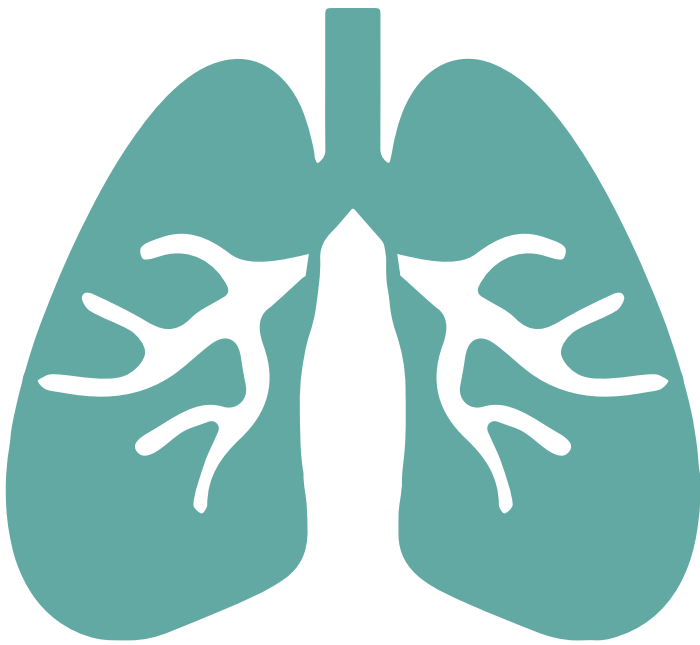


Treatment Duration for Uncomplicated Community-Acquired Pneumonia: The Evidence in Support of 5 Days





Executive Summary

National consensus guidelines created jointly by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) recommend 5 days of antibiotic therapy for adult patients with community-acquired pneumonia (CAP) who have been afebrile for 48 hours and have no more than 1 CAP-associated sign of clinical instability.

Patients with uncomplicated CAP treated at many hospitals, including hospitals participating in the Michigan Hospital Medicine Safety Consortium (HMS), continue to get longer treatment durations without evidence to support that these longer durations lead to better outcomes. The 5-day treatment duration is directly or indirectly supported by the following:

- Five (5) randomized controlled trials, plus an additional sub-group analysis, which demonstrate no significant difference in key outcomes for short versus extended-course antibiotics including clinical improvement, bacteriological improvement, radiographic resolution, adverse effects, mortality, recurrence, and length of hospital stay.
- Three (3) quasi-experimental studies, plus a follow-up study, which demonstrate no significant difference in key outcomes for short versus extended-course antibiotics including treatment failure, recurrence, mortality, length of hospital stay, and re-admission.
- Two (2) systematic reviews with meta-analyses, based on 20 randomized controlled trials collectively, which demonstrate no significant difference in effectiveness and safety of short versus extended-course antibiotic therapy including clinical failure, mortality, and bacterial eradication.

A detailed, annotated list of key references in support of 5-day antibiotic treatment duration for uncomplicated CAP patients follows.



Haas MK, Dalton K, Knepper BC et al. Effects of a Syndrome Specific Antibiotic Stewardship Intervention for Inpatient Community Acquired Pneumonia. *Open Forum Infect Dis.* 2016;3(4):ofw186

A quasi-experimental study conducted by the Antimicrobial Stewardship Program (ASP) at the University of Colorado. The ASP convened a multidisciplinary workgroup to develop a pneumonia guideline and CPOE admission order set for non-ICU CAP. The implementation strategy included electronic dissemination of guidelines to clinicians and multiple educational sessions performed by hospitalists who were part of the workgroup. The guideline recommended a 5-day course of a fluoroquinolone-sparing regimen for uncomplicated pneumonia.

Median duration of therapy decreased from 10 to 7 days ($P < 0.0001$). Levofloxacin prescriptions at discharge decreased from 60% to 27% ($P < 0.001$).

Frequency of clinical failure (a composite outcome of re-admission due to pulmonary infection (1% vs 6%), in-hospital mortality (1% vs 0%), treatment failure (5% vs 4%), recurrence (2% vs 4%), 30-day mortality (0% vs 0%)) was the same pre and post intervention (7% vs 10%; $p = .53$).



Unranga A, Espana P, Bilbao et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. *JAMA Intern Med.* 2016;176(9):1257–65

Randomized Clinical Trial (RCT)—The intervention arm was treated until afebrile for 48 hours and no more than one pneumonia associated instability (per IDSA guidelines), but with a 5-day minimum. The control arm's treatment duration was determined by physicians. Outcomes were clinical success rates (resolution or improvement of signs and symptoms related to pneumonia without further antibiotic therapy) and CAP symptom questionnaire scores. They had planned to look at clinical cure, all-cause mortality, and major complications as the primary outcome but there were too few events. There were no differences in clinical success rates or CAP questionnaire score between intervention and control group. Median treatment duration was 5 days in the intervention group and 10 days in the control group.

There were no significant differences for time until clinical improvement, days to return to normal activity, radiographic resolution (Day 30), adverse effects (Day 30), in-hospital mortality, 30-day mortality, in-hospital complications, recurrence by day 30, and length of hospital stay. Readmission by day 30 was more common in control group (6.6% vs 1.4%, $P = 0.02$).

In the intervention group, 70.1% qualified for and received 5 days of therapy. There were 13/162 protocol violations that were not included in the per protocol analysis. Of the cohort (intervention and control group), 80% were treated with a quinolone, 11% with beta-lactam alone, and 9% with a beta-lactam and macrolide.



3. Avdic E, Cuschinotto LA, Hughes AH, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis 2012;54 (11):1581-7.

Quasi-experimental study performed at Johns Hopkins with education and postprescription review and feedback of treatment provided to patients with CAP.

Treatment duration was 5 days for pneumonia patients without immunocompromising conditions or structural lung disease, 7 days for moderately immunocompromised and/or structural lung disease, and 10-14 day for patients with poor clinical response or significantly immunocompromised.

Median duration of therapy went from 10 to 7 days. The Pre-intervention period was in 2008 and at that time 58% of patients received moxifloxacin. The intervention period was in 2010 and 58% received ceftriaxone + azithromycin.

There was no difference in LOS and 30-day re-admission rates were higher in the pre-intervention group (though not statistically significant).



4. Li DX et al. Sustained Impact of an Antimicrobial Intervention for Community-Acquired Pneumonia. Infect Control Hosp Epidemiol 2016; 37:1243-1246.

A follow-up study 3 years after the intervention was performed in Reference 3. There was no difference in length of stay or hospital re-admission compared to the original study period 3 years prior. Median duration of antibiotics for CAP remained at 7 days.



5. Li JZ, Winston LG, Moore DH, Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med. 2007;120 (9):783-90.

Meta-analysis: Included 15 RCT and 10/15 used azithromycin, 2/15 beta-lactam, and 2/15 with fluoroquinolones. Only two were specifically about hospitalized patients. There was no difference in clinical failure between shortcourse and extended course regimens. No difference in risk of mortality or bacterial eradication. Subgroup analysis, there was trend toward favorable clinical efficacy for the short course regimens in all antibiotic classes.

Conclusion was that mild-moderate CAP can be safely and effectively treated with an antibiotic regimen of 7 days or less.

6.

Leophante P, Choutet P, Gaillat J, et al. Efficacy of a ten-day course of ceftriaxone compared to a shortened five-day course in the treatment of community-acquired pneumonia in hospitalized adults with risk factors. *Med Mal Infect* 2002; 32:369-81.

French RCT study: Patients were randomized to 5-day IV ceftriaxone followed by 5 day placebo IM versus 5 days IV ceftriaxone followed by 5 days ceftriaxone IM.

The primary criterion for success was being afebrile on day 10. There was no difference between the groups. Secondary criteria was clinical normalization at day 10, cure (clinical/radiological at day 30/45), and absence of new antibiotic starts before day 30/45. Fewer patients had clinical and radiographic normalization in the 10-day treatment group, but other secondary endpoints were not different between treatment arms.

Patients had to also have a risk factor for inclusion—age ≥ 65 , tobacco ≥ 10 ppd, chronic alcoholism, non-decompensated underlying disease, and malnutrition or obesity. No patients with malignancies or immunosuppression were included.

7.

Dimopoulos G, Mathaiou DK, et al. Short versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. *Drugs*. 2008;68(13):1841-54.

Systematic review which included 5 RCTs for adults. The main outcome for clinical success was defined as complete resolution or improvement of symptoms and signs of CAP which was assessed at the end of therapy evaluation visit.

There was no difference in effectiveness and safety of short versus long course antimicrobial therapy. A subgroup analysis also found no difference for patients treated with no more than 5-day short course vs 7-day long course regimen—but 5 vs 7 included gemifloxacin trial, telithromycin trial, and ceftriaxone trial (see above ref 6).

8.

File TM Jr. Mandell LA, et al. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicenter, double-blind study. *J Antimicrob Chemother* 2007;60:112-20.

A double blind, multicenter RCT comparing 5 days versus 7 days of gemifloxacin for CAP. The 5-day treatment arm was non-inferior to 7-day treatment arm with respect to clinical, bacteriological, and radiological efficacy.

9.

Moussaoui R, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community-acquired pneumonia: randomized, double blind study. *BMJ* 2006;332:1335.

A RCT performed in the Netherlands. The intervention was IV amoxicillin X 3 days followed by no further antibiotics or oral amoxicillin for 5 days. At day 3 of therapy they rated four respiratory symptoms. Patients who had improved by ≥ 2 points on this scale, afebrile, and able to take oral medications were then randomized.

20.4% did not improve enough to be randomized. There was no significant difference in length of stay, clinical cure, bacteriological success, and radiological success at day 10 and day 28.

The study excluded patients with a PSI > 110 , severe CAP and immunosuppressed patients (neutropenia, HIV infection with AIDS, ICU, *S.aureus* pneumonia, empyema, primary immunodeficiency, and asplenia).

10.

Dunbar LM, Wunderink RG et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003;37:752-60.

A RCT comparing 5 days of levofloxacin 750 mg daily vs 10 days of levofloxacin 500 mg daily. Fevers resolved more frequently at Day 3 in the short course arm. There was no difference in clinical success rates or microbiologic eradication rates.

11.

Foolad F, Huang A et al. Impact of a Multi-faceted Stewardship Intervention on Duration of Antibiotic Therapy for the Treatment of Community-Acquired Pneumonia. *ID Week*; 2016 Oct 26-30; New Orleans, LA. Abstract 1029.

A quasi-experimental study performed at University of Michigan and Medical College of Wisconsin with interim analysis. A stewardship intervention including CAP guideline update, pharmacist education, prescriber education, and prospective audit and feedback was implemented. The recommended duration of therapy was based on IDSA guidelines (applying clinical stability criteria).

There was a significant decrease in the median duration of therapy 7 vs 8 days ($P<0.001$). There was also a decrease use in high risk CDI antibiotics—ceftriaxone, cefpodoxime, and levofloxacin ($P<0.05$).

There was no difference in mortality, length of stay, re-admission for pneumonia, or incidence of CDI. In the abstract 44.4% of patients in the intervention group met criteria for 5 days and 37% received 5 days and 47.3% in the pre-intervention group met criteria for 5 days and 10% received 5 days.

12.

Shorr, AF et al. A Multicenter, Randomized, Double- Blind, Retrospective Comparison of 5- and 10 day Regimens of Levofloxacin in a Subgroup of Patients Aged > 65 years with Community-Acquired Pneumonia. Clinical Therapeutics 2005. 27;1251-1259.

This study was a subgroup analysis of reference 10 that only included analysis of elderly patients > 65 years (41.3% in the 5 day group had COPD). Clinical success was similar between 5 and 10-day regimens.

13.

Vaughn, VM et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized with Pneumonia: A Multihospital Cohort Study 2019. 171;153-163.

A retrospective cohort study conducted using data from 43 hospitals within the Michigan Hospital Safety Consortium (6481 total general care medical patients with pneumonia). The aim of this study was to examine not only outcomes associated with excess duration of antibiotic therapy, but also the predictors of excess therapy.

At the conclusion of the study, it was found that ~68% of patients received excess antibiotic therapy, with a majority (92.3%) of the excess therapy being prescribed on discharge. It was also found that a longer duration of antibiotics was associated with antibiotic-associated adverse events reported by patients after discharge.

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