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# Is shorter better? Duration of therapy for common bacterial infections in adults

Randomized controlled studies conducted over the last decade have indicated that a shorter duration of antibiotic therapy is just as effective as longer treatment.

**ABSTRACT:** Antimicrobial resistance is a looming threat to our society's health. Physicians need simple strategies for antimicrobial stewardship that can be readily incorporated into everyday practice. Addressing duration of therapy is one

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of these key strategies. Every day of antibiotic exposure beyond that which is necessary to cure the infection increases the risk of adverse events and antimicrobial resistance without providing additional benefits. We focus on the adult population and commonly encountered conditions: community-acquired pneumonia, intra-abdominal infections, skin and soft tissue infections, osteomyelitis, complicated urinary tract infections, and gram-negative bacteremia. The treatment of these common infections overlaps in primary and acute care practices. Recent literature suggests shorter duration of therapy is as effective as longer durations for these infections.

**W**ithout a concerted societal effort, antimicrobial resistance is predicted to kill more people than cancer by the year 2050.<sup>1</sup> The human cost is staggering, with one death occurring every 3 seconds.<sup>1</sup> Appropriate use of antibiotics is one of the key strategies that can prevent this looming existential threat. Addressing the duration of treatment, and thus overall antibiotic exposure, is a simple practice change that all physicians can make. We focus on the duration of treatment for common bacterial infections in adults seen in community and hospital practices, based on the latest evidence in the literature.

## Community-acquired pneumonia

Historically, community-acquired pneumonia treatment ranged from 7 to 10 days;<sup>2</sup> however,

new data suggest that shorter durations of therapy are as effective. In 2007, the Infectious Diseases Society of America community-acquired pneumonia guidelines recommended that 5 days of treatment may be adequate in patients who are afebrile for 48 to 72 hours, and who do not have more than one of the following clinical signs of instability: heart rate greater than 100 beats/minute, respiratory rate greater than 24 breaths/minute, systolic blood pressure less than 90 mmHg, or arterial oxygen saturation less than 90% on room air.<sup>3</sup>

These recommendations were validated by a multicentre, randomized, noninferiority trial in Spain.<sup>4</sup> Noninferiority trials compare the effectiveness of a new regimen against a standard therapy; if the new regimen is not worse than the comparator within a defined amount, it is considered “noninferior” to the standard therapy and can be recommended for use. At day 5, hospitalized patients were randomly assigned to an intervention group or a control group. In the intervention group, researchers stopped giving antibiotics if patients reached clinical stability based on the Infectious Diseases Society of America guidelines; in the control group, the treatment duration was determined by physicians per usual practice. Primary outcome was defined as improvement in or resolution of signs and symptoms of community-acquired pneumonia at day 10 and day 30. Median duration of therapy was 5 days in the intervention group versus 10 days in the

control group. Clinical success at day 30 was similar between the two groups. These results demonstrated that Infectious Diseases Society of America community-acquired pneumonia guideline recommendations regarding shorter duration can be safely implemented in many hospitalized patients.<sup>4</sup>

In 2018, a meta-analysis of 21 clinical studies, 19 of which were randomized controlled trials, that involved 4861 patients demonstrated that a short course of antibiotics ( $\leq 6$  days) was just as effective as longer treatment durations, regardless of the type of antibiotic used. The analysis included inpatient and outpatient studies of treatment with various antibiotics, such as azithromycin, quinolones, and  $\beta$ -lactams; there were no differences in clinical cure or relapses. In addition, patients who received a shorter course of treatment had lower mortality, likely due to fewer serious adverse effects from antibiotics.<sup>5</sup>

Most recently, Dinh and colleagues demonstrated that 3 days of therapy was noninferior to 8 days of therapy in non-ICU patients with moderately severe community-acquired pneumonia. This multicentre, double-blind, randomized, placebo-controlled trial was conducted in France. Patients with lung abscess, massive pleural effusion, known immunosuppression, health care-associated pneumonia, or aspiration pneumonia were excluded. Patients who achieved clinical stability after 3 days of treatment with  $\beta$ -lactams were then randomly assigned to receive a placebo or amoxicillin plus clavulanate for 5 additional days. Clinical cure by day 15 was similar between the placebo and treatment groups, and there was no difference in 30-day mortality rate.<sup>6</sup>

### Synopsis

Based on cumulative research in the past 20 years, a short duration of therapy for community-acquired pneumonia (minimum of 3 days) is as effective as longer durations for most patients in outpatient or inpatient settings, and reduces the risk of adverse drug reactions. This applies to non-ICU hospitalized patients with clinical improvement by day 3, without known immunosuppression, lung abscess, or empyema. In the outpatient setting, it is important for clinicians to reassess patients

between days 3 and 5 in the clinic or by phone to ensure they are clinically stable and can safely stop their antibiotics.

### Intra-abdominal infections

According to the 2010 Infectious Diseases Society of America guidelines, the recommended duration of treatment for established intra-abdominal infections is 4 to 7 days unless adequate source control is not achievable.<sup>7</sup> In clinical practice, however, many patients are typically treated for 10 to 14 days.

## Without a concerted societal effort, antimicrobial resistance is predicted to kill more people than cancer by the year 2050.

In 2015, the STOP-IT trial determined that outcomes were similar between patients who received antibiotics for 4 days after source control and those who had a longer course of therapy (median duration of 8 days). This was an open-label trial that included 23 sites across the United States and Canada. Patients were enrolled if they had leukocytosis, fever, or gastrointestinal dysfunction due to peritonitis with adequate surgical source control. They were randomly assigned to receive antibiotics until 2 days after resolution of fever, leukocytosis, and ileus (control group) or to receive a fixed duration of 4 days post source control (intervention). The maximum duration of therapy was capped at 10 days for the control group. The mean Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score was 10 (approximately 10% risk of mortality), and one-third of the patients had intra-abdominal infections related to the colon or rectum. One-third of the patients underwent percutaneous drainage as their primary source control procedure. Outcomes were similar between the groups for the composite primary endpoint (consisting of surgical-site infection, recurrent intra-abdominal infection, and death).<sup>8</sup> In a post-hoc analysis, patients with colonic source

of infection, steroid use, APACHE II score greater than 15, and hospital-acquired infections had an increased risk of treatment failure; however, this was not prevented by longer antibiotic duration.<sup>9</sup> A prospective, open-label study by Montravers and colleagues showed that even for critically ill ICU patients, longer duration of treatment did not provide additional benefits once surgical source control was achieved.<sup>10</sup>

### Synopsis

Most patients with intra-abdominal infection benefit from a shorter duration of antibiotics (between 4 and 7 days) after source control is achieved. Those who are immunocompromised or do not have adequate source control may require a longer duration of treatment depending on individual clinical scenarios.

### Skin and soft tissue infections

Skin and soft tissue infections include a broad range of presentations from cellulitis and abscess to necrotizing fasciitis. In general, the 2014 Infectious Diseases Society of America guidelines recommended that most skin and soft tissue infections be treated for 5 to 10 days.<sup>11</sup> In clinical practice, however, patients often receive antibiotics for longer periods than recommended. A retrospective analysis of 322 hospitalized patients conducted by Jenkins and colleagues in 2010 indicated that the median duration of antibiotic treatment for cellulitis and cutaneous abscess was 13 days; however, the authors felt that half these patients could have benefited from a shorter duration of treatment because they did not have complicating factors.<sup>12</sup>

In a double-blind, placebo-controlled trial by Hepburn and colleagues, 87 patients were randomly assigned to receive 5 days versus 10 days of antibiotics for uncomplicated cellulitis. Patients were recruited from primary care clinics and the emergency department of a tertiary care hospital, and were excluded if they had bacteraemia, sepsis, or deep-seated skin and soft tissue infections, such as abscess, fasciitis, myositis, osteomyelitis, or septic arthritis. The primary outcome was resolution of infection by day 14 and no recurrence by day 28. In both groups, 98% of patients improved by day 14 without further relapse. The authors concluded that there was no difference in clinical outcome in patients

who received 5 versus 10 days of therapy, and found that even though many patients still had substantial edema and erythema at day 5, it appeared to resolve on its own as long as improvement was seen within the first 5 days.<sup>13</sup>

### Synopsis

Five days of treatment with antibiotics can be considered for patients with uncomplicated cellulitis with clinical improvement. In the outpatient setting, it is recommended that the patient be reassessed in person or by phone on day 5 to ensure there is clinical improvement prior to stopping the antibiotics. Patients with complicating factors such as deep-seated infections (e.g., abscess, osteomyelitis), immunosuppression, diabetic foot infection with poor source control, peripheral arterial disease, or persistent ulcers may require longer therapy.<sup>13</sup>

### Osteomyelitis

Traditionally, patients receive at least 4 to 6 weeks of antibiotics for osteomyelitis. This practice stems from clinical studies dating back to the 1970s.<sup>14</sup> Occasionally, up to 3 months of treatment may be recommended for diabetic foot osteomyelitis without surgical debridement.<sup>15</sup> These recommendations are often based on retrospective observational studies, some of which are of low quality.

A meta-analysis of 15 studies, which was published in 2019, summarized the latest evidence on this controversial topic. Five of the studies were randomized controlled trials, but only two focused on adult patients. Of the other 10 retrospective observational studies, only three were graded as good quality. When all the studies were combined, there was no significant difference in treatment failure rates between short and long durations of therapy (> 4 to 6 weeks).<sup>15</sup> However, given the pathophysiological and therapeutic differences between pediatric and adult osteomyelitis, we focus only on the two adult randomized controlled trials.

The first trial by Tone and colleagues compared 6 versus 12 weeks of antibiotic treatment for diabetic foot osteomyelitis without surgical intervention in 40 patients. Patients with peripheral arterial disease or gangrene and those who required bone resection were excluded. The primary outcome was remission of diabetic

foot osteomyelitis within 12 months. There was no difference in remission rates between the 6-week and 12-week groups; 26 patients (65%) were in remission. However, patients in the 12-week group experienced more gastrointestinal side effects from antibiotics. The main

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limitation of this study was the small number of patients included, which may have affected its power to detect a difference between the two groups.<sup>16</sup>

The second trial, a multicentre, open-label, noninferiority, randomized controlled study compared 6 weeks versus 12 weeks of antibiotic treatment in patients with pyogenic vertebral osteomyelitis. The primary outcome was remission, defined as sustained lack of fever, pain, and inflammatory syndrome (C-reactive protein < 10 mg/L) 12 months after the end of treatment; this was determined by an independent committee that was not aware of the duration of treatment each patient received. In the trial, 359 patients were randomly assigned to the treatment groups. Clinical cure at 1 year was achieved in 91% of patients in each group. However, those with *Staphylococcus aureus* infection had a higher risk of failure, regardless of treatment duration.<sup>17</sup>

Additionally, a pilot, prospective, randomized noninferiority trial by Gariani and colleagues published in 2020 was the first study to show that 3 weeks of antibiotic therapy after partial surgical debridement was noninferior to 6 weeks for diabetic foot osteomyelitis in terms of remission rate. The trial included 93 patients, and the median number of surgical

debridement was one. After a median follow-up period of 11 months, 78% of the patients remained in remission. The two treatment groups had similar results. The authors plan to conduct a follow-up randomized controlled trial with a larger number of patients and a smaller margin of difference (10% instead of 25%) to validate the results of this study.<sup>18</sup>

### Synopsis

Six weeks of antibiotic treatment is likely sufficient for most cases of osteomyelitis. Emerging evidence suggests that durations as short as 3 weeks of antibiotic treatment may be sufficient in patients with partial surgical debridement for diabetic foot osteomyelitis.<sup>18</sup>

### Complicated urinary tract infections

Short-duration antibiotic treatment for female uncomplicated cystitis is well established in the Infectious Diseases Society of America 2011 guidelines.<sup>19</sup> Conversely, the duration of treatment for complicated urinary tract infections (pyelonephritis and male cystitis) is less clear.

Eliakim-Raz and colleagues conducted a systematic review of eight randomized controlled trials with 2515 patients, which compared treatment of less than 7 days to longer treatment in both community and hospitalized patients with pyelonephritis or septic urinary tract infection. Clinical failure, defined as no resolution of signs and symptoms of urinary tract infection or need to change antibiotic at the end of treatment, was the primary outcome. No significant differences in treatment failure were found, including in those who received  $\beta$ -lactams. In a small subset of 100 patients with urogenital abnormalities, longer treatment was more favorable.<sup>20</sup>

For male patients, evidence is mounting to support a shorter duration of treatment, such as 7 days compared with 14 days. In a retrospective study by Drekonja and colleagues, the outpatient records of 33 336 male veterans were reviewed, and 4449 index cases (13.3%) had recurrences of urinary tract infection. In a multivariate logistic regression analysis, a treatment duration of less than 7 days was not associated with early recurrence of infection. However, a treatment duration of 7 days or longer was associated with

a higher risk of late recurrence (> 30 days after initial treatment). This could be due to selection bias, where patients with underlying risk factors for urinary tract infection were given longer treatments.<sup>21</sup> The results of this study were subsequently confirmed by Germanos and colleagues.<sup>22</sup> In their study, patients with any urogenital abnormality, recent surgery or catheterization, and immunosuppression were excluded. Of the 573 patients included in the study, 32 (5.6%) had recurrence of urinary tract infection. Longer treatment duration was associated with a twofold increased risk of recurrent urinary tract infection, even after the exclusion of men with urologic abnormalities. One possible explanation is that prolonged antibiotic exposure can alter the gastrointestinal microbiome, which in turn can affect urogenital flora and lead to recurrent urinary tract infection. The authors also showed that antibiotic choice was not associated with urinary tract infection recurrence; however, most patients received fluoroquinolones, and less than 5% of patients received a  $\beta$ -lactam.<sup>22</sup> Finally, an outpatient, double-blind, placebo-controlled, randomized trial by Drekonja and colleagues further supported the results of previous observational studies by illustrating that ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days for men with afebrile urinary tract infection.<sup>23</sup> In their trial, 272 patients were randomly assigned to the treatment groups. More than 90% of patients in each group achieved symptom resolution by day 14, and recurrence of urinary tract infection symptoms was also comparable in the two groups. However, only ciprofloxacin and trimethoprim/sulfamethoxazole were used; it is unclear if the same duration applies to treatment with  $\beta$ -lactams or nitrofurantoin.<sup>23</sup>

### Synopsis

Seven days of antibiotic treatment may be adequate in complicated urinary tract infection, including pyelonephritis and male cystitis. Treatment duration in men with established prostatitis remains unclear; further studies are required.

### Uncomplicated gram-negative bacteremia

Gram-negative bacteremia accounts for 33% to 45% of hospital- and community-acquired

bacteremia, respectively.<sup>24</sup> Patients typically receive 14 days of antibiotic treatment for uncomplicated bacteremia, as durations in guidelines range from 7 to 14 days.<sup>24</sup> Clinicians often prescribe a longer duration to err on the side of caution due to the severity and potential mortality associated with bacteremia.

**The evidence is clear that overuse of antibiotics can lead to collateral damage, resulting in development of bacterial resistance.**

The first multicentre, randomized, noninferiority trial on uncomplicated bacteremia was conducted by Yahav and colleagues<sup>25</sup> in 2019. In their trial, 604 patients were randomly assigned to the short (7 day) or long (14 day) duration treatment group if they were hemodynamically stable for at least 48 hours by day 7 of their hospital stay. Immunocompromised patients, those without source control for infection, and those with polymicrobial bacteremia were excluded. The urinary tract was the main source of infection (69%), followed by intra-abdominal infections (12%). Males comprised slightly less than half of all patients. *Escherichia coli* was the most

commonly identified bacterium (63%). The primary outcome measure was 90-day all-cause mortality, relapse or complications related to initial bacteremia, hospital readmission, or prolonged hospitalization (> 14 days). The results indicated that 7 days of antibiotic treatment was noninferior to 14 days of treatment. In addition, patients in the short-duration treatment group were able to return to their baseline activities sooner than those in the long-duration treatment group. However, the results of this study may not be applicable to pathogens such as *Pseudomonas* and *Acinetobacter*, which comprised only a small percentage of those treated in this trial.<sup>25</sup>

In a second multicentre, randomized, noninferiority trial published by von Dach and colleagues in 2020, 504 patients were randomly assigned to C-reactive protein (CRP)-guided antibiotic treatment, fixed 7-day therapy, or fixed 14-day therapy (control group).<sup>26</sup> The CRP-guided group discontinued antibiotics once CRP declined by 75% from the peak level, with treatment capped at 14 days. To be enrolled, patients had to be afebrile for 24 hours by day 5 and could not have poor source control or severe immunosuppression. Median antibiotic duration was 7 days in the CRP-guided group. Similar to Yahav and colleagues, urinary tract infections were the main source of infection. Males comprised approximately one-third of all patients. Both CRP-guided and 7-day treatment strategies were noninferior to 14 days of

**TABLE.** Antibiotic treatment duration based on infection source.

Type of infection	Duration
Mild to moderate community-acquired pneumonia	3 days*
Intra-abdominal infection	4–7 days after source control attained
Skin and soft tissue infection such as cellulitis (excluding deep-seated infections)	5 days*
Osteomyelitis (diabetic foot and vertebral) <sup>†</sup>	3–6 weeks for diabetic foot osteomyelitis 6 weeks for vertebral osteomyelitis
Complicated urinary tract infection <ul style="list-style-type: none"> <li>• Pyelonephritis (male and female)</li> <li>• Male cystitis</li> </ul>	7 days 7 days
Uncomplicated gram-negative bacteremia (primarily from urinary or intra-abdominal sources, with adequate source control)	7 days*

\*applies only to patients who are clinically stable and have source control for infection

<sup>†</sup>infectious diseases consultation is strongly recommended to individualize the duration of treatment

treatment for clinical failure at 30 and 90 days. Patients with *Pseudomonas* or *Acinetobacter* infections were not included in the study.<sup>26</sup>

### Synopsis

The duration of treatment for uncomplicated gram-negative bacteremia from primarily urinary and intra-abdominal sources can be as short as 7 days in select patients who have clinical improvement by day 5, are not immunocompromised, and have adequate source control.

### Summary

The invention of antibiotics in the 1940s was accompanied by the dogma that using “too little” antibiotics may lead to bacterial resistance and recurrence of infections. As a result, prescribers often instructed their patients to complete their prescribed antibiotic course, even when they had recovered clinically. Current literature suggests the contrary; the evidence is clear that overuse of antibiotics can lead to collateral damage, resulting in development of bacterial resistance.<sup>27</sup> In the last decade, a number of randomized controlled studies have revealed that a shorter duration of antibiotic therapy is just as effective as longer treatment. This principle applies to many common infections [Table].

As the number of newly developed antibiotics declines, it is of utmost importance to preserve our present antibiotics by providing patients with appropriate durations of treatment; in most cases, the old adage “less is more” holds true for common bacterial infections. ■

### Competing interests

None declared.

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## The duration of treatment for uncomplicated gram-negative bacteremia from primarily urinary and intra-abdominal sources can be as short as 7 days.

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