Optimal duration of antibiotic treatment in Gram-negative infections

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Purpose of review
Whilst many guidelines recommend limiting the use of antibiotics because of the increase in antimicrobial resistance (AMR), this strategy becomes challenging when dealing with severe infections in critically ill patients. Moreover, some Gram-negative bacilli (GNB) can exhibit mechanisms of resistance that make the patient more vulnerable to recurrence of infections. We reviewed recent data on the optimal duration of antibiotic therapy in these patients.

Recent findings
Apart from having no additional clinical benefit at a certain point after initiation, antibiotics might have negative effects. Prolonged antibiotic exposure has been associated to development of AMR and represents a strong reason to avoid long courses of antibiotic therapy in GNB infections. Recent data suggest that also patients with severe infections, in whom source control is adequate, can be managed with short-course antibiotic therapy.

Summary
The optimal duration of antibiotic therapy depends on many factors, but overall, many infections in the critically ill can be treated with short-course antibiotic therapy (7 days or less). The integration of signs of resolution, biomarkers, clinical judgment, and microbiologic eradication might help to define this optimal duration in patients with life-threatening infections caused by GNB.

Keywords
antibiotic, antibiotic stewardship, antibiotic therapy, Gram-negatives, pneumonia, sepsis

INTRODUCTION

Whereas most intensivists are concerned with antibiotic decision-making early in the course of the disease, primarily focusing on getting the spectrum and timing of antibiotic therapy in patients with septic shock right, much of the exposure of patients to antibiotics is determined by the total duration of antibiotic therapy. Remarkably, this important aspect of therapy gets disproportionately less attention by most clinicians, leading to antibiotic therapy duration for established infections that continues beyond 1 and even 2 weeks in many patients.

Duration of antibiotic therapy in the critically ill is important for a number of reasons. Apart from having no additional clinical benefit at a certain point after initiation, antibiotics have negative effects, many of which are linked to the duration of exposure. For most antibiotics, toxicity is considered to be limited, and whereas this may be true for commonly used drugs such as penicillins, other drugs such as aminoglycosides, colistin, vancomycin, are less harmless and paradoxically often required in patients at a higher risk of side effects because of comorbidities or acute organ dysfunction. More importantly nowadays, the link between prolonged antibiotic exposure and development of antimicrobial resistance (AMR) is a more pressing reason to avoid long courses of antibiotic therapy; equally important is the impact of antibiotic therapy on the microbiome, although many of these effects are incompletely understood today.

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Curr Opin Infect Dis 2018, 31:606–611
DOI:10.1097/QCO.0000000000000491

KEY POINTS

- Duration of antibiotic therapy is a linked to antibiotic resistance development but rarely a priority in antibiotic decision-making.
- Antibiotic therapy is often continued beyond what is recommended in international guidelines for many common infections in the ICU.
- Optimal duration balances antimicrobial efficacy (i.e. bacterial killing) and side effects such as toxicity and development of resistance.
- For common infections in critically ill immunocompetent patients, antibiotic therapy can be limited to 7 days or less provided the spectrum and dosing is appropriate and the source of infection is controlled.

A HISTORICAL PERSPECTIVE ON DURATION OF ANTIBIOTIC THERAPY

The duration of antibiotic therapy has evolved over time [1]. Early after the discovery of antibiotics, duration of therapy was often limited to a few days, and most patients recovered without relapses [2]. In the 1950s and 1960s, it became standard practice to continue antibiotics until the patient was cured. Remarkably, also the fear of inducing resistance has led to recommendations of avoiding short courses and completing antibiotic therapies to avoid AMR development. Also, the fact that antibiotics are considered well tolerated has been an important contributor to the standard practice of continuing antibiotics until a few days after resolution of signs and symptoms. Given the current threat of AMR – clearly linked to antibiotic exposure – and recent insights on the impact of antibiotics on the microbiome, this needs to be reconsidered [3▪].

This tendency to continue antibiotics until after a patient had recovered was also influenced by commercial interests from pharmaceutical companies manufacturing antimicrobial drugs. Limiting antibiotics to a short course only would undoubtedly impact the profits made from this new class of drugs and jeopardize future development of new compounds.

Except for a number of selected infections, such as urinary tract infections where a short-course therapy has been the standard for some time, it became common to continue antibiotics for up to 2 or 3 weeks. Particularly, in situations where it was difficult to evaluate the clinical response of patients, such as in the ICU, or where additional risks and newly developed drugs put patients at increased risk of infections, such as in cancer or immunosuppressive chemotherapy, prolonged therapy became common. It is only in recent years that for severe infections in the ICU, shorter courses are being considered [4], although in many infections, antibiotic treatment is often continued beyond what is currently recommended in many guidelines, and what has been studied in randomized controlled trials.

WHAT ARE THE DETERMINANTS OF ANTIBIOTIC DURATION?

The first and obvious consideration is that antibiotics only will have effects in patients with infections. Although this may sound obvious, many patients in the ICU receive antibiotic therapy because of the fear of missing a life-threatening infection in a severely ill patient. Whereas this low threshold may be justified in a number of situations, for example, patients with shock and suspected infection, continuing antibiotics after confirmation that no infection was present should be avoided, even if this is limited to 3–5 days.

The goal of antibiotic therapy is to rapidly reduce the number of pathogenic bacteria at the site of infection and avoid spread of the infection or invasion of other organs or the bloodstream. The more effective the antibiotic therapy is in reaching this goal, the shorter the antibiotic therapy duration can be. The duration of antibiotic therapy can as such not be disconnected from other elements that determine antibiotic efficacy in the treatment of infection such as patient factors, treatment factors and pathogen factors. A high-dose antibiotic therapy in an immunocompetent patient may be discontinued earlier compared with an immunocompromised patient; a moderately dosed therapy may need to be continued for a longer time to have the same clinical effect as a high-dose treatment in the same patient with the same infection.

The immune status of the patient may be an important reason to continue antibiotic therapy for established infections; immunocompromised patients have reduced ability to clear residual infection. Other patient factors include the site of infection, severity of illness including extracorporeal therapies, and other determinants of pharmacokinetics. Treatment factors include antibiotic dose and method along with route of administration, as well as type of antibiotic as the mechanism of action may differ in terms of bacterial killing. Finally, also the pathogen characteristics such as inoculum size, virulence, susceptibility, biofilm formation capacity will also determine the effect of the antibiotic, and therefore required duration of therapy.

For patients with confirmed infections, duration of antibiotic therapy is governed by the interaction between the host, the pathogen and the antibiotic,

Table 1. Prerequisites for shortening antibiotic therapy in critically ill patients

Improvement in clinical signs and symptoms
Timely and adequate source control (where considered relevant)
Confirmed susceptibility of the pathogen to the antibiotic administered
Adequately and preferably pharmacokinetic/pharmacodynamic optimized antibiotic dosing

and a number of prerequisites need to be fulfilled for further shortening antibiotic therapy can be considered (Table 1).

AVAILABLE DATA IN BACTERAEMIA

Optimal antimicrobial treatment duration for nonfermentative Gram-negative bacilli (NF-GNB) bloodstream infection (BSI) remains unclear. At present, there are no specific guidelines that focus on NF-GNB. The Infection Disease Society of America (IDSA) guidelines for management of intravascular catheter-related BSI because of NF-GNB recommend 7–14 days of therapy in the absence of complications based on consensus opinion of experts. This broad recommendation acknowledges high recurrence rates and long-term mortality following GNB-BSI [5].

Nelson *et al.* [6] conducted a retrospective study that included 117 and 294 patients received short (7–10 days) and long (>10 days) courses of antimicrobial therapy for uncomplicated NF-GNB BSI, respectively [1]. After adjustment for the propensity to use a short course of therapy, risk of treatment failure was higher in patients receiving short compared with long courses of antimicrobial agents [hazard ratio 2.60, 95% confidence interval (CI) 1.20–5.53, $P = 0.02$].

GUIDELINES AND CURRENT RECOMMENDATIONS FOR HOSPITAL-ACQUIRED PNEUMONIA AND VENTILATOR-ASSOCIATED PNEUMONIA

The integration of biomarkers, clinical judgment, and microbiologic eradication might help to define a shorter duration for some ventilator-associated pneumonia (VAP) episodes because of NF-GNB [7]. The best-known evidence comes from classic articles, such as Chastre *et al.* [8] in a randomized controlled trial (RCT) that compared the use of 8 vs. 15 days found no differences in the main population but in the subgroup of VAP caused by NF-GNB, a higher percentage of patients developed documented recurrence in the 8-day group (41 versus 26%). More recently, another RCT conducted by Kollef *et al.* found that comparing 7 days of doripenem with 10 days of imipenem in patients with VAP caused by GNB [9]. The 7-day course arm was found to have nonsignificant higher rates of clinical failure and mortality compared with the 10-day course arm, but this contrast was probably because of differences between the antibiotics under study. Interestingly, the Clinical Pulmonary Infection Score (CPIS) was similar for the first 8 days of treatment and remained stable in the 1-week course with doripenem but in the 10-day arm continued to decrease in the 10-day imipenem course.

An important part in analysis interpretation is the pattern of resolution and a recent task force [10] has published, which would be the primary endpoints to be incorporated in clinical trials that compare treatment options for BSI in adults. Whilst, for *Staphylococcus aureus* BSI studies, a primary outcome of success at 90 days was defined by survival and no microbiologically confirmed failure, for GNB BSI studies, a primary outcome of survival at 90 days was supported by a secondary outcome of success at day 7. In addition, the taskforce proposed that for pilot studies of GNB BSI, a primary outcome of success at day 7 was defined by the following elements: survival, resolution of fever and symptoms related to BSI source, stable or improved Sequential Organ Failure Assessment (SOFA) Score and negative blood cultures.

As described elsewhere [11], patients with VAP caused by NF-GNB, including *Pseudomonas aeruginosa*, might exhibit a higher rate of recurrence with short-duration therapy compared with a long-duration therapy group. These results have led the American Thoracic Society (ATS) in 2005 to recommend short-duration therapy for VAP, with the exception of VAP with NF-GNB, including *P. aeruginosa* VAP [12]. New updated guidelines for VAP have been recently published. The International European Respiratory Society (ERS)/European Society of Intensive Care Medicine (ESICM)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Asociación Latinoamericana del Tórax (ALAT) guidelines [13▪] for the management of hospital-acquired pneumonia and VAP were published in 2017 whilst the American guidelines for Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia were released in 2016 by the IDSA/ATS [14]. Both guidelines concur and recommend a 7-day course of antimicrobial therapy rather than a longer duration. Whilst, the IDSA/ATS guideline made a strong recommendation even in NF-GNB, the European guideline made a less rigid approach in case of immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotizing pneumonia that are all situations where a higher

prevalence of NF-GNB is to be expected. Moreover, the European guidelines recommended extending treatment duration for more than a week in accordance with microbiology findings [such as extended or pan-drug-resistant pathogens, methicillin-resistant *S. aureus* (MRSA) or if concurrent bacteraemia].

ANTIBIOTIC DURATION IN INTRAABDOMINAL INFECTIONS

Intra-abdominal infections (IAI) remain among the most challenging infections to manage in the ICU, and antibiotic use in these patients is often extensive because of inadequate source control (often justified), or the need to cover a broad range of pathogens as these are often polymicrobial infections [15]. Recent data suggest that also patients with severe infections, in whom source control is adequate, can be managed with short-course antibiotic therapy.

Montravers *et al.* randomized ICU patients with IAI at day 8 to either a 15 day course or discontinuation [16▪▪]. They found no difference in mortality, and that antibiotic-free days were (not surprisingly) higher in the 8-day course (about 5 days). No difference in multidrug resistance (MDR) development was observed between the two groups, but when looking at patients infected with *P. aeruginosa*, the authors found a staggering 59% MDR emergence in the 15-day treatment arm, compared with 21% in the 8-day arm.

Furthermore, Hassinger *et al.* [17] studied the patients included in the STOP-IT trial that were considered at the highest risk of treatment failure and concluded that prolonged antimicrobial therapy does not prevent treatment failure. From this cohort, it was also evident that patients with IAI who were treated with percutaneous drainage do not require longer duration of therapy [18].

BIOMARKERS IN DECISION-MAKING

Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have shown a benefit to decrease antibiotic duration. A recent meta-analysis, that included 5136 patients, produced evidence that among all the PCT-based strategies (initiation, discontinuation, or combination of antibiotic initiation and discontinuation strategies) only using PCT for antibiotic discontinuation can reduce both antibiotic exposure and short-term mortality in a critical care setting [19▪▪]. It should be noted that the reduction in antibiotic exposure was small (1.6 days) and total duration in the PCT-guided groups still varied between 5 and 10 days, so similar duration of antibiotics were found when compared with standard treatment duration for many infections.

An interesting approach is to determine the bacterial cause in order to tailor antibiotic duration; Ankomah *et al.* [20] performed a subgroup analysis of data from a prospective cohort study of 505 patients admitted with pneumonia and found that admission levels of PCT were lowest in *P. aeruginosa* infections and highest in pneumococcal infections, though this difference did not reach statistical significance.

Many published studies have found contradictory results and the vast majority of them have only analysed the performance of biomarkers without a clinical component. On the contrary, an interesting concept has been the combination of a clinical score – CPIS – and a spot serum PCT-guided protocol in order to shorten the duration of antibiotic treatment in patients with VAP, mainly caused by NF-GNB [21]. Whilst the results are extracted from a very small population (24 patients in the PCT group and 26 patients in the conventional group), they, interestingly found that the PCT group had a greater number of antibiotic-free days alive during the 28 days after VAP onset than the conventional group and 12.5% of the PCT and 26.9% of the conventional group, respectively, developed a recurrent VAP episode compatible with superinfections.

FUTURE DIRECTIONS: NEW STRATEGIES TO OPTIMIZE ANTIBIOTIC DURATION

Several projects are currently in the pipeline that will shed light for antibiotic duration in GNB infections such as PIRATE project (NCT03101072): a multicentre, noninferiority, informatics-based point-of-care RCT will randomly assign adult hospitalized patients receiving microbiologically efficacious antibiotic(s) for GNB to 14 days of antibiotic therapy, 7 days of therapy or an individualized duration determined by clinical response and 75% reduction in peak CRP values. The primary outcome will be the incidence of clinical failure at day 30; secondary outcomes will include clinical failure, all-cause mortality and incidence of *Clostridium difficile* infection in the 90-day study period [22].

Pseudomonas aeruginosa might be one of the most debated pathogens for antibiotic treatment duration. Treatment of persistent infections is additionally hampered by adaptive resistance, because of the growth state of this pathogen in the patient including the microorganism's ability to grow as a biofilm [23]. One of the several unique characteristics and pathogenic properties of this pathogen are due by an intense neutrophilic response resulting in significant damage to host tissues and often exhibit resistance to antibiotics leading to mortality. Siempos *et al.* [24] reported a VAP recurrence over 25% from pooled data when *P. aeruginosa* was the causative pathogen. Acute

respiratory distress syndrome (ARDS) and shock on the day of diagnosis of the first VAP episode was found to be associated with VAP recurrence. Planquette *et al.*, more recently, analyzing 314 patients with *P. aeruginosa*-VAP found that treatment failure was frequent (35.7%) and associated with a high rate of recurrence (20.1%) [25]. Also from France, the impact of the duration of antibiotics on clinical events in patients with *P. aeruginosa* VAP (iDIAPASON) trial (NCT02634411) has been recently started [26]. This will be a randomized, open-label noninferiority trial, to be conducted in ICUs, comparing the impact of duration of antibiotic therapy on mortality and recurrence of *P. aeruginosa* -VAP (8 days or 15 days). The primary outcome will be a composite endpoint combining 90-day mortality and *P. aeruginosa*-VAP recurrence rate during hospitalization in the ICU.

CONCLUSION

The general trend observed in recent years is definitely that short-course antibiotic therapy can be safely used in hospitalized patients with common infections, including pneumonia, urinary tract infection and IAI, as evidenced by a recent systematic review on this topic in hospitalized patients [27▪▪]. Short-course antibiotic therapy was found to achieve clinical and microbiologic resolution without adverse effects on mortality or recurrence and showed a trend towards a lower emergence of MDR (−9.0%, 95 CI −19.1 to 1.1%). Many of these studies included patients in the ICU, and it is probably time to start thinking more seriously about shortening antibiotic therapy in patients with confirmed infections in the ICU [4].

Undeniably, it is hard to determine what the 'optimal duration' of antibiotic therapy exactly is for an individual patient. Conceptually this would be the duration of antibiotic exposure required to have the maximal clinical effect with absent or minimal toxicity or side effects. From this it follows that this can probably not be standardized, as this effect will be determined by more than just the antibiotic and the (standard) dose the patient receives, without considering patient and pathogen characteristics. So long enough to treat the infection adequately, and short enough to avoid toxicity and side effects. The latter depends on how important treatment duration is in the occurrence of side effects. Duration of antibiotic exposure has been linked to increased prevalence of antibiotic resistance, but in terms of the effect on the microbiome, a (very) short course may already be enough [28]. Current recommended duration of antibiotic therapy for different indications is summarized in Table 2.

Table 2. Proposed duration of antibiotic therapy for different types of infection with Gram-negative pathogens in critically ill patients[a]

Type of infection	Proposed duration (days)
Ventilator-associated pneumonia	7–10
Hospital-acquired pneumonia	7–10
Community-acquired pneumonia	5–7
Complicated intraabdominal infection	5–7
Bacteremia	10–14

[a]Patients who are considered immunocompetent and not deteriorating, and in whom source control was adequate. Duration refers to the total duration of adequate antibiotic therapy (which could include more than one antibiotic in this period).

It would be naive to think that optimal duration would be a set number of days for a particular infection, as is now advised for many infections in critically ill patients. It is even more striking that we tend to think in weeks or multitudes thereof, and obviously there is no biological rationale to explain why 7 days would be the threshold for effectiveness of antibiotic therapy. This also exemplifies how random antibiotic duration, also in randomized controlled trials, is determined.

When determining the duration of therapy, probably, other factors need to be considered. In this context, we would currently typically focus on difficult-to-treat patients or pathogens, that are often not included in the randomized controlled trials on duration of antibiotic therapy; examples include immunocompromised patients, critically ill patients, specific infection foci, *P. aeruginosa* infections, among others and probably with good reasons. The challenge is to identify patient and/or pathogen characteristics that can be used to safely stop antibiotics well within the 7-day standard duration. These factors could include source control or the lack thereof, inoculum size, susceptibility, antibiotic dose used and probably many more.

Acknowledgements

None.

Financial support and sponsorship

J.J.D.W. is Senior Clinical Investigator at the Research Foundation – Flanders (Belgium) (FWO).

Conflicts of interest

J.J.D.W. has consulted for AtoxBio, MSD, Pfizer, Bayer and Accelerate (honorarium paid to institution). I.M.-L. has consulted for MSD, Bayer, and Accelerate (honorarium paid to institution) and acts a principal investigator for Polyphor.

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