Get shorty!

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A recent randomized controlled trial to evaluate the efficacy of a fixed, short antimicrobial treatment was published in May of this year (1). This interesting study brings to the fore the importance of evaluating, with proper methodology, one of the most disputable aspects of antimicrobial treatments, the duration. When supported by strong evidence or expert statements, shortening courses of antimicrobial treatments are an important component of antimicrobial stewardship programs (2). The course of therapy must be defined as the time period during which therapeutic concentrations are maintained at the site of infection, instead of the time during which an antimicrobial treatment is administered. This definition puts emphasis on the importance of a thorough evaluation before starting a short treatment. For example, the most recent Infectious Diseases Society of America (IDSA) skin and soft tissue guidelines suggest a treatment as short as five days for cellulitis (3). This duration might not apply to a patient with cellulitis and chronic arterial insufficiency of the lower limbs. Successful abbreviated treatment courses depend on several factors linked to host (immune status), pathogen (susceptibility, low spontaneous mutation rate, extracellular, rapid multiplication), infection site (accessible site, not as biofilm, no foreign body, not life-threatening, not in an abscess – low pH, or any other factors that inhibit antimicrobial action) and therapeutic agents (bactericidal, rapid onset of action, lack of propensity to induce mutants, good penetration in tissues, active against nondividing bacteria).

This strategy has several theoretical or demonstrated advantages. There is a clear link between bacterial resistance and shorter courses of antimicrobial treatments. It reduces the selective pressure on bacterial flora and, therefore, prevents emergence of resistance. Upper respiratory tract infections treated for ≥5 days in children increased the risk of pharyngeal carriage of resistant *Streptococcus pneumoniae* (4). Prophylaxis for >48 h after cardiovascular surgery was associated with increased bacterial resistance in enterobacteriaceae and enterococci (5). However, one must remember that a useless short course is still the worst strategy and strength should also be put on avoiding the treatment of conditions that do not require antimicrobial treatments such as asymptomatic bacteriuria, upper respiratory viral infections and viral otitis media, etc.

Other advantages of short therapy are increased compliance, reduced direct (related to the acquisition of an antimicrobial treatment) and indirect (associated with administration of intravenous antimicrobial treatments, adverse effects, length of stay, etc) costs, lower risk of adverse events and drug-drug interactions. The main drawback of a shorter treatment is the risk of lower efficacy that may be associated with additional treatment (probably with a broader spectrum because the patient failed the previous treatment), significant morbidity and hospital admissions/readmissions. There is a lower limit under which short therapy becomes ineffective and that is why we need sound studies to support it. Several studies have demonstrated the limit in shortening treatments because they were associated with unfavourable outcomes. Single-dose treatments for uncomplicated cystitis have been consistently shown to be less successful than longer courses (6) and treating *Staphylococcus aureus* bacteremia for <14 days was associated with higher relapse rates (7).

In the 2010, *Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America*, the recommended duration of an established infection was four to seven days in patients with adequate source control (8). At this time, it was graded as a B-III (moderate evidence coming mainly from expert opinion and descriptive studies). For some indications, suggested treatment or prophylaxis was even shorter. For stomach or proximal jejunum perforations, when source control was achieved, prophylactic antibiotics directed against aerobic Gram-positive cocci for 24 h were considered to be adequate, unless patients were undergoing treatment to reduce gastric acidity or were known for gastric malignancy. In these cases, antimicrobial therapy covering a mixed flora was recommended for the same duration. Penetrating bowel injuries repaired within 12 h, any intraoperative contamination by enteric contents, acute appendicitis without perforation, and abscess or local peritonitis should be treated with an antimicrobial treatment with mixed flora coverage for <24 h.

The recent multicentre randomized controlled trial published by Sawyer et al (1) presents evidence to support a four-day treatment for complicated intra-abdominal infections, instead of the four to seven days suggested in the aforementioned guidelines. A total of 518 patients were enrolled and underwent randomization; 260 were assigned to a control group that received antimicrobial treatments until two days after the resolution of their sepsis (based on systemic inflammatory response syndrome criteria) and 258 received a fixed four-day course of therapy. To be included in the study, patients needed to have undergone an intervention to achieve source control. The choice of the antimicrobial agent was not dictated by the protocol but was considered acceptable if consistent with IDSA guidelines. The most frequently used antimicrobial treatment was piperacillin-tazobactam in 54% of patients. Baseline characteristics in the two groups were very similar. In the control group, patients received antimicrobial treatments for a median duration of eight days (interquartile range five to 10 days) versus four days (interquartile range four to five days) in the experimental group. The main outcomes of this study, surgical site infection and recurrent intra-abdominal infection or death, were almost identical in both groups; 21.8% in the experimental group versus 22.3% in the control group (absolute difference −0.5 percentage point [95 % CI −7.0 to 8.0] [P=0.92]). The study had several strengths including a large sample size and randomized design, but above all, it included patients with

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different severities of illness and methods for source control (percutaneous versus surgical). Authors report several limitations: results are applicable only to immunocompetent patients with adequate source control; there was an important rate of nonadherence to the protocol in both groups creating a bias toward the null hypothesis; and the sample size to assert equivalence between groups was not reached. However, this is the best study available because it brings appreciable additional evidence to limit the duration of antimicrobial treatment to four days in similar patients. Hopefully, this study will achieve higher impact than the IDSA guidelines, because recent data show that patients with intra-abdominal infections are treated for an mean duration of 10 to 14 days (9).

Even if it is a very imprecise science, most IDSA guideline authors have made an important effort to delineate the best duration of treatment for most infections. As you will see, these recommendations are frequently supported by low- to moderate-quality evidence (Table 1).

Most of the IDSA guidelines have been published for more than five years. Consequently, in the updated version, new shorter options may be available and the level of evidence to support some of the current recommendations may be stronger. Several studies aiming to evaluate shorter antimicrobial treatments are recruiting (www.clinicaltrials.gov). Of interest, seven versus 14 days comparison for bloodstream infections caused by enterobacteriaceae, (SHORTEN study) two days versus seven days versus two to seven days based on C-reactive protein monitoring in the treatment of acute exacerbations of chronic obstructive pulmonary disease, and seven versus 14 days for patients admitted in the intensive care unit with bacteremia (BALANCE study). The latter is a multicentre randomized controlled trial being conducted in 13 hospitals in Canada. The results of this study will be particularly interesting because it aims to enroll patients with bacteremia from different sources. It is also remarkable that a group of Canadian researchers are leaders in this domain. The selection of the optimal duration of prescription remains and is largely an art rather than a science, and additional trials are needed to continue to identify the best duration of antimicrobial treatment and maximize efficacy by lowering the associated side effects.

TABLE 1
Shorter recommended treatment for frequent infections in adults seen in hospitals, from the Infectious Diseases Society America guidelines

Type of infectious disease	Suggested treatment duration	Suggested clinical criteria/comments	Grading of evidence	Year of publication
Intravascular infections				
Catheter-related blood stream infections (10)	5–7 days	Coagulase-negative *Staphylococcus* species with catheter removal	B-III, moderate evidence from expert opinion and descriptive studies	2009
	10–14 days	Coagulase-negative *Staphylococcus* species + antibiotic lock therapy if catheter is retained		
	7–14 days	*Enterococcus* species, Gram-negative bacilli	C-III, poor evidence from expert opinion and descriptive studies	
	14 days	For *Staphylococcus aureus* and *Staphylococcus lugdunensis* 14 days can be considered if: not diabetic; immunocompetent; catheter is removed; no prosthetic intravascular device; no evidence of endocarditis; no metastatic foci of infection; and fever and bacteremia are resolved within 72 h of antimicrobial initiation	A-II, good evidence from at least one RCT or high-quality observational studies	
	4–6 weeks	*S aureus* and *S lugdunensis* with positive criteria for shorter duration	B-II, moderate evidence from at least one RCT or high-quality observational studies	
Endocarditis (11)	14 days	Combination therapy (Penicillin/ceftriaxone + gentamicin) for viridans group and *Streptococcus bovis* (MIC ≤0.5 µg/mL)	IB, general agreement, data derived from a single RCT or nonrandomized studies	2005
		MSSA (uncomplicated right-sided)	IA, general agreement, data derived from multiple RCTs	
	4 weeks	Viridans group and *S bovis* (MIC ≤0.5 µg/mL) with penicillin or ceftriaxone monotherapy	IA, general agreement, data derived from multiple RCTs	
		Enterococcal-native valve endocarditis susceptible to penicillin and gentamicin + symptoms of illness ≤3 months		
	6 weeks	Native MSSA or MRSA (complicated right-sided or left-sided)	IA, general agreement, data derived from multiple RCTs	
		Prosthetic MSSA or MRSA valve endocarditis	IB, general agreement, data derived from a single RCT or nonrandomized studies	
		Prosthetic viridans group and *S bovis* endocarditis		
	8 weeks	Native or prosthetic valve enterococcal endocarditis caused by strains resistant to penicillin, vancomycin and aminoglycosides	IIaC, weight of evidence/opinion is in favour of usefulness/efficacy, experts opinion	
Lower/upper respiratory infections				
Acute bacterial rhinosinusitis (12)	5–7 days	Uncomplicated acute bacterial rhinosinusitis, might not apply to elderly with underlying illnesses and patients with immunosuppression	Weak recommendation, low- to moderate-quality evidence	2012
Community-acquired pneumonia (13)	5 days	Afebrile for 48–72 h	Level 1 (high)	2007
		Not more than one of: heart rate >100/min; respiratory rate >24/min; systolic blood pressure <90 mmHg; arterial O_2 saturation of <90% on room air; able to maintain oral intake; normal mental status	Evidence from well-conducted, RCTs	

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TABLE 1 – CONTINUED
Shorter recommended treatment for frequent infections in adults seen in hospitals, from the Infectious Diseases Society America guidelines

Type of infectious disease	Suggested treatment duration	Suggested clinical criteria/comments	Grading of evidence	Year of publication
Lower/upper respiratory infections – CONTINUED				
Hospital-associated pneumonia, ventilator-associated pneumonia and health care-associated pneumonia (14)	7 days 14 days	Initially appropriate therapy, good clinical response Nonfermenting Gram-negative bacilli	Level 1 (high) Evidence from well-conducted, randomized controlled trials	2005
Skin and soft tissue infections (3)				
Nonpurulent sexually transimitted infection	5 days	Might be extended if the infection has not improved within this time period	Strong recommendation, high-quality evidence	2014
Impetigo/echtyma	7 days	Oral treatment is suggested in patients with numerous lesions and during outbreaks	Strong recommendation, moderate-quality evidence	
Pyomyositis	14 days		Strong recommendation, low-quality evidence	
Urinary tract infection				
Catheter-associated urinary tract infection (15)	3 days	Women, without upper urinary tract infection symptoms, indwelling catheter removed	B-II, moderate evidence from at least one RCT or high-quality observational study	2010
	5 days	Levofloxacin 750 mg in patients not severely ill	B-III, moderate evidence from expert opinion and descriptive studies	
	7 days 10–14 days	All patients with prompt resolution of symptoms All patients with delayed response	A-III, strong evidence from expert opinion and descriptive studies	
Uncomplicated cystitis (16)	1 day 3 days 5 days	Fosfomycin 3 g Quinolones, TMP-SMX, β-lactam agents (3–7 days) Nitrofurantoin	A-I (except β-lactam that are graded B-I), good evidence from more than one RCT	2011
Uncomplicated Pyelonephritis (16)	5 days 7 days	Levofloxacin 750 mg daily Ciprofloxacin 1000 mg daily	B-II, moderate evidence from expert opinion and descriptive studies	
	14 days	TMP-SMX double strength twice-daily, β-lactam agents (10–14 days)	A-I (TMP-SMX), good evidence from more than one RCT	
Others				
Bacterial meningitis (17)	7 days 10 days 14 days 21 days	*Neisseria meningitidis* and *Haemophilus influenzae* *Streptococcus pneumoniae* *Streptococcus agalactiae* *Listeria monocytogenes* and aerobic Gram-negative bacilli	A-III, strong evidence coming mainly from expert opinion and descriptive studies	2004
Complicated intra-abdominal infection (8)	4–7 days	Patients with adequate source control	B-III, moderate evidence coming mainly from expert opinion and descriptive studies	2010

MIC Minimum inhibitory concentration; MRSA Methicillin-resistant Staphylococcus aureus; *MSSA Methicillin-sensitive* S aureus; *RCT Randomized controlled trial; TMP-SMX Trimethoprim/sulfamethoxazole*

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