DISEASE MANAGEMENT

Base the antibacterial treatment of community-acquired pneumonia on disease severity and other factors

Community-acquired pneumonia is a common infectious disease that is treated with antibacterial monotherapy or combination therapy. Recommended initial empirical antibacterial regimens are based on disease severity and presence of predisposing risk factors for specific pathogens.

Risk is higher in some individuals

Community-acquired pneumonia (CAP) is defined as pneumonia occurring in the community setting in a patient who has had no contact with the healthcare system.[1] In terms of the pathogenic spectrum and, thus, management and prognosis, it differs from community-onset healthcare-associated pneumonia.[1]

Prominent risk factors related to the development of CAP include chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus and smoking. Although the elderly individuals are frequently affected with CAP, it is not yet known whether age is an independent risk factor or whether it reflects concomitant risk factors (e.g. co-morbidity and a higher rate of prior antibacterial therapy).[1,2]

This article summarizes a recent review by Thiem et al. on the antibacterial treatment of CAP.[1]

Pathogenic spectrum influenced by risk factors

Although pneumonia is associated with a diverse spectrum of aetiological pathogens, *Streptococcus pneumoniae* is the most frequently isolated in patients with CAP.[3] Other pathogens of importance include *Chlamydophila pneumoniae*, Gram-negative Enterobacteriaceae, *Haemophilus influenzae*, *Legionella* species, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, anaerobes and respiratory viruses.[1] The spectrum of causative organisms varies by geographical location.

Of note, there are a number of modifying risk factors that will predispose a patient to infection with a specific pathogen.[3] For instance, chronic corticosteroid therapy (at a daily dose equivalent to prednisolone ≥10 mg), recent broad-spectrum antibacterial therapy for >7 days in the previous month and the presence of malnutrition or structural pulmonary disease elevate the risk of infection with *P. aeruginosa*.[1,3]

Base treatment on disease severity …

The cornerstone of CAP treatment is monotherapy or combination therapy with antibacterials, with initial empirical antibacterial regimens recommended based on disease severity and the presence of predisposing risk factors for specific pathogens.[1] Table I lists the antibacterials most commonly recommended in current guidelines.[2,4-6]

The severity of pneumonia may be assessed by various means, including the Pneumonia Severity Index or, in patients aged ≥65 years, the CURB-65 or CRB-65.[1] However, as misclassifications (in either direction) may occur, management decisions should not be based solely on a prognostic score.[1]

… and other factors

Other factors, such as an individual patient's characteristics (e.g. the ability to take oral medication, sufficient compliance and adequate social support), the overall clinical picture (e.g. renal impairment) and, most importantly, assumptions on the likely pathogenic spectrum and antibacterial resistance in the geographical region should also be considered when treating patients with CAP.[1] The extensive use of antibacterials for infectious diseases is associated with increasing pathogenic resistance and a resulting increase in the risk of treatment failure, complications and death.[1] Considering the current patterns of antibacterial resistance is, therefore, essential when making treatment decisions.

The tolerability profile and potential for drug interactions of the agent should also be considered when choosing an antibacterial.[1] The typical adverse events and important drug interactions specific to the major antibacterial classes used in the treatment of CAP are presented in table II.

If low risk, treat based on the absence…

In patients with low-risk CAP in ambulatory care without predisposing factors for specific pathogens, the pathogen spectrum is relatively narrow.[1] In light of this, and given the importance of preventing the avoidable emergence of pathogen resistance, empirical antibacterial treatment should not be unnecessarily broad, with oral antibacterials selected on the basis of their favourable compatibility and bioavailability.[1] Under such circumstances, the antibacterial most frequently recommended is an aminopenicillin such as

1172-0360/12/0005-0015/$19.95

amoxicillin with or without a β-lactamase inhibitor[2,4,5] (*Patient care guidelines*). However, US guidelines[6] recommend a macrolide as the first choice of therapy.

Although macrolides (e.g. azithromycin, clarithromycin and roxithromycin) and doxycycline may be used in patients with penicillin intolerance or hypersensitivity,[2,4-6] with levofloxacin and moxifloxacin serving as alternatives to the aminopenicillins, the pathogen spectrum covered by these antibacterials is considered excessive in low-risk CAP.[2,4,5] The use of ciprofloxacin should be avoided because of its inadequate activity against *S. pneumoniae*[7] and its potential to promote fluoroquinolone resistance.[2,4-6]

A course of antibacterial therapy of at least 5 days, with cessation 2–3 days following clinical recovery, is recommended.[1] However, a treatment duration of 3 days is sufficient for azithromycin owing to its long half-life.[1]

… or presence of risk factors

In the presence of predisposing factors, the pathogenic spectrum may potentially include, among others, anaerobes, Enterobacteriaceae, *Legionella* species and *Staphylococcus aureus*, in addition to *H. influenzae* and *S. pneumoniae*. In such cases, empirical antibacterial treatment with a β-lactam plus a β-lactamase inhibitor (e.g. amoxicillin/clavulanic acid, which is active against *S. aureus*, most β-lactamase-producing Enterobacteriaceae and anaerobes) is recommended[2,4-6] (*Patient care guidelines*). Although levofloxacin and moxifloxacin have a high oral bioavailability, a half-life permitting once-daily administration and demonstrated efficacy, the benefits of these agents in light of the good overall prognosis of low-risk CAP should be weighed against their adverse events and the possibility of promoting fluoroquinolone resistance.[1,5,8]

Combination therapy with a β-lactam, a β-lactamase inhibitor and a macrolide is warranted in suspected primary infection or co-infection cases with *C. pneumoniae*, *Legionella* species or *M. pneumoniae*[2,4,5] (*Patient care guidelines*).

In patients who have previously received antibacterial therapy, a drug class different from that used during pretreatment should be selected.[1]

Table I. Antibacterial options in the empirical treatment of community-acquired pneumonia (CAP) based on current guidelines, as reviewed by Thiem et al.[1]

Antibacterial (suggested daily dosage)	Low-risk CAP	Hospitalized, non-severe CAP	Hospitalized, severe CAP	CAP with risk factors	CAP with risk factors for *Pseudomonas* infection[a]
Aminopenicillin					
Amoxicillin (3×750–1000 mg oral)	✓				
β-Lactam + β-lactamase inhibitor					
Amoxicillin/clavulanic acid (2×875/125 mg oral)		✓[b]		✓	
Ampicillin/sulbactam (3×3000 mg IV)		✓			
Piperacillin/tazobactam (3×4500 mg IV)			✓		✓
Sultamicillin (2×750 mg oral)				✓	
Other β-lactams					
Cefepime (3×2000 mg IV)					✓
Cefotaxime (3×2000 mg IV)		✓	✓		
Ceftazidime					✓
Ceftriaxone (1×2000 mg IV)		✓	✓		
Cefuroxime (3×1500 mg IV)		✓			
Fluoroquinolones					
Ciprofloxacin (3×400 mg IV)					✓
Levofloxacin (1×500 mg oral)	✓	✓	✓	✓	✓
Moxifloxacin (1×400 mg oral)		✓		✓	
Macrolides					
Azithromycin (1×500 mg oral)	✓				
Clarithromycin (2×500 mg oral)	✓				
Roxithromycin (1×300 mg oral)	✓				

a Antibacterial pretreatment within the previous 3 mo, chronic obstructive pulmonary disease or corticosteroid therapy.
b Daily dosage: 3×2200 mg IV.
IV = intravenous; ✓ indicates that the antibacterial is recommended for empirical treatment in the patient population.

Table II. Typical adverse events and important drug interactions associated with β-lactams, fluoroquinolones and macrolides, as reviewed by Thiem et al.[1]

β-Lactams	Fluoroquinolones	Macrolides
Typical adverse events		
Blood count alterations, diarrhoea, drug fever, nausea, skin rash, vomiting	Confusion, delirium, dizziness, gastrointestinal events, hallucinations, photosensitivity, somnolence[a]	Gastrointestinal events, ototoxicity, ventricular arrhythmias
Important drug interactions		
Uricosuric agents: lower β-lactam excretion	Antiarrhythmics, QT-interval prolonging agents: may induce ventricular arrhythmias Competition by ciprofloxacin with other agents for CYP1A2 (e.g. aminophylline, mirtazapine, warfarin): higher competitor agent concentrations	Antiarrhythmics, QT-interval prolonging agents: may induce ventricular arrhythmias CYP3A4-inducing agents (e.g. carbamazepine, phenytoin, rifampicin): lower macrolide concentration Competition with other agents for CYP3A4 (e.g. digoxin, HMG-CoA reductase inhibitors [statins], verapamil, warfarin): higher competitor agent concentrations

a Because of their potential to cause CNS adverse events, fluoroquinolones should be used with caution in elderly patients, especially those with known cognitive impairment or overt dementia.

CYP = cytochrome 450.

Intravenous and/or oral therapy for non-severe infection in hospitalized patients

The spectrum of underlying pathogens in hospitalized patients with non-severe pneumonia is not necessarily different from those in ambulatory patients with low-risk CAP.[1] However, given the differences in patient characteristics (i.e. a higher proportion of elderly patients with greater comorbidity and a higher prevalence of antibacterial pretreatment), a higher prevalence of anaerobes, Enterobacteriaceae, mixed pathogen infections and multiresistant pathogens is possible.[1]

Therefore, initial empirical antibacterial therapy with an aminopenicillin plus a β-lactamase inhibitor (e.g. amoxicillin/clavulanic acid or ampicillin/sulbactam) is frequently recommended[2,4-6] (*Patient care guidelines*). Alternatives include the cephalosporins cefuroxime, ceftriaxone or cefotaxime.[1] Combination therapies that include a fluoroquinolone or macrolide have not been shown to be more beneficial than β-lactam monotherapy, with the exception of the subgroup of patients with proven *Legionella* pneumonia.[9,10] The use of fluoroquinolones (i.e. levofloxacin or moxifloxacin) is also an option, but the risk of adverse effects and development of resistance should be considered.[1]

Apart from macrolides and fluoroquinolones (which have high oral bioavailability), antibacterials should initially be administered intravenously to hospitalized patients to ensure that doses are sufficient to obtain effective concentrations.[2,4-6] Once the patient is clinically stable (usually occurs within the first 2 or 3 days of therapy), the patient can be switched from intravenous to oral antibacterial therapy.[2,4-6]

Usual total treatment duration is ≤7 days

The most appropriate duration of antibacterial therapy for CAP is a subject of debate.[1] A meta-analysis of various antibacterials has suggested a regimen of ≤7 days for the treatment of adults with mild to moderate pneumonia, with consistent results among each antibacterial class (i.e. β-lactams, fluoroquinolones, ketolides and macrolides).[11] Provided that clinical stability has been achieved, a treatment duration of at least 5 days (as the shortest duration) is recommended by the German guidelines;[5] however, a duration of >7 days is not generally recommended, except in the case of proven infections with *P. aeruginosa*, for which a treatment duration of 15 days appears appropriate.[2,4-6] Shorter treatment durations may be justified by daily clinical assessments of the patient with special emphasis on signs and symptoms indicative of treatment failure.[2,5]

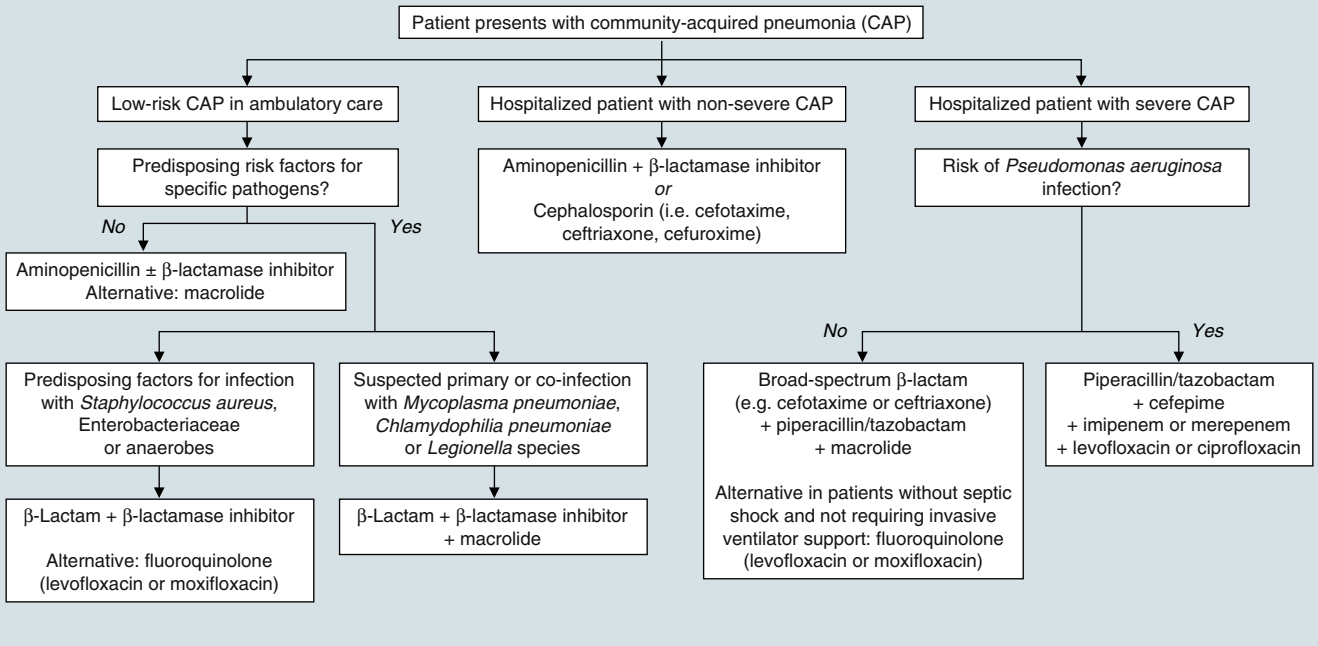
Of note, the pharmacokinetic properties of azithromycin differ markedly from those of other macrolides. Following the completion of therapy, azithromycin maintains high tissue concentrations for at least 3 days, implying that 3–5 days' therapy with azithromycin is equivalent to 7–10 days' therapy with another macrolide.[12,13]

Combination therapy needed for severe infection

The pathogenic spectrum in severe CAP is broader than that in non-severe CAP.[1] *S. pneumoniae* is the leading causal pathogen, followed by *H. influenzae*, *S. aureus*, *L. pneumophila* and Enterobacteriaceae, especially *Escherichia coli* and *Klebsiella* species, and *P. aeruginosa*.[1]

1172-0360/12/0005-0017/$19.95

Patient care guidelines



Suggested empirical treatment of community-acquired pneumonia in patients without penicillin intolerance or hypersensitivity based on current guidelines,[2,4-6] as reviewed by Thiem et al.[1]

The following antibacterial classes have shown sufficient antibacterial activity in severe CAP: ureidopenicillins with a β-lactamase inhibitor (piperacillin plus sulbactam or tazobactam), broad-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime), carbapenems (imipenem, meropenem, ertapenem), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and macrolides (erythromycin, clarithromycin, azithromycin).[1] While fluoroquinolone monotherapy would cover the aforementioned pathogens,[2,4-6] limited data are available on its use in hospitalized patients with severe CAP and no data are available on its use in patients with septic shock or invasive ventilator support.[1] Therefore, combination therapy is usually recommended.[2,4-6]

In patients with severe CAP without predisposing factors for *P. aeruginosa* infection, the combination of a broad-spectrum β-lactam (e.g. cefotaxime or ceftriaxone), piperacillin/tazobactam and a macrolide is recommended as first-line therapy[2,4-6] (*Patient care guidelines*). In those patients without septic shock and not requiring invasive ventilator support, monotherapy with levofloxacin or moxifloxacin is a potential alternative. Combination therapy with piperacillin/tazobactam, cefepime, imipenem or meropenem plus either levofloxacin or ciprofloxacin is recommended in patients with a predisposition for *P. aeruginosa*,[2,4-6] with ceftazidime, a β-lactam with activity against *Pseudomonas* species, but weaker (compared with other β-lactams) activity against *S. pneumoniae* and *S. aureus*, being another potential alternative.[1]

Combination therapy with an aminoglycoside (e.g. amikacin, gentamicin or tobramycin) plus a macrolide appears promising, but the pathogenic spectrum covered by aminoglycosides is rather narrow. In addition, aminoglycosides achieve low tissue levels in lung parenchyma, carry a high toxicity potential (especially nephro- and ototoxicity) and require serum concentration monitoring. In contrast, high tissue levels and a substantially lower rate of toxicity have been observed with macrolides and fluoroquinolones.[1]

The mandatory treatment duration for hospitalized patients with severe pneumonia is currently unknown,[1] although lower recurrence has been observed in cases of proven *Pseudomonas* infection following 15 days' therapy in one study.[14] The German guidelines recommend 15 days' therapy for severe *Legionella* pneumonia.[5]

Consider timing and adjuvant therapy

The following are important factors to take into account when treating patients with CAP:[2,4-6]

- Time from admission to the first administration of an antibacterial in hospitalized patients. As this is considered

prognostically important, antibacterial therapy should be started as soon as the diagnosis is established.

- *Clostridium difficile*-associated diarrhoea. Commonly emerges during or after antibacterial therapy (risk is highest with cephalosporins, clindamycin and fluoroquinolones) and typically occurs in hospitalized patients with co-morbidity and ongoing acid suppression therapy. Prevention strategies include adequate hygiene and contact precautions and, if possible, the preferential use of lower risk antibacterials.
- Hypoxaemia. As this is an established risk factor for mortality, oxygen should be given as soon as possible in patients with proven arterial hypoxaemia.
- Volume depletion. May occur secondary to fever and/or tachypnoea, acute confusional states, dementia or the presence of dysphagia in elderly patients. Hydration status should be assessed and managed.

Differentiate a delayed response from treatment failure

For the majority of patients, clinical stability is usually achieved within 3 days of treatment initiation.[1] However, treatment failure, manifesting as either progressive pneumonia or a lack of response to the initial therapy, is possible. Progressive pneumonia (defined as progressive clinical deterioration with respiratory failure and the development of shock necessitating treatment in the intensive care unit, vasopressor therapy and ventilator support) occurs in ≈5–10% of patients and has a poor prognosis.[2,4-6] It is important to identify the infectious cause and provide cardiocirculatory and respiratory support.[1]

A lack of response is characterized by the persistence of initial symptoms without apparent clinical deterioration and has a better prognosis overall.[5,6] However, approximately half of these patients are experiencing only a delayed response, which would not necessarily require a change in treatment. Differentiating a delayed response from a true non-response is not easy, thus warranting a careful re-evaluation of the treatment, particularly the initial choice of antibacterial(s), and further diagnostic efforts.[1]

Disclosure

This review was adapted from *Drugs & Aging* 2011; 28 (7): 519-37[1] by Adis editors and medical writers. The preparation of these articles was not supported by any external funding.

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1172-0360/12/0005-0019/$19.95