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

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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.

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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.
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.

2. Antibiotic underdosing is frequent in the
critically ill patient

Correct dosing implies achieving adequate pharmacody-
namic (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, capil-
ary 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 chal-
enges, renal replacement therapy and vasopressors. There-
fore antibiotic concentration variability is to be expected in
a large number of critically ill patients [5]. In these popula-
tions, 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
centration 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 concen-
tration 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
every 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.

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Early dose</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>16/2 g q6h (Cl)</td>
<td>4/0.5 g q8h</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g q6h (Cl)</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g q8h (Cl)</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>2 g q8h (Cl)</td>
<td>2 g q12h</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1 g q8h (over 3 h)</td>
<td>500mg q6h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q6h (over 3 h)</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>9mg/kg q24h</td>
<td>5mg/kg q24h</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>9mg/kg q24h</td>
<td>5mg/kg q24h</td>
</tr>
<tr>
<td>Ciprofloxacine</td>
<td>600mg q12h</td>
<td>400mg q12h</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>500mg q8h</td>
<td>750mg q24h</td>
</tr>
</tbody>
</table>

Adapted from Ref. [4]. These doses are only intended for patients
without renal failure. CI, continuous infusion.
However, individual PK variability poses great difficulties to the achievement of that goal. Therapeutic drug monitoring [16] and population PK [8,21] has been proposed to accomplish it. Nevertheless, the clinical efficacy of these strategies to achieve adequate concentrations and decrease infection mortality has never been properly evaluated.

Furthermore, in critically ill patients, the classic antibiotic PD targets can prove to be sub-optimal. McKinnon et al. [22], evaluating ceftazidime and cefepime PD, showed that a larger T > MIC, as high as 100%, was necessary to achieve clinical cure and bacteriologic eradication. Similar findings were noted in a population with febrile neutropenia [23]: the T > MIC of responders was 83%, whereas non-responders had a T > MIC of only 59%. In addition, optimal antibacterial activity of concentration dependant antibiotics was only achieved when its maximum concentration was very high, 8 to 12 times greater than MIC [24,25], and these are seldom easily achieved, especially when using conventional dosing [7]. Continuous infusion of β-lactam antibiotics has been proposed to help achieving those therapeutic targets. Despite the PK benefits with this strategy, studies have repeatedly failed to show a mortality benefit [26].

High antibiotic concentrations and adequate therapeutic targets may be especially important early in infection course, especially in patients with septic shock, with increased Vd and renal hyperfiltration (Fig. 1). Furthermore, these high antibiotic doses may also be essential to overcome the impact of high bacteria MICs.

In an interventional study, pharmacodynamic modeling was used to empirically treat hospital acquired pneumonia in critically ill patients with a high risk of antibiotic resistant Pseudomonas aeruginosa [27]. With a 3-hour infusion regimen of either cefepime or meropenem at very high doses (2 g every 8 hours) mortality decreased from 21.6% to 8.5% (P = .029) compared with a historical control. Antibiotic and/or dose de-escalation was possible in 66.2%, according to microbiological results.

3. Sustained high antibiotic doses may be deleterious

When the critically ill septic patient responds to the antibiotic therapy, the described hemodynamic changes tend to progressively normalize. Accordingly, the PK changes, especially the increased Vd, will probably also slowly return to normal and the antibiotic dose needed to maintain adequate serum levels will become lower. This has already been shown for aminoglycosides [28]. Besides, antibiotic accumulation can easily occur in the patient who develops organ failure [29], and failure to reduce dosage can be associated with accumulation and toxicity.

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**Fig. 1** Proposed approach to antibiotic dosing. Initial loading dose should account for the large volume of distribution. A high antibiotic dose should be maintained during the first 48 to 72 hours if there is any suspicion of increased clearance and no organ failure. Finally, dose adjustment should be performed whenever bacteria with a low MIC are isolated, creatinine clearance normalizes, or there is sepsis resolution.
Therapeutic drug monitoring has been shown to facilitate the achievement of adequate target antibiotic concentration [30] and also to avoid overexposure. Unfortunately, in clinical practice, this is only largely available for vancomycin and aminoglycosides, although $\beta$-lactam concentration monitoring data is increasing and seems to be also useful [16]. Nevertheless the ideal therapeutic targets for most antibiotics are largely unknown, as we have already discussed.

There is evidence from $\beta$-lactam antibiotics PK studies, that both underdosing and toxic accumulation are common in the clinical setting [31]. Aubert et al studied 92 patients receiving cefazidime: low concentrations were found in 36.9% whilst potentially toxic levels were unveiled in 27.2% [32]. In another cohort of 21 patients receiving cefepime [33], large variability of trough concentration was noted. Furthermore, 2 patients presented very high toxic levels. Despite the fact that both had toxic neurologic manifestations, these were only attributed to an antibiotic adverse reaction after the serum levels were reported to the physicians in charge. In fact, antibiotic accumulation and toxicity are often underdiagnosed [34], especially when they are associated with antibiotics not routinely monitored in clinical practice. Similarly, in a cohort of febrile neutropenia patients without renal failure (Cr Cl higher than 50 mL/min), high cefepime plasma concentrations and neurological toxicity was noted in 6 of 30 patients, a median of 4 days after starting therapy [35]. High vancomycin trough serum concentration may also be associated with nephrotoxicity and aggressive dosing is nowadays recommended [36] for difficult-to-treat infections, although there are scarce data to support this approach.

Moreover, antibiotics may interfere with mitochondria function or recovery in patients with severe sepsis or septic shock [37,38]. This is even more common in patients experiencing declining renal or hepatic function [37].

In the responding patient, due to antibiotic efficacy and to source control, bacterial load necessarily decreases. Furthermore, when the causing agent with a low MIC is identified, the intended concentration targets may be reduced, as these concentration targets are usually defined to the “worst case scenario,” to achieve coverage of the least sensitive bacteria, usually $P$ aeruginosa [13,27,31]. Therefore, maintenance of the initial or even of the recommended, conventional dosing is often unnecessary (Fig. 1).

In fact, a target concentration of 20 mg/L of gentamicin was found adequate to treat critically ill patients. This concentration was based on the $Pseudomonas$ spp MIC of 2 mg/L and an intended peak/MIC ratio of 10 [39]. Consequently if a lower MIC was found less antibiotic would also provide adequate Peak/MIC ratio. The same was true for vancomycin. Dose efficacy was linked to an antibiotic area under the concentration time curve/MIC of at least 400 [40]. Consequently dose could be safely reduced for the treatment of more sensitive bacteria, with lower MIC. In addition, lower doses of $\beta$-lactams can easily provide the adequate T > MIC in the presence of lower MIC [41].

4. Dose modulation: a broader and innovative view of de-escalation

Antibiotic de-escalation, that is, the adequation of the antibiotic spectrum to the isolated microorganisms, has been shown to be safe and largely feasible in patients with a good response to the initial antibiotic therapy. The same helps to decrease antibiotic exposure and is an accepted policy to reduce the induction and emergence of resistance [42].

Accordingly dose modulation is a strategy that combines the front-line use of a variable, larger than conventional, antibiotic dose, selected on the basis of PK and infection characteristics, followed, a few days later, by dose reduction to diminish unnecessary antibiotic exposure. In fact, in patients responding to therapy and recovering from the infection, there is commonly hemodynamic improvement [43], with weaning of vasopressors, negative fluid balance, and normalization of cardiac, renal, and hepatic function, which will also lead to progressive antibiotic PK normalization. Therefore, after hemodynamic recovery, if the patient is stable and there is evidence of clinical response, it is probably safe to reduce the antibiotic dose to reduce the risk of antibiotic toxicity.

Besides, when a low MIC is found, lower than conventional antibiotic concentrations can easily attain the PD targets needed to treat the infection and, therefore, dose modulation is also desirable. Consequently, microbiological information including MIC is most useful in the intensive care unit setting.

Dose reduction is actually usually performed in clinical practice, in the form of oral switch, often used to discharge infected patients who can complete their treatment in ambulatory and this has been shown to be safe.

5. Selection of resistance

A criticism to this strategy may be its possible association with the risk of promoting resistance when the lower antibiotic doses are used. In fact, in a study addressing $P$ aeruginosa ability to acquire resistance in vivo, the authors were able to show, in patients who had a second infection caused by this microorganism, that the late isolates almost always had substantially higher MICs to the previously used antibiotics [44].

Selection of resistance to antibiotics appears to be strongly associated with suboptimal antimicrobial exposure, that may be prevented by the achievement of adequate PK/ PD parameters [45]. On the contrary, resistance induction seems to be related to high bacteria inoculum and suboptimal antibiotic exposure. In an in vitro study a very high fluoroquinolone trough concentration was necessary to avoid the derepression of resistant clones, meaning the proliferation of bacterial mutants with the highest MIC, when a large inoculum was used [46]. However, resistance only became
significant after at least three days of this sub-optimal antibiotic exposure [47].

Similarly a sub-optimum meropenem exposure to *P. aeruginosa* was associated with a mutant subpopulation derepression, even with a T > MIC of 100%. Inhibition could only be achieved, at least in vitro, by a ratio of meropenem trough concentration to MIC of 6.2 (or adding tobramycin). Again, this was only noted after 3 days of antibiotic therapy [48].

There is some evidence that duration of antibiotic therapy may safely be reduced in VAP [49,50] as well as in blood stream infections [51] to no longer than 8 days. We speculate that concentrating the largest weight of antibiotics at the front-end, to ensure more rapid bacterial killing may help to further decrease the duration of antibiotic therapy, although studies in critically ill patients addressing this issue are needed.

In stable patients with a satisfactory immune system, after an adequate source control and clinical improvement, antibiotic dose should probably be reduced, guided by therapeutic drug monitoring, the bacteria MIC and the evolution of patient PK. This strategy is due to occur mainly during the last few days of therapy and consequently no deleterious impact in terms of emergence of resistance should be noted. Accordingly, reducing the length of exposure and modulating the dose of antibiotics seems to be safe and will possibly improve efficacy.

We acknowledge the need to appropriately test this strategy. We think that both animal models and clinical trials may be designed to test the use of higher initial antibiotic doses and modulation of antibiotic dosing after clinical stabilization (namely, weaning of vasoressors and spontaneous negative fluid balance), all according to bacteria MIC and PK parameters.

### 6. Conclusion

In conclusion, we propose the concept of dose-modulation, that globally means concentrating the largest weight of antibiotics at the front-end, when the microbial load is necessarily higher, the infection is not under control and patient Vd and Cl are above normal and nibbling off antibiotic dose after the first days, when there are signs of clinical response and the sepsis syndrome is improving. In the critically ill septic patient the concept of front-line antibiotic dose variability, according not only to patient characteristics as Vd, Cr Cl, and albumin concentration but also microorganism idiosyncrasies, namely its MIC and presumed bacterial load, should be used. Selection of the antibiotic is not enough; one has to decide its dose. Therefore dose modulation strategy may, on one hand, avoid initial front-line antibiotic underdosing, potentially improving antibiotic effectiveness and decreasing the induction of multi-drug-resistant microorganisms and, on the other hand, promote biosafety, decreasing antibiotic exposure time and avoiding overexposure and toxicity.

### References


**Glossary**

**AUC:** Area under the concentration time curve  
**CI:** Drug clearance  
**Cr Cl:** Creatinine clearance  
**MIC:** Minimum inhibitory concentration  
**PD:** Pharmacodynamics  
**PK:** Pharmacokinetics  
**T > MIC:** Antibiotic concentration time over bacteria MIC  
**Vp:** Ventilator-associated pneumonia  
**Vd:** Volume of distribution