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EDITORIAL

Should the Clinical Pharmacologist Play a Role in the Multidisciplinary Team Managing Severe Necrotizing Soft-Tissue Infections?

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Necrotizing soft-tissue infections (NSTIs) are uncommon severe bacterial infections characterized by a high morbidity and mortality rate, frequently requiring intensive care unit (ICU) admission because of the occurrence of septic shock and multiorgan failure [1]. Recently, several viewpoints focused on the challenges concerning the treatment of critically ill patients affected by severe NSTIs, specifically highlighting the key role of multidisciplinary assessment and management [2–4]. It has been suggested that the implementation of a synchronized multidisciplinary team, coordinated by the intensivist and including the surgeon, the infectious disease specialist, the clinical microbiologist, and the dermatologist, may become a cornerstone in the management of critical patients with NSTIs. In this regard, a multidisciplinary taskforce coupled with implementation of a specific bundle has proven to improve the outcome of severe NSTIs, leading to faster improvement of end-organ damage and a decrease in the mortality rate [5, 6].

Should the clinical pharmacologist play a role in this multidisciplinary team? In the last update of the Surviving Sepsis Campaign [7], it is recommended that the dosing schedule of antimicrobials should be optimized according to accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties in patients with sepsis or septic shock. Consistently, given the remarkable clinical complexity of critically ill patients affected by severe NSTIs, the clinical pharmacologist could provide aid in selecting the best-tailored dosing schedule of administered antimicrobials, by implementing PK/PD concepts and an adaptive therapeutic drug monitoring (TDM) approach.

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Why are PK/PD concepts and an adaptive TDM strategy so fundamental in this setting? We may identify four major determinants (Fig. 1):

1. Extensive fluid resuscitation, capillary leakage, hypoalbuminemia, end-organ damage, and the requirement for extracorporeal supports as continuous or intermittent renal replacement therapy (especially when applying a high ultra-filtration flow rate) may lead to PK alterations in patients with sepsis, causing an increased volume of distribution and deranged clearance [8, 9].
2. Serum concentrations may not always adequately predict tissue exposure in patients with NSTIs, with the ratio between the tissue area under the concentration–time curve (AUC) and plasma AUC generally lower for the hydrophilic antimicrobials (e.g., beta-lactams, daptomycin) than for the lipophilic antimicrobials (e.g., linezolid) [10]. Furthermore, tissue hypoperfusion due to the necrotic process may impair antimicrobial penetration into the infection site, especially for hydrophilic agents, leading to tissue underexposure [11].
3. Specific PK features of critical patients with NSTI, namely large fluid losses from open wounds, recurrent debridements (every 12–24 h in the first days after ICU admission), and negative pressure wound therapy, may lead to subtherapeutic antimicrobial concentrations owing to "augmented extracorporeal clearance", a specific alteration commonly seen in challenging pharmacological scenarios (e.g., major burn victims) affecting mainly hydrophilic antimicrobials [5, 11, 12]. Large fluid resuscitation (up to 5–10 L/day of crystalloids and colloids in the first 48 hours), second only to that required by major burn victims, is usually implemented in critical care patients affected by severe NSTIs, as a result of significant fluid losses from open wounds and surgical debridements. Additionally, negative pressure wound therapy contributes to fluid losses and increased elimination of hydrophilic antimicrobials [13]. Con-

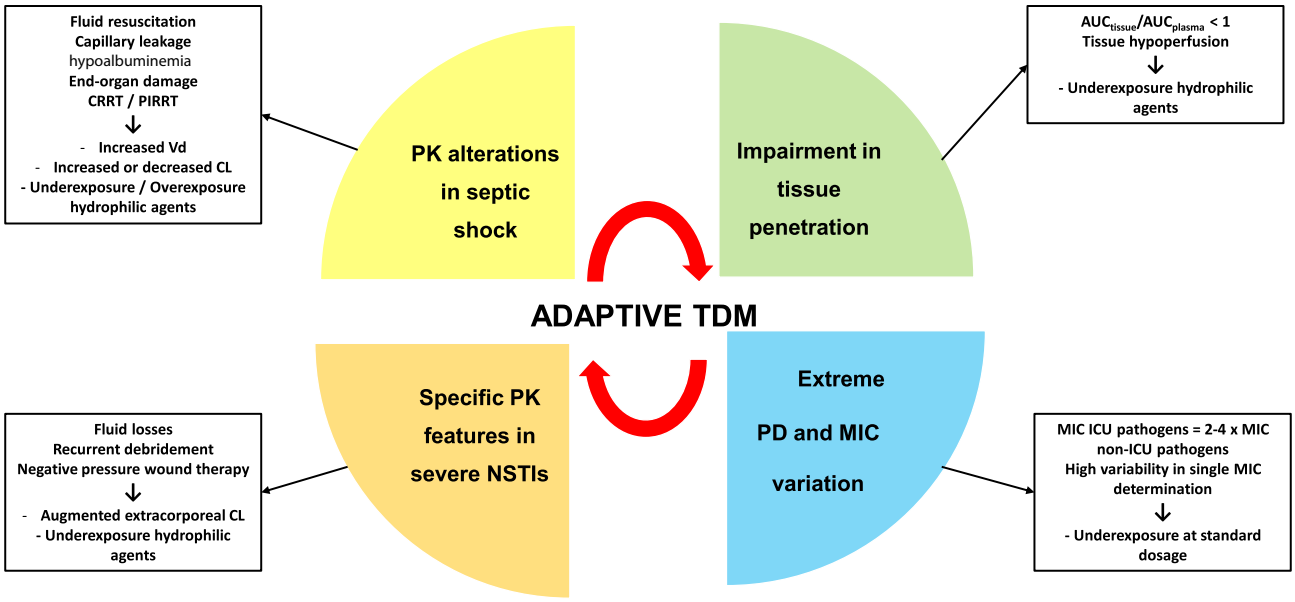

Fig. 1 Main determinants involved in the requirement for adaptive therapeutic drug monitoring (TDM) in critical patients with necrotizing soft-tissue infections (NSTIs). *AUC* area under the concentration–time curve, *CL* clearance, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit, *MIC* minimum inhibitory concentration, *PD* pharmacodynamic, *PIRRT* prolonged intermittent renal replacement therapy, *PK* pharmacokinetic, *Vd* volume of distribution

sequently, these specific PK features of severe NSTIs strongly affect both the volume of distribution and clearance of hydrophilic antibiotics, calling for *ab initio* optimization of antibiotic exposure through implementation of altered dosing strategies [10].

4. The borderline susceptibility of the ICU bacterial clinical isolates, which may commonly exhibit minimum inhibitory concentrations (MICs) two- to four-fold higher than those observed among isolates coming from other hospital wards, may affect the effectiveness of antimicrobial treatment [9]. As antibiotic effectiveness depends on appropriate attainment of the targeted PK/PD indexes (e.g., t>MIC, peak/MIC and/or AUC/MIC), the higher the MICs of the ICU bacterial isolates is, the higher the drug exposure (in terms of trough concentration and/or peak concentration) should be for guaranteeing optimal target achievement. Furthermore, the use of a punctual MIC value to guide antibacterial dosing may not always be appropriate because of imprecise and highly variable measurements associated with MIC determination, especially with automated testing methods [14]. Broth microdilution is the reference standard for antimicrobial susceptibility testing according to the European Committee for Antimicrobial Susceptibility Testing and the Clinical and Laboratory Standards Institute, and being the most accurate method should be preferred for correctly determining the MIC of a clinical isolate. Punctual MIC measurements should be regarded as an estimate of a pathogen's susceptibility, and TDM-guided dosing adjustments should take care of any potential MIC variation [15].

Given the abovementioned alterations, the achievement of an optimal PK/PD target in ICU critically ill patients is often unpredictable if drug concentrations are not measured in each patient. Implementation of an adaptive TDM strategy coupled with monitoring of tissue antibiotic concentrations, if feasible, may represent the only way to truly tailor antimicrobial dosing and optimize tissue exposure in critical patients with NSTIs.

According to the latest guidelines for the management of NSTIs [16], the association of a broad-spectrum beta-lactam with daptomycin or linezolid is recommended for the empiric treatment of NSTIs. Both daptomycin and beta-lactams are hydrophilic agents whose plasmatic and tissue concentrations may be extremely affected by different physiopathological conditions. In Table 1, advice for dosing optimization of the most common agents used for the management of NSTIs is provided. A higher than standard dose should be administered for concentration-dependent agents (e.g., up to 10–12 mg/kg of daptomycin), while an extended/continuous infusion (EI/CI) coupled with higher doses should be implemented for time-dependent agents (e.g., meropenem at 1–1.5 g every 6 h by EI/CI). These enhanced dosing schedules may overcome large fluid losses from open wounds and recurrent debridements and PK alterations caused by septic shock [8–10]. Larger loading doses (e.g., 2 g for meropenem or 6.75 g for

Table 1 Dose optimization of the most common agents used for the management of critical patients with necrotizing soft-tissue infections (NSTIs)

Antibiotic	Solubility features	PK/PD target for efficacy	Standard dosing schedule	Loading dose in case of severe NSTI[a]	Maintenance dose in case of severe NSTI[a]	Augmented renal clearance	Acute kidney injury
Concentration-dependent agents							
Daptomycin	Hydrophilic/ lipophilic	AUC/MIC >666	8–10 mg/kg	≥ 10–12 mg/kg	≥ 10–12 mg/kg	≥ 12 mg/kg	Consider full dose in the first 48 h in the case of moderate-to-severe acute kidney injury Consider dose reduction after 48 h if renal impairment persists
Time-dependent agents							
Piperacillin-tazobactam	Hydrophilic	100% $fT_{>4–8MIC}$	4.5 g q6h	6.75 g	4.5 g q6h EI/CI	4.5 g q4–6h EI/CI	Consider full dose in the first 48 h in the case of moderate-to-severe acute kidney injury Consider dose reduction after 48 h if renal impairment persists
Meropenem	Hydrophilic	100% $fT_{>4–8MIC}$	1 g q8h	2 g	1–1.5 g q6h EI/CI	1.5 g q6h EI/CI	Consider full dose in the first 48 h in the case of moderate-to-severe acute kidney injury Consider dose reduction after 48 h if renal impairment persists
Linezolid	Lipophilic	AUC/MIC 80–120 85–100% $fT_{>MIC}$	600 mg q12h	600 mg	450–600 mg q8h	450–600 mg q8h	Consider full dose in the first 48 h in the case of moderate-to-severe acute kidney injury Consider dose reduction after 48 h if renal impairment persists

AUC area under the concentration–time curve, *CI* continuous infusion, *EI* extended infusion, *h* hours, *MIC* minimum inhibitory concentration, *PD* pharmacodynamic, *PK* pharmacokinetic, *q6h* every 6 hours, *q8h* every 8 hours, *q12h* every 12 hours

[a]Large fluid losses from open wounds and recurrent debridement every 12–24 hours added to PK alterations caused by septic shock (large increase in the volume of distribution coupled with clearance variations)

piperacillin-tazobactam) are required for time-dependent antibiotics at the start of therapy before applying EI/CI. In patients with moderate or severe acute kidney injury, the dosing schedule should not be reduced in the first 48 hours for both time- and concentration-dependent agents, as acute kidney injury may often be transient in patients with NSTIs. In the presence of augmented renal clearance possibly occurring in the first phase of septic shock, EI/CI may be the crucial strategy for maximizing PK/PD target attainment of time-dependent antibiotics [8–10]. A more aggressive dosing schedule of hydrophilic antibiotics may be also required for solving the issue of serum concentrations often not reflecting tissue concentrations. Conversely, tissue exposure is not expected to be significantly altered for lipophilic agents (e.g., linezolid), thus standard dosing approaches may be optimal in the majority of cases.

The abovementioned altered dosing strategies may be needed to achieve an optimal PK/PD target in critical patients with NSTIs (namely $AUC_{0–24}$/MIC ≥ 666 mg/L for daptomycin and 100% $fT_{>4–5MIC}$ for beta-lactams [15]). Accordingly, routine implementation of a TDM-guided approach should be encouraged in this setting, also considering that these higher than standard dosages could sometimes be required even in the presence of severe organ damage, as previously reported [11, 17]. Notably, TDM-guided dosing adjustments should take care of any potential MIC variation [15]. If precise MIC values assessed by broth microdilution are unavailable, an MIC-based dose adjustment may be based on the following strategies. The European Committee for Antimicrobial Susceptibility Testing and the Clinical and Laboratory Standards Institute clinical breakpoints should be taken as the target value to determine the optimal PK/PD attainment for wild-type strains. For strains considered in vitro resistant according to an MIC value above the clinical breakpoint, a margin of at least a two-fold dilution could be used for individual target attainment calculations [14].

In this setting, the clinical pharmacologist should act like a real detective. Observation, deduction, and knowledge should represent essential qualities for properly choosing the best therapeutic strategy. The clinical pharmacologist should move from bench to the bedside, for carefully addressing the PK and PD issues exhibited by each patient, providing a real-time antimicrobial optimization. In many countries, including the USA and UK, this skill is usually provided by the clinical pharmacist [18]. Notably, both clinical pharmacologists and clinical pharmacists should have a valuable expertise in critical care and in antimicrobial therapy to optimize treatment in patients with NSTIs. The "one dose fits all" approach may be grossly flawed and hazardous when applied in the setting of critical patients with NSTIs, and we believe the clinical pharmacologist could add significant knowledge in the multidisciplinary taskforce managing severe NSTIs in referral centers, becoming, why not, the 'cherry on top'.

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