Journal of Critical Care (2013) **28**, 341–346

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Journal of Critical Care

Dose modulation: A new concept of antibiotic therapy in the critically ill patient?☆,☆☆,★

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Keywords:
Antibiotics;
Pharmacokinetics;
Dose;
Modulation;
Intensive care unit

Abstract Considerable evidence has shown that adequate antibiotic therapy is of utmost importance in the critically ill septic patient. However, antibiotic concentration may be insufficient early in infection course. We propose the concept of dose modulation, meaning front-line variability of antibiotic dose, according to patient and microorganism characteristics, followed by its reduction after clinical response and patient recovery. Therefore, dose modulation means concentrating the largest weight of antibiotics at the front-end, when the microbial load is higher and the pharmacokinetic changes poses the highest risk of underdosing and nibbling off antibiotic dose, when the sepsis syndrome is improving, guided by pharmacokinetic and pharmacodynamic data.

1. Adequate antibiotic therapy: drug but also dose selection

The accumulation of evidence that both front-line antibiotic inappropriateness and late appropriateness had significant impact on the outcome of infections in severe sepsis and septic shock patients led to the concept of antibiotic de-escalation, meaning that a large-spectrum antibiotic regimen should immediately be started front-line to assure coverage of the pathogen and clinical success. Combination antibiotic therapy has also been proposed in order to enlarge antibacterial spectrum and it may improve patient outcomes, especially in septic shock patients [1]. In parallel, antibiotic streamlining should be done as soon as there is evidence of clinical response and microbiological results are available, to reduce antibiotic pressure and avoid the emergence of antimicrobial resistance [2]. This has been shown to be safe in critically ill patients [3].

Several authors also pointed out that not only should antibiotic therapy be appropriate and early but also antibiotic dose should be maximized to ensure adequate bactericidal concentration as soon as possible [4,5].

However, the concept of dose maximization is ill-defined and, in our opinion, did not translate into the clinical arena.

☆ Funding: None.
☆☆ Competing interests: None declared.
★ Authors' Contributions: JG-P and J-AP both search literature, developed the concept, analyzed, data and wrote the manuscript.
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http://dx.doi.org/10.1016/j.jcrc.2012.11.018

In fact, in daily unit rounds, antibiotic selection is very often discussed, but antibiotic dose selection is rarely the matter of debate. Antibiotics are usually prescribed in a traditional pattern, using the usual dose: in the empirical setting, taking only into account the existence or not of renal or liver dysfunction, and as directed therapy, only considering the susceptibility pattern of the microorganism. Moreover, dose is usually maintained throughout treatment course, although significant pharmacokinetics (PK) changes occur from the resuscitation to the recovery phase of the severe sepsis/septic shock patient.

Dose is a very important concept and we think that dose decision is also key to success, as antibiotic efficacy is mainly dependent on bacteria exposure to the antibiotic at the infection site.

Table 1 Proposed doses of antibiotics in the early and late phase of severe sepsis

Antibiotic	Early dose	Adjusted dose
Piperacillin/tazobactam	16/2g q6h (CI)	4/0.5g q8h
Cefotaxime	2g q6h (CI)	1g q8h
Ceftazidime	2g q8h (CI)	1g q8h
Cefepime	2g q8h (CI)	2g q12h
Imipenem	1g q8h (over 3h)	500mg q6h
Meropenem	1g q6h (over 3h)	1g q8h
Gentamycin	9mg/kg q24h	5mg/kg q24h
Tobramycin	9mg/kg q24h	5mg/kg q24h
Ciprofloxacin	600mg q12h	400mg q12h
Levofloxacin	500mg q8h	750mg q24h

Adapted from Ref. [4]. These doses are only intended for patients without renal failure.
CI, continuous infusion.

2. Antibiotic underdosing is frequent in the critically ill patient

Correct dosing implies achieving adequate pharmacodynamic (PD) targets as soon as possible, according to the antibiotic killing characteristics. This is mainly dependent on antibiotic dosing and PK. Dosing in critically ill patients is especially challenging due to the increased volume of distribution (Vd), secondary to volume resuscitation, capillary leak and decreased concentration of serum proteins. Also the increased renal and hepatic clearance (Cl) sometimes noted in patients without organ failure may further decrease drug concentration and half-life [5,6].

These PK changes are quite common in the critically ill population, namely the increase in the Vd [7,8], even in the presence of organ failure [9,10]. In addition, increase in the creatinine (Cr) Cl has been shown to be present in a large number of patients and it seems to be impossible to extrapolate it from commonly used formulas [11]. This increase in Cr Cl is more common in young post-trauma patients, although age is not by itself predictive of a higher Cr Cl [12].

Several commonly used therapeutic procedures in critically ill patients are also associated with PK changes and fluid shifts, namely surgical interventions, invasive ventilation, transfusions, the performance of fluid challenges, renal replacement therapy and vasopressors. Therefore antibiotic concentration variability is to be expected in a large number of critically ill patients [5]. In these populations, therapeutic drug monitoring is especially advisable and dose adjustment to the specific patient should always be considered [4].

In critically ill septic patients conventional dosing has been shown to provide inadequate concentrations of β-lactams [13], vancomycin [14], and aminoglycosides [9], implying the need for higher than traditionally recommended doses even in patients with organ failure (Table 1). This is especially important in the beginning of antibiotic therapy, as the drug concentration after the initial loading dose is only dependent on the drug Vd and the dose itself [9,10]. Therefore, failure to acknowledge these PK changes in the critically ill population may lead to sub-therapeutic antibiotic concentrations [10]. In fact this increase in Vd has been shown to be independent of age, renal failure or sepsis severity [9,13].

The dose and schedule of maintenance doses should be decided on the basis of the intended target concentrations and Cl [10] and should also be increased in patients with a high Cr Cl. It should be noted that commonly used formulas may easily fail to unveil an increased Cr Cl, and therefore, direct measurement is recommended [11].

In a critically ill population (N = 52) treated with β-lactam antibiotics, the authors noted that 42% had trough concentration below the bacteria minimal inhibitory concentration (MIC) despite their intended therapeutic target of time above minimal inhibitory concentration (T > MIC) of 100%. Besides, 72% of patients had even lower T > MIC when their Cr Cl was above 130 mL/min [15]. The same was noted in a larger population, mostly receiving β-lactam antibiotics by continuous infusion, in which roughly half of the patients had a steady-state concentration below the intended target of four times the MIC [16].

Dose adaptation may be useful not only due to patient characteristics but also due to microorganism idiosyncrasies. High antibiotic doses may be necessary for the treatment of infections associated with a high bacterial load or inoculum, namely, some of those presenting as severe septic shock (eg, peritonitis). In fact, at least in vitro, some sensitive bacteria show an inoculum effect, meaning a diminished susceptibility or even resistance to an antibiotic as the size of the inoculum increases [17,18]. This inoculum effect, if present in vivo, may lead to therapeutic failure, reinforcing the need for a higher antibiotic dosage in the critically ill. There is some evidence that both C-reactive protein [19] and procalcitonin [20] correlate with the bacterial load and may be used to identify those patients with high bacterial inoculum.

Ideally, individualized dosing strategies should account for the altered PK and pathogen susceptibility in each patient.