

2015

New evidence prompts rethinking the clinical management of community acquired pneumonia in patients admitted to general medical services.

J. Timothy Caldwell
jtcaldwe@med.wayne.edu

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>

 Part of the [Medical Education Commons](#), [Respiratory Tract Diseases Commons](#), and the [Translational Medical Research Commons](#)

Recommended Citation

Caldwell JT. New evidence prompts rethinking the clinical management of community acquired pneumonia in patients admitted to general medical services. *Clin. Res. Pract.* July 2015;1(2):eP1029. doi: 10.22237/crp/1437147323

This Critical Analysis is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

New evidence prompts rethinking the clinical management of community acquired pneumonia in patients admitted to general medical services.

Erratum

This article was originally published with an erroneous abstract.

New evidence prompts rethinking the clinical management of community acquired pneumonia in patients admitted to general medical services

J. TIMOTHY CALDWELL, B.S., Wayne State University, Detroit, MI

ABSTRACT A critical appraisal and clinical application of Postma DF, van Werkhoven CH, van Elden LJR, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med.* 2015;372(14):1312-1323. doi:[10.1056/NEJMoa1406330](https://doi.org/10.1056/NEJMoa1406330).

Keywords: Community-acquired pneumonia, beta-lactam

Clinical Context

Mr. W is a 68 year old man with a past medical history significant for hypertension and vitamin D deficiency who presented to the emergency department (ED) with a 2-day history of worsening shortness of breath, productive cough, pleuritic chest pain, and fevers as high as 101°F/38.3°C. The patient was diagnosed with community-acquired pneumonia (CAP), treatment was initiated with moxifloxacin, and he was admitted to the general floor for inpatient management.

Clinical Question

What is the appropriate first-line antibiotic for the treatment of community-acquired pneumonia in an adult patient requiring admission to a general floor?

Research Article

Postma DF, van Werkhoven CH, van Elden LJR, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med.* 2015;372(14):1312-1323. doi:[10.1056/NEJMoa1406330](https://doi.org/10.1056/NEJMoa1406330).

Literature Review

Community acquired pneumonia has long been an important cause of morbidity and mortality¹. In an effort to limit the burden that CAP has on patients, guidelines have been instituted that direct physicians to administer antibiotics empirically based on the severity of clinical presentation^{2,3}. The application of such guidelines has been correlated with improved outcomes⁴, but also with an increase in the use of, and subsequent resistance to macrolide and fluoroquinolone antibiotics^{5,6}.

J. TIMOTHY CALDWELL, B.S., is an MD/PhD student in the M3 year of his clinical training at Wayne State University School of Medicine, and a Senior Student Editor of the journal.



In investigating the proper choice for initial antibiotic therapy, this author first turned to the joint guideline statement from the 2007 Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) recommended by the Centers for Disease Control (CDC)² Those authors clearly recommend a β -lactam plus macrolide OR fluoroquinolone as first line therapy, stating that β -lactams alone were found to be inferior with “level-1 evidence”, however all of the trials cited are retrospective or prospective observational studies⁷⁻¹⁰. These recommendations are somewhat at odds with those provided by the British Thoracic Society in 2009, which recommend oral amoxicillin monotherapy for low-severity CAP³. A 2012 Cochrane Review on the subject investigated the utility of adding atypical coverage to empiric therapies and found no benefit¹¹. Furthermore, the authors of that study were unable to find a quality randomized controlled trial (RCT) comparing β -lactam monotherapy to said therapy plus a macrolide and emphasized the need for such a study.

In order to find RCTs investigating this question that may have been completed since the publication of the Cochrane Review, PubMed and Google Scholar were searched using the term “community-acquired pneumonia” and either “lactam” or “trial”. Results published before 2012 or in a non-English language were excluded. 2 studies were identified. In order to check for possible missed studies, UptoDate was queried for “community acquired pneumonia” and those articles searched for reference to relevant RCTs, of which none were found. Furthermore, the 2 studies found did not reference any previous studies; one stated none could be found upon their search.

The first study, published in 2014 by Garin et al., was a randomized non-inferiority trial comparing β -lactam monotherapy to β -lactam-macrolide combinations in moderately-severe CAP¹². The authors used an open, block-randomization strategy that included 580 patients after randomization. Using an intention-to-treat (ITT) strategy and non-inferiority margin of 8%, the authors did not find non-inferiority for β -lactam monotherapy for the primary endpoint of clinical stability at 7 days. Furthermore, the authors found an increased rate of readmission in the β -lactam monotherapy group on secondary analysis, although other outcomes were not different between the two groups. The second study, published in 2015 by Postma et al. and critically appraised in this work, used a cluster-randomization with crossover strategy to compare the non-inferiority of β -lactam monotherapy to β -lactam-macrolide and fluoroquinolone monotherapy¹³. It included 2283 patients, and unlike the Garin et al. study, did find non-inferiority for β -lactam monotherapy as initial antibiotic therapy. It was chosen for appraisal because of its larger sample size and strength of study design, which eliminated several potential sources of bias.

Critical Appraisal

The article in question represents level 1 evidence, according to the SORT classification¹⁴. Though not blinded, it was an RCT study with crossover that utilized ITT strategy for analysis of primary outcome measures. Number needed to treat determination is not applicable to this article. The study design involved multiple centers in the Netherlands that were individually randomized to preferentially use either β -lactam monotherapy, β -lactam-macrolide, or fluoroquinolone monotherapy for initial therapy for the treatment of CAP requiring admission to a general ward. Each center utilized all three strategies in staggered, rotating blocks of 4 months on all patients who met criteria for admission to a general floor with suspected CAP. Adherence was defined as initiation of therapy with the proper agent(s), regardless of any changes that were made to the regimen after the fact. The study was designed and powered to demonstrate non-inferiority of β -lactam monotherapy with a primary outcome of 90-day all-cause mortality. Secondary outcomes were length of hospital stay, complication rate, and time to initiation of oral therapy.

The appraised study was well designed and executed, and as such has a number of important strengths, some of which will be discussed here. The first and most important is that the prospective, randomized nature of the study prevents a substantial source of bias seen in previous observational studies that compared the regimens in question. In any retrospective or observational study it is impossible to determine if some uncontrollable factor influenced treatment decision (such as how sick the patient “looked”). By predetermining what antibiotic regimen all patients in a given time period would receive as initial therapy for their CAP, selection biases secondary to variations in admission criteria, population-based illness severity, institutional-level practice, and perceived severity of illness at presentation were minimized. Furthermore, this randomization strategy minimized any delay that may have resulted from patient-level randomization, and also may have contributed to better protocol adherence. The second strength (which may also be considered a weakness, see below) was that adherence was defined as initiating the proper regimen, without penalty for changing agents as the physician felt necessary. This realistically reflects clinical practice, and in some ways allows for determination of the impact that initial therapy had on outcome, regardless of eventual therapy. Finally, the multicenter nature of



the study coupled with staggered start strategy helped to diminish the impact that institutional practice or seasonal variation in disease patterns would have on the validity and generalizability of the results.

The major potential limitation for application to clinical practice is the fact that only administration of initial therapy as assigned was required for adherence. With such a strategy, the primary outcome of 90-day mortality could theoretically remain unaffected even if β -lactam monotherapy was ineffective, so long as the regimen was switched in a timely manner. However, the authors demonstrate fairly tight adherence to the initial therapy amongst all study groups (albeit less-so in the β -lactam monotherapy group), and the lack of significant difference in secondary outcome measures of length of hospitalization and complication rate argue against the negative effect of this strategy. Another potential critique involves the use of a non-inferiority strategy; unfortunately, the lack of an established standard of care and the unethical nature of a placebo-controlled trial make a superiority trial in this case difficult. Additionally, a very conservative 3% noninferiority margin was utilized (compared to, for example the 8% used by Garin et al. above¹²) which helps to abate one of the biggest weaknesses of such trials, namely the relative ease of demonstrating noninferiority with a large predetermined margin. That being said, it is important to remember that demonstrating non-inferiority is not the same as demonstrating equivalence or superiority. Finally, the catchall category of β -lactam monotherapy makes application of these results difficult. Because the authors did not stratify their results by the choice of β -lactam therapy, it is possible in theory that positive results from (for example) ceftriaxone may have overshadowed more negative results from amoxicillin alone.

Clinical Application

The determination of which initial antibiotic to use in the setting of CAP requiring admission to a general ward can be difficult at times, and is often guided by many factors such as perceived efficacy of possible treatments, patient allergies, and antimicrobial stewardship. The last of these is important moving forward, especially given the broad coverage and good oral availability of fluoroquinolones, as resistance to macrolide and fluoroquinolone therapy has been clearly demonstrated^{5,6}. This study provides evidence that initial treatment with β -lactam monotherapy is an appropriate treatment approach, possibly sparing the use of additional broad-spectrum antibiotics.

Despite this, the results of this study must be carefully interpreted within the context of local communities. The patient population studied by Postma et al. is not necessarily representative of certain global populations, especially those in other countries or with poorer access to care. Furthermore, the pathogen distribution in an area would play an important role: for example, an area with high prevalence of atypical organisms would be poorly served by initial treatment with β -lactam monotherapy. The choice of initial β -lactam may also be difficult, as this study does not offer guidance on specific agent selection. These concerns aside, this study provides a good foundation for the necessary further study/replication and poses a unique challenge to the existing guidelines for the treatment of CAP.

Take-home points:

1. For patients like Mr. W who present with CAP requiring admission to a general ward, β -lactam monotherapy may be appropriate for the empiric treatment of their suspected pneumonia.
2. In light of increasing antibiotic resistance, the principles of antimicrobial stewardship dictate that the risk of benefit be weighed against the risk of harm. In light of this new evidence, empiric therapy with β -lactam monotherapy is reasonable.
3. Guidelines are sometimes based on poorer quality evidence than many think, and as such their recommendations must be interpreted carefully and critically. Furthermore, when new evidence becomes available, existing guidelines may require reevaluation.

References

1. Thomas CP, Ryan M, Chapman JD, et al. Incidence and cost of pneumonia in medicare beneficiaries. *Chest.* 2012;142(4):973-981.



Caldwell JT. New evidence prompts rethinking the clinical management of community acquired pneumonia in patients admitted to general medical services. *Clin. Res. Pract.* July 2015;1(2):eP1029. doi: [10.22237/crp/1437147323](https://doi.org/10.22237/crp/1437147323)

2. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* March 1, 2007;44(Supplement 2):S27-S72.
3. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax.* October 1, 2009 2009;64(Suppl 3):iii1-iii55.
4. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: Playing by the rules. *Arch Intern Med.* 2009;169(16):1525-1531.
5. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet.* 2007 Feb 10;369(9560):482-90. doi:[10.1016/S0140-6736\(07\)60235-9](https://doi.org/10.1016/S0140-6736(07)60235-9)
6. Fuller JD, Low DE. A review of streptococcus pneumoniae infection treatment failures associated with fluoroquinolone resistance. *Clin Infect Dis.* July 1, 2005;41(1):118-121.
7. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med.* 1999;159(21):2562-2572.
8. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states*: 1993, 1995, and 1997. *Chest.* 2001;119(5):1420-1426.
9. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching us community hospitals. *Ann Pharmacother.* 2000 Apr;34(4):446-52.
10. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia*: Analysis of a hospital claims-made database. *Chest.* 2003;123(5):1503-1511.
11. Eliakim-Raz N, Robenshtok E, Shefet D, et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev.* 2012 Sep 12;9:CD004418. doi: [10.1002/14651858.CD004418.pub4](https://doi.org/10.1002/14651858.CD004418.pub4)
12. Garin N, Genné D, Carballo S, et al. B-lactam monotherapy vs β -lactam–macrolide combination treatment in moderately severe community-acquired pneumonia: A randomized noninferiority trial. *JAMA Intern Med.* 2014 Dec;174(12):1894-901. doi: [10.1001/jamainternmed.2014.4887](https://doi.org/10.1001/jamainternmed.2014.4887).
13. Postma DF, van Werkhoven CH, van Elden LJR, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med.* 2015 Apr 2;372(14):1312-23. doi: [10.1056/NEJMoa1406330](https://doi.org/10.1056/NEJMoa1406330)
14. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract.* 2004 Jan-Feb;17(1):59-67.

