansion of the abbreviations.

Aerosolized Antibiotics for P aeruginosa *ICU Pneumonia:* Aerosolized antibiotics consisting of aminoglycosides or colistin have been evaluated in patients with pneumonia with the underlying illnesses of cystic fibrosis or lung transplantation. Inhaled aminoglycosides lead to high drug concentrations in lung tissue, whereas serum concentrations are negligible. In patients with cystic fibrosis, inhaled tobramycin achieved 25 times the MIC for *P aeruginosa* in sputum, whereas serum concentrations were negligible.[135]

Aerosolized colistin has been used successfully in anecdotal reports of pneumonia therapy and a retrospective case-control study,[136] usually as a supplement to IV therapy.[137-141] In a prospective randomized trial of aerosolized colistin in 100 patients with VAP, favorable outcome was essentially the same as control patients receiving aerosolized saline (about 50%).[142] With respect to combinations of aerosolized antibiotics, aerosolized colistin and tobramycin have been used for recalcitrant pneumonia with MDR *P aeruginosa* in patients with cystic fibrosis. Aztreonam inhalation solution has been approved for patients with cystic fibrosis infected with *P aeruginosa*.

CONCLUSIONS

MDR *P aeruginosa* represents an emerging problem in ICUs owing to multiple bacterial resistance mechanisms. Based on assessment of in vitro studies, animal models, PK/PD data, and extensive clinical literature, we recommend an antipseudomonal β-lactam antibiotic in combination with an aminoglycoside or an antipseudomonal quinolone. The increasing resistance of *P aeruginosa* to quinolones may be a limiting factor. If possible, constant infusion of the β-lactam antibiotic should be used, for it provides more intense activity against this bacterium for a

longer period of time and decreases labor costs (nursing and pharmacy time). Once-daily aminoglycoside dosing is superior pharmacodynamically and also more convenient. The duration of the aminoglycoside therapy should be limited to <5 days if possible. Polymyxins (colistin) are used in some ICUs because these agents often remain the only antibiotics that exhibit activity against MDR *P aeruginosa*. A pragmatic algorithmic treatment approach of empirical antibiotic therapy for ICU pneumonia is presented.

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