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EXPERT REVIEWS

Treatment of community-acquired pneumonia

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Community-acquired pneumonia is the sixth leading cause of death in the USA. Adherence to the 2007 Infectious Diseases Society of America/American Thoracic Society community-acquired pneumonia guidelines has been associated with improved clinical outcomes. However, choice between guideline-recommended treatments is at the discretion of the prescribing clinician. This review is intended to discuss the characteristics of these treatment options including dosing frequency, dose adjustment for renal/hepatic dysfunction, serious/common adverse events, drug interactions, lung penetration, pharmacokinetic-pharmacodynamic target and effect of obesity to help guide antimicrobial selection. An increasing portion of patients are receiving expanded empiric coverage for methicillin-resistant *Staphylococcus aureus* as recommended by the American Thoracic Society and Infectious Diseases Society of America for healthcare-associated pneumonia. However, this expanded coverage may not be achieving the desired improvements in clinical outcomes. We expect this increasingly diverse spectrum of patients with pneumonia to eventually result in the merger of these two guidelines to include all patients with pneumonia.

Keywords: dose optimization • empiric therapy • lung penetration • obesity • pharmacodynamics • pharmacokinetics

Community-acquired pneumonia (CAP) affects 5.6 million Americans and 915,900 Americans aged 65 and over per year [1,2]. It is the sixth leading cause of death in the USA and is responsible for 600,000 hospitalizations of geriatric patients.

The Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) provide numerous guideline-recommended therapeutic options for the treatment of CAP [3]. While the selection of agent has not been associated with clinical success or mortality, the provision of guideline-recommended therapy has been linked to improved clinical outcomes [4–6]. This review will provide a summary of the IDSA/ATS guideline recommendations for adults with CAP emphasizing factors associated with patient- and drug-specific factors. Patient factors to be discussed include allergy history, concomitant medications and disease states as well as kidney/liver function. Drug-specific factors will focus on factors affecting antimicrobial pharmacokinetics (PK) and pharmacodynamics (PD) with an emphasis on lung penetration and obesity.

Outpatient treatment of CAP

The IDSA/ATS guidelines recommend that patients with CAP in the outpatient setting or on a general medicine ward typically receive antimicrobial coverage for *Streptococcus pneumoniae*, *Haemophilus influenzae* and atypical pathogens (*Chlamydophila pnuemoniae*, *Mycoplasma pnuemoniae*, *Legionella*) [3].

Previously healthy & have not used antimicrobials within 3 months

Treatment options for these patients include:

1. Azithromycin, clarithromycin or erythromycin (strong recommendation)
2. Doxycycline (weak recommendation)

Macrolides/ketolide

Drug characteristics: Drug characteristics for antimicrobials used in the treatment of CAP are shown in Table 1. Erythromycin is rarely used for CAP due to its frequent dosing, inhibition of CYP450 3A4 and gastrointestinal side effects. Clarithromycin is favored by some clinicians due to its potency against *S. pneumoniae*. However, it also inhibits CYP450 3A4 and is associated with metallic taste. Therefore, azithromycin is the most commonly used macrolide. Reasons for this include its once-daily dose, shortened duration of treatment due to its extended half-life and relative lack of CYP450 3A4 inhibition.

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Telithromycin is a ketolide that was designed to overcome the low- (efflux) and high-level (alteration of the 50S ribosomal binding site) macrolide resistance. The appeal of its *in vitro* potency and once-daily dosing have been diminished by the reports of hepatotoxicity that have resulted in removal of telithromycin's indications for acute sinusitis and acute exacerbations of chronic bronchitis [7]. Telithromycin's use can also be limited by its potent inhibitor of CYP450 3A4 and lack of an intravenous formulation.

Lung penetration: Macrolides are lipophilic agents and have high concentrations in the lungs (epithelial lining fluid [ELF] to plasma concentration ratio >1) [8]. This will be beneficial; especially in extracellular microorganisms (i.e., *S. pneumonia, Moraxella catarhalis, H. influenzae*) since ELF is the likely infection site for these pathogens [8].

Effect of obesity: To our knowledge, the only data come from a study of patients with *Helicobacter pylori* [9]. Two groups of non-diabetic naïve *H. pylori*-positive patients, a control group (BMI <25 kg/m^2) and study group (BMI ≥25 kg/m^2), received pantoprazole 40 mg for 2 weeks plus amoxicillin 1 g three times a day, and clarithromycin 250 mg three times a day, for the first week. *H. pylori* eradication was less common for BMI ≥25 kg/m^2 than BMI <25 kg/m^2 (55 vs 85%, $p < 0.005$). However, it is difficult to extrapolate these findings as it is unknown which drug(s) was/were affected by patient weight.

Dose optimization: Macrolides are as concentration-independent antibiotics [10]. The percentage of time above the minimal inhibitory concentration (MIC), also known as T>MIC, is the PK-PD parameter best associated with microbial killing for erythromycin and clarithromycin, whereas the ratio of the area under curve (AUC) to the MIC (AUC/MIC) best correlates with azithromycin's activity [10]. Mechanisms to improve the PK-PD target for an oral formulation of T>MIC include using more frequent daily dosing or an extended-release formulation. Mechanism to improve T>MIC for intravenous formulations will be discussed later as most data supporting the approaches used come from β-lactams. Clarithromycin is the only macrolide with a commercially available extended-release formulation. Drugs whose activity is best associated with the AUC/MIC ratio should be dosed as infrequently as possible to enhance patient compliance. Other countries have used alternative azithromycin regimens to achieve this (500 mg daily for 3 days, 2 g as a single dose), but these approaches are not approved by the US FDA for CAP. The guidelines do not address azithromycin dosing recommendations.

Doxycyline

Drug characteristics: Doxycyline's use is limited in patients with CAP due to the weak recommendation for use in the IDSA/ATS guideline. Doxycycline does not require an adjustment for hepatic or renal function. It can also cause photosensitivity if proper precautions (i.e., sunscreen, long sleeve clothing) are not taken to minimize the risk. Doxycline should be avoided in pregnant patients.

Lung penetration: Doxycycline is a lipophilic agent with excellent lung penetration. The drug concentration ratio in sputum/plasma ranged from 0.33 to 1.2 (mean 0.71) with 100–200 mg after 14–28 days therapy in patients with cystic fibrosis [11].

Effect of obesity: We were unable to find any data describing the impact of obesity on the PK, effectiveness or safety of doxycycline.

Dose optimization: Tetracyclines are optimized with a T>MIC ≥50% and an AUC/MIC of 2–4 times the MIC value [12]. A 200 mg intravenous (iv.) or per os (p.o.) q12h is recommend in CAP since 100 mg iv. or p.o. q12h will take 5 days to achieve optimal concentrations [13]. At higher concentrations (8- to 16-times the MIC), doxycycline exhibits concentration-dependent killing and post-antibiotic effect.

Presence of comorbidities or recent use of antimicrobials/immunosuppressive agents

According to the IDSA/ATS guidelines, people with diabetes mellitus, asplenia, alcoholism, cancer or those with heart, lung, liver, renal or immunosuppressive comorbidities should receive expanded antimicrobial coverage [3]. The receipt of antimicrobials within 3 months or immunosuppressive drugs also places a person into this category. These patients can be treated with one of two recommended regimens.

1. Monotherapy with moxifloxacin, gemifloxacin or levofloxacin 750 mg
2. An oral β-lactam (or ceftriaxone administered intramuscularly) plus a macrolide
   a. Oral β-lactam:
   (i) Preferred: High-dose amoxicillin or amoxicillin-clavulanate
   (ii) Alternatives: cefpodoxime and cefuroxime

Fluoroquinolones

Drug characteristics: Fluroquinolones are commonly used agents for CAP as their ability to be used as monotherapy, relative lack of CYP450 3A4 inhibition and direct iv. to p.o. conversion. Gemifloxacin is not commonly used due to the current lack of an intravenous formulation approved for use in the USA as well as an increased risk of rash in younger patients and females. Empiric use of gemifloxacin has been supported by some to prevent delays in tuberculosis treatment due to its lack of potency against *Mycobacterium tuberculosis* [14,15]. However, others still suggest that a 5- to 10-day course of any fluoroquinolone should not produce a meaningful delay in diagnosis compared with patients treated with other antimicrobials [16]. These agents are all administered once daily. While none of these agents requires dose adjustment for hepatic dysfunction, only moxifloxacin is not adjusted for renal function. Chelation with di- or tri-valent cations can decrease fluroquinolone exposure by 90%. There is also an increased potential for Torsade de pointes due to QTc prolongation in patients receiving fluoroquinolones in persons who have a history of QTc prolongation and/or receive drugs that prolong the QT

Table 1. Empiric treatment options for community-acquired pneumonia.

Drug	Dose	Times per day	Route	Setting for use	CYP450, P-glycoprotein or MAO-I interactions	Renal dose adjustment	Adverse drug reactions (frequent)	Adverse drug reactions (serious)
Erythromycin	250–500 mg	3–4	p.o.	Out	CYP450 3A4 (moderate), P-glycoprotein inhibitor	No	GI intolerance	QT prolongation, hypersensitivity reaction (e.g., angioedema, anaphylaxis, Stevens–Johnson syndrome, toxic epidermal necrolysis)
Clarithromycin	500 mg	2	p.o.	Out	CYP450 1A2 (weak), 3A4 (strong), P-glycoprotein inhibitor	CrCl <30	Metallic taste, GI intolerance	QT prolongation, ↑ LFT, hypersensitivity reaction (e.g., angioedema, anaphylaxis, Stevens–Johnson syndrome, toxic epidermal necrolysis)
Azithromycin	1 dose – 2 g 3d – 500 mg 5d – Zpack (day 1: 500 mg, days 2–5: 250 mg)	1	p.o., iv.	Out In	CYP1A2 (weak), P-glycoprotein inhibitor	No	GI intolerance	QT prolongation, hypersensitivity reaction (e.g., angioedema, anaphylaxis, Stevens–Johnson syndrome, toxic epidermal necrolysis)
Telithromycin	400 mg	1	p.o.	Out	CYP450 2D6 (weak), 3A4 (strong) inhibitor	CrCl <30	GI intolerance	QT prolongation. Life-threatening respiratory failure in myasthenia gravis patients
Doxycycline	100 mg	2	p.o., iv.	Out	CYP450 3A4 (weak) inhibitor	No	GI intolerance	Photosensitivity, permanent tooth discoloration (avoid during pregnancy, age <8 years)
Moxifloxacin	400 mg	1	p.o., iv.	Out In ICU	None	No	Confusion, dizziness	QT prolongation, hypo/hyperglycemia, tendon inflammation/rupture
Levofloxacin	750 mg	1	p.o., iv.	Out In ICU	None	CrCl <50	Confusion, dizziness	QT prolongation, hypo/hyperglycemia, tendon inflammation/rupture
Gemifloxacin	320 mg	1	p.o.	Out	None	CrCl <40	Rash (particularly in females <40 years old)	QT prolongation, hypo/hyperglycemia, tendon inflammation/rupture
Amoxicillin	250–500 mg	2–4	p.o.	Out	None	CrCl <30	Rash	Anaphylactic reaction

The data presented in this table are primarily from the FDA-approved prescribing information for each antimicrobial and Micromedex [100].
CrCl: Creatinine clearance; CYP450: Cytocrome P450; GI: Gastrointestinal; ICU: Intensive care unit; im.: Intramuscular; In: Inpatient; LFT: Liver function tests; MAO: Monoamine oxidase; Out: Outpatient; RF: Risk factors for *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*.

Table 1. Empiric treatment options for community-acquired pneumonia (cont.).

Drug	Dose	Times per day	Route	Setting for use	CYP450, P-glycoprotein or MAO-I interactions	Renal dose adjustment	Adverse drug reactions (frequent)	Adverse drug reactions (serious)
Amoxicillin/ Clavulanate	500 mg	2–3	p.o.	Out	None	CrCl <30	Diarrhea, rash	Anaphylactic reaction
Cefuroxime	500 mg	2	p.o.	Out	None	CrCl <10	Diarrhea, rash	Anaphylactic reaction
Cefpodoxime	200 mg	2	p.o.	Out	None	CrCl <30	Diarrhea, rash	Anaphylactic reaction
Ceftriaxone	1–2 g	1	iv.	In ICU	None	No	Induration (im.)	Anaphylactic reaction, biliary sludging
Cefotaxime	1–2 g	2–3	iv.	In ICU	None	CrCl <50	Diarrhea, rash	Anaphylactic reaction
Ceftaroline	600 mg	2	iv.	In ICU	None	CrCl <50	Positive Coombs' test without hemolysis	Anaphylactic reaction, hemolytic anemia
Ampicillin/ sulbactam	1.5–3 g	4	iv.	In ICU	None	CrCl <30	Diarrhea, rash	Anaphylactic reaction
Ertapenem	1 g	1	iv.	In ICU	None	CrCl <30	Diarrhea	Seizures
Piperacillin/ Tazobactam	4.5 g	4	iv.	ICU-RF	None	CrCl <40	Diarrhea	Anaphylactic reaction
Ceftazidime	2 g	3	iv.	ICU-RF	None	CrCl <50	Diarrhea	Anaphylactic reaction
Cefepime	1–2 g	2–3	iv.	ICU-RF	None	CrCl <60	Positive direct Coombs' test (without hemolysis; 16%), diarrhea	Anaphylactic reaction, seizure
Imipenem/ Cilastatin	500 mg 1 g	3–4	iv.	ICU-RF	None	CrCl <70	Rash, diarrhea	Seizures
Meropenem	1 g	3	iv.	ICU-RF	None	CrCl <50	Headache, diarrhea	Seizures
Doripenem	500 mg	3	iv.	ICU-RF	None	CrCl <50	Headache, diarrhea	Seizures
Aztreonam	2 g	3–4	iv.	ICU-RF	None	CrCl <30	Neutropenia, ↑ LFT	Anaphylactic reaction
Gentamicin	7 mg/kg	1	iv.	ICU-RF	None	CrCl <70	Nephrotoxicity	Nephrotoxicity, ototoxicity, neurotoxocity
Tobramycin	7 mg/kg	1	iv.	ICU-RF	None	CrCl <70	Nephrotoxicity	Nephrotoxicity, ototoxicity, neurotoxocity

The data presented in this table are primarily from the FDA-approved prescribing information for each antimicrobial and Micromedex [100].
CrCl: Creatinine clearance; CYP450: Cytocrome P450; GI: Gastrointestinal; ICU: Intensive care unit; im.: Intramuscular; In: Inpatient; LFT: Liver function tests; MAO: Monoamine oxidase; Out: Outpatient; RF: Risk factors for *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*.

Table 1. Empiric treatment options for community-acquired pneumonia (cont.).

Drug	Dose	Times per day	Route	Setting for use	CYP450, P-glycoprotein or MAO-I interactions	Renal dose adjustment	Adverse drug reactions (frequent)	Adverse drug reactions (serious)
Amikacin	20 mg/kg	2	iv.	ICU-RF	None	CrCl <70	Nephrotoxicity	Nephrotoxicity, ototoxicity, neurotoxocity
Ciprofloxacin	400 mg	3	iv.	ICU-RF	None	CrCl <30	Confusion, dizziness	QT prolongation, hypo/hyperglycemia, tendon inflammation/rupture
Vancomycin	15 mg/kg	2	iv.	ICU-RF	None	CrCl <70	Rash, Redman syndrome (with fast infusion)	Nephrotoxicity with other concomitant nephrotoxic agents
Linezolid	600 mg	2	iv.	ICU-RF	MAO inhibitors (contraindicated)	No	Headache, diarrhea, thrombocytopenia	Lactic acidosis, neuropathy, serotonin syndrome
Telavancin	10 mg/kg	1	iv.	ICU-RF	None	CrCl <50	Metallic taste, insomnia, headache, psychiatric disturbance, proteinuria	Anaphylactic reaction, QT prolongation, nephrotoxicity

The data presented in this table are primarily from the FDA-approved prescribing information for each antimicrobial and Micromedex [100].
CrCl: Creatinine clearance; CYP450: Cytocrome P450; GI: Gastrointestinal; ICU: Intensive care unit; im.: Intramuscular; In: Inpatient; LFT: Liver function tests; MAO: Monoamine oxidase; Out: Outpatient; RF: Risk factors for *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*.

interval. Likewise, fluorquinolones may cause hypoglycemia or hyperglycemia. There have been reports of tendon inflammation or rupture with fluoroquinolones, particularly in people ≥65 years of age.

Lung penetration: Several studies have demonstrated good lung penetration of fluoroquinolones. The lung to plasma concentration ratio (mean) of moxifloxacin and levofloxacin ranged from 3.53 to 6.78 and 1.16 to 3.95, respectively [17,18].

Effect of obesity: To our knowledge, no data are available regarding the effect of obesity on gemifloxacin PK. For levofloxacin, one PK study of 15 obese persons receiving a single levofloxacin dose of 750 mg suggested that no dosing alteration was needed [19]. However, the AUC and the clearance showed increased variability in the obese group. We do not recommend a dosage alteration at this time because of the limited data regarding daily levofloxacin doses >750 mg. Moxifloxacin PK have been evaluated in 12 morbidly obese patients (weight 98–166 kg, BMI 43.0–58.2 kg/m^2) scheduled for gastric bypass surgery [20]. The mean plasma PK values were comparable to historical controls of normal weight patients. Therefore, no dosing alterations are required for patients receiving moxifloxacin.

Dose optimization: *In vitro* studies suggest that C_{max}: MIC is the PK-PD target for Gram-negative bacteria, especially *Pseudomonas aeruginosa* and AUC:MIC was suggested for *S. pneumoniae* [10]. In humans, the optimal ratios of AUC/MIC for *S. pneumoniae* is ≥30–50 [21]. For Gram-negative pathogens, an AUC/MIC ≥125 was associated with clinical cure in patients with moderate-to-severe infections [22]. An AUC/MIC <100 has also been found to increase the development of resistance in patients with Gram-negative infections [23].

Oral β-lactams & ceftriaxone

IDSA/ATS guideline-recommended options:

Drug characteristics: All β-lactams used as empiric therapy for CAP have common adverse reactions such as diarrhea and rash. Of the recommended agents, only ceftriaxone is not adjusted in renal insufficiency. High-dose amoxicillin, 3–4 g/day with or without clavulanate, is preferred by the guideline to overcome penicillin-resistant *S. pneumoniae*. Other recommended oral β-lactams include cefpodoxime and cefuroxime (500 mg twice daily). Ceftriaxone can be administered once daily as an intramuscular or intravenous injection.

Lung penetration: β-Lactams are hydrophilic antibiotics and have marginal concentration in the lungs (ELF to plasma concentration ratio <1) [8].

Effect of obesity: To our knowledge, there are no PK data regarding the effect of obesity on aminopencillins or cefpodoxime. Based on the water composition of adipose which is 30%, an expert opinion has suggested an empirical dosing factor of 0.30-times the difference

between total body weight (TBW) and ideal body weight (IBW) for dosing of penicillins.

Dosing weight = IBW + 0.3 (TBW – IBW)

This approach has yet to be validated in PK or outcomes studies [24].

Dose optimization: β-Lactams exhibit time-dependent antibacterial activity and T>MIC is the PK-PD target [10]. Turnidge proposed different T>MIC for the bacteriostatic effect in non-neutropenic patients (20–34% for penicillins, 35–55% for cephalosporins) [25]. Craig and Andes found good correlation between 85 and 100% cure rate and greater than 40% of T>MIC for *S. pneumoniae* and *H. influenza* in patients with otitis media [26]. Kays *et al*. found all oral β-lactams achieved T>MIC of >40% for penicillin-sensitive *S. pneumoniae*. Only cefaclor failed to achieve a T>MIC of >40% for penicillin-intermediate *S. pneumoniae* [27].

Inpatient treatment of CAP in the general medical ward

These patients can be treated with one of two options:

1. Monotherapy with levofloxacin or moxifloxacin
2. Intravenous β-lactam PLUS a macrolide (may use doxycycline if a macrolide is not an option)
   a. Preferred β-lactam: cefotaxime, ceftriaxone and ampicillin
   b. Alternative: Ertapenem

Intravenous β-lactam

Drug characteristics: Cefotaxime is an alternative to ceftriaxone that requires more doses per day and requires an adjustment for renal insufficiency. Ceftriaxone non-susceptible *S. pneumoniae* (MIC >1 mg/l) has been identified in 6.5–8.7% of isolates in recent studies [28,29]. Some geographic areas may have higher rates of ceftriaxone non-susceptibility due to higher rates of *S. pneumoniae* serotypes that are more likely to be non-susceptible to ceftriaxone (19 A: 51.4%, 35 B: 29.7%) [29]. Data regarding the impact of ceftriaxone non-susceptible *S. pnuemoniae* on clinical outcomes are extremely limited [30]. One study compared 10 patients with non-susceptible *S. pneumoniae* isolates to 20 patients with susceptible isolates. The time to clinical cure was 4 days longer in patients with non-susceptible isolates ($p = 0.51$). There was no difference in infection-related length of stay, overall length of stay, hospital readmissions or deaths. Ertapenem is administered once a day and requires dose adjustment in renal insufficiency. Tigecycline is another option for these patients and was not addressed by the CAP guideline. However, tigecycline's utility is limited by nausea/vomiting and reports of increased mortality compared with standard therapy in meta-analyses [31–33].

Lung penetration: Cephalosporins are hydrophilic antibiotics and have very low concentration in the lungs (ELF to plasma concentration ratio <1) [8]. Ertapenem is also hydrophilic antibiotic and showed poor lung penetration (ELF to plasma concentration ratio <0.5).

Effect of obesity: A single-center, prospective, open-label study evaluated the soft tissue penetration of cefuroxime in six women with a BMI ≥40 kg/m^2 and concluded that soft tissue interstitial concentrations were inadequate [34]. Cefotaxime PK were evaluated in 12 normal weight (90–110% IBW) and 11 obese (190–210% IBW) people [35]. The authors found that obese persons had an increased volume of distribution and clearance. However, the authors concluded that a dose alteration should be based on body surface area, not body weight. Ertapenem PK have been evaluated in 30 healthy volunteers in three BMI groups (10 per group), normal weight (BMI 18.5–24.9 kg/m^2), class I–II obesity (BMI 30–39.9 kg/m^2) and class III obesity (BMI ≥40 kg/m^2), who received a 1 g dose [36]. The authors found that the target attainment rate for ertapenem in isolates with a MIC >0.5 μg/ml was suboptimal and larger doses were likely needed regardless of patient weight. Therefore, a dosing alteration of ertapenem based on patient weight is not recommended.

Dose optimization: T>MIC is the PD target for cephalosporins and ertapenem [10,37]. Data regarding methods for dose optimization are limited due to the limited stability time of ampicillin and the long half-life for ceftriaxone and ertapenem.

Inpatient treatment of CAP in the ICU

Patients with risk factors for multidrug-resistant organisms

1. Preferred regimens:
   a. Cefotaxime, ceftriaxone OR ampicillin-sulbactam PLUS EITHER.
   b. Azithromycin OR
   c. Anti-pneumococcal fluoroquinolone (levofloxacin, moxifloxacin)
2. Penicillin allergic patients: Aztreonam plus antipneumococcal fluoroquinolone.

Aztreonam

Drug characteristics: Aztreonam is typically reserved for use in patients who have a severe allergic reaction to a β-lactam. Aztreonam has no clinically reliable coverage against Gram-positive bacteria and therefore must be combined with an agent that is active against *S. pneumoniae*. It shares many qualities with ceftazidime (dosing frequency, antimicrobial spectrum and route of elimination) due to an identical side chain. The only documented allergic reactions to aztreonam have been in patients who are also allergic to ceftazidime.

Lung penetration: Aztreonam is a hydrophilic agent with poor lung penetration (ELF to plasma concentration ratio <0.5) [38].

Effect of obesity: Aztreonam PK were studied in 10 critically ill, intubated patients (one obese patient) with a lower respiratory tract infection. The obese patient had a higher volume of distribution and drug clearance, resulting in a lower AUC [39]. Therefore, maximum FDA-approved aztreonam doses (i.e., 2 g every 6 h for normal renal function) should be used for obese patients. Hites *et al*. suggested routine therapeutic drug monitoring of β-lactams in obese critically ill patients since PK can be changed by obesity itself as well as by critical illness like severe sepsis or septic shock [40].

Dose optimization: Like other β-lactams, aztreonam is concentration-independent antibiotic whose activity is best linked to T>MIC [37].

Patients at risk of multidrug-resistant organisms

In cases where *P. aeruginosa* is a concern, the recommendation is:

1. Anti-pseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem OR meropenem) PLUS one of the following options:
   a. Ciprofloxacin OR levofloxacin 750 mg
   b. Gentamicin, tobramycin OR amikacin PLUS azithromycin
   c. Last option: Aminoglycoside PLUS an antipneumococcal fluoroquinolone
2. If community-associated methicillin-resistant *S. aureus* is a concern: Add vancomycin OR linezolid.

Anti-psuedomonal β-lactams

Drug characteristics: Piperacillin/tazobactam or cefepime are the more commonly used agents for these patients. This is due to the association of increased carbapenem use and the development of carbapenem-resistant *P. aeruginosa* or *Acinetobacter*. Recent data suggest the concomitant use of piperacillin/tazobactam and vancomycin may increase the risk of nephrotoxicity [41–43]. Cefepime has been associated with neurologic adverse events, including seizures. A study of 100 critically ill patients receiving cefepime found that patients experiencing neurotoxicity were more likely to have chronic kidney disease and were less likely to have their dose appropriately adjusted for renal insufficiency [44]. However, neurotoxicity has been observed in patients without renal failure [45].

Imipenem, meropenem and doripenem have *in vitro* activity against *P. aeruginosa* and *Acinetobacter*. However, doripenem was not granted an indication for hospital-acquired pneumonia by the FDA on the basis of increased mortality with doripenem therapy. The FDA prescribing information for imipenem and meropenem lists similar seizure rates. However, meropenem has a FDA indication for pediatric meningitis, whereas the only study of imipenem for this condition was stopped after 7 of the 21 children had seizures [46].

Lung penetration: ELF to plasma concentration ratio of tazobactam was almost 1, but lung penetration of piperacillin is very poor as it is expected due to hydrophilicity [47]. Lung penetration of cefepime is about the same as piperacillin (ELF to plasma concentration ratio <1) [48]. Lung penetration of carbapenems is the similar to other β-lactams (ELF to plasma concentration ratio <1) [49–51].

Effect of obesity: A BMI ≥30 kg/m^2 has been reported as having worse cure rates in complicated intra-abdominal infections (86 vs 65%; 95% CI: 1–47%) in patients receiving piperacillin/tazobactam 3.375 g q6h [52]. The only data regarding meropenem PK is from a study presented only in abstract form. Drug concentrations were recorded in nine patients with class III obesity and then compared with historical controls. Volume of distribution and drug clearance were increased in the study population by 38 and 28%, respectively. However, these changes had minimal impact on T>MIC (<3%) [53]. Therefore, no dosage adjustment is recommended for obesity with meropenem.

Dose optimization: Piperacillin/tazobactam is a time-dependent antibiotic and T>MIC is recommended for the optimal PD target [37]. More frequent dosing, continuous infusion and extended infusion dosing are all methods that have been used to optimize achievement of the PK-PD target. Recently, Falagas *et al*. evaluated clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam in a systemic review and meta-analysis [54]. The six studies included that used piperacillin/tazobactam observed a lower mortality with extended or continuous infusion than intermittent dosing (relative risk: 0.55; 95% CI: 0.34–0.89). Similar rates of target attainment have been shown for cefepime 2 g q12h (67%) and cefepime 1 g q8h (67%) [55]. Tam *et al*. demonstrated higher probability of achieving cefepime's PK-PD target with higher doses or extended infusions [56]. Ludwig *et al*. evaluated more frequent dosing of imipenem and prolonged infusions of meropenem against multidrug-resistant *P. aeruginosa* [55]. Similar target attainment rates were found for imipenem 1 g q8h (69%) and imipenem 0.5 g q6h (72%). Likewise, meropenem 1 g q8h as a 3 h infusion (84%) and meropenem 2 g q8h (30 min infusion) (84%) achieved similar target attainment rates. Lorente *et al*. also evaluated continuous versus intermittent infusion of meropenem in patients with ventilator-associated pneumonia (VAP) due to Gram-negative bacilli [57]. This was a retrospective cohort trial, which compared meropenem 1 g q6h (6 h infusion) versus meropenem 1 g q6h (30 min infusion) with both groups receiving tobramycin 7 mg/kg/24 h. Clinical cure rate was significantly higher with continuous infusion in *P. aeruginosa* (odds ratio: 8.25; 95% CI: 1.33–51.26) as well as all cases (odds ratio: 6.44; 95% CI: 1.97–21.05). The aforementioned meta-analysis was unable to reach statistical significance when analyzing the mortality benefit from extended or continuous infusions of carbapenems (relative risk: 0.66; 95% CI: 0.34–1.30) [54].

Anti-psuedomonal non-β-lactams

Drug characteristics: Ciprofloxacin doesn't have clinically reliable activity against *S. pneumoniae*, so the IDSA/ATS guidelines only recommend its use for CAP with multidrug-resistant organisms due to its activity against *P. aeruginosa.* Aminoglycosides are associated with nephrotoxicity and ototoxicity due to their narrow therapeutic index.

Lung penetration: Like other fluoroquinolones, ciprofloxacin has excellent lung penetration (ELF to plasma concentration ratio >1) [58]. Due to hydrophilicity, lung penetration of aminoglycosides is very poor (ELF to plasma concentration ratio <0.5) [59–61].

Effect of obesity: Ciprofloxacin was studied in 17 obese subjects (mean BMI 36.4 kg/m^2) and 11 normal-weight volunteers (mean BMI 23.3 kg/m^2) [62]. Renal and systemic clearance and

volume of distribution were significantly greater in the obese group. When normalized for TBW, the volume of distribution remained increased. The distribution of ciprofloxacin in adipose tissue was not complete, leading the authors to recommend using adjusted body weight for dosing. The results suggested that higher doses of ciprofloxacin may be needed to achieve targeted concentrations. Hollenstein *et al.* compared soft tissue concentrations of ciprofloxacin in 12 obese subjects (mean weight 122 ± 22.6 kg) and 12 lean subjects (mean weight 59 ± 8.6 kg) [63]. Each volunteer received 2.85 mg/kg of ciprofloxacin intravenously based on TBW. Significantly higher plasma peak (9.97 vs 2.59 mg/ml) and trough (0.44 vs 0.19 mg/ml) concentrations of ciprofloxacin were found in obese persons ($p < 0.05$). However, there was no difference in concentration–time curves for samples obtained from interstitial fluid of muscle and subcutaneous fat. The authors recommend using TBW to achieve similar tissue concentrations in obese patients, but the safety of this approach requires validation.

For morbidly obese patients where the TBW/IBW ratio >2, a dosing weight correction factor of IBW plus 40% excess body weight (EBW) (where EBW = TBW – IBW) is used. In a study investigating aminoglycoside PK in 1708 patients, it was found that dosing weight correction factors to give equivalent predicted peak aminoglycoside concentrations with a 2 mg/kg loading dose were 0.43-times the EBW plus IBW for overweight patients [64].

Data regarding dose optimization: Aminoglycosides are concentration-dependent antibiotics and have a prolonged post-antibiotic effect [37,65]. These properties allow aminoglycoside's once-daily regimen with high peak concentration and long drug-free time except pregnancy, cirrhosis, volume-overloaded, burn and dialysis patients [65]. C_{max}/MIC is recommended PD target for optimal aminoglycoside's efficacy against Gram-negative bacteria. C_{max}:MIC >8 is recommended to prevent development of resistant pathogens and C_{max}/MIC of 8–10 is required to have about 90% of clinical cure rate in Gram-negative bacteria infections [66].

Anti-MRSA agents

Drug characteristics: Vancomycin should be reserved for MRSA since β-lactams are more effective than vancomycin against methicillin-sensitive *S. aureus* [67]. There has been a great deal of discussion in the literature about the impact of target vancomycin troughs on nephrotoxicity rates. Increasing vancomycin trough concentrations have been associated with an increased risk of nephrotoxicity [68–70]. However, the empiric weight-based dosing regimen intended to achieve a target trough of 15–20 mg/ml has yet to be associated with nephrotoxicity [71]. Linezolid, another option for these patients, has several advantages compared with vancomycin including no adjustment for renal dysfunction, no therapeutic drug monitoring, superior lung penetration and an oral formulation with excellent bioavailability. Both linezolid and vancomycin are associated with similar rates of thrombocytopenia [72]. Linezolid has mild monoamine oxidase inhibitor properties and should not be used with selective serotonin reuptake inhibitors to avoid serotonin syndrome. Telavancin is currently FDA approved for hospital-acquired pneumonia, but studies in CAP are lacking. The main concerns with telavancin are QTc prolongation, nephrotoxicity and the requirement of a serum pregnancy test in women of childbearing age prior to therapy.

Lung penetration: Lung penetration of vancomycin was studied in several studies and showed poor penetration. ELF to plasma concentration ratio ranged from 0.05 to 0.41 [73]. Linezolid is lipophilic antibiotic and has very good bioavailability. It has good concentrations in the lungs (ELF to plasma concentration ratio >1) with oral dosage form as well as iv. forms [74].

Effect of obesity: Vancomycin PK have been extensively investigated and the results have been summarized in a consensus review [75]. The consensus review recommends dosing vancomycin based on TBW in obese patients. The effect of obesity on linezolid PK has been controversial. The impact of obesity on linezolid absorption was evaluated in four men and a woman with a BMI >35 kg/m^2 (weight 106–136 kg) before and 3 months after Roux-en-Y gastric bypass surgery [76]. The patients had a 25% decrease in TBW after bypass surgery (weight 83–99 kg). There was no effect on the mean bioavailability (1.14), but the mean $AUC_{0-\infty}$ increased after bypass surgery to (42 vs 99 mg*h/l, $p < 0.001$). This is because linezolid CL was significantly associated with TBW ($r^2 = 0.58$). Meagher *et al.* evaluated the population PK of linezolid in 318 adults (weight 37–200 kg) [77]. Creatinine clearance and weight significantly affected linezolid clearance, but explained only 16% of the variance. Another population PK study of 455 Japanese patients (30–190.5 kg) observed weight was a significant covariate for clearance and volume of distribution [78]. Bhalodi *et al.* evaluated linezolid PK in adults with a BMI of 30–39.9 kg/m^2 (4 males/6 females) and 40–54.9 kg/m^2 (10 females) [79]. No body weight descriptor was associated with Vc or CL, which resulted in similar mean AUC_T (130 vs 109 μg*h/ml, $p = 0.32$) or mean C_{max} (21 vs 19 μg/ml, $p = 0.24$) values. However, volume of distribution was significantly associated with TBW ($r^2 = 0.524$), adjusted body weight ($r^2 = 0.587$), lean body weight ($r^2 = 0.495$) and IBW ($r^2 = 0.398$). A dose increase to linezolid 600 mg every 8 h can be considered given the risk versus benefit to an individual patient.

Data regarding dose optimization: The guideline-recommended dose of vancomycin is 30–45 mg/kg/day and the recommended trough concentration is 15–20 mg/ml. Moise-Broder *et al.* investigated various PD parameters (AUC:MIC vs % T>MIC) in *S. aureus* lower respiratory infections [80]. Clinical and microbiological response was higher in patients with AUC:MIC ≥400. As previously mentioned, increased vancomycin troughs are associated with nephrotoxicity. However, vancomycin concentrations increase regardless of whether vancomycin is the cause of nephrotoxicity or not. Therefore, more data regarding the cause of nephrotoxicity are needed to help

guide vancomycin dosing regimens. Several investigators have studied the impact of continuous infusion of vancomycin with conflicting results both in terms of effectiveness and nephrotoxicity [81–85]. However, this approach should not be more effective given that vancomycin's activity is linked to AUC/MIC. The results were not consistent among the studies.

Linezolid efficacy is affected by AUC/MIC and %T>MIC. A PK-PD analysis of 288 patients identified an AUC/MIC of 80–120 was associated with clinical success and 100% T>MIC increased the likelihood of success [86]. This range is in agreement with a mean AUC/MIC of 83 associated with stasis for staphylococci found in a murine model [87].

Expert commentary

The creation of healthcare-associated pneumonia by the hospital-acquired pneumonia guidelines has increased the number of patients with pneumonia receiving empiric coverage for MRSA who would have previously been treated by the CAP guidelines. However, recent studies have shown that the addition of MRSA coverage may not alter clinical outcomes [88–90]. Initial treatment failure has been found to be more predictive of mortality than inappropriate empiric therapy [89]. Therefore, further data are needed to help identify patients at risk of initial treatment failure and methods to minimize this risk.

The two most commonly used antimicrobials for coverage of atypical pathogens in CAP are azithromycin and fluoroquinolones. Each of these drugs has faced increased scrutiny recently in regards to their safety. Azithromycin has specifically faced concerns regarding cardiovascular mortality [91]. However, the small increase in myocardial infarction is offset by a decrease in all-cause mortality [92]. Fluoroquinolones have been associated with an increased risk of tendon rupture in people >65 years of age and those receiving steroids resulting in the addition of a black box warning to the FDA prescribing information for all fluoroquinolones [93,94]. Given the widespread use of fluoroquinolones for multiple indications, further risk stratification is needed to identify the spectrum of risk in elderly patients.

Obese people with CAP have a lower 30-day mortality rate than non-obese patients (hazard ratio: 0.53; 95% CI: 0.29–0.98) [95]. However, this does not mean that the survival rates of obese patients could not be further improved with individualized dosing regimens. We have previously found that TBW, not BMI, is best linked to the PK of several antimicrobials [96–99]. Therefore, pharmacokinetic data are needed to derive these individualized regimens and outcomes studies are needed to evaluate the effectiveness and safety of these regimens.

Lung penetration is often considered to be an important factor in antimicrobial selection for CAP. However, we are unaware of any data supporting the superiority of antimicrobials with increased lung penetration. Therefore, the primary goal should be to achieve drug concentrations with the selected antimicrobial to maximize the likelihood of clinical success while minimizing the development of toxicity or antimicrobial resistance.

Five-year view

A call for consolidation of the pneumonia guidelines is needed. This is particularly true given the overlap between the CAP and hospital-acquired pneumonia has only increased with the introduction of healthcare-associated pneumonia within the hospital-acquired pneumonia guidelines. This will provide a common treatment pathway for all patients that is evidence-based without having to decipher which guideline applies for a particular patient with pneumonia. Research is also needed to help improve the long-term outcomes of patients with pneumonia. Antimicrobial selection plays a role in short-term outcomes, but it is unclear what factors are responsible for the high long-term mortality rates in these patients. A focus on risk versus benefit ratio of CAP treatment options for geriatric patients is particularly needed provided the increased risk of adverse events from fluoroquinolones and increased risk of drug interactions from treatment of concomitant diseases in this population.

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Key issues

- Community-acquired pneumonia (CAP) is the sixth leading cause of death in the USA.
- Guideline-recommended therapy is associated with improved clinical outcomes in CAP.
- The introduction of healthcare-associated pneumonia has increased the prescribing of empiric treatment for methicillin-resistant *Staphylococcus aureus*, without an improvement in patient outcomes.
- Dose optimization can help increase the likelihood of positive clinical outcomes.
- Selection of antimicrobials with increased lung penetration is logical, but their superiority has not been demonstrated in clinical trials.
- Risk stratification of the risks of fluoroquinolone therapy in the elderly is needed.
- Nephrotoxicity has been associated with increased vancomycin trough concentrations or the use of vancomycin with piperacillin/tazobactam and/or concomitant nephrotoxins (i.e., aminoglycosides).

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