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# Rational Antibiotic Use: How Much Can Duration of Antibiotic Therapy Be Shortened?

## Akılcı Antibiyotik Kullanımı: Antibiyotik Tedavi Süresi Ne Kadar Kısaltılabilir?

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### Abstract

Infectious diseases are conditions with significant consequences in terms of public health while associated mortality, morbidity, and complications can be prevented. Disease severity and duration can be shortened by means of rational antimicrobial therapy. It is important to obey main rational antibiotic use rules ie. to collect and examine appropriate culture specimens before treatment, identify potential microbial agents, consider the pharmacological properties of the antibiotic, determine whether combined antibiotics are indicated, review the host factors and indications for antibiotic therapy modification, and monitor response to antibiotic therapy while planning antibiotic therapy. Once correct diagnosis has been made, the correct antibiotic must be administered via the correct route, at an effective dose, at optimum intervals, and for an appropriate length of time for rational antimicrobial therapy. However, knowledge concerning the optimal duration of treatment is limited. Patients generally receive antibiotic therapy for 10–14 days. Prolonged treatment is also common. Duration of antimicrobial therapy may be a confusing issue for clinicians due to problems of resistance and toxicity. A healthy bacterial ecosystem (i.e. a normal flora) is essential to remain healthy. Antibiotic use can alter the normal bacterial flora in humans, which generally leads to the emergence of multidrug-resistant (MDR) bacteria and side effects such as diarrhea. Infections caused by MDR bacteria result in increased disease and mortality rates and extended hospital stays, as well as increased costs. Studies aimed at shortening the duration of treatment have reported that a 3–5 day treatment period in some of the community-acquired infections and one-week period in some of the nosocomial infections may be sufficient. Based on the patients' individual characteristics and clinical responses to treatment, short-term antibiotic therapy may be administered in selected patient groups both in community-acquired and healthcare-associated infections. Rational antibiotic therapy, together with observation of response to treatment and optimal treatment durations (which remain to be determined) can prevent adverse outcomes associated with long-term antibiotic use such as antibiotic-related side effects and development of MDR bacteria.

**Keywords:** Duration of antibiotic therapy, short-term antibiotic therapy, antibiotic stewardship, pneumonia, rational antibiotic therapy

### Öz

Enfeksiyon hastalıkları, akılcı antimikrobiyal tedavi ile mortalite, morbidite ve komplikasyonların önlenilebileceği, hastalık şiddet ve süresinin kısaltılabileceği, halk sağlığı açısından önemli sonuçları olan hastalıklardır. Antibiyotik tedavisi planlanırken; antibiyotik tedavisinin gerekçelerinin saptanması, tedavi öncesi uygun örnek alınması ve incelenmesi, etken olabilecek mikroorganizmaların belirlenmesi, antibiyotiğin farmakolojik özelliklerinin bilinmesi, kombine antibiyotik endikasyonunun olup olmadığının belirlenmesi, konakçı faktörlerinin gözden geçirilmesi, antibiyoterapi değiştirme endikasyonlarının saptanması ve antibiyotik tedavisine yanıtın izlenmesi ilkelerine uyulmalıdır. Akılcı antimikrobiyal tedavi için doğru tanı sonrası doğru antibiyotik en uygun yoldan, etkin dozda, optimum aralıklarla, uygun süreyle verilmelidir. Ancak, başlanan tedavinin optimal süresine ilişkin bilgiler kısıtlıdır. Hastalar çoğunlukla 10–14 gün antibiyotik tedavisi almaktadır. Tedavi süresinin uzatıldığı durumlarla da sıkça karşılaşmaktadır. Antimikrobiyal tedavi süresinin uzunluğu, direnç ve toksisite sorunları nedeniyle klinisyenlerin kafasını karıştıran bir sorun oluşturmaktadır. Sağlıklı kalmak için, sağlıklı bir bakteri ekosistemine, yani normal floraya ihtiyaç vardır. Antibiyotik kullanımı, insanlardaki normal bakteriyel floranın değişmesine bu da genelde çoklu antibiyotik dirençli bakterilerin ortaya çıkmasına ve ishal gibi yan etkilerin görülmesine neden olabilmektedir. Çok ilaca dirençli bakterilerin yol açtığı enfeksiyonlar, hastalığın ve ölüm oranlarının artması ve hastanede geçirilen sürenin uzaması ile sonuçlanmakta, ayrıca tedavi maliyetlerinde de artışa neden olmaktadır. Tedavi süresinin kısaltılmasına yönelik çalışmalarda bazı toplum kaynaklı

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enfeksiyonlarda 3-5 günlük, bazı hastane kaynaklı enfeksiyonlarda bir haftalık tedavi süresinin yeterli olabileceği belirtilmektedir. Gerek toplum kaynaklı gerekse hastane kaynaklı enfeksiyonlarda seçilmiş hasta gruplarında hastaların bireysel özellikleri ve tedaviye klinik cevapları da göz önüne alınarak kısa süreli antibiyotik tedavisi verilebilir. Tedavi yanıtının izlenmesi ve belirlenecek optimum tedavi süresi ile birlikte akılcı antibiyotik uygulaması antibiyotik ilişkili yan etki ve çok ilaca dirençli enfeksiyon gelişimi gibi uzun süreli antibiyotik kullanımının getireceği olumsuzlukları önleyebilecektir.

**Anahtar Kelimeler:** Antibiyotik tedavi süresi, kısa süreli antibiyotik, antibiyotik yönetimi, pnömoni, akılcı antibiyotik tedavisi

## Introduction

Mortality, morbidity, aclinical severity, and complications associated with infectious diseases are preventable and may be reduced via rational antimicrobial therapy<sup>[1]</sup>. The discovery of antibiotics in the mid-twentieth century dramatically reduced morbidity and mortality resulting from infectious diseases and led to major changes in healthcare<sup>[2]</sup>.

The massive increase in the use of medicines, particularly antimicrobial drugs in recent years, has led to higher antibiotic resistance rates and costs and become an increasingly common cause of delays in proper treatment due to drug toxicity and diagnostic masking<sup>[2]</sup>. These problems gave rise to a new concept: rational drug use. Accordingly, patients should receive appropriate antimicrobials suitable to their clinical needs and individual characteristics, at an appropriate dose, for an appropriate period of time, and at the lowest cost<sup>[3]</sup>. World Health Organization estimates that more than 50% of drugs are prescribed, dispensed, or sold inappropriately. In addition, half of patients fail to take their medicine properly<sup>[4]</sup>. This situation is no different in Turkey, and is in fact even more alarming. The aggregate consumption of systemic antimicrobials for 2011 was calculated as 46.70 [Defined Inhabitant Dose (DID)-defined daily dose per 1000 inhabitants per 24 h], and among these drugs, the aggregate consumption of systemic antibacterial drugs was calculated as 42.28 DID<sup>[5]</sup>. Unfortunately these rates place Turkey the first among European countries in antimicrobial consumption<sup>[6]</sup>. These data demonstrate the absolute necessity of practicing rational antibiotic therapy. In the rational use of medicines (RUM) concept, responsibility lies with the doctor prescribing the medicine, the pharmacist dispensing the medicine under appropriate conditions, the nurse administering the medicine, and the patient receiving the treatment<sup>[4]</sup>. It is apparent that the issue is multidimensional. Our aim in this article is not to discuss all of these dimensions, but to examine the importance of treatment duration as one component of RUM and to raise awareness of this issue.

## Rational Antimicrobial Therapy

For rational antimicrobial therapy, an accurate diagnosis should be followed by administering the correct antibiotic via the most appropriate route, at an effective dose, at optimum intervals, and for an appropriate period of time<sup>[7,8]</sup>.

However, there is limited information regarding optimal treatment duration. Patients generally take antibiotics for 10-14 days while more prolonged treatment is also common. The duration of antimicrobial treatment can be a confusing issue for clinicians due to problems with antibiotic resistance and toxicity<sup>[9]</sup>. Some of the problematic multidrug-resistant (MDR) pathogens are carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, extended-spectrum  $\beta$ -lactamase (ESBL) producer and carbapenem-resistant *Enterobacteriaceae*, and methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>[10]</sup>. The best way to reduce the emergence of MDR nosocomial strains is the rational use of antimicrobials<sup>[11]</sup>. This requires following guidelines for diagnosis and treatment, implementing antimicrobial de-escalation, avoiding the treatment of colonizations, monitoring serum levels of antimicrobials, and determining the appropriate duration of antibiotic therapy<sup>[12]</sup>.

## The Basic Principles of Rational Antibiotic Use

There are several principles that should guide clinicians while planning of antibiotic therapy. These include identifying the indication for antibiotic use, obtaining and analyzing an appropriate specimen before initiating treatment, and identifying the likely causative microorganisms. Also important are knowing the pharmacological properties of the antibiotic, evaluating host factors, and determining whether there are indications for combined antibiotic use. Finally, indications for changing antibiotherapy should be determined and treatment response must be monitored<sup>[13]</sup>. These principles are indispensable for all clinicians and particularly for Infectious Diseases and Clinical Microbiology specialists. The factors influencing antibiotic use are presented in Table 1.

1. First, questioning the need for antibiotics is important in preventing unnecessary antibiotic use, particularly in viral infections<sup>[14]</sup>. There is evidence showing that antibiotics are not necessary for many cases of respiratory tract infections and that the patient's immune system is capable of fighting minor infections. Although the Turkish Ministry of Health has called attention to the misuse of antibiotics in treating influenza through recent public service advertisement campaigns, it is clear that both the public and physicians need constant reminders and that these campaigns should be repeated. Another incorrect but common practice is the prolonged use of antibiotics as prophylaxis after clean surgical procedures<sup>[15]</sup>.

**Table 1. Factors influencing antibiotic use**

Patient factors	Usage at incorrect dose or duration
	Mistrust of patient to physician
	Requests for nonindicated antibiotic use
	Using medicines based on advice from nonmedical persons and obtaining them from pharmacies without a prescription
	Nonadherence to lifestyle changes recommended to complement medical treatment and recommended follow-up during treatment
Physician factors	Adequate and current scientific knowledge
	Relationships with the pharmaceutical industry
	Outdated information
	Habit
Institutional factors	Workload and staff number
	Infrastructure
	Relationships with health personnel
	Relationships with regulatory agencies
Physician-related social factors	Cultural and social factors
	Economic and legal factors

2. When antibiotherapy is indicated, appropriate culture samples obtained before initiating treatment enable the selection of a more effective spectrum and facilitate a faster treatment response, thus reducing any possible delays due to treatment-based diagnosis<sup>[2]</sup>. Narrow-spectrum antibiotics may be prescribed based on culture results, which reduces possible antibiotic resistance. Antibiotic use can alter the normal bacterial flora in humans, often leading to the emergence of MDR bacteria and side effects such as diarrhea. Antibiotic resistance has become a major global health problem. One of the best examples of the importance of performing bacteriological culture prior starting treatment is patients with chronic conditions such as vertebral osteomyelitis due to the high incidence of tuberculosis in Turkey<sup>[16,17]</sup>.

3. The pharmacological properties and tissue distribution of drugs are also important when selecting antibiotics<sup>[18,19]</sup>. In central nervous system infections, antibiotics with good penetration into the cerebrospinal fluid must be selected for successful treatment. Antibiotics which are unable to reach therapeutic levels in some tissues should not be preferred. It should be kept in mind that obesity and cachexia may influence drug doses.

4. After establishing an indication for antibiotic use and obtaining appropriate samples, failure to evaluate the possible causative microorganisms may result in the selection of incorrect treatment, even if an antibiotic with high target tissue penetration is selected. Inability to test for antibiotic drug

level, bactericidal activity, or synergy are also seen as important problems<sup>[19,20]</sup>.

5. Both antibiotic and patient characteristics are important in treatment selection. Comorbidities and drug interactions are generally overlooked during antibiotic selection. The Infectious Diseases Society of America (IDSA) 2016 guidelines for antibiotic stewardship emphasize that this may result in low or high serum concentration of the given drug and lead to treatment failure; therefore, serum concentrations of many drugs, particularly amikacin, vancomycin, and voriconazole, should be assessed in order make necessary dose adjustments<sup>[2]</sup>.

6. The need for combination antibiotic treatment should also be evaluated. Although combination antibiotic therapy is recommended for specific illness such as multidrug-resistant *A. baumannii* infections, tuberculosis, and brucellosis, it has been emphasized that not all antibiotic combinations are beneficial<sup>[21,22]</sup>. Lepper and Dowling<sup>[23]</sup> clearly demonstrated in 1951 that penicillin alone is more effective in the treatment of pneumococcal meningitis than the combination of penicillin and chlortetracycline. The mortality rate was 21% among patients treated with penicillin monotherapy, compared to 79% among those treated with combined penicillin and chlortetracycline. Another study involving pediatric meningitis demonstrated the superiority of monotherapy over an antagonistic drug combination. Mathies et al.<sup>[24]</sup> treated a group of children with bacterial meningitis using only ampicillin or ampicillin + chloramphenicol + streptomycin combination. They reported 4.3% mortality among 140 children treated only with ampicillin and 10.5% among 124 children treated with combination antibiotics, which resulted in a significant difference. However, further studies suggest that clinically significant antagonism may also occur in patients with disrupted host defense mechanisms (e.g. cancer such as leukemia, neutropenia) or in serious infections (e.g. meningitis, endocarditis), and that this in vitro antagonism is not clinically significant in patients with normal host defense mechanisms<sup>[25,26]</sup>. In addition, the best known example of chemical antagonism related to route of drug administration is between aminoglycosides and antipseudomonal penicillins. These drugs chemically antagonize each other in the serum and should not be infused together<sup>[27]</sup>.

7. Policies for the rational use of antibiotics suggest reducing the use of antibiotics in industrial areas such as livestock production. Numerous studies have demonstrated a causal link between the antibiotics used to prevent infections in livestock animals and increasing antibiotic resistance in human pathogens<sup>[28-30]</sup>.

## Consequences of Irrational Drug Use

The most common problems in irrational drug use are inattention to route of drug administration, treatment duration, and dosage.

The excessive and unnecessary use of medicines, using multiple medicines without indication, consuming medicine with liquids other than water, using expired medicines, and inappropriate self-treatment outside physicians' recommendations are examples of irrational drug use<sup>[31]</sup>. Failure to practice RUM may result in lower treatment adherence, unwanted outcomes due to drug interactions, development of resistance to certain drugs, repeated or prolonged illnesses, higher incidence of adverse events, and increased treatment costs<sup>[32,33]</sup>.

## Normal Flora

The normal human flora is one of the natural mechanisms of resistance against microorganisms. It starts forming at birth and is composed primarily of bacteria<sup>[34]</sup>. The composition of normal flora varies in different body sites and is affected by age, gender, hormonal changes, nutritional properties, and personal hygiene habits<sup>[35]</sup>. Intestinal flora plays an important role in vitamin K synthesis and nutrient absorption. It also has a protective effect against colonization and proliferation of pathogenic microorganisms. This effect is explained with the concept of bacterial interference, which refers to the competition between flora bacteria and pathogenic bacteria for nutrients, colonization sites, cell surface receptors, and other attachment sites<sup>[36,37]</sup>. For example, the anaerobic components of the intestinal flora inhibit the proliferation of *Salmonella* bacteria. Colicins are proteins encoded by plasmids which are synthesized by intestinal bacterial flora. These proteins bind to specific cell surface receptors on the target bacteria and induce cell lysis or attack specific intracellular components such as ribosomes. In the intestine, colicins are fatal for *Escherichia coli* and *Salmonella* and *Shigella* species<sup>[38]</sup>.

## The Normal Flora and Antibiotics

A healthy microbial biosystem (i.e., a normal flora) is necessary to stay healthy. The use of antibiotics may cause changes in the normal bacterial flora, often leading to the emergence of antibiotic-resistant bacteria and to side effects such as diarrhea<sup>[4,39]</sup>. Infections caused by resistant bacteria result in higher rates of disease and mortality and extended hospital stays, as well as increased treatment costs<sup>[40]</sup>.

Antibiotic resistance is ability of bacteria to proliferate and cause infection despite the presence of an antibiotic. Using antibiotics for inappropriate reasons or in inappropriate ways may cause bacteria to become resistant to medical treatment<sup>[41]</sup>. Although antibiotics are known to have short-term effects on the human microbiota, recent evidence shows that the effects of some antibiotics persist for longer periods. Both molecular and conventional approaches have demonstrated that the administration of antibiotics is followed by the emergence of a bacterial community in the microbiota that is either particularly sensitive or is resistant to the antibiotic<sup>[42-47]</sup>.

Antibiotherapy disturbs the balance of the normal flora. This balance is closely related to the duration of antibiotherapy. Especially with treatment lasting longer than 7 days, resistant strains have been shown to remain in the microbiota for up to 2 years<sup>[42]</sup>.

## Treatment Duration

Treatment of 7-14 days is generally sufficient for many of the infectious diseases, but individualizing the duration of antibiotic treatment has recently gained attention. Main factors influencing treatment duration are the virulence of the agent, comorbidity, clinical severity of the disease, presence of bacteremia, complications, and treatment response<sup>[48-50]</sup>.

Short-term therapy increases treatment adherence and patient satisfaction while reducing costs and side effects<sup>[49]</sup>. However, in spite of these positive aspects, the use of short-term therapy is limited among physicians due to doubt regarding the adequacy of treatment, concerns of relapse, and the belief that it will increase complication, mortality, and sequelae rates<sup>[49]</sup>.

Prolonged antibiotic use is a practice that may cause collateral damage, new infection with MDR microorganisms, infection of other patients with MDR microorganisms, and increased morbidity, mortality, and costs<sup>[49]</sup>.

"Collateral damage" refers to the unwanted effects observed in the bacterial ecology as a result of inappropriate or excessive use of antibiotics<sup>[51]</sup>. These effects manifest as superinfection with different bacteria or selection for resistant bacteria and the subsequent colonization/infection with MDR bacteria. The antibiotics most often associated with collateral damage are third-generation cephalosporins, fluoroquinolones, and carbapenems. Currently potential agents of collateral damage include MRSA, vancomycin-resistant enterococcus, ESBL-producing Gram-negative bacilli, and multidrug-resistant *Acinetobacter* spp. and *Clostridium difficile*. The growing use of extended-spectrum antibiotics, particularly in hospital settings, has made the problem of collateral damage more common. When deciding on the antibiotic therapy possible collateral damage must be considered in addition to the benefits of treatment<sup>[51]</sup>.

## Community-acquired Pneumonia

Efforts to shorten the duration of antibiotic therapy are most notable in the area of community-acquired pneumonia. The problems of antibiotic resistance, side effects, and cost have always been the driving forces behind such efforts.

Peltola et al.<sup>[52]</sup> carried out a study to investigate whether parenteral  $\beta$ -lactamase administered for 4 days was as effective as 7 days as parenteral antimicrobial therapy for



pediatric inpatients. A group of patients aged 3 months to 15 years who had bacterial pneumonia, other respiratory tract infections, sepsis-like infections, and other acute infections were prospectively and randomly assigned to groups given parenteral penicillin or cefuroxime group for 4 or 7 days. In addition to blood and throat cultures, etiology was investigated by serology for 23 different agents. A probable etiology was not identified for 96 of the 154 children included in the study. The authors concluded that shortening parenteral  $\beta$ -lactamase treatment to 4 days for infections treated parenterally was safe, cost-effective, ecologically appropriate, and lowered the risk of hospital-acquired infection.

Schrag et al.<sup>[53]</sup> investigated whether short-term, high-dose amoxicillin treatment reduced the risk of posttreatment carriage of resistant *Streptococcus pneumoniae* in children with respiratory tract infections. The study included 795 children aged between 6 and 59 months old who were prescribed antibiotics for respiratory tract diseases. The children were randomly assigned to amoxicillin regimens of 90 mg/kg (n=398) daily for 5 days or 40 mg/kg (n=397) daily for 10 days. Nasopharyngeal samples obtained from the patients on days 0, 5, 10, and 28 were analyzed for carriage of penicillin-resistant *S. pneumoniae*. On day 28, the risk of carrying penicillin-resistant pneumococci was significantly lower in the short-term, high-dose group (24%) compared to the standard course group (32%). Short-term, high-dose therapy had a stronger protective effect and treatment adherence was higher in families with 3 or more children.

Dunbar et al.<sup>[54]</sup> investigated the efficacy of 10 day 500 mg and 5 day 750 mg levofloxacin regimens in the treatment of atypical community-acquired pneumonia. The research was conducted in the USA as a randomized-controlled, double-blind, multicenter study. Of the 528 patients, 149 were diagnosed with atypical community-acquired pneumonia caused by *Legionella pneumophila*, *Chlamydia pneumoniae*, or *Mycoplasma pneumoniae*. Twenty-six of those were lost to follow-up and excluded, leaving 123 included in the analysis. The patients' initial symptoms and clinical presentation were reevaluated on day 3 of treatment and 7-14 days after the final dose of active drug. The clinical success rate was 95.5% for the 750 mg group and 96.5% for the 500 mg group. In the post-treatment analysis (31-38 days after treatment), relapse occurred in 2% of the patients in both treatment groups. Patients receiving the high-dose, short-term therapy showed significantly greater fever reduction and symptom regression on day 3 of treatment.

In a study performed in Turkey<sup>[55]</sup>; Kiter<sup>[55]</sup> analyzed the efficacy and safety of azithromycin (a single daily dose of 500 mg for 3 days) in the outpatient treatment of adults with nonsevere community-acquired pneumonia. The study included 11 patients diagnosed in an outpatient clinic with community-

acquired pneumonia based on clinical and radiological findings. Ten (91%) of the 11 patients showed full recovery, 1 (9%) had relapse, and 2 (18%) experienced side effects related to treatment. Azithromycin therapy at 500 mg/day for 3 days was reported to be safe and effective in the outpatient treatment of nonsevere community-acquired pneumonia, with a high rate of treatment adherence.

Socan<sup>[56]</sup> compared the use of an azithromycin regimen of 500 mg on the first day followed by 250 mg for 4 days (group 1) to a regimen of 500 mg for 3 days (group 2) in the treatment of atypical pneumonia. Success rates were 80% in group 1 and 88% in group 2. Azithromycin had similar efficacy in treating adult atypical pneumonia when the same total dose was administered over 3 or 5 days.

In another study<sup>[57]</sup>, 100 adult patients diagnosed with community-acquired atypical pneumonia were randomly given azithromycin either as a single dose of 1.5 g or as 500 mg for 3 days. Both groups had a clinical success rate of 97.9%. It was concluded a single dose of 1.5 g azithromycin can be an alternative to the standard 3-day azithromycin regimen in the outpatient treatment of atypical pneumonia.

Hoepelman et al.<sup>[58]</sup> compared treatment with amoxicillin/clavulanic acid for 10 days and azithromycin for 3 days in patients with acute lower respiratory tract infection. Of the 144 patients included in the study, 123 had chronic bronchitis with type 1 acute exacerbation, 3 had pneumonia, and 18 had purulent bronchitis. Treatment success was 95% in the azithromycin group and 90% in the amoxicillin/clavulanic acid group. Success rates for the two groups were 77-66% at 30-day follow-up and 66-59% at 60-day follow-up, respectively. Mild adverse events occurred in 27 patients in the azithromycin group and 24 patients in the amoxicillin/clavulanic acid treatment group. The authors concluded that a 3-day regimen of oral azithromycin was as clinically and microbiologically effective as a 10-day amoxicillin/clavulanic acid regimen in treating acute lower respiratory tract infections.

Tellier et al.<sup>[59]</sup> compared the efficacy and safety of 5- and 7-day oral telithromycin regimens and a 10-day clarithromycin regimen in patients with mild to moderate community-acquired pneumonia in a multicenter, double-blind, randomized-controlled study. The patients received telithromycin for 5 days (159 patients), telithromycin for 7 days (161 patients), or clarithromycin for 10 days (146 patients). Test-of-cure assessment after treatment showed clinical cure rates for telithromycin were 89.3% (5 days) and 88.8% (7 days), compared to 91.8% for clarithromycin. Eradication rates in the respective treatment groups were 95.8%, 96.7%, and 88.5% for *S. pneumoniae*; 88.0%, 84.0%, and 88.2% for *Haemophilus*

*influenza*; and 1/1, 4/5, and 3/4 for *Moraxella catarrhalis*. Telithromycin was found to have similar efficacy and safety to 10-day clarithromycin therapy.

In a meta-analysis of randomized controlled studies comparing short-term and long-term antibiotic regimens<sup>[60]</sup>, 15 studies including 2796 patients were evaluated. Short-term regimens used in the studies included azithromycin (n=10),  $\beta$ -lactamase (n=2), fluoroquinolones (n=2), and ketolides (n=1); of the long-term regimens, the same antibiotic was used in 3 studies while antibiotics in the same class were used in 9. In general, no differences were observed between short-term and long-term regimens in terms of clinical failure [Odds ratio (OR): 0.89, 95% confidence interval (CI): 0.78–1.02], mortality (OR: 0.81, 95% CI: 0.46–1.43) or bacteriological eradication (OR: 1.11, 95% CI: 0.76–1.62).

El Moussaoui et al.<sup>[61]</sup> performed a randomized, double-blind, placebo-controlled study among mild to moderate community-acquired pneumonia patients who improved after 3 days of intravenous treatment to compare the effectiveness of discontinuing treatment after 3 or 8 days. Patients who improved after receiving intravenous amoxicillin for 3 days were randomly administered oral amoxicillin (n=63) or a placebo (n=56) 3 times a day for 5 days. Clinical success, symptoms, radiological findings, and adverse events were evaluated on days 10 and 28. The results showed no difference between amoxicillin treatment for 3 days or 8 days in mild to moderate community-acquired pneumonia.

There have been very few prospective, well controlled studies in which the same antibiotic was used at the same dosage, only varying the treatment duration. However, these few studies suggest that azithromycin administered for less than 7 days (as short as 3 days) had similar efficacy with azithromycin given for longer durations in mild to moderate community-acquired pneumonia<sup>[60,61]</sup>. The IDSA/American Thoracic Society guidelines currently recommend at least a 5-day course of antibiotics for adult patients with community-acquired pneumonia<sup>[50]</sup>. Similarly, the British Thoracic Society guidelines recommend a course of 7 days when treating mild to moderate community-acquired pneumonia<sup>[62]</sup>. The Pediatric Infectious Diseases Society and IDSA state that shorter treatment durations are more effective than a 10-day course in children with community-acquired pneumonia<sup>[62,63]</sup>. Longer treatment should be considered for severe disease, bacteremic *S. aureus* pneumonia, or patients with cavitary lung disease. Outpatient care should be coordinated after discharge from hospital, as most patients with community-acquired pneumonia have long-term symptoms such as fever, cough, labored breathing, chest pain, expectorating, fatigue, or gastrointestinal symptoms. Comorbidities, especially cardiopulmonary or neurological disease, are the most common cause of early rehospitalization among clinically stabilized patients<sup>[64,65]</sup>.

In conclusion, current evidence indicates that mild to moderate community-acquired pneumonia can be effectively and safely treated with antibiotic therapy of 7 days or less. Reducing patients' antibiotic exposure may curb the rising rates of resistance to antimicrobial drugs, lower costs, and improve patient satisfaction and tolerance.

## Ventilator-associated Pneumonia (VAP)

In patients hospitalized for any reason, pneumonia that develops within 48 hours after admission or within 48–72 hours after discharge and was not incubating during hospitalization is defined as nosocomial pneumonia<sup>[66]</sup>. Nosocomial pneumonia that develops at least 48 hours after endotracheal intubation in patients who do not exhibit the clinical picture of pneumonia or any clinical findings suggesting pneumonia at time of intubation and who receive invasive mechanical ventilation is defined as VAP<sup>[49]</sup>. VAP is a common healthcare-associated infection, seen in approximately 15–20% in patients admitted to intensive care units (ICU)<sup>[67]</sup>.

Studies investigating shortening treatment durations have suggested that 1 week of treatment may be sufficient<sup>[68,69]</sup>. The IDSA guidelines updated in July 2016 recommend 7-day treatment for both hospital-acquired pneumonia and VAP, and specify that the treatment can be extended to 14 days in cases caused by pathogens such as *A. baumannii* and *P. aeruginosa*<sup>[48]</sup>. However, short-term treatment is rarely given in daily practice.

In a study conducted in our hospital<sup>[49]</sup> we evaluated the effectiveness of individualized treatment duration in VAP patients based on clinical response to an initial 5 days of antimicrobial treatment. The duration of antibiotic therapy was determined according to predetermined criteria and a 5-day clinical examination. Patients were divided into short-term (7–10 days) and long-term (>10 days) antibiotic treatment groups. Nineteen patients were in the first group and 30 patients were in the second group. The groups were statistically equivalent in terms of demographical and clinical properties, Glasgow Coma Scale score, Clinical Pulmonary Infection Score (CPIS), and  $\text{PaO}_2/\text{FiO}_2$  ratio at time of VAP diagnosis ( $p>0.05$ ). The number of antibiotic-free days was  $15.6\pm 6.2$  in the short-term treatment group and  $8.3\pm 7.5$  days in the long-term treatment group ( $p<0.0001$ ). One patient in the short-term and 4 patients in the long-term treatment groups died within 28 days after treatment ( $p=0.348$ ). The most common microorganisms in both groups were *A. baumannii* and *P. aeruginosa*. It was determined that treatment duration may be reduced to 1 week for VAP patients who show early clinical and laboratory response by monitoring fever, CPIS,  $\text{PaO}_2/\text{FiO}_2$  ratio, CRP, and procalcitonin values.

Klompas et al.<sup>[70]</sup> reported that patients with minimal and stable ventilator settings may be eligible for early discontinuation of antibiotic treatment. Of the 1290 patients in their study,

259 were treated for 1–3 days and 1031 were treated for >3 days. There were no differences between patients who received short- or long-term treatment in terms of time to extubation, mortality, or time to discharge. The main finding of the study was that assessing serial ventilator settings can help clinicians identify patients eligible for early discontinuation of antibiotic treatment.

There are also recent studies reporting that monitoring procalcitonin may enable treatment duration to be shortened, particularly in hospital-acquired pneumonia while concluding that procalcitonin may be a powerful antibiotic management tool<sup>[49,71,72]</sup>.

### Pyelonephritis/Catheter-associated Urinary System Infection

Short-term treatment may also be used for patients with pyelonephritis or catheter-associated urinary system infections. Sandberg et al.<sup>[73]</sup> evaluated the efficacy of ciprofloxacin for 7–14 days in females with community-acquired acute pyelonephritis (AP). One hundred twenty-six patients were given a 7-day course and 122 were given a 14-day course of ciprofloxacin. Treatment success rates were 97% and 96%, respectively. The authors concluded that “Females with AP, including elderly women and patients with severe infection, can be successfully and safely treated in 7 days with oral ciprofloxacin, and therefore, short-term antibiotics should be preferred in this age of increasing resistance”.

A clinical study was carried out with 506 patients to compare the efficacy of 750 mg levofloxacin once daily for 5 days with ciprofloxacin twice a day for 10 days in treating complicated urinary tract infections or AP<sup>[74]</sup>. Success rates at the end of treatment were 88.3% for levofloxacin and 86.7% for ciprofloxacin. There was no statistical difference between the results.

Another study<sup>[75]</sup> included 192 patients with catheter-associated urinary tract infection and compared treatment durations of 3–5 days and 14 days. Seventy-seven of the patients were given a 3–5-day course. Both treatment durations provided similar clinical results, highlighting the fact that short-term therapy may be used in the treatment of catheter-associated urinary tract infections.

### Acute Otitis Media (AOM)

AOM is a common pediatric infection that may lead to serious health problems in rare cases. One of the most controversial issues in pediatric AOM treatment is the use of antibiotics. Antibiotic therapy is recommended for children between 6 and 23 months with symptoms of earache for at least 48 hours

or a fever of 39 °C or higher<sup>[76]</sup>. It is not necessary to initiate antibiotic therapy for AOM in the absence of severe symptoms. If there is no improvement or worsening of symptoms in 48–72 hours, the child should be reevaluated and may require antibiotics. However, the duration of antibiotic therapy for pediatric AOM is a subject of debate. It has been stated that there is no difference between short-term (<7 days) and long-term (7–14 days) antibiotic treatment. In a randomized study organized by Hoberman et al.<sup>[77]</sup> and implemented in two centers in the USA, children diagnosed with AOM were randomly assigned to 10-day or 5-day courses of amoxicillin-clavulonic acid treatment. Clinical failure was defined as worsening of the signs or symptoms of infection during follow-up or the incomplete resolution of AOM signs and symptoms at the end of treatment. Secondary outcomes were relapse of otitis media, nasopharyngeal bacterial colonization rates, and parents' satisfaction with treatment. Clinical failure was seen in 34% of the 10-day course group and 16% of the 5-day course group. At least 50% reduction in AOM symptoms was seen in 91% of the children in the 10-day treatment group and only 80% of children in 5-day treatment group. There was no significant difference between the groups in terms of residual middle ear effusion after treatment. The rate of AOM recurrence was similar between the groups, and was higher among children with residual effusion regardless of treatment received. There were also no differences between the 10-day and 5-day treatment groups in rates of nasopharyngeal colonization with penicillin-resistant bacteria, adverse events, and parent satisfaction. It was stated in a meta-analysis regarding AOM<sup>[78]</sup> that a 5-day short-term course of antibiotics is an effective treatment for AOM. The analysis concludes by stating that “with the estimated cost savings, improved convenience, and lower antibiotic resistance, short-term antibiotic therapy has the potential to significantly reduce antibiotic usage in regions where 10-day treatment is accepted as the standard”.

### Complicated Intraabdominal Infections (cIAI)

The optimal duration of antimicrobial therapy for cIAI in critically ill surgical patients is unknown. Recent evidence suggests that short-term (4 days) treatment may be effective, but there are limited data for the patients with severely critical disease. In a study by Smith et al.<sup>[79]</sup>, 1679 cIAI patients were divided into short-term (≤7 days) and long-term (>7 days) antimicrobial treatment groups. The short-term regimen was 5 days and the long-term regimen was 14 days. Treatment failure occurred in 39% in patients receiving short-term therapy and 63% in patients receiving long-term therapy ( $p<0.001$ ). Treatment duration was found to be correlated with treatment failure (OR: 2.886;  $p=0.006$ ). There was no difference in mortality between the groups (OR: 0.738;  $p=0.461$ ). The authors concluded that “A

short course of antibiotic therapy after source control in surgical patients with critical cIAI yielded results similar to previous studies and supported the safety of this method in critical patients". In another study<sup>[80]</sup>, the authors stated that "Data obtained from noninferiority trials of short-term antimicrobial treatment for IAIs indicate the global superiority of short-term therapy". Hence, determining whether source control has been achieved is imperative for short-term therapy.

### Catheter-associated Bloodstream Infection

Catheter-associated bloodstream infections are among the leading healthcare-related infections causing severe morbidity and increased costs<sup>[81]</sup>. Most catheter-associated bloodstream infections can be prevented by taking universal preventive measures.

#### Universal preventive measures:

1. Enhancing collaborative performance using checklists and bundles,
2. Educating the personnel who place and maintain catheters,
3. Maximal sterile barrier precautions,
4. Chlorhexidine skin antisepsis.

If the incidence of catheter-associated bloodstream infection is not reduced to acceptable levels after implementing these universal measures, technological innovations such as coated catheters and antimicrobial-impregnated dressings as well as antimicrobial lock solutions should be considered. Although many experts claim that a certain period of antibiotic therapy is necessary, these infections can be resolved by catheter removal, without the need for further antibiotic treatment. It has been reported that except for endovascular infections such as septic thrombosis, endocarditis, and metastatic infections, a 5–7 day course of antibiotics course is sufficient after catheter removal<sup>[82]</sup>.

### Osteomyelitis

The management of osteomyelitis requires a multidisciplinary approach combining debridement and antimicrobial treatment. Many therapeutic regimens have been designed to prevent, cure, or suppress osteomyelitis<sup>[83]</sup>. Defining treatment for these patients is difficult for several reasons. These difficulties include debridement, the effectiveness of antibiotics, heterogeneity of clinical condition and pathogens, and the need for years of follow-up to demonstrate long-term remission. Another important problem is the limited number of randomized controlled studies. Many recommendations for the treatment of osteomyelitis are based on expert opinion and not on the results of randomized-controlled studies. Therefore, standardization of

treatment has not been possible. Swiontkowski et al. conducted a study comparing clinical outcomes of 93 osteomyelitis patients treated with a protocol including debridement followed by 5–7 days of intravenous antibiotics and oral treatment for 6 weeks to those of 22 patients treated with the same surgical protocol and intravenous antibiotics for 6 weeks. The authors reported that the treatment was 91% successful regardless of the active microorganism and emphasized that prolonged intravenous antibiotic therapy is not necessary for clinical recovery in adult patients with chronic osteomyelitis<sup>[84]</sup>. In a study comparing 6 weeks and 12 weeks of treatment in patients with pyogenic vertebral osteomyelitis, both were reported to be equally effective<sup>[85]</sup>. Another study aimed at identifying the optimal duration of antibiotic use after chronic osteomyelitis surgery demonstrated no difference in recovery between a treatment of 6 weeks and longer treatments<sup>[86]</sup>. A review of articles published between 1968 and 2000 to determine the best approach to antibiotic therapy for osteomyelitis revealed that although no optimal duration was defined for antibiotherapy, most researchers treated patients for about 6 weeks. The authors stated that despite 30 years of research, the available literature on osteomyelitis treatment is insufficient to determine the best antibiotic, route of administration, and treatment duration<sup>[87]</sup>.

### Prosthetic Joint Infections

Deep infection of the implant site is a destructive complication typically resulting in pain, extended hospital stays, and increased medical costs<sup>[88]</sup>. The treatment of such infections generally involves surgery and antimicrobial treatment. Although debridement and one-stage revision has been successful in selected cases, the current standard surgical procedure for managing prosthetic hip infections (PHI) is staged exchange arthroplasty (SEA) which involves total debridement of infected tissues and removal of all components, followed by a period of antibiotic treatment and eventual re-implantation of a new prosthesis<sup>[89]</sup>. An antibiotic-loaded cement spacer (ALCS) is used both as a temporary hip joint implant as well as a way to directly apply local antibiotic<sup>[90]</sup>. Studies have shown that ALCS provides *in vivo* high efficacy with antibiotic levels much higher than those achieved by systemic antibiotics and maintains levels far above the required therapeutic concentration for several months<sup>[91,92]</sup>. Therefore, ALCS implantation has become a common approach. Although SEA is successful, the optimal duration of systemic antibiotic treatment has not been determined. In a study in which ALCS was used in 114 patients with PHI, Stockley et al.<sup>[93]</sup> reported successful infection control in 87.7% (100/114) without prolonged systemic antibiotic therapy. In a multicenter study, Nelson et al.<sup>[94]</sup> applied a prospective, randomized protocol to 28 patients with infected total knee and hip arthroplasties (22



hip and 6 knee); one group was treated with debridement and ALCS, the other with debridement and systemic antibiotherapy. The mean follow-up period was about 3 years (6 months–5.6 years). The results of both groups were similar in terms of relapse and treatment success. However, due to a lack of comparative studies of the appropriate duration of SEA using ALCS, the interim use of ALCS could not be evaluated. In that sense, a study by Hsieh et al.<sup>[90]</sup> was the first to compare the outcomes of short- and long-term systemic antibiotic therapy in patients with infected hip arthroplasty undergoing SEA with ALCS. The study included 99 patients, 46 who received standard (4–6 weeks) antibiotic treatment and 53 who received short-term (1 week) treatment, and the average follow-up period was 43 months (24–60 months) regardless of infection. The success rate in both groups was approximately 90%. The authors also stated that 5 patients (11%) in the long-term treatment group developed complications related to antibiotic use, while patients in the short-term treatment group had shorter hospital stays and lower medical expenses<sup>[95]</sup>. In another study comparing 6 weeks and 12 weeks of postoperative antibiotic therapy in the treatment of prosthetic joint infections, the 6-week antibiotic course was reported to be sufficient<sup>[96]</sup>. Although the literature

contains many studies investigating length of treatment, there is still a need for randomized controlled studies to determine optimal treatment durations.

## Conclusion

In conclusion, the inappropriate or excessive use of antibiotics may manifest as superinfection with different bacteria, selection for resistant bacteria, and subsequent colonization/infection with MDR bacteria, which are referred to as collateral damage. The potential collateral damage should be considered in addition to the benefits of treatment when choosing antibiotic therapy. With better antibiotic stewardship, the benefits can be enhanced while reducing antibiotic-related collateral damage. Short-term antibiotic therapy may be administered to selected patient groups both in community- and hospital-acquired infections based on patients' individual characteristics and their clinical response to treatment (Table 2). The negative consequences of prolonged antibiotic use, such as antibiotic-related side effects and resistance, can be prevented by practicing the rational use of antibiotics together with treatment response monitoring and establishing optimum treatment durations.

**Table 2. Studies evaluating short- and long-term antibiotic use**

Study	Disease	Short-term regimen	Long-term regimen	Patient number	Conclusion
Socan <sup>[56]</sup>	Community-acquired pneumonia	Azithromycin, 3 days	Azithromycin, 5 days	148	No difference in clinical success
Hoepelman et al. <sup>[58]</sup>	Community-acquired pneumonia	Azithromycin, 3 days	Amoxicillin/clavunate, 10 days	144	No difference in clinical success
Peltola et al. <sup>[52]</sup>	Community-acquired pneumonia	Cefuroxime or penicillin G, 4 days	Cefuroxime or penicillin G, 7 days	154	No difference in clinical success
Dunbar et al. <sup>[54]</sup>	Community-acquired pneumonia	Levofloxacin, 5 days	Levofloxacin, 10 days	528	No difference in clinical success
Yilmaz et al. <sup>[49]</sup>	Ventilator-associated pneumonia	7–10 days of therapy based on 5-day clinical evaluation	>10 days of therapy based on 5-day clinical evaluation	49	No difference in clinical success Number of days without antibiotics was higher in patients who received short-term treatment
Sandberg et al. <sup>[73]</sup>	Pyelonephritis	Ciprofloxacin, 7 days	Ciprofloxacin, 14 days	248	No difference in clinical success
Jarrell et al. <sup>[75]</sup>	Catheter-associated urinary tract infection	3–5 days of therapy based on clinical evaluation	14 days of therapy based on clinical evaluation	192	No difference in clinical success
Hoberman et al. <sup>[77]</sup>	Acute otitis media	Amoxicillin/clavulonic acid, 5 days	Amoxicillin/clavulonic acid, 10 days	520	No difference in clinical success
Swiontkowski et al. <sup>[84]</sup>	Osteomyelitis	Debridement + 5–7 days IV + 6 weeks oral antibiotic	Debridement + 6 weeks IV antibiotic	115	No difference in clinical success
Bernard et al. <sup>[85]</sup>	Osteomyelitis	6 weeks antibiotic	12 weeks antibiotic	359	No difference in clinical success
Nelson et al. <sup>[94]</sup>	Infected knee and total hip arthroplasty	Debridement + antibacterial ALCS	Debridement + systemic antibiotherapy	28	No difference in clinical success
Bernard et al. <sup>[95]</sup>	Prosthetic joint infections	6 weeks antibiotic	12 weeks antibiotic	144	6-week treatment is adequate

ALCS: Antibiotic-loaded cement spacer, IV: Intravenous

## Ethics

**Peer-review:** Externally and internally peer-reviewed.

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Concept: G.Y., S.A., U.K., Design: G.Y., S.A., U.K., Data Collection or Processing: G.Y., S.A., U.K., Analysis or Interpretation: G.Y., S.A., U.K., Literature Search: G.Y., S.A., U.K., Writing: G.Y., S.A., U.K.

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