

Investigation and Management of Community-Acquired Pneumonia (CAP) Frequently Asked Questions

1. Why was this algorithm developed?

Emergency department physicians were seeking guidance about best antimicrobial therapy for common infectious diseases in light of increasing interest around issues of antimicrobial stewardship, emergency department efficiency, and patient safety. This 2016 update was developed to consider new evidence, resistance issues, and evolving standards.

2. How was this algorithm developed?

In 2012, the Toronto Central Local Health Integration Network (LHIN) convened a small working group to develop a CAP algorithm, which was then vetted through electronic peer review, and finally a consensus meeting of stakeholders. Human Factors Engineering consultants were employed to optimized algorithm design.

For the 2016 revision, antimicrobial stewardship experts, coupled with ER physicians and internists were gathered to review potential modifications. Additionally, electronic survey of general internists and a Twitter survey were used to gauge standards of care. Questions for this revision are included below, with an accompanying discussion.

3. What are the most notable changes or updates to the 2016 algorithm?

- a. Low-risk patients suitable for discharge should be defined by a CRB-65 score of 0 AND an oxygen saturation of at least 92% on room air.
- b. Recommended first-line outpatient therapy for CAP is now amoxicillin 1g po bid.
- c. Recommended first-line inpatient non-ICU therapy for CAP is now amoxicillin-clavulanate 875mg/125mg po bid OR cefotaxime 1g iv q8h or ceftriaxone 1g iv q24h. Consideration for adding azithromycin empirically should only be given during the months of June through October.
- d. Recommended duration of therapy for all CAP is now 5-7 days.

4. Should CRB-65 continue to be used for severity and risk stratification?

CRB-65, a tool that has been validated in at least 14 studies, involving almost 400 000 patients, remains a well-validated tool.¹ However, concern regarding the absence of oxygen saturation was raised, based on a Canadian study of

Emergency Department CAP that was published around the time of the previous revision. In an observational study from Edmonton, patients discharged with an oxygen saturation of less than 92% were found to have higher subsequent hospital admission rates and higher mortality compared to those discharged with an SaO₂ of at least 92%.² A second publication looked at the incremental value of adding oxygen saturation <90% to CRB-65 in low-risk patients, and found that it improved performance. Despite the limitations of these observational studies, the working group and consensus panel felt that the evidence supporting the additional criterion for discharge from the Emergency Department of an SaO₂ ≥ 92% is appropriate.

5. Is amoxicillin-clavulanate monotherapy still appropriate first-line therapy for outpatient CAP?

Prior recommendations for amoxicillin-clavulanate were based on the need to cover both *Streptococcus pneumoniae* and *Haemophilus influenzae*. However, amoxicillin-clavulanate confers no advantage over amoxicillin for *S. pneumoniae* (because the mechanism of resistance is a penicillin binding protein, rather than a beta-lactamase, and so beta-lactamase inhibition with clavulanic acid provides no advantage). Additionally, *H. influenzae* is a relatively uncommon cause of CAP^{3,4}, and beta-lactamase production (i.e. amoxicillin resistance) occurs in less than a quarter of cases. A Cochrane review showed no preference of one agent over another. Accordingly, there was consensus that amoxicillin is appropriate first-line therapy for CAP.

Additionally, discussion moved to dosing for amoxicillin. The Cochrane review identified amoxicillin 1g tid as having poor tolerability compared to other regimens.⁵ Because 875mg bid of amoxicillin had previously been used and recommended (when included in the amoxicillin-clavulanate formulation), experts were comfortable recommending 1g bid for amoxicillin. Alternatively, amoxicillin 750mg po tid would also be acceptable.

6. In patients with non-ICU inpatient CAP, should atypical coverage be “+/- azithromycin”?

Several areas of research informed the decision-making, acknowledging (as with the 2012 CAP algorithm and FAQ) that this is an area of considerable controversy. Influential data came from epidemiological studies on CAP, showing that atypical bacteria—especially *Legionella* species—comprise only a small portion of all cases of CAP.^{3,4,6} Additionally, the value of adding macrolide therapy routinely to CAP therapy has now been investigated with 2 randomized controlled trials with somewhat disparate results. A Dutch RCT showed that there was no difference in 90-day mortality or hospital length-of-stay between beta-lactam monotherapy, respiratory fluoroquinolone monotherapy, and beta-lactam + macrolide combination therapy.⁷ A Swiss

RCT showed that beta-lactam monotherapy failed to reach non-inferiority compared with beta-lactam + macrolide combination therapy in a primary end-point exploring proportion of patients reaching “clinical stability” by day 7.⁸ Finally, the consensus panel considered data from Public Health Ontario showing that a) the number of diagnosed cases of Legionellosis in Ontario has been steadily rising, and b) the overwhelming majority of cases occur in the months June through October.

Balancing all of this information, the consensus panel concluded that most patients with non-ICU inpatient CAP do not require the addition of atypical bacteria for inpatient treatment of CAP. For clinicians wishing to consider the addition of a macrolide for Legionella coverage, that consideration should primarily be given only in the months of June through October and during Legionellosis outbreaks.

7. For patients admitted with CAP, should corticosteroids be administered?

This was considered following the publication of a systematic review out of McMaster University.⁹ Looking at almost 2000 mostly low-risk patients, Siemieniuk et al. found that adjunctive corticosteroids might improve clinically important outcomes such as mortality, ICU admission, and length of stay, at a cost of a 50% increase in episodes of hyperglycemia. The consensus panel concluded that there was insufficient evidence and enough concern for harm that routine corticosteroid therapy cannot be supported.

8. Should we include duration of therapy for patients admitted with CAP?

The Consensus panel felt strongly that duration of therapy is important to address in this algorithm for all patients, not just those discharged from the Emergency Department.

Unfortunately, duration of therapy has not been well studied. Several studies have strongly suggested that treatment durations beyond 7 days are unnecessary.¹⁰⁻¹³ Additionally, a recent RCT (published after the Consensus Panel met), demonstrated that therapy can be stopped at day 5 if body temperature was 37.8C or less for 48 hours and they had no more than 1 CAP-associated sign of clinical instability.¹⁴

Although most consensus panel members were comfortable treating CAP for 5 days, a University of Toronto Department of Medicine survey showed the strongest support for 5-7 days of therapy. Because of the lack of high-quality evidence supporting routine durations of 5 days, the panel has opted for 5-7 days.

References

- 1 McNally, M., Curtain, J., O'Brien, K. K., Dimitrov, B. D. & Fahey, T. Validity of British Thoracic Society guidance (the CRB-65 rule) for predicting the severity of pneumonia in general practice: systematic review and meta-analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners* **60**, e423-433, doi:10.3399/bjgp10X532422 (2010).
- 2 Majumdar, S. R., Eurich, D. T., Gamble, J. M., Senthilselvan, A. & Marrie, T. J. Oxygen saturations less than 92% are associated with major adverse events in outpatients with pneumonia: a population-based cohort study. *Clin Infect Dis* **52**, 325-331, doi:10.1093/cid/ciq076 (2011).
- 3 Holter, J. C. *et al.* Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis* **15**, 64, doi:10.1186/s12879-015-0803-5 (2015).
- 4 Jain, S. *et al.* Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med* **373**, 415-427, doi:10.1056/NEJMoa1500245 (2015).
- 5 Pakhale, S. *et al.* Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev* **10**, CD002109, doi:10.1002/14651858.CD002109.pub4 (2014).
- 6 Gadsby, N. J. *et al.* Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia. *Clin Infect Dis* **62**, 817-823, doi:10.1093/cid/civ1214 (2016).
- 7 Postma, D. F. *et al.* Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med* **372**, 1312-1323, doi:10.1056/NEJMoa1406330 (2015).
- 8 Garin, N. *et al.* beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med* **174**, 1894-1901, doi:10.1001/jamainternmed.2014.4887 (2014).
- 9 Siemieniuk, R. A. *et al.* Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med* **163**, 519-528, doi:10.7326/M15-0715 (2015).
- 10 Li, J. Z., Winston, L. G., Moore, D. H. & Bent, S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. *Am J Med* **120**, 783-790, doi:10.1016/j.amjmed.2007.04.023 (2007).
- 11 Dimopoulos, G. *et al.* Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis. *Drugs* **68**, 1841-1854 (2008).
- 12 Choudhury, G. *et al.* Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia--a propensity-adjusted analysis. *Clin Microbiol Infect* **17**, 1852-1858, doi:10.1111/j.1469-0691.2011.03542.x (2011).
- 13 Avdic, E. *et al.* Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis* **54**, 1581-1587, doi:10.1093/cid/cis242 (2012).
- 14 Uranga, A. *et al.* Duration of Antibiotic Treatment in Community-Acquired Pneumonia. *JAMA Internal Medicine*, doi:10.1001/jamainternmed.2016.3633 (2016).