ARTICLE

Controversies in the management of community-acquired pneumonia in adults

Emily Tucker
Infectious Diseases Physician[1]

Maeve O'Sullivan
Editor[2]

Lisa Waddell
Senior Editor[2]

[1] Royal Adelaide Hospital
[2] Therapeutic Guidelines Limited

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SUMMARY

Community-acquired pneumonia (CAP) is a common infectious syndrome in Australia and a leading global cause of morbidity and mortality. It drives a significant amount of antimicrobial prescribing in Australia.

Accurate assessment and stratification of CAP severity is important. However, adequate evaluation is challenging and controversy remains about the optimal method.

Streptococcus pneumoniae is the most commonly identified bacterial pathogen causing CAP. As such, oral amoxicillin monotherapy is the mainstay of empirical therapy for low-severity CAP. The need to start empirical therapy for pathogens such as *Mycoplasma pneumoniae* and *Legionella* species in low-severity CAP remains controversial; evaluating the causative pathogen on clinical grounds alone is difficult.

Oral antibiotics recommended for CAP (e.g. amoxicillin, doxycycline) have excellent bioavailability and may be used instead of intravenous therapy in some hospitalised patients.

A duration of 5 days of antibiotic therapy is recommended in clinical practice guidelines for patients with uncomplicated CAP who meet stability criteria at follow-up.

Introduction

Community-acquired pneumonia (CAP) is a common infectious syndrome in Australia,[1] and a leading global cause of morbidity and mortality.[2] In Australia, CAP drives a significant amount of antimicrobial prescribing.[3]

There remains uncertainty and controversy in CAP management because of variability in clinical presentation, the breadth of potential pathogens, and key evidence gaps, which contributes to variation in guideline recommendations.

This article reviews some key questions and controversies in CAP management for adults, including severity stratification, antibiotic choice and duration, and the use of adjuvant corticosteroids. It does not address the challenges associated with diagnosing CAP in adults, and does not consider pneumonia caused by nonbacterial pathogens (e.g. SARS-CoV-2, influenza A and B).

Clinical assessment versus pneumonia severity scoring tools to assess severity

In adults with CAP, assessment of severity is an important step when selecting empirical antibiotic therapy and determining location of care. Adequate evaluation is challenging, and controversy remains about the optimal method.

Formal pneumonia severity scoring tools (e.g. Pneumonia Severity Index [PSI][4] and CURB-65[5])* are recommended in some international guidelines;[6,7] however, they have limited sensitivity and specificity because they were validated to identify risk of mortality, they do not consider potential pathogens, and they have limitations in identifying patients who are likely to deteriorate.[8] Furthermore, such tools are only relevant to the population in which they have been validated.[9] For example, some studies in Aboriginal and Torres Strait Islander peoples with high-severity CAP have reported a poor association between scoring tool results and 30-day mortality.[10] Thus, such tools can only aid clinical judgement; they cannot replace it.

For these reasons, Australian guidelines[11] do not recommend the use of a specific scoring tool to assess severity, but instead list features that may indicate the need for hospital admission (e.g. respiratory rate 22 breaths per minute or more, heart rate 100 beats per minute or more) or intensive care support (e.g. signs of severe acute respiratory insufficiency or acute extrapulmonary organ dysfunction). These features are based on modified clinical parameters

* The PSI calculator and CURB-65 calculator show the clinical parameters included in these tools.

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identified in studies of pneumonia severity and consensus expert opinion.

Regardless of the method used to assess CAP severity, most guidelines divide severity into 3 categories, based predominantly on recommended location of care:

- low-severity CAP is usually managed in the community
- moderate-severity CAP is usually managed in hospital without intensive care support
- high-severity CAP is usually managed in hospital and may require intensive care support.

Using location of care as a surrogate for severity has limitations as it does not account for individual patient considerations, including comorbidities, social circumstances, functional status, ability to tolerate or absorb oral therapy, risk of deterioration and goals of care. For example, some patients with low-severity CAP will be admitted to hospital predominantly for other needs (e.g. a concurrent medical problem such as hip fracture).

How broad should empirical antimicrobial therapy be?

Most patients with CAP never have a causative pathogen identified, so empirical therapy that targets *Streptococcus pneumoniae* (the most common causative bacterial pathogen) is recommended.[12] The choice of empirical antibiotic therapy for CAP aims to strike a balance between limiting exposure to unnecessarily broad-spectrum antibiotics and ensuring patients at risk of infection with less common pathogens receive adequate treatment.

For adults with **low-severity CAP** in Australia, first-line empirical antibiotic therapy is narrower-spectrum amoxicillin monotherapy, because *S. pneumoniae* resistance to penicillin is low (less than 1% in the Australian community setting in 2021). The rates of *S. pneumoniae* resistance to macrolides and tetracyclines are higher (approximately 20% and 10% respectively).[1]

Some patients, depending on disease severity, exposure risk and clinical features, require antimicrobial therapy against a broader range of pathogens.[6] For example, patients in tropical regions of Australia may be exposed to pathogens such as *Burkholderia pseudomallei* and *Acinetobacter baumannii*, particularly in the wet season.[13-15]

While the backbone of empirical therapy for CAP is beta-lactam antibiotics, these do not have activity against pathogens such as *Mycoplasma pneumoniae*, *Legionella* species, *Chlamydophila* (*Chlamydia*) *pneumoniae* and *Coxiella burnetii*. The need to start empirical antibiotic therapy for such pathogens is controversial, particularly in low- and moderate-severity CAP; data are limited and conflicting.[6,16] *M. pneumoniae*, *C. burnetii* and *Chlamydophila (Chlamydia)* species most often cause low- and moderate-severity CAP; *Legionella* species are more likely to cause high-severity CAP.[12] For adults with low-severity CAP, the decision to replace amoxicillin monotherapy with either doxycycline or a macrolide to target these organisms is challenging. Historically, CAP was categorised as typical or atypical based on patient presentation; however, evidence has shown that it is difficult to accurately predict the causative organism based on clinical presentation alone.[2]

For adults with low-severity CAP who also have a significant medical comorbidity (e.g. advanced heart, liver or kidney disease, or frailty), initial combination therapy with amoxicillin and either doxycycline or a macrolide is recommended, because the consequences of empirical therapy being incorrect are more serious, particularly if there is a possibility that follow-up may not occur.[6,17]

When doxycycline or a macrolide is indicated for low- or moderate-severity CAP, doxycycline is preferred. A systematic review and meta-analysis showed doxycycline was noninferior to macrolides or fluoroquinolones when used as monotherapy.[18] Compared with macrolides, doxycycline has a better adverse effect profile, causes fewer drug interactions, and is less likely to cause *Clostridioides difficile* infection.[19]

For **moderate-severity CAP** in Australia, benzylpenicillin in combination with doxycycline or a macrolide is recommended, because of the significant risk of patient deterioration.[17,20] For **high-severity CAP**, the high mortality risk outweighs the potential for adverse effects with combination therapy, so antibiotic therapy with activity against a broader range of pathogens (*S. pneumoniae*, *Legionella pneumophila* and Gram-negative Enterobacterales) is recommended.[6,17]

Amoxicillin+clavulanate is not recommended as initial empirical therapy for CAP, or for intravenous to oral switch. The dosage of amoxicillin for CAP produces adequate concentrations to treat *Streptococcus pneumoniae* with a higher penicillin minimum inhibitory concentration,† without the unnecessarily broader-spectrum activity of clavulanate.[21] Also, amoxicillin+clavulanate provides a lower total dose of amoxicillin, and causes more adverse effects than amoxicillin monotherapy.[11]

† The minimum inhibitory concentration (MIC) is a measure of the lowest concentration of a drug required to stop the visible growth of a specific organism in vitro.

Oral versus parenteral antimicrobial therapy in hospitalised adults

Patients admitted to hospital with CAP have traditionally been treated with intravenous antibiotics;[6] however, many of the oral antibiotics used for CAP, including amoxicillin, doxycycline and macrolides, have excellent bioavailability.[22] The dogma that intravenous administration is superior to orally administered antibiotic therapy has been challenged and overturned in numerous infectious syndromes.[23] Oral antibiotic therapy has many advantages compared with intravenous therapy, including avoidance of an intravenous cannula, lower drug and healthcare costs, and reduction in length of hospital stay.[23,24]

Data to support equivalent efficacy of oral versus parenteral therapy in CAP are limited, and predominantly involve paediatric populations and fluoroquinolones.[25,26] A recent systematic review and meta-analysis did not find that oral antibiotic therapy had a negative impact on outcome or mortality in hospitalised patients, but results were limited by the quality and heterogeneity of the included studies.[26] An earlier retrospective cohort study and meta-analysis of patients treated exclusively with oral antibiotics in hospital, excluding those who could not take oral therapy or had severe disease, found no difference in mortality but there was a reduction in length of stay and drug costs with an oral-only approach.[24]

Internationally, there is no consensus regarding when parenteral antibiotics are recommended. Australian and British guidelines recommend oral antibiotics as first-line therapy for moderate-severity CAP, whereas US guidelines recommend intravenous antibiotics for patients admitted to hospital for CAP.[6,7,11] Clinical judgement is required to select suitable patients in the absence of any alternative evidence-based methodology. Ongoing advances in rapid diagnostics and data analytics will hopefully close this evidence gap and provide a more precise approach to selecting the route of antibiotic administration.

Can the duration of antimicrobial therapy be shortened?

For patients with uncomplicated CAP (regardless of severity) who achieve clinical stability, international clinical practice guidelines recommend a duration of 5 days of antibiotic therapy.[6,7] Recent meta-analyses of randomised controlled trials (RCTs) have also demonstrated that a duration of therapy of 7 days or shorter is equivalent to 7 to 14 days of antibiotic therapy, which was historically considered standard for CAP.[12,27-29] Shortening the standard duration has many potential benefits including a reduced risk of antibiotic-associated harms (including adverse events and antimicrobial resistance), improved adherence to therapy, and lower healthcare costs.[27] Longer durations of therapy are recommended for complicated infections (e.g. pneumonia complicated by empyema or infective endocarditis) and for directed therapy to treat certain pathogens such as *Mycobacterium tuberculosis*.[6]

The duration of therapy studied in RCTs varies. A few key high-quality studies are of interest. A Spanish RCT found that ceasing antibiotic therapy after a median of 5 days, based on clinical stability criteria, was noninferior to 10 days therapy.[30] A recent French multicentre noninferiority RCT highlighted the potential to further shorten this duration to 3 days in certain hospitalised patients; stopping beta-lactam antibiotic therapy after this time was noninferior to 8 days of treatment.[31] Approximately 40% of the included patients had more severe disease (classified as risk class 4 and 5 according to the PSI scoring tool). Less than half of the patients screened for inclusion met the eligibility criteria for the study, emphasising that the results are not generalisable to all patients, particularly those who do not have a rapid response to therapy.

Use of clinical stability criteria (e.g. temperature, blood pressure, heart rate, oxygenation) to guide cessation of antibiotics has been used in most trials. Failure to achieve clinical stability within 5 days was associated with worse outcomes, including higher mortality.[32] This finding emphasises the importance of close patient follow-up. If a patient has not responded to therapy, particularly at day 5, assess for complications of pneumonia, review the choice of initial empirical therapy, and look for an alternative source of infection or inflammatory response.[6]

Despite evidence to support a shorter duration of antibiotic therapy for CAP, prolonged therapy is still commonly prescribed.[33] This is not without risk: a large cohort study of general medicine patients with pneumonia in the USA found that each excess day of treatment was associated with a 5% increase in the odds of antibiotic-associated adverse effects.[34]

What is the role of adjunctive corticosteroids for high-severity CAP?

Corticosteroid use for hospitalised patients with CAP, particularly those who are critically unwell, has been the subject of multiple clinical trials that have produced conflicting results.[35-37] To date, adjunctive corticosteroids have not routinely been recommended for patients with CAP managed either in the community or in hospital, unless existing

evidence supports their use (e.g. patients with CAP who have an acute exacerbation of chronic obstructive pulmonary disease or who have refractory septic shock).[6,38]

In response to recently published high-quality RCTs, a meta-analysis and meta-regression of these RCTs evaluated the safety and efficacy of corticosteroids in 3367 patients hospitalised with CAP.[35-37] The authors found the all-cause mortality at 30 days was significantly lower in the corticosteroid group (6.15%) than in the control group (9.06%; risk ratio 0.67, 95% confidence interval 0.53 to 0.85, p=0.001).[35] Corticosteroid therapy was not associated with an increased risk of developing any adverse effect compared with standard of care.

For patients who are critically unwell with CAP current evidence suggests corticosteroids should be used, administered within 24 hours of diagnosis of high-severity CAP. Careful selection of patients to meet strict eligibility criteria is essential. These criteria include intensive care unit admission, the presence of respiratory failure requiring initiation of (at minimum) high-flow oxygen, and consideration of relative contraindications to corticosteroids. Evidence gaps remain. The choice of corticosteroid, timing of commencement, and dosing and duration of therapy have varied between studies, and the optimal approach is yet to be determined.

Conclusion

Community-acquired pneumonia is common and contributes a significant burden of disease globally, yet many uncertainties and controversies regarding management remain. Recent advances in knowledge are promising but further research is required to close many evidence gaps, with the aim to reduce the morbidity and mortality associated with CAP while ensuring antibiotics are used judiciously. ≺

Conflicts of interest: Emily Tucker, Maeve O'Sullivan and Lisa Waddell are members of the expert group for Therapeutic Guidelines: Antibiotic *version 17 (under review).*

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