BC Provincial Antimicrobial Clinical Expert Group (PACE)

Community Acquired Pneumonia (CAP): Duration of Antibiotic Therapy in Hospitalized Adults

Commentary

How did we get to 3 days of therapy for CAP?

Historically, CAP was treated with 10 to 14 days of antibiotic therapy. However, shorter durations of therapy have been evaluated and recommended by various organizations over the last couple decades.

IDSA/ATS CAP guidelines from 2019 recommend CAP to be treated for a minimum of 5 days then stopped in those meeting clinical stability criteria and without complications (e.g., lung abscess). Clinical stability criteria were first detailed by Halm (1998) in a pivotal analysis from the Pneumonia Patient Outcomes Research Team (PORT) prospective observational study conducted in the United States and Canada. They evaluated time to stability, individually and collectively, for multiple parameters: systolic blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, ability to eat, and normalized mental status. The median time to stability of all parameters was 3 days and patients with more severe pneumonia at presentation took the longest to recover.

Multiple meta-analyses of randomized controlled trials that have shown short course therapy for CAP (7 days or less) to be equivalent to longer courses of therapy (Li 2007; Tansarli 2018; Furlan 2019). We have extracted the relevant trials from these analyses, specifically those that included a prominent proportion of hospitalized patients. Only trials with a short course arm of <7 days were included to evaluate 3 and 5 day regimens. Furthermore, trials of short course azithromycin have been excluded due to its long tissue half-life.

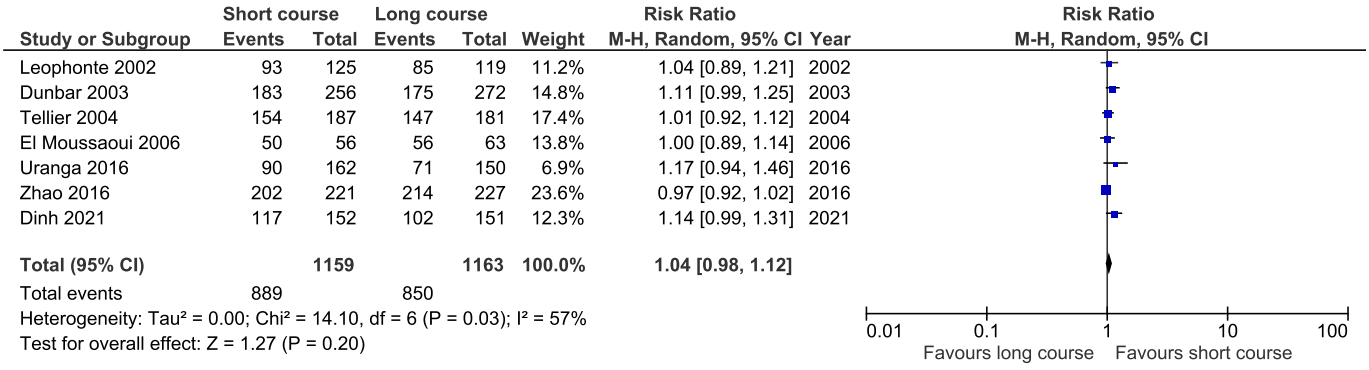
Table 1. Randomized controlled trials including hospitalized CAP with a trial arm of <7 days total therapy.

Reference	Severity	Regimen		Clinical Cure (ITT population)		Time of clinical evaluation
		Short Course	Long Course	Short Course	Long Course	
Léophonte 2002	Inpt	Ceftriaxone IV for 5 days	Ceftriaxone IV for 5 days, followed by ceftriaxone IM for 5 days	74% (93/125)	71% (85/119)	Day 10
Dunbar 2003	Inpt/Outpt	Levofloxacin IV/PO for 5 days	Levofloxacin IV/PO for 10 days	72% (183/256)	64% (175/272)	7-14 days after last antibiotic dose
Tellier 2004	Inpt/Outpt	Telithromycin PO for 5 days	Clarithromycin PO for at least 10 days (range 10-14)	82% (154/187)	81% (147/181)	Days 17-21
El Moussaoui 2006	Inpt	Amoxicillin IV for 3 days	Amoxicillin IV fo 3 days followed by amoxicillin PO for 5 days	89% (50/56)	89% (56/63)	Day 10
Zhao 2016	Inpt/Outpt 87% CURB-65=0 55% hospitalized	Levofloxacin IV 5 days	Levofloxacin IV/PO for at least 7 days (range 7-14)	91% (202/221)	94% (214/227)	End of treatment

Reference	Severity	Regimen		Clinical Cure (ITT population)		Time of clinical evaluation
		Short Course	Long Course	Short Course	Long Course	
Uranga 2016	Inpt	Beta-lactam+/- macrolide or fluoroquinolone for 5 days then stop if clinically stable	Beta-lactam+/- macrolide or fluoroquinolone for as per treating physician (median 10 days)	56% (90/162) 92% (147/162)	49% (71/150) 89% (132/150)	Day 10 Day 30
Dinh 2021	Inpt	Beta-lactam monotherapy for 3 days	Beta-lactam monotherapy for 3 days, followed by amox-clav PO for 5 days	77% (117/152)	68% (102/151)	Day 15

Meta-analysis of these trials was performed using Review Manager 5.4.1. Pooled risk ratio and 95% confidence intervals for clinical cure at short term follow-up were calculated. The Mantel-Haenszel random effects model was used.

Figure 1. Relative risk of clinical cure with short course (3 to 5 days) versus long course therapy for hospitalized CAP.



Pooling outcomes from 7 randomized controlled trials showed no statistically significant difference in clinical cure rates between short and long duration therapy.

The trial by Uranga (2016) should be highlighted as it was the first to validate the IDSA/ATS clinical stability criteria to stop antibiotics for hospitalized CAP. In this randomized controlled trial, hospitalized patients with CAP who met IDSA/ATS clinical stability criteria at day 5 were randomized to stop antibiotics (intervention group) or continue according to physician usual practice (control group). Patients received antibiotic therapy typically used in BC hospitals (beta-lactam +/- macrolides, or fluoroquinolones). Patients in the intervention arm received a median therapy duration of 5 days while the control group received a median 10 days of therapy. A sizeable proportion had more severe pneumonia, approximately 40% of patients had a baseline Pneumonia Severity Index (PSI) class of IV-V, correlating with 9-25% mortality. Clinical success at day 10 and 30 in the intervention group was non-inferior to the control group. Interestingly, patients in the control group had significantly more hospital readmission by day 30 than in the intervention group. This trial validated that clinical stability criteria could be safely applied after 5 days of therapy for hospitalized CAP.

While most trials used 5 days of therapy in the short course arm, two trials used 3 days (el Moussaoui 2006; Dinh 2021). Both showed similar cure rates between 3 days and 8 days of therapy. The most recent trial (Dinh 2021) enrolled patients admitted with CAP, defined as one acute clinical sign compatible with pneumonia (e.g., dyspnea, cough, purulent sputum, or crackles), fever above 38°C, and new pulmonary infiltrate on chest radiography. All patients received initial beta-lactam monotherapy (to avoid confounding by azithromycin's long tissue half-life). Approximately 40% of patients had a baseline PSI class of IV-V. Patients who met clinical stability criteria after 72 hours of therapy were then randomized to 5 days of oral placebo (intervention) or 5 days of oral amoxicillin-clavulanate (control). Clinical cure at day 15 for the intervention group was non-inferior to control, results that remained consistent across post-hoc subgroup analyses by age and initial PSI score. This trial validates that clinical stability criteria can be safely applied after 3 days of therapy for hospitalized CAP.

Similar results have been described in large, observational studies. Klompas (2022) evaluated hospitalized patients treated for pneumonia in 4 US hospitals. Both community and hospital acquired pneumonia were included. Patients with a median oxygen saturation of ≥95% on room air during day 1 and 2 of antibiotic therapy were identified, and antibiotic treatment for 1-2 days was compared with 5-8 days. After propensity-matching, those treated with 1-2 days of antibiotics had less overall antibiotic exposure and shorter hospitalization than those treated for 5-8 days. There was no difference in mortality or hospital readmission.

While not directly comparable, findings from the ventilator-associated pneumonia (VAP) literature further support short durations of therapy for mild pneumonia. In a randomized controlled trial of mild VAP (Singh 2000), as defined by a low Clinical Pulmonary Infection Score, patients were treated with 3 days of ciprofloxacin (intervention) versus 10-21 days of antibiotics (control). Short term outcomes were similar between groups, with the exception of increased ICU length of stay and increased superinfections in the control group. An analogous observational study (Klompas 2017) identified patients treated for mild VAP with minimal and stable ventilator settings (defined as positive end-expiratory pressure of ≤5 cm H2O and fraction of inspired oxygen ≤40% for 3 days). Those treated with short course therapy (1-3 days) were compared with long course therapy (>3 days). After propensity-matching, the short course therapy had no difference in time to extubation alive, ventilator death, time to hospital discharge alive, or hospital death.

The totality of literature to date consistently shows that short durations of therapy, as little as 3 days, are safe and effective for the treatment of pneumonia that has early and prompt clinical response.

Are patients with CAP that improve within 3 days of therapy even admitted to hospital?

The existing literature is clear on the spectrum of illness typically admitted to hospitals. The landmark study by Halm (1998) found a relatively even proportion of patients in each of PSI class I through IV (21-27% each), though fewer with PSI class V (8%). This distribution is similar to the pragmatic, non-industry sponsored, pneumonia clinical trials of the past decade (Uranga 2016, Dinh 2021).

Moreover, nearly one-fifth of patients admitted to hospital and treated for CAP have normal temperature, respiratory rate, oxygen saturation, and white blood cell count on the day of admission (Klompas 2020). The median time to clinical stability for admitted CAP is 3 days (Halm 1998). Antibiotics are continued for 3 days or longer after reaching clinical stability in one-third of hospitalized pneumonia (Klompas 2020). There are substantial opportunities for reducing antibiotic exposure in patients hospitalized with pneumonia.

Bacterial CAP doesn't improve within 3-5 days?

All of the trials included in this analysis included a broad range of patients with syndromic CAP. Thus, the distribution of pathogens broadly reflects what has been found in prospective observational studies of hospitalized CAP.

The trial by Léophonte (2002) identified an etiologic pathogen in about 35% of enrolled patients. *Streptococcus pneumonia* was identified in 6% of blood cultures and 13% of respiratory cultures. *Haemophilus influenzae* was identified in 9% of patients.

The trial by Dunbar (2003) identified an etiologic pathogen in about 37% of enrolled patients. About 8% had *Streptococcus pneumoniae*, though bacteremia was uncommon (14 cases). *Haemophilus influenzae/parainfluenzae* was identified in 9% of patients.

The trial by Tellier (2004) identified an etiologic pathogen in about 32% of enrolled patients in the relevant trial arms (telithromycin 5 day and clarithromycin 10 day). About 14% had Streptococcus pneumoniae, though bacteremia was uncommon (18 cases). A further 11% had *Haemophilus influenzae*.

The trial by El Moussaoui (2006) detected an etiologic pathogen in about 54% of enrolled patients. About 30% of patients had *Streptococcus pneumoniae* detected, including approximately 12% with bacteremia.

The trial by Zhao (2016) identified an etiologic pathogen in about 8% of enrolled patients. The majority were *Streptococcus pneumoniae* identified by urinary antigen testing.

The trial by Uranga (2016) identified an etiologic pathogen in about 20% of enrolled patients. The majority were *Streptococcus pneumoniae* (16% of enrolled patients).

The trial by Dinh (2021) identified an etiologic pathogen in about 12% of enrolled patients. The majority were *Streptococcus pneumoniae*, though bacteremia was rare (4 cases).

In summary, identification of an etiologic pathogen ranged from 8% to 50% of enrolled patients in randomized controlled trials of treatment duration in predominantly hospitalized CAP. *Streptococcus pneumoniae* was nearly universally the most common bacterial pathogen identified. While bacteremia was rare, these patients were not excluded from the trials. There is no evident signal in the literature that short course therapy of 3-5 days is less effective for confirmed bacterial CAP in those with early and prompt clinical response.

This is all the more important with the recognition that most patients admitted to hospital with CAP do not have an etiologic pathogen detected. When a pathogen is detected, respiratory viruses are twice as common as bacteria. The CDC EPIC prospective observational study identified bacterial pathogens in only 14% of 2259 hospitalized CAP patients (Jain 2015). The ultimate goal is to identify the shortest effective treatment duration for bacterial CAP, in order to minimize the harms of overtreatment for far more common viral CAP.

What about immunocompromised patients with CAP?

Immunocompromised patients are historically underrepresented in pneumonia trials. Some of the trials reviewed explicitly excluded immunocompromised patients (Léophonte 2002, Tellier 2004, Dinh 2021), while others excluded only certain forms of immunocompromise (e.g., splenectomy, solid organ transplant, neutropenia, advanced HIV; Dunbar 2003, el Moussaoui 2006, Zhao 2016, Uranga 2016). Despite this limitation, there are no studies to the contrary to suggest immunocompromised patients require longer treatment for CAP, especially if they have early and prompt clinical response.

Who is not appropriate for 3 days therapy with CAP?

Patients who do not have an early and prompt clinical response may not be appropriate for short duration of therapy. Clinical stability criteria that have been validated in randomized controlled trials (Uranga 2016, Dinh

2021) can be used to support clinical judgment. Patients with more severe pneumonia at presentation trend towards taking longer to reach clinical stability (Halm 1998).

Patients who are not responding as expected to CAP therapy, particularly by day 5, should be evaluated for potential complications of pneumonia as well as alternative etiologies for their respiratory or infectious syndrome. A particularly important complication to rule out would be spread of infection to the pleural space (i.e., complicated parapneumonic effusion or empyema). Such patients require source control and longer durations of therapy.

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