Duration of antibiotic therapy in Gram-negative infections: is shorter better?

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Antimicrobial resistance (AMR) is a major global threat that has recently captured the attention of physicians all over the world[1]. Limiting antibiotic exposure is of utmost importance in the fight against AMR as it has been well established that prolonging duration of antibiotics increases the incidence of multidrug resistant pathogens[2,3]. Moreover, using unnecessarily prolonged antibiotic courses exposes the patient to the risks of antibiotic-related adverse effects, including *Clostridiodes difficile* infection, and increases hospital length of stay (LOS) and health costs. However, shortening antibiotic therapy in certain settings may be associated with a higher risk of treatment failure and relapse.

Hence, determining the right duration for antibiotic therapy (DOT) remains a challenging question notably for Gram-negative bacilli (GNB) and multidrug-resistant Gram-negative bacteria (MDR-GNB) that account for a vast proportion of hospital-acquired or ventilation-associated pneumonias (HAP/VAP), intra-abdominal infections (IAI), bloodstream infections (BSI) and urinary tract infections (UTI). These pathogens are of particular concern as they have been associated with high morbidity and mortality and are often seen in patients with comorbidities or

Figure. Factors contributing to the decision of gram-negative duration of therapy

in immunocompromised hosts (ICH)[4]. With the recent emergence of MDR-GNB, many novel antibiotics including cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, imipinem-cilastin-relebactam and meropenem-varbobactam have been a welcome addition to the armamentarium in the treatment of various hospital acquired infections[5]. However, the recently published trials did not draw firm recommendations about the optimal DOT. Moreover, published studies addressing the DOT for GNB in various infection sites mostly included Enterobacterales, with underrepresentation of non-fermenting organisms and MDR-GNB.

Starting with HAP/VAP, while the duration of 7 days of antibiotic therapy has been established and recommended by the Infectious Diseases Society of America / American Thoracic Society (IDSA / ATS) and the European Societies,

ongoing studies such as the DATE trial are investigating shortening the regimen treatment of VAP to 4 days[6]. However, one should be careful generalising the evidence to non-fermenting (NF) GNB. First, organisms like *Acinetobacter* spp., and *Stenotrophomonas* spp. are not commonly represented in the trials. Second, the optimal DOT of *P. aeruginosa* pneumonia is yet uncertain and prolonged duration might be needed particularly in patients with secondary bacteremia, MDR strains and slow response to therapy. The iDIAPASON study is a randomised control trial (RCT) published this year and showed no difference in mortality between 8 and 15-day antibiotic for *P. aeruginosa* VAP. However, patients who received a shorter course were twice as likely to have *P. aeruginosa* VAP recurrence[7].

As for IAI, it is well established that the cornerstone of effective treatment is adequate source control (ASC). However, shortening the DOT should be done carefully and with close patient monitoring, as studies have shown conflicting results and included different patient populations with variable outcomes; while some showed no significant difference in intensive care unit (ICU) stay, LOS and mortality rate between patients who received short (< 7 days) and long (> 7 days) antibiotics after ASC[8], the recent CABI RCT showed that 23.5% of patients who received less than 10 days of antibiotics had a relapse of IAI[9]. A current multicenter study being conducted in the UK, the EXTEND trial, is aiming at comparing 28 days of antibiotics to the standard duration in patients in intensive care units (ICU) with IAI with up to 180 days of follow-up[10]. Thus, more robust data is needed to make standardised clinical guidance on DOT for IAI.

When it comes to BSI including MDR-GNB, there is no need to prolong DOT beyond 7 days based on the most recent guidance[11]. Recent studies including patients with extended spectrum beta lactamase (ESBL) producing *E. coli* showed no difference between short and long duration of treatment of uncomplicated GN-BSI in mortality and recurrence of bacteremia[12,13]. This also applies to catheter-
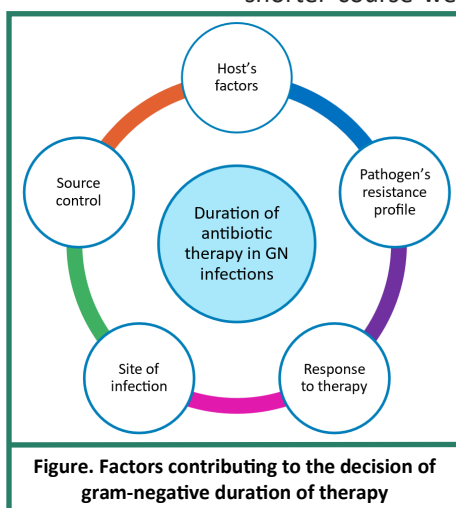
related GNB BSI where DOT can be shortened to 7 days if the central line is removed[14]. As for patients with febrile neutropenia and BSI, uncertainty remains about the optimal DOT as one should take into consideration the patient's degree of immunosuppression and severity of infection. In a recently published study, there was a successful attempt in decreasing antibiotic treatment to 7 days without increasing the risk of infection complications in patients with febrile neutropenia after implementing the 4th European Conference on Infections in Leukemia (ECIL-4) recommendations[15]. Nonetheless, it is difficult to generalise the current findings to some pathogens such as *P. aeruginosa*. Studies showing that a short DOT is as effective as long DOT in the treatment of *P. aeruginosa* BSI excluded patients with persistent bacteremia and those with metastatic infectious foci[16]. In fact, *P. aeruginosa* BSI tends to occur in immunocompromised or ICU patients or those with co-morbidities and treatment duration should vary according to the primary source of bacteremia, host factors and susceptibility of the isolate. As for BSI caused by other MDR-GNB, there are no published studies to guide on the optimal DOT in various infection sites.

Finally, although the guidelines for the DOT in pyelonephritis still recommend a variable duration according to the choice of drug and the presence of an abscess, there is a tendency towards shortening the treatment in patients with UTI and secondary bacteremia to 7 days including those caused ESBL-producing Enterobacterales[17,18]. This strategy might also apply to afebrile UTI in men when treated with trimethoprim / sulfamethoxazole or ciprofloxacin as both drugs are highly excreted in the urine[19]. However, one should be careful when treating a complicated acute prostatitis as studies have shown that a shorter course was associated with earlier relapse and therefore a 14-day course is still recommended[20].

It is also important to highlight that the evidence on the optimal DOT for GNB infections in ICH is scarce, and this population is of particular interest as their inadequate innate and adaptive immune systems may alter the infection course and its outcome. Prolonging antibiotic duration might be needed to achieve an effective cure; however, it is a double-edged sword as it might predispose the ICH to future colonisation and infections with resistant pathogens[21]. Meanwhile, a patient centered approach should be the cornerstone for deciding on DOT for GNB infections in ICH.

While recent studies have supported shorter antibiotic regimens in some scenarios, further studies are still needed to draw definitive conclusions in various sites of infection and when dealing with different GN pathogens and host factors. The new paradigm is to treat infections only for as long as it is necessary taking into consideration the patient's host factors, the pathogen's resistance profile, the rapidity of response to therapy, the site of infection and adequacy of source control.

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