Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections

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Despite the large number of suggestions available in the literature, the optimal duration of antibiotic treatment remains an individual decision mainly based on clinical criteria. Shorter but equally effective regimens would reduce the side effect rates, including both antibiotic resistance and drug expenses. Although several prospective, randomized trials and meta-analyses with the aim of comparing a standard duration with a shorter one for most bacterial infections have been published, to date most current recommendations carry little weight, as they are based on expert opinions or practical experience. This review will briefly touch upon the clinical evidence of short-course versus long-course antibiotic therapy for the most common community- and hospital-acquired bacterial infections.

Keywords: duration of antibiotic therapy, antibiotic resistance, appropriate therapy

Introduction

The discovery of antibiotics greatly improved the quality of life in the twentieth century. Following the introduction of penicillin into clinical practice, there was extensive use of antibiotics both in humans and in animals. However, widespread antibiotic use has created strong selective pressure, which has consistently resulted in the emergence and spread of resistant bacteria.1–3

Although increasing the duration of patient exposure to antimicrobials is known to increase the likelihood of colonization with resistant organisms and despite the large number of suggestions in the literature concerning antibiotic therapy (AT) duration for different bacterial infections, choosing the moment to interrupt antibiotic treatment remains an individual decision based mainly on clinical criteria.4

In recent years, a novel approach for determining the necessity and optimal duration of AT is the use of biomarkers, such as procalcitonin (PCT) levels, opening the door to individualized treatment that might allow the overall duration of AT to be reduced.5 Recently, in a systematic review, Agarwal and Schwartz6 showed that PCT-guided treatment was associated with significantly reduced antimicrobial exposure in intensive care unit (ICU) patients (effect sizes 19.5%–38%) without worsening the mortality rate.

This review will briefly touch upon the clinical evidence of short-course versus long-course AT for the following community- and hospital-acquired bacterial infections: tonsillo-pharyngitis; acute bacterial sinusitis (ABS); community-acquired pneumonia (CAP); hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP); urinary tract infections (UTIs); intra-abdominal infections (IAIs); bone and joint infections (BJIs); bloodstream infections (BSIs); and infective endocarditis (IE).

Tonsillo-pharyngitis

Current guidelines suggest penicillin for 10 days as the first choice for AT for patients affected by acute group A β-haemolytic Streptococcus (GABHS) pharyngitis.7 Several studies carried out during the 1990s clearly demonstrated that second- and third-generation cephalosporins and azithromycin exert the same or better efficacy in terms of bacterial eradication with a much shorter AT course (3–5 days) compared with penicillin (10 days).8

Recently, in a Cochrane review on AT duration for GABHS pharyngitis in children (aged 1–18 years; one study included patients aged up to 25 years), Altamimi et al.9 found that short-course (3–6 days) AT with oral antibiotics (mostly patients were treated with azithromycin) had a lower risk of early clinical treatment failure, but no significant differences in early microbiological treatment failure or in late clinical recurrence were found. Importantly, the overall risk of late microbiological recurrence was worse in the short-duration treatment. If late microbiological recurrence is considered clinically important, it is a reason to choose long-course AT, given the fact that we aim to avoid complications of GABHS. However, when studies on low-dose azithromycin were excluded, no significant differences were found (OR 1.06, 95% CI 0.92–1.22) (Table S1, available as Supplementary data at JAC Online).9
ABS

The current Infectious Diseases Society of America (IDSA) guidelines recommend that 5–7 day AT should be administered for uncomplicated ABS in adults, whereas a longer course (10–14 days) is recommended in children.10 The findings of a meta-analysis carried out by Falagas et al.11 suggest that short-course (3–7 days) AT has an effectiveness similar to longer-course (6–10 days) treatment for adult patients with uncomplicated ABS. However, the authors stress the importance of the clinician’s own assessment: AT should not be inappropriately shortened in a patient who fails to respond adequately to the regimen administered (Table S1, available as Supplementary data at JAC Online).11

CAP

The optimal duration of AT is an open question due to the lack of sufficient randomized clinical trial (RCT) data. The current IDSA guidelines for treatment of CAP recommend that non-critically ill hospitalized patients with CAP should be treated for at least 5 days and that the treatment should be continued for 72 h after the patient becomes afebrile.

In the early 2000s, Dunbar et al.12 showed that levofloxacin is as effective at a dosage of 750 mg/day for 5 days as it is at a dosage of 500 mg/day for 10 days for the treatment of mild to moderate CAP. Overall, in the clinically evaluable population, the clinical success rates were 92.4% for the group treated with 750 mg and 91.1% for the 500 mg group, whereas the microbiological eradication rates were 93.2% and 92.4% in the 750 and 500 mg groups, respectively.12 More recently, the efficacy of short-course AT for mild to moderate CAP in adults and children was investigated by Dimopoulos et al.13 in a meta-analysis of seven RCTs. Overall, no differences were found between short- and long-course AT regarding clinical and microbiological success, relapses, mortality and adverse events, and no differences were found in subset analyses of adults or children (Table S1, available as Supplementary data at JAC Online).13

Finally, a recent RCT evaluated the effect of PCT-based guidelines versus standard guidelines on antibiotic use in community-acquired lower respiratory tract infections (LRTIs). Patients were randomized to antibiotic administration based on a PCT algorithm with predefined cut-off ranges for initiating or stopping antibiotics or according to standard guidelines. In patients with LRTIs, a strategy of PCT guidance compared with standard guidelines gave similar rates of adverse outcomes, as well as lower rates of antibiotic exposure and antibiotic-associated adverse events.16

HAP and VAP

To date, few studies have been conducted on the optimal duration of therapy for patients with HAP and VAP. The established practice is that most patients receive antibiotics for 10–14 days while those infected with non-lactose-fermenting organisms such as Pseudomonas aeruginosa are treated for 14–21 days. However, evidence suggests that patients infected with susceptible pathogens experience rapid microbiological eradication and significant improvement in clinical signs and symptoms of pneumonia within only 6 days of receiving appropriate AT.15 Micek et al.16 and Ibrahim et al.17 demonstrated that patients experienced similar resolution of clinical signs and symptoms, with mean durations of therapy of 6.0 and 8.6 days, respectively, compared with patients treated for longer durations. More recently, in a Cochrane review, Pugh et al.18 assessed the effectiveness of short-course AT for HAP, particularly patients with VAP. Overall, eight studies were included. The analysis found that a short course (7–8 days) of antibiotics compared with a long course (10–15 days) reduced the recurrence of VAP due to multiresistant organisms. Moreover, both antibiotic regimens resulted in similar rates of adverse outcomes. However, when infections due to non-fermenting Gram-negative bacilli were analysed, recurrence was greater after short-course therapy (OR 2.18, 95% CI 1.14–4.16). Finally, it was found that a PCT-guided strategy significantly reduced antibiotic exposure and selective pressure with no apparent adverse outcomes (Table S1, available as Supplementary data at JAC Online).18

UTIs

The recent IDSA guidelines on the management of acute uncomplicated cystitis and pyelonephritis in women recommend treating cystitis with antibiotics for 3–7 days or with a single dose of fosfomycin, whereas AT for acute pyelonephritis is recommended for 5–7 days with an oral quinolone and 14 days with a β-lactam agent or trimethoprim/sulfamethoxazole.19

In a Cochrane review, Lutters and Vogt-Ferrier20 showed that short-course AT (3–6 days) with oral antibiotics (mostly patients were treated with quinolones) is effective for the treatment of uncomplicated UTIs (UTIs) in elderly (>60 years old) women (Table S1, available as Supplementary data at JAC Online). However, when a single-dose regimen was compared with short- or long-course AT, a higher rate of persistent UTI at short-term follow-up (<2 weeks), but not at long-term follow-up (>2 weeks), was observed. No differences in clinical failure were found.20 Similarly, in another systematic review in young and middle-aged women with uUTIs, Milo et al.21 did not find clinical differences between short-course (3 days) and long-course (5–10 days) regimens in clinical success, while short-course treatment was less effective in microbiological eradication (Table S1, available as Supplementary data at JAC Online). Moreover, in a meta-analysis of four RCTs, Kyriakidou et al.22 observed that short-course (7–14 days) AT had an effectiveness similar to longer-course (14–42 days) treatment for adolescent and adult patients with acute pyelonephritis (Table S1, available as Supplementary data at JAC Online).

For catheter-associated UTI, international experts recommend a short course (7 days) of antibiotics in patients who have prompt resolution of symptoms, but a long course (10–14 days) in those with a delayed response or with bacteraemia.23

Finally, the IDSA guidelines for the treatment of asymptomatic bacteriuria recommended a duration of AT of 3–7 days in pregnant women.24 In an updated systematic review on the duration of AT for asymptomatic bacteriuria during pregnancy, Widmer et al.25 concluded that a single-dose regimen of antibiotics may be less effective than the 7 day regimen (Table S1, available as Supplementary data at JAC Online).
IAIs

The duration of AT of IAIs has not yet been standardized, as the relevant data in the literature are both heterogeneous and incomplete, dealing with patients in very different clinical situations.26,27 The most recent update of IDSA guidelines published in 2010 encourages short-course therapy (4–7 days) in patients with adequate surgical source control.28 The conclusions of a meta-analysis carried out by Snelling et al.29 on the duration of AT in cases of advanced paediatric appendicitis suggest that limiting the duration of antibiotic use to only 3 days is not associated with higher rates of intra-abdominal abscesses or wound infection. In an Italian RCT, Basoli et al.30 found that a shorter (3 days) duration of ertapenem is as clinically and microbiologically effective as a standard 5 day treatment schedule in patients presenting with mild to moderately severe community-acquired localized peritonitis. However, the duration of AT in critically ill surgical patients, including those with inadequate source control, is a unresolved issue. For these patients, the therapy should be guided by the intra-operative findings and should be discontinued if the patient is afebrile and has normal white blood cell counts at the time of AT cessation.32

BJIs

Unfortunately, to our knowledge, no well-designed RCTs have established the effective duration of AT for osteomyelitis and prosthetic joint infections (PJIs).31 Acute haematogenous osteomyelitis is best managed with a 4–6 week course of appropriate AT, whereas chronic osteomyelitis is generally treated with antibiotics and surgical debridement. The excision of all sequestra along with any infected bone and soft tissue is the cornerstone of the management of chronic osteomyelitis. The duration of AT for the latter is unclear: reports range from 4–6 weeks to several months. As a general principle, for the first step (4–6 weeks) the antibiotics should be administered intravenously rather than orally. When effective oral antibiotics are not available, parenteral antibiotic administration on an outpatient basis can be considered.32

The management of PJIs is based on the timing of infection, type of infection, condition of the implant, the soft tissue and patient co-morbidities. In patients with a stable implant, a pathogen susceptible to antimicrobial agents active against surface-adhering microorganisms (e.g. rifampicin), uncompromised soft tissue and a short (<3 weeks) duration of symptoms of infection, a conservative approach (retention of implant) is possible. After the debridement, patients with hip prostheses should be treated for 3 months and those with knee prostheses for 6 months.31,33 More recently, Puhto et al.34 observed that an AT duration of 3 months in knee prostheses and 2 months in hip prostheses is as good as standard AT duration for the management of patients treated with a conservative approach.

Conversely, a two-stage exchange procedure is recommended. This is the first choice in patients with compromised soft tissue and difficult-to-treat bacteria, whereas use of a one-stage revision should be restricted to selected cases. In the two-stage exchange approach, the interval of AT duration without any foreign material between surgeries should be a minimum of 6 weeks.31,33 Recently, Bernard et al.35 compared AT for 6 weeks with a 12 week treatment in 144 PJIs. Although the surgical treatment procedure was not homogeneous in the study population, no significant difference in curing the infection was observed. If there is any doubt about persistent infection before reimplantation (failure of inflammatory markers or clinical signs of infection), a new debridement should be planned. At the second-stage surgery, a further set of specimens for culture and histopathological examination should be taken in the same manner prior to the implantation of a new prosthesis. As a general principle, AT should not routinely be administered after the second-stage surgical procedure if the tissue specimens for culture and histopathological examination show no growth and no acute inflammation. Nevertheless, if the specimens indicate an active infection, further surgical debridement with another course of AT should be performed.36

BSIs

According to the international Surviving Sepsis Campaign guidelines, sepsis should be treated for 7–10 days, whereas the duration of the AT should be longer in patients with a slow response, undrained foci of infection or immunological deficiencies.37 In a meta-analysis on the duration of AT for BSIs, Havey et al.38 found no significant differences in clinical cure, microbiological cure and survival between shorter (5–7 days) and longer (7–21 days) AT for the management of bacteraemic patients. However, data were available only in 155 patients with primary neonatal bacteraemia or secondary BSIs due to S. aureus, whereas data from patients with catheter-related BSIs were not included. Overall, short-course (<10 days) AT was commonly prescribed in patients with catheter-related BSIs or those with bacteraemia related to pneumonia, UTI, IAI or skin and soft tissue infection. Moreover, longer-course regimens were recommended by the majority of respondents for BSIs due to Staphylococcus aureus, whereas shorter regimens were recommended in those due to coagulase-negative staphylococci. Gram-negative and other Gram-positive bacteria did not influence the AT duration.39 The longer-course AT for BSIs due to S. aureus is likely because of a high incidence of metastatic and relapse infections. As a general principle, BSIs due to S. aureus can be treated with a 2 week course in patients without evidence of endocarditis, thrombophlebitis or metastatic infections, in those without foreign bodies and in patients with effective clinical (defervescence within 72 h) and microbiological (blood cultures negative within 48–96 h) response.40 However, the introduction into clinical practice of rapidly bactericidal antibiotics such as daptomycin is likely to reduce the AT duration in BSIs due to S. aureus.41 Finally, PCT-guided treatment for the management of BSIs appears highly effective to reduce antibiotic exposure without increasing the mortality rate.42

IE

The IDSA and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines suggest that patients with uncomplicated native valve endocarditis (NVE) should be treated
with a 4 week course of AT, whereas the duration of the AT should be longer (≥6 weeks) in patients with complicated NVE (e.g. peri-valvular abscess or septic metastatic complications) or with prothet-ic valve endocarditis (‘PVE’).\textsuperscript{43,44} A short course with 2 weeks of drug administration should be a feasible option in selected un-complicated cases due to penicillin-susceptible oral streptococci or group D streptococci treated with a combination of penicillin G (or amoxicillin or amoxycillin) or ceftriaxone and an aminoglyco-side (gentamicin or netilmicin).\textsuperscript{45,46} Uncomplicated staphylococ-cal right-side IE in intravenous drug users can be treated with a short course (2 weeks) of penicillinase-resistant penicillin alone or combined with an aminoglycoside.\textsuperscript{47}–\textsuperscript{51} On the other hand, NVE due to enterococci in patients with a history of ≥3 months of symptoms should be treated for 6 weeks.\textsuperscript{44} Moreover, IE due to enterococci with a multiresistance phenotype (e.g. resistance to aminoglycosides, β-lactams and vancomycin) should be treated with a longer course of AT (≥8 weeks) with newer antibiotics or β-lactam combinations.\textsuperscript{43,44}

Finally, the duration of AT after surgery is controversial. As a general principle, if valve cultures are positive, a new complete course of AT should be started, whereas if valve cultures are negative the patient should complete the pre-operative course of AT.\textsuperscript{43,44} On this point, Morris et al.\textsuperscript{52} performed a retrospective study in New Zealand to determine the AT duration after valve surgery. The authors observed that a 2 week post-surgical course of AT was not associated with higher relapse rates if valve culture results were negative.\textsuperscript{52} More recently, a Spanish retrospective study carried out by Muñoz et al.\textsuperscript{53} found that short-course (median 15 days) post-operative AT has a similar effectiveness to longer-course (median 32 days) treatment for patients who underwent surgery for IE and had a high risk of complications (short course of AT before surgery, embolic events, extension of infection beyond the valve and positive valve culture). Moreover, on multivariate analysis, IE due to Streptococcus viridans or Streptococcus bovis was independently associated with short-course AT.\textsuperscript{53}

Conclusions
In the early 2000s the concept of appropriate AT was introduced according to the following limiting criteria that can be termed ‘microbiological’: lack of antibiotic treatment of a microbiologically confirmed infection, use of AT without activity against the identified pathogen, and administration of an antibiotic to which the microorganism responsible for the infection is resistant.\textsuperscript{54} The same concept of appropriateness was subsequently extended to include ‘pharmacological’ criteria such as inappropriate dosage, inappropriate intervals between doses, lack of antibiotic concentration monitoring (whenever required) and combining with antibiotics or other drugs that may interfere with each other. The same concept can now be further extended to ‘other’ criteria, such as inappropriate site of care (a good example is the hospitalization of patients with CAP according to standardized score systems), inappropriate timing (delay in starting empirical AT soon after the clinical diagnosis) and inappropriate AT duration [frequently too short for BJIs and frequently too long for respiratory tract infections (RTIs)]. The last factor can play a major role in clinical and microbiological outcomes, in the incidence of side effects, in cost containment and in the development of bacterial resistance.\textsuperscript{55,56} Concerning the onset of bacterial resistance, clinical studies and in vitro models have clearly demonstrated that longer-duration AT courses are associated with higher rates of resistance.\textsuperscript{57–59}

In conclusion, most published studies on AT duration would suggest that antimicrobials can be administered for a shorter period with advantages in terms of side effects, antibiotic resistance containment and costs. These recommendations are based on sufficient evidence for RTIs and UTIs, but carry little weight for all other diagnoses. Well-designed, prospective RCTs to compare a standard AT duration with a shorter one would be desirable and advisable for most common community- and hospital-acquired bacterial infections.

Transparency declarations
None to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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