

Appropriate Use of Short-Course Antibiotics in Common Infections: Best Practice Advice From the American College of Physicians

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Description:

Antimicrobial overuse is a major health care issue that contributes to antibiotic resistance. Such overuse includes unnecessarily long durations of antibiotic therapy in patients with common bacterial infections, such as acute bronchitis with chronic obstructive pulmonary disease (COPD) exacerbation, community-acquired pneumonia (CAP), urinary tract infections (UTIs), and cellulitis. This article describes best practices for prescribing appropriate and short-duration antibiotic therapy for patients presenting with these infections.

Methods:

The authors conducted a narrative literature review of published clinical guidelines, systematic reviews, and individual studies that addressed bronchitis with COPD exacerbations, CAP, UTIs, and cellulitis. This article is based on the best available evidence but was not a formal systematic review. Guidance was prioritized to the highest available level of synthesized evidence.

Best Practice Advice 1:

Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).

Best Practice Advice 2:

Clinicians should prescribe antibiotics for community-acquired pneumonia for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.

Best Practice Advice 3:

In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, trimethoprim–sulfamethoxazole (TMP–SMZ) for 3 days, or fosfomycin as a single dose. In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP–SMZ (14 days) based on antibiotic susceptibility.

Best Practice Advice 4:

In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.

Primary care physicians prescribe antibiotics in 10% of all outpatient visits (1, 2). In 2014, outpatients received more than 250 million courses of antibiotics in the United States, and at least 30% were considered unnecessary and often continued for too long, particularly for bronchitis and sinusitis (3–5). Antimicrobial overuse, particularly with broad-spectrum antibiotics, drives resistance and causes adverse events in up to 20% of patients, ranging from allergic reactions to *Clostridioides difficile* infections (2, 6). The American College of Physicians (ACP) and the Centers for Disease Control and Prevention have recognized antibiotic-resistant infections as a national threat, with an estimate of more than 2.6 million illnesses and 35 900 deaths annually and with incidence of resistant infections of 6.1 per 10 000 person-days after receipt of antibiotics (7–9).

Clinicians, especially general internists, play a key role in antimicrobial stewardship, and quality improvement strategies can improve antimicrobial prescribing (10, 11). We define appropriate antibiotic use as prescribing the right antibiotic at the right dose for the right duration for a specific condition (5). When clinically safe and supported by evidence, shortening the duration of antibiotic therapy decreases overall antibiotic exposure, reducing the selection pressure for resistant organisms as well as a patient's risk for adverse effects from antibiotics. For several types of infections, studies and meta-analyses have shown that compared with longer courses of antibiotics, shorter courses show similar clinical outcomes with fewer drug-related adverse events (12–15). Despite evidence and guidelines supporting shorter durations of antibiotic use, many physicians do

not prescribe short-course therapy, frequently defaulting to 10-day courses regardless of the condition (5, 16). Even infectious disease subspecialists do not consistently recommend short-course treatment for uncomplicated infections (14). Often, clinicians prescribe longer durations to prevent development of antibiotic resistance. However, there is no evidence that taking antibiotics beyond symptom resolution reduces antibiotic resistance; in fact, resistance is a documented side effect of prolonged antibiotic use due to natural selection pressure (17). The purpose of this best practice advice is to describe appropriate use of shorter durations of antibiotic therapy for common bacterial infections seen in both inpatient and outpatient health care settings.

Methods

We conducted a narrative literature review of published clinical guidelines that addressed bronchitis with chronic obstructive pulmonary disease (COPD) exacerbations, community-acquired pneumonia (CAP), urinary tract infections (UTIs), and cellulitis (Table; Appendix Table). We also reviewed other relevant studies from the peer-reviewed literature. This article is based on the best available evidence but was not a formal systematic review. Guidance was prioritized to the highest available level of synthesized evidence. We did not evaluate the quality of the guidelines or the studies. This article was reviewed and approved by ACP's Scientific Medical Policy Committee (SMPC), whose members are physicians trained in internal medicine and its subspecialties and which includes experts in evidence synthesis. At each conference call, all members of the SMPC declared all financial and nonfinancial interests.

Table. Summary of the ACP Best Practice Advice on Appropriate Use of Short-Course Antibiotics in Common Infections

Condition	Patient Population	Available Guidelines and Evidence*	Best Practice Advice
Acute bronchitis	Adults with COPD	GOLD guideline (18) Meta-analysis of 21 studies comparing ≤5 vs. >5 days (19)	Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).
Community-acquired pneumonia	All adults who are not immunocompromised†	IDSA/ATS guideline (20)	Clinicians should prescribe antibiotics for community-acquired pneumonia for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.
Urinary tract infection: uncomplicated bacterial cystitis	Nonpregnant adult women†	IDSA/ESCMID guideline (21)	In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, TMP-SMZ for 3 days, or fosfomycin as a single dose.
Urinary tract infection: uncomplicated pyelonephritis	Nonpregnant adults†	IDSA/ESCMID guideline (21) Recent systematic review (22) 3 recent RCTs (23-25)	In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP-SMZ (14 days) based on antibiotic susceptibility.
Nonpurulent cellulitis	All adults	IDSA guideline (26) NICE guideline (27) 1 recent RCT (28)	In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.

ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IDSA = Infectious Diseases Society of America; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; TMP-SMZ = trimethoprim-sulfamethoxazole.
 * The Scientific Medical Policy Committee prioritized the highest available level of synthesized evidence: clinical guidelines, followed by systematic reviews, and then individual studies.
 † Available evidence in these patient populations is not robust enough to include in this summary table.

Appendix Table. Search Strategy Documentation

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Databases searched	PubMed ACCESSSS Smart Search Infectious Diseases Society of America guidelines
Additional sources	UpToDate Cochrane Library www.bradspellberg.com/shorter-is-better
Keywords	"Antibiotic Duration" or "short duration antibiotics" + "acute bronchitis" OR "community acquired pneumonia" OR "pyelonephritis" OR cystitis OR "cellulitis"

* The committee developed this best practice advice based on a narrative review of published clinical guidelines, augmented with select systematic reviews and individual studies.

The target audience for this article is all internists, family physicians, and other clinicians, and the target patient population is symptomatic adults with acute bronchitis with COPD exacerbations, CAP, UTIs, or cellulitis. Disease processes were defined on the basis of clinical guidance. Although most patients with these infections will be seen in the outpatient setting, these best practice advice statements also apply to patients who present in the inpatient setting. Advice presented here is based on the assumption that a patient has the right diagnosis and the right antibiotic prescribed. If a patient is not improving with appropriate antibiotics, it is important for the clinician to reassess for other causes of symptoms rather than defaulting to a longer duration of antibiotic therapy; a longer duration should be considered the exception and not the rule. These best practice advice statements may not apply to patients with complicated anatomy (such as bronchiectasis) or recent history of resistant bacterial infections.

COPD Exacerbation and Acute Uncomplicated Bronchitis

Best Practice Advice 1: Clinicians should limit antibiotic treatment duration to 5 days when managing patients with COPD exacerbations and acute uncomplicated bronchitis who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume).

Rationale

Acute uncomplicated bronchitis, defined as an acute respiratory infection with a normal chest radiograph, is typically a self-limited infection of the large airways, usually caused by a virus (29). The ACP has previously recommended against initiating antibiotic treatment in patients with bronchitis unless pneumonia is suspected (9). In COPD, however, antibiotics are recommended if there is a high pretest probability of a bacterial cause; this best practice advice focuses on available data on short-course antibiotics in this patient population. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends treating COPD exacerbations with antibiotics in patients who have clinical signs of a bacterial infection (presence of increased sputum purulence in addition to increased dyspnea, and/or increased sputum volume) (18). The choice of antibiotic should be based on effective treatment of the most commonly reported bacterial pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*) and may include an aminopenicillin with clavulanic acid, a macrolide, or a tetracycline (18, 19, 30). Although the GOLD report recommends 5 to 7 days of antibiotics for COPD exacerbations in general, a separate meta-analysis (21 randomized controlled trials [RCTs]; $n = 10\,698$ patients) that focused specifically on short-course antibiotic use in acute exacerbations of chronic bronchitis and COPD showed no difference in clinical improvement between groups that included patients receiving short-course antibiotics (mean, 4.9 days) versus long treatment (mean, 8.3 days) (19). Subanalysis of different antibiotic classes likewise showed no difference between duration groups (19).

Community-Acquired Pneumonia

Best Practice Advice 2: Clinicians should prescribe antibiotics for community-acquired pneumonia for a minimum of 5 days. Extension of therapy after 5 days of antibiotics should be guided by validated measures of clinical stability, which include resolution of vital sign abnormalities, ability to eat, and normal mentation.

Rationale

This article defines CAP as pneumonia in nonimmunocompromised patients presenting with fever, productive cough with purulent sputum, dyspnea, and pleuritic chest pain. Antibiotic recommendations for empirical therapy should cover common pathogens, such as *S pneumoniae*, *H influenzae*, *Mycoplasma pneumoniae*, and *Staphylococcus aureus*, and atypical pathogens, such as *Legionella* species, and typically include amoxicillin, doxycycline, or a macrolide for healthy adults or a β -lactam with a macrolide or a respiratory fluoroquinolone in patients with comorbidities. Current evidence based on meta-analyses and RCTs supports use of shorter-duration antibiotics in the treatment of CAP. Highlighting this body of evidence, the 2019 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guideline for the treatment of CAP recommends a minimum of 5 days of antibiotics but qualifies this recommendation to include validated measures of clinical stability, such as resolution of vital sign abnormalities, ability to eat, and normal mentation (20). These guidelines were based on moderate-quality evidence, including 3 meta-analyses and multiple RCTs.

A 2018 meta-analysis included in the IDSA/ATS guideline clearly defined short-course antibiotics for the treatment of CAP (31). It assessed 21 studies of CAP, of which 19 were RCTs, and concluded that short-course treatment (≤ 6 days) was as effective as longer treatment, with fewer serious adverse events (risk ratio, 0.73 [95% CI, 0.55 to 0.97]) and lower mortality (risk ratio, 0.52 [CI, 0.33 to 0.82]) (31). Despite evidence supporting shorter durations, a retrospective cohort study evaluated data from 6481 patients admitted with CAP to 43 Michigan hospitals from 2017 to 2018 and showed that nearly two thirds of patients received antibiotics for longer than the shortest effective duration consistent with the guidelines outlined by IDSA (15). Antibiotics prescribed at discharge accounted for 93% of prescriptions that had excess duration, and each additional day carried a 5% increased risk for antibiotic-associated adverse events without any benefits.

Further evidence supporting shorter antibiotic use came from a recent multicenter noninferiority RCT, which randomly assigned 312 patients with CAP who were at day 5 of their antibiotic regimen to follow the IDSA/ATS guidelines for clinical stability outlined earlier if no further fever occurred for 48 hours or to receive antibiotics for a duration determined by the clinician (32). There were no significant differences in clinical success at day 10 or 30 and no difference in CAP symptom scores at day 5 or 10 despite high rates of severe pneumonia in both groups. The researchers were able to safely limit antibiotic treatment to 5 days in 70% of patients in the intervention group.

UTI: Uncomplicated Cystitis and Pyelonephritis

Best Practice Advice 3: In women with uncomplicated bacterial cystitis, clinicians should prescribe short-course antibiotics with either nitrofurantoin for 5 days, trimethoprim–sulfamethoxazole (TMP–SMZ) for 3 days, or fosfomycin as a single dose. In men and women with uncomplicated pyelonephritis, clinicians should prescribe short-course therapy either with fluoroquinolones (5 to 7 days) or TMP–SMZ (14 days) based on antibiotic susceptibility.

Rationale

Urinary tract infections are among the most common bacterial infections requiring medical care. They are typically defined by both pathophysiology (cystitis and pyelonephritis) and complexity. Complicated UTIs (those occurring in the setting of structural or functional abnormalities of the genitourinary tract, including but not limited to obstruction and instrumentation) and UTIs in pregnant women are not covered here. Further, acute bacterial prostatitis is not included in this guidance given the complexity of diagnosis and prolonged treatment duration. Infectious cystitis, defined as acute inflammation of the bladder mucosa, is a common reason for antibiotic use in healthy women. *Escherichia coli* accounts for more than 75% of all bacterial cystitis, and empirical antibiotics should therefore target this organism (21). In women with uncomplicated cystitis, the IDSA/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline recommends treatment durations depending on the type of antibiotic, including 5 days of nitrofurantoin, 3 days of TMP–SMX, or a single dose of fosfomycin (21). Of note, fluoroquinolones are highly efficacious in 3-

day regimens but have high propensity for adverse effects and thus should not be prescribed empirically and should instead be reserved for patients with a history of resistant organisms.

Pyelonephritis, defined as inflammation of the renal parenchyma, occurs in more than 250 000 patients in the United States yearly, resulting in costs as high as \$2.1 billion (33). The IDSA/ESCMID guideline focuses only on female patients and recommends either an oral fluoroquinolone for 7 days or TMP–SMX for 14 days for treatment of patients with pyelonephritis not requiring hospitalization (21). Data are insufficient to recommend oral β -lactams for pyelonephritis (21). Since publication of the IDSA/ESCMID guideline, 1 meta-analysis has assessed shorter-course therapy for pyelonephritis in both men and women and reported no significant difference overall in clinical failure with fluoroquinolones except in patients with complicated UTI, in whom microbiologic failure was lower in the longer-treatment group (22). Three recent RCTs have assessed further decreasing duration of treatment with fluoroquinolones to 5 days; all 3 showed that a 5-day course was noninferior to a 10-day course, with clinical cure rates upward of 93% (23–25).

Due to concerns about high rates of resistance with corresponding failure rates, the IDSA/ESCMID guideline recognizes that TMP–SMX should not be used alone as an empirical therapy without culture and susceptibility testing in pyelonephritis (21). However, the increasing prevalence of fluoroquinolone resistance in *Enterobacteriaceae* requires reevaluation of the efficacy of shorter courses of antibiotic classes other than fluoroquinolones as targeted therapy for pyelonephritis when susceptibility is known (12). A multicenter trial comparing 7 days of ciprofloxacin versus 14 days of TMP–SMX found clinical cure in 96% of patients in the ciprofloxacin group compared with 85% in the TMP–SMX group; however, 18.4% of all uropathogens in the study were resistant to TMP–SMX (34). Subanalysis identified a clinical cure rate of 92% in strains susceptible to TMP–SMX. Another recent study showed that shorter courses using TMP–SMX may be effective. This multicenter retrospective study of 272 women with pyelonephritis found that a 7-day course of TMP–SMX may be effective for women with susceptible *E coli* pyelonephritis compared with a 7-day course of ciprofloxacin, with similar rates of recurrent UTI within 30 days (33). More RCTs are needed to assess shorter courses of TMP–SMX when information on antimicrobial susceptibility is available.

Cellulitis

Best Practice Advice 4: In patients with nonpurulent cellulitis, clinicians should use a 5- to 6-day course of antibiotics active against streptococci, particularly for patients able to self-monitor and who have close follow-up with primary care.

Rationale

Skin and soft tissue infections (SSTIs) can be challenging to diagnose because of their variable presentation, cause, and severity (26). Over the past 10 to 15 years, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of SSTI, which has likely contributed to the increase in frequency of SSTIs in both the inpatient and outpatient settings (12, 26). Approximately 6.3 million physician office visits per year are attributable to SSTIs. Purulent SSTIs, including furuncles, carbuncles, and abscesses, commonly respond to incision and drainage and are not discussed here. Nonpurulent SSTIs include necrotizing infections, cellulitis, and erysipelas. Cellulitis presents as a diffuse, superficial, spreading skin infection without pus collection and is typically caused by bacterial invasion in the skin, often involving MRSA and streptococci (26). Treatment recommendations include a cephalosporin, penicillin, or clindamycin, except for patients whose cellulitis is associated with penetrating trauma or who have evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or systemic inflammatory response syndrome; in these cases, inclusion of another antimicrobial effective against both MRSA and streptococci is recommended (26).

The 2014 IDSA guideline recommends that patients should receive antibiotics for uncomplicated cellulitis but that clinicians should consider extending treatment if the infection has not improved after 5 days (26). The more recent 2019 National Institute for Health and Care Excellence (NICE) guideline recommends a course of 5 to 7 days (27). The NICE guideline reported on findings from 2 systematic reviews on antibiotic course length (12, 35). The first review (35) included 1 RCT ($n = 87$) that found no significant differences in clinical outcomes between 5 or 10 days of therapy with a fluoroquinolone (levofloxacin) (36); this study was also reported in the IDSA guideline. The second systematic review (12) included 2 RCTs (37, 38) comparing oxazolidinone antibiotics (linezolid and tedizolid) for treatment of cellulitis. In both trials, 6 days of tedizolid was compared with 10 days of linezolid or tedizolid, with an overall similar clinical response in both the intention-to-treat and per protocol analyses, suggesting that a shorter course is adequate (37, 38). More recently, the DANCE (Duration of Antibiotic Therapy for Cellulitis) RCT compared a 6-day course of a

penicillin (flucloxacillin) with the standard 12-day course and found overall similar rates of cure, but with wide CIs that could neither confirm nor refute shorter versus longer therapy (28). Further study is needed to evaluate the optimal duration of antibiotic therapy for SSTIs.