REVIEW ARTICLE

Dosing of antibiotics in critically ill patients: are we left to wander in the dark?

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KEY WORDS

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ABSTRACT

Critically ill patients are frequently affected by acute kidney injury accompanied by dysfunction of other systems and organs. Sepsis is common in this population and remains a major cause of multiorgan dysfunction syndrome, indicating a crucial role in efficient antibiotic treatment. However, such treatment is particularly difficult due to altered pharmacokinetic profile in these patients, dynamic changes in their clinical status and, in many cases, need for renal replacement therapy (RRT). Current guidelines concerning the dosing of antibiotics in this patient population are not particularly reliable because they are based on studies involving small and heterogeneous groups of patients, often treated with different RRT modalities. Our paper reviews the basic pharmacokinetic and pharmacodynamic parameters as well as other factors that should be considered while devising a proper therapeutic approach for this patient population.

Introduction Critically ill patients are frequently affected by acute kidney injury (AKI) accompanied by dysfunction of other systems and organs. It is usually observed during the course of severe sepsis or septic shock as well as a result of extensive injuries or burns, but can also occur after cardiac and aortic surgery, complex abdominal surgery, cell and organ transplantation,[1-3] in patients undergoing intensive chemotherapy, or during the course of fulminant liver failure. A significant number of those cases are further complicated by a secondary infection. Since the prognosis in these patients is very poor, with the mortality rate reaching from 80% to 90%, selecting appropriate antibiotic regimen is crucial for the clinical outcome. Unfortunately, the rules guiding this process are extremely complex in this population, increasing the risk of either under- or overtreatment. Administering subtherapeutic doses of antibiotics may lead to a decreased efficiency of therapy and development of resistant bacterial strains. On the other hand, high doses can be harmful to vital organs such as the kidneys, bone marrow, and liver, resulting in a significantly worse prognosis.

Since the majority of drugs are excreted by the kidney, renal function should always be taken into account. Elderly patients, who have a lower glomerular filtration rate (GFR) due to age and comorbidities, are much more prone to AKI; therefore, an estimation of their kidney function is crucial for appropriate drug dosing.[4-6] Unfortunately, due to different equations used for estimating the GFR (Modification of Diet in Renal Disease or the Cockcroft-Gault formula), the results of the studies vary even between similar age groups.[4]

Several factors may contribute to increased difficulties in establishing proper dosing regimen in critically ill patients (TABLE 1). Most importantly, drug pharmacokinetics in this highly heterogeneous group is altered to varying extent compared with the healthy population. Additionally, their clinical state and drug pharmacokinetics can fluctuate significantly on the day-to-day basis. Therefore, indicators routinely employed in designing the antibiotic regimen in individuals without organ dysfunction are entirely inadequate in this group of patients. Not taking these disparities into consideration can result in inappropriate antibiotic treatment and becomes the underlying cause of therapeutic failure. In TABLE 2, the pharmacokinetic-pharmacodynamic profiling of selected antibiotics is presented.

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TABLE 1 Factors contributing to the difficulties in establishing precise guidelines for antibiotic dosing in critically ill patients with acute kidney injury

differences in baseline characteristics (age, sex, body mass and surface, fat tissue and muscle tissue content)
altered drug pharmacokinetics (individual variations) – changes in volume of distribution
hypoalbuminemia
changes in renal clearance
commonly observed disturbances in drug metabolism in the liver (individual variations)
dynamic changes in patient's clinical state and organ function
renal replacement therapy – various techniques and their modifications – differences in ultrafiltrate and dialysate flow rates – various dialysis membranes – varying treatment times

Volume of distribution Volume of distribution (Vd) constitutes one of the most important factors affecting antibiotic dosing in critically ill patients, and its inaccurate assessment may lead to serious clinical errors. Sepsis is present in a substantial number of these patients leading to the damage to vascular endothelium with an increase of capillary permeability and redistribution of fluid into the extracellular compartment. As a result, Vd of water-soluble antibiotics increases with a subsequent drop in their concentration to the subtherapeutic level. This phenomenon can be further perpetuated by the vasodilatation and fluid loading during resuscitation, intravenous drug administration, or parenteral nutrition, as well as water retention due to oliguria or anuria. In the early phase of treatment, Vd is significantly increased in critically ill patients, with the exception of some antibiotics such as meropenem and ciprofloxacin.[7]

TABLE 2 Pharmacodynamic and pharmacokinetic parameters of selected antibiotics[7,11,16,19,43-45]

	Concentration- vs. time-dependent	Vd, l/kg	Protein binding capacity, %	Main elimination route	Comments
gentamycin	concentration	0.2–0.3	<30	renal	optimal C_{max}/MIC ≥8–10
tobramycin	concentration	0.2–0.3	<30	renal	
amikacin	concentration	~0.25	0–11	renal	
cefazolin	time	~0.14	74–86	renal	a 2 × increase in Vd in critically ill reported
cefepime	time	0.23–0.29	16–20	renal	
cefotaxim	time	0.15–0.55	27–38	renal	
ceftazidime	time	0.23	17–21	renal	
ceftriaxone[a]	time	0.09–0.2	85–95	hepatic	
cefuroxime	time		33–50	renal	
ciprofloxacine[a]	concentration	1.8–2.7	20–40	renal	optimal AUC_{24}/MIC >125 for Gram(–), >40 for Gram(+)
levofloxacine	concentration	1.05–1.6	24–38	renal	a Vd is not increased in critically ill
ampicilin	time	0.29	1–28	renal	
clavulanate	–	0.3	30	hepatic	
vancomycin	time/concentration	0.4–1.0	50–55	renal	
piperacilin	time	0.18	16	renal	
tazobactam	time	0.18–0.33	20–23	renal	
imipenem	time	0.23	20	renal	a Vd is not increased in critically ill
meropenem[a]	time	0.21–0.29	2	renal	a MIC ≤2 mg/l MIC = 4 mg/l or meningitis
linezolid	time/concentration	0.57–0.71	31	hepatic	optimal AUC_{24}/MIC ~50 for *S. pneumoniae* and 82 for *S. aureus*
daptomycin	concentration	0.1–0.13	90–93[a]	renal	a 84%–88% for CrCl <30 l/min
fluconazole[a]	time	0.6–0.65	12	renal	a it undergoes postfiltration reabsorption therefore in anuric patients on CRRT its clearance ↑ necessitating dose ↑
itraconazole	time	10	~99	hepatic	
voriconazol	time	4.6	58	hepatic	

Abbreviations: AUC_{24} – area under the concentration-time curve after 1 dose during 24 h, C_{max} – peak serum concentration, CrCl – creatinine clearance, CRRT – continuous renal replacement therapy, MIC – minimal inhibitory concentration, Q – number of hours between each antibiotic dose, Vd – volume of distribution

TABLE 3 Stages of acute kidney injury according to Kidney Disease: Improving Global Outcomes[8]

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 ml/kg/h for >12 h
3	3.0 × baseline, or increase in serum creatinine ≥4.0 mg/dl (≥353.6 mmol/l), or initiation of RRT, or decrease in eGFR <35 ml/min/1.73 m^2 for patients <18 years	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

Abbreviations: eGFR – estimated glomerular filtration rate, RRT – renal replacement therapy

An increase in Vd can result in lower efficiency of antibiotic removal during renal replacement therapy (RRT) and difficulties in reaching the minimal concentration (C_{min}) of an antibiotic required for maintaining its therapeutic action throughout treatment.

Disturbances of renal function Critically ill patients are diagnosed with various stages of AKI, although in some of them renal function can still remain intact, particularly in the early phases of the disease. TABLE 3 presents in detail the stages of AKI and their diagnostic criteria established within the last decade and recently accepted by the Kidney Disease: Improving Global Outcomes.[8] The frequency of AKI in critically ill patients reaches from 50% to 65%, and while in one-third of the cases it occurs as a late complication, in approximately two-thirds it is being diagnosed within the first 24 hours after admission to the intensive care unit (ICU).[9,10] Among patients diagnosed with stage 3, approximately 50% requires RRT. Importantly, in contrast to end-stage kidney disease, renal clearance does not remain constant but rather fluctuates in time.

It has to be emphasized that disturbances of renal function are not limited to GFR, but also affect the process of tubular secretion and reabsorption. This is particularly important in the case of antibiotics that undergo postfiltration reabsorption, such as fluconazole. Its clearance increases in patients with AKI and anuria undergoing continuous RRT (CRRT), necessitating an increase or even doubling of the amount of administered drug.[11]

An interesting phenomenon described in critically ill patients, which has been gaining an increasing attention in recent years, is augmented renal clearance (ARC). This term refers to enhanced renal elimination of circulating solute, and its diagnosis relies on GFR values (calculated on the basis of measurements of serum creatinine and 8–24-hour urine collection sample) that are 10% higher than normal, or above 130 ml/min/1.73 m^2.[12,13] ARC can result in underdosing of antibiotics and other life-saving drugs, leading to therapeutic failure. Early diagnosis of this disorder can contribute to successful treatment by allowing to compensate the enhanced elimination of antibiotics by the kidneys by increasing their dosage, shortening the dosing intervals, or administering them through intravenous infusion. ARC can also affect individuals with intact renal function during forced diuresis (administration of large volume of intravenous fluids or diuretics), administration of vasoactive medications, increase in cardiac output and, in the case of sepsis, induced vasodilation. It has been observed most commonly among relatively young, previously healthy patients with trauma, surgery, burns, or sepsis, particularly when vasoactive drugs were administered.[12,14] For example, Udy et al.[12] reported that 85% of young patients with severe head trauma who received intravenous hypertonic saline infusions and/or vasopressor agents (in order to maintain adequate cerebral perfusion) were diagnosed with ARC. In a retrospective study published by Grootaert et al.,[15] ARC affected 30% of 1317 patients hospitalized in the surgical ICU.[15]

Decreased serum protein binding Serum albumin concentration is another important factor to be taken into consideration while prescribing antibiotic regimen. By increasing the fraction of unbound drug, which is able to move freely between various compartments, hypoalbuminemia leads to an increase in drug Vd and a decrease in its serum concentration.[16] Moreover, uremia, low pH, presence of heparin, and some other drugs may further decrease serum protein binding ability.[16]

This phenomenon has the strongest effect in the case of antibiotics with the highest protein binding capacity and in such circumstances, it may be directly responsible for treatment failure. Achieving therapeutic serum peak concentrations can be accomplished by a significant increase in the dosage of such antibiotics.

Renal replacement therapy Critically ill patients are usually treated by one of the forms of CRRT: continuous veno-venous hemofiltration, hemodiafiltration, or hemodialysis (CVVHF, CVVHDF, CVVHD, respectively) or sustained low-efficiency dialysis (SLED). Molecules are transported across the filter membrane by the mechanism of convection (driven by the pressure gradient – CVVHF), diffusion (driven by the concentration gradient – CVVHD, SLED) or both (CVVHDF). Unfortunately, employing CRRT

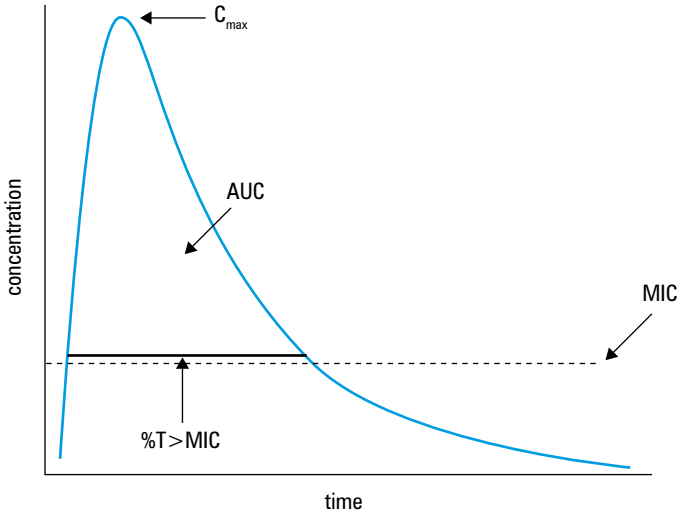

FIGURE Basic pharmacokinetic and pharmacodynamic parameters
Abbreviations: see **TABLE 1**

techniques complicates dosing of antibiotics to a significantly higher extent than standard hemodialysis. It is predominantly due to the high number of variables, including Vd, flow of the dialysis fluid, replacement fluid infusion site (pre- or postdilution mode), type and surface of the used membrane and the different ratio of delivered to prescribed RRT dose. In CRRT, the most important parameter determining drug clearance is the ultrafiltration rate.[17] Dosing adjustments of selected intravenous antibiotics in patients with renal dysfunction are presented in **TABLE 4**. However, since those adjustments are based on low ultrafiltration rates (1–2 l/h), in the case of more intensive treatment (currently often performed) the proposed dosing should be modified. In patients treated with hemodialysis, the doses should be given after the procedure. In the case of SLED, it is necessary to maintain an appropriate time interval between drug administration and the procedure.

There is some controversy about who should be responsible for the management of AKI in the ICU as well as the commencement of RRT and the choice of an appropriate method. The practice varies across countries. According to Srisawat et al.,[18] in the years 2000–2001, CRRT was more often prescribed by intensivists than nephrologists in Northern Europe (84.6% vs. 7.7%), Southern Europe (41.7% vs. 8.3%), Asia (88.9% vs. 0%), and Australia (100% vs. 0%), and more often by nephrologists than intensivists in North and South America (62.5% vs. 25% and 80% vs. 20%, respectively).[18] We feel that it should be a shared decision-making process involving nephrologists and intensive-care practitioners, if necessary in cooperation with a pharmacist, particularly in severe cases. Such cooperation can foster a deeper understanding of the pathophysiology of organ dysfunction and the mechanisms and procedures involved in continuous therapies.

Pharmacokinetics and pharmacodynamics: basic parameters and models Antibacterial efficiency of antibiotics in vivo can be described using pharmacokinetic and pharmacodynamic parameters. Pharmacokinetics follows the time course of a given drug in the body and provides us with the information on the absorption rate, Vd, and elimination through excretion or metabolism. It also describes changes in drug concentration with time using such parameters as the peak serum level (C_{max}), the trough level (C_{min}), and area under the concentration-time curve (AUC) after one dose (**FIGURE**).[7,19] Pharmacodynamics studies the interactions between the drug and the microorganism and the relationship between its concentration and antibacterial effect. This effect is usually described by minimal inhibitory concentration (MIC), which is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro (**FIGURE**). Nowadays, many laboratories can inform the clinicians about MIC.

Several pharmacokinetic/pharmacodynamic models have been constructed using the above parameters, three most popular being: C_{max}/MIC, %T >MIC, and AUC_{24}/MIC.[12,19] They quantify the activity of an antibiotic, describing the relationship between the concentration of the drug in bodily fluids and other pharmacokinetic parameters and the effect of the drug exerted on a given microorganism. C_{max}/MIC is simply a measure of how many times the peak serum concentration of a given antibiotic is higher than MIC. A clear advantage of this model is the necessity of drawing only one blood sample for the calculation. %T >MIC is the percentage of a dosage interval in which the serum drug concentration remains above the MIC. The AUC_{24}/MIC ratio is determined by dividing the AUC_{24} by the MIC. The target AUC_{24}/MIC values are determined by the type of the pathogen. The formulas to calculate these models are given below.

Formula for %T >MIC calculation[7]:

$$\%T>MIC = \ln \frac{D}{Vd \times MIC} \times \frac{t1/2}{0.693} \times \frac{100}{\tau}$$

Formula for calculation AUC_{24}/MIC[7]:

$$AUC_{24}/MIC = \frac{D}{Vd \times MIC} \times \frac{t1/2}{0.693} \times \frac{24}{\tau}$$

Classification of antibiotics based on pharmacokinetic and pharmacodynamic models Generally, antibiotics can be divided into two main groups based on the mechanism of their bacteriocidal effect: concentration- and time-dependent (**TABLE 2**). However, there are some antibiotics with mixed properties, with time-dependent killing but prolonged persistent effects.

Concentration-dependent antibiotics Concentration-dependent antibiotics, including aminoglycosides, fluorochinolones, daptomycin, amphotericin B, should be administered in high doses

TABLE 4 Dose adjustments of selected intravenous antibiotics in patients with renal dysfunction[7,12,43-56]

Antibiotics	Normal renal function	CrCl 30–50 ml/min	CrCl 10–30 ml/min	CrCl <10 ml/min	HD	CRRT	Comments
aminoglycosides							
gentamicin	1–2.5 mg/kg Q8–12 h or 4–6 mg/kg Q24 h	1–2.5 mg/kg Q12 h	1–2.5 mg/kg Q24 h (<20 ml/min Q48 h) TDM	LD: 1–2.5 mg/kg MD: Q48–72 h TDM	LD: 2–3 mg/kg MD: 1–1.5 mg/kg Q48–72 h (aHD) TDM in systemic Gram(–) infections 1.5–2 mg/kg Q48–72 h	all CRRT: LD: 2–3 mg/kg MD: 1–1.5 mg Q24–36 h TDM in systemic Gram(–) infections 1.5–2 mg/kg Q24–48 h	use of ideal body weight dialyzable ~50%
tobramycin	1–2.5 mg/kg Q8–12 h or 4–6 mg/kg Q24 h	1–2.5 mg/kg Q12 h	1–2.5 mg/kg Q24 h (<20 ml/min Q48 h) TDM	LD: 1–2.5 mg/kg MD: Q72 h TDM	LD: 2–3 mg/kg MD: 1–1.5 mg/kg Q48–72 h (aHD) TDM in systemic Gram(–) infections 1.5–2 mg/kg Q48–72 h	all CRRT: LD: 2–3 mg/kg MD: 1–1.5 mg Q24–36 h TDM in systemic Gram(–) infections 1.5–2 mg/kg Q24–48 h	use of ideal body weight dialyzable 25%–70%
amikacin	5–7.5 mg/kg Q8 h or 15–20 mg/kg Q24 h	5–7.5 mg/kg Q12 h	5–7.5 mg/kg Q24 h (<20 ml/min LD and TDM)	LD: 5–7.5 mg/kg MD: TDM	LD: 5–7.5 mg/kg MD: 5–7.5 mg/kg Q48–72 h (aHD) TDM	LD: 10 mg/kg MD: 7.5 mg/kg Q24–48 h TDM	use of ideal body weight dialyzable ~20%
fluoroquinolones							
ciprofloxacin	400 mg Q8–12 h	400 mg Q8–12 h	200–400 mg Q18–24 h or 75–50% of the dose Q12 h	200–400 mg Q24 h or 50% of the dose Q12 h	200–400 mg Q24 h (aHD)	All CRRT: 200–400 Q12–24 h	dialyzable <10%
levofloxacin	500 mg Q24 750 mg Q24 h	250 mg Q24 h 750 mg Q48 h	LD + 250 mg Q48 h LD + 500 mg Q48 h	LD + 250 mg Q48 h LD + 500 mg Q48 h	LD + 250 mg Q48 h (aHD) LD + 500 mg Q48 h (aHD)	LD: 500–750 mg MD: CVVHF 250 mg Q24 h, CVVHD 250–500 Q24 h, CVVHDF 250–750 mg Q24 h	poorly dialyzable
β-lactams							
cefazolin	1–2 g Q6–8 h	1–1.5 g Q8–12 h	0.5–1 g Q12 h	0.5–0.75 g Q18–24 h	0.5–1 g Q24 h or 1–2 g Q48–72 (aHD)	LD: 2 g MD: CVVHF 1–2 g Q12 h CVVHD/HDF 1 g Q8 h or 2 g Q12 h	dialyzable 20%–50%
cefepime	2 g Q12 h	2 g Q12–24 h	1–2 g Q24 h	0.5–1 g Q24 h	LD: 1–2 g MD 0.5–1 g Q24 h or 1–2 g Q48–72 h (aHD)	LD: 2 g MD: CVVHF 1–2 g Q12 h CVVHD/HDF 1 g Q8 h or 2 g Q12 h	dialyzable ~60%
cefotaxime	2 g Q6–8 h	2 g Q6–12 h	2 g Q6–12	2 g Q24 or 1 g Q6–12	1–2 g Q24 (aHD)	CVVHF 1–2 g Q8–12 h, CVVHD 1–2 g Q8 h, CVVHDF 1–2 g Q6–8 h	dialyzable 70%–100%
ceftazidime	1–2 g Q8 h	1–2 g Q12 h	1–2 g Q24 h	1–2 g Q48–72 h	LD: 1–2 g MD: 0.5–1 g Q24 h or 1–2 g Q48–72 h (aHD)	LD: 2 g MD: CVVHF 1–2 g Q12 h CVVHD/HDF 1g Q8 h or 2g Q12 h	dialyzable 50%–100%
ceftriaxone	1–2 g Q12–24 h	1–2 g Q124 h	1–2 g Q24 h	1–2 g Q24 h	1–2 g Q24 h	2 g Q12–24 h	poorly dialyzable
cefuroxime	0.75–1.5 g Q8 h	0.75–1.5 g Q8 h	0.75–1.5 g Q12 h	0.75–1.5 g Q24 h	0.75–1.5 g Q24 h (aHD)	0.75–1.5 g Q12 h	dialyzable 25%

carbapenems							
imipenem	500 mg Q6 h	500 mg Q8 h	250 mg Q6–12 h	250 mg Q12 h	250 mg Q12 h (aHD) after HD	LD 1 g, MD: CVVHF 250 mg Q6 h or 500 mg Q6–8 h, CVVHD 250 mg Q6 h or 500 mg Q8 h, CVVHDF 250–500 mg Q6 h	500 mg Q8 h for MIC ≤2 mg/l, and 500 mg Q6 h for MIC ≥4 mg/l, *Pseudomonas spp* and deep seated infections
meropenem	0.5–2 g (usually 1 g) Q8 h	0.5–2 g (usually 1 g) Q12 h	50% of the dose Q12 h	50% of the dose Q24 h	LD 1 g: MD: 500 mg Q24 (aHD)	LD 1 g, MD: CVVHF 0.5 Q8 h CVVHD/CVVHDF 0.5 g Q6–8 h or 1 g Q8–12 h	dialyzable
vancomycin	LD: 25–30 mg/kg MD: 15–20 mg/kg Q8–12 h	15–20 mg/kg Q24 h	15–20 mg/kg Q24 h (<20 ml/min TDM)	15–20 mg/kg MD – TDM	LD 15–25 mg/kg, aHD reload with 5–10 mg/kg or base on TDM	LD 15–25 mg/kg, MD: CVVHF 1 g or 10–15 mg/kg Q24 h; CVVHD 1g or 10–15 mg/kg Q24 h; CVVHDF 1g Q24 h or 7.5–10 mg/kg Q12	
metronidazole	500 mg Q8 h	500 mg Q8 h	500 mg Q12 h	500 mg Q12 h or 50% of the dose Q8 h	500 mg Q8–12 h (aHD)	500 mg Q6–12 h	dialyzable 50%–100% reduce dose in severe liver disease
ampicillin	1–2g Q4–6 h	1–2 g Q6–12 h	1–2 g Q6–12 h	1–2 g Q12–24 h	1–2 g Q12–24 h	LD: 2 g, MD: CVVHF 1–2 g Q8–12 h; CVVHD 1–2g Q8 h; CVVHDF 1–2g Q 6–8 h	dialyzable in 20%–50%
piperacilin/ tazobactam	3–4.5 g Q6–8 h	3–4.5 g Q6–8 h	3–4.5 g Q8 h	3–4.5 g Q8 h	3–4.5 Q12 h	3–4.5 g Q6–8 h	dialyzable in 20%–50%
linezolid	600 mg Q12 h	600 mg Q12 h	600 mg Q12 h	600 mg Q12 h	600 mg Q12 h (aHD)	600 mg Q12 h (controversy over supplemental doses)	dialyzable 20%–50%
daptomycin	6–8 mg/kg Q24 h	6–8 mg/kg Q24 h	6–8 mg/kg Q48 h	6–8 mg/kg Q48 h	6–8 mg/kg Q48 h (aHD)	CVVHF/CVVHDF 4–6 mg/kg Q24 or 8 mg/kg Q48 h; CVVHD 8 mg/kg Q48 h SLED should be initiated within 8 h after the dose	dialyzable in ~30% pts with severe sepsis and significant ↑ of liver clearance may benefit from continuous iv infusion
fluconazole prophylaxis noninvasive candidiasis invasive candidaisis	LD 200 mg, MD 200 mg Q12–24 h LD 800 mg, MD 400 mg Q24 h	LD 200 mg, MD 100 mg Q12–24 h LD 800 mg, MD 200 mg Q24 h	LD 200 mg, MD 100 mg Q24 LD 400–800 mg, MD 200 mg Q24 h	LD 200 mg, MD 50 mg Q12–24 h LD 400–800 mg, 100 mg Q24 h	100% aHD or 200–400 mg Q48–72 h or 100–200 mg Q24 h	LD 400–800 mg, MD: CVVHF 200–400 mg Q24 h, CVVHD/HDF 400–800 mg Q24 h	it undergoes postfiltration reabsorption therefore in anuric pts on CRRT with UF ≥2 l/h its clearance ↑ necessitating ↑ doses even more (to 500–600 mg Q12 h)
itraconazole (orally)	200 mg Q12–24 h	200 mg Q12–24 h	200 mg Q24 h	100 mg Q24 h	100 mg Q24 h (aHD)	100 mg Q24 h	it undergoes postfiltration reabsorption therefore in anuric pts on CRRT with UF ≥2 l/h its clearance ↑ necessitating ↑ doses even more (to 500–600 mg Q12 h)
voriconazole	LD 6 mg/kg MD 3–4 mg/kg Q12	should be avoided	should be avoided	should be avoided	should be avoided	should be avoided	poorly dialyzable should be avoided in pts with CrCl <50 ml/min due to accumulation

Abbreviations: aHD – after hemodialysis, CVVHD – continuous venovenous hemodialysis, CVVHDF – continuous venovenous hemodiafiltration, CVVHF – continuous venovenous hemofiltration, HD – hemodialysis, LD – loading dose, MD – maintenance dose, pts – patients, SLED – sustained low-efficiency dialysis, TDM – therapeutic drug monitoring, UF – ultrafiltration, others – see TABLE 2

once per 24 hours in order to obtain high values of C_{max}/MIC to maximize killing, followed by very low troughs to minimize toxicity. In such antibiotics as aminoglycosides, and fluorochinolones, a single-dose approach not only enhances drug efficacy and decreases toxicity but also allows for the so called postantibiotic effect, when persistent suppression of bacterial growth is observed after the concentration falls below the MIC.[20-22] Therefore, for this group, the other useful model describing bacteriocidal efficacy is AUC_{24}/MIC.

Time-dependent antibiotics Time-dependent antibiotics, including cephalosporins, carbapenems, and penicillins, exert their optimal bactericidal effect when unbound drug concentration is maintained above the MIC for the longest period of time, and %T >MIC is the best predictor of their efficacy. It is estimated that %T >4–6 × MIC should reach from 40% to 100%, depending on the antibiotic and the type of bacteria as well as on infection severity.[23] After administering the loading dose, time-dependent antibiotics should be readministered in several lower doses per 24 hours. Intravenous infusion constitutes an ideal delivery route for this group of agents; however, it is not always feasible due to the limited stability of some of them (e.g., meropenem). Nevertheless, the comparison between standard administration (1 g every 12 h) and intravenous infusion (500 mg bolus followed by 2 g/24 h) in patients treated by CVVHDF showed that both methods achieved similar stable target concentrations of meropenem in serum, as published by Langgartner et al.[24]

In the case of β-lactam antibiotics, which are characterized by a high rate of elimination during RRT and insignificant postantibiotic effect, the option of continuous intravenous infusion maintaining their concentration above the MIC during 90%–100% of the dosing interval, is indeed very tempting, particularly in patients with difficult infections.[25] Employing such a strategy would allow to decrease the total antibiotic dose (lower toxicity, lower costs) and, at the same time, to increase its efficacy. Indeed, the results of several in-vitro studies justify application of continuous intravenous infusion of β-lactams; however, the available clinical data is not sufficient to fully support such therapeutic modality.[25] Moreover, two recently published meta-analyses comparing bolus vs. continuous infusion of β-lactams did not find significant differences between these two approaches in terms of their antibacterial efficiency or patients' mortality.[26,27] Alternatively, an approach involving extended 3-hour infusion of β-lactam antibiotics has been proposed.[28] Continuous antibiotic infusions can also benefit patients with ARC.

Time- and concentration-dependent antibiotics AUC_{24}/MIC is the most reliable predictor of antibiotic efficacy in this group (vancomycin, linezolid, tetracyclines, azithromycin), and it is also related to the type of the pathogen involved.

Practical remarks **The loading dose** Renal failure per se does not necessitate any modifications in the loading dose of antimicrobials. Nevertheless, increase in Vd, which is commonly present in this group of patients, warrants a proportional dose increase and – in some critically ill septic patients with AKI and fluid overload – even its doubling may be required. Taccone et al.[29] recently conducted a multicenter, prospective study in 80 patients admitted to four Belgian ICUs with the diagnosis of severe sepsis or septic shock, in 36% of them accompanied by AKI. %T >4 × MIC was calculated after the loading dose of various β-lactam antibiotics (ceftazidime, cefepime, or meropenem). A targeted pharmacokinetic profile recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) was achieved in 75% of the patients receiving meropenem, but only in 16% of cefepime-treated, in 28% of ceftazidime-treated, and 44% of piperacillin/tazobactam-treated patients.[29,30]

In some circumstances, the persistence of high levels of antibiotic after the administration of a loading dose (e.g., in the case of nephrotoxic aminoglycosides) may be prevented by properly setting the parameters of CRRT. For example, as reported by Taccone et al.,[31] a routinely prescribed loading dose of amikacin (10 mg/kg) may prove to be insufficient to achieve the C_{max} values recommended by the EUCAST for highly pathogenic bacteria such as *Enterobacteriaceae* or *P. aeruginosa*. On the other hand, administering higher doses of the drug in oliguric patients may lead to persistence of its toxic levels in the late phase of the therapy, even despite continuous RRT. In such cases, high-volume CVVHF or initiating the SLED procedure a few hours after administration may be helpful in reducing the C_{min} of the antibiotic.[31,32]

In the majority of cases, it is simply impossible to define the pathogenic bacteria at the beginning of treatment. Then, when calculating the loading dose of an antibiotic, one should target the MIC value for the most resistant bacteria among those commonly isolated in the particular environment, e.g., a hospital ward. Data published annually by the EUCAST may also prove helpful.[30] Loading doses for selected antibiotics are presented in TABLE 4.

Dose modification during treatment During further stages of treatment, antibiotic doses have to be modified on regular basis depending on the changes in Vd and clearance. Improvement in the patient's clinical state is usually accompanied by a decrease in Vd and therefore requires dose reduction. In contrast, a decline in clinical status may require an increase in dose. Triginer et al.[33] investigated the pharmacokinetics of gentamicin in 40 patients with Gram(–) sepsis. On the second day of treatment, after intensive hydrating

TABLE 5 Target aminoglycosides and vancomycin serum concentrations for serious infections[7,52,57-61]

	Peak (C_{max})	Trough (C_{min})
gentamycin/tobramycin	5–8 mg/l	<2 mg/l
amikacin	20–25 mg/l 25–40 mg/l[a]	<10–8 mg/l
vancomycin	–	10–15 mg/l 15–20 mg/l[a]

a in life-threatening infections

regimen had been undertaken, average Vd was 0.43 l/kg, and the dose required to achieve target serum concentration was 5.14 mg/kg/24 h, while on the fifth day both values decreased significantly and reached 0.29 l/kg and 3.98 mg/kg/24 h, respectively (P <0.001). During the period of the study, kidney function did not change. In patients with AKI, the improvement of the general clinical status and renal function leads to increased drug clearance and decreased serum concentration.

Therapeutic drug monitoring Under such circumstances, monitoring serum drug concentrations would certainly prove extremely helpful. However, in today's clinical practice, it is only feasible for aminoglycosides and glycopeptides. Due to the particularly narrow therapeutic window of these antibiotics and their high nephrotoxicity, monitoring of their serum levels in critically ill patients should be obligatory. Usually, they are obtained with the third dose or after dose adjustment and then troughs rechecked after a few days. Trough concentrations need to be checked 30 minutes before the next dose, and peak concentrations from 30 to 45 minutes after the end of intravenous infusion of the drug. The desired aminoglycosides and vancomycin serum concentrations for serious infections are presented in TABLE 5. While for aminoglycosides, both peak and trough serum concentrations are equally important for therapy efficacy and safety, in the case of vancomycin, which has a significant time-dependent component, only troughs are necessary for routine monitoring.

Unfortunately, therapeutic drug monitoring is not available in the case of β-lactams, a group of antibiotics most commonly used in critically ill patients. Since it has been recently shown that a significant number of patients from this group had subtherapeutic levels of β-lactams, the possibility of their serum levels monitoring becomes crucial, especially that some of these agents may cause severe side effects, e.g., neurological complications in the case of cefepime (particularly in patients with renal failure).[34,35]

Current recommendations If therapeutic drug monitoring is not possible, published recommendations are used to establish the proper dosing regimens. Unfortunately, their reliability in this particular population is being questioned due to the fact that they are often based on pharmacological studies conducted in relatively small groups of patients. These groups are usually highly heterogeneous, including patients with various values of renal clearance, treated with different RRT modalities, using different types of filters and various combinations of procedural parameters that are all ultimately highly important for the total clearance value. Moreover, clinical studies referred to in these recommendations often date back to the times when less intense RRT was clearly favored in clinical practice. This reality practically translates into doses of antibiotics that are inadequate for our patients.

In a recent study, Ocampos-Martinez et al.[36] reported that as many as 53% of the ICU patients with sepsis treated with continuous intravenous infusion of vancomycin administered according to the currently accepted guidelines had too low serum concentrations of this antibiotic on the first day of treatment, and 33% – on the second.

Seyler et al.[37] analyzed concentrations of four β-lactam antibiotics administered (according to the guidelines) to 53 patients with *P. aeruginosa*-related septic shock and treated with CVVHF/HDF. Too low concentrations were reported in 19% of the patients receiving meropenem, in 29% treated with piperacillin and tazobactam, in 47% treated with ceftazidime, and in all patients receiving cefepime.

Is serum procalcitonin useful for guiding antibiotic therapy? Over the last years, it has been suggested that serum procalcitonin may be used to support clinical decision for initiation and duration of antibiotic therapy in critically ill patients with severe infections, and even procalcitonin-based algorithms were presented.[38,39] However, while some investigators found it effective in reducing antibiotic exposure with no change in mortality and treatment failure, others warn against wide adoption of the strategy in the critical-care setting.[38-41] In the largest randomized study so far, which included 1200 critically ill patients from nine Danish ICUs, Jensen at al.[42] showed that procalcitonin-guided therapy not only did not improve survival, but also increased duration of renal and respiratory failure and prolonged admission to the ICU, and therefore should not be recommended until further research is done.[42] Large trials are ongoing to determine the safety of antibiotic sparing procalcitonin strategies in intensive care.

Conclusions In conclusion, successful treatment of infections in critically ill patients requires not only the basic knowledge of pharmacokinetics and pharmacodynamics of antibiotics and expertise in conducting RRT, but also careful vigilance in the continuous assessment of the patients' clinical state and organ function. Dramatic changes in the clinical state commonly observed in this group of patients warrant daily verification and adjustment of therapeutic approaches.

Therapeutic drug monitoring based on the serum levels, if possible, should be attempted.

Shortage of reliable data regarding antibiotic dosing in critically ill patients poses an enormous clinical dilemma. Most recent studies suggest that routine treatment modalities are inadequate in a significant number of patients, certainly contributing to high mortality rates in this population. Consequently, there is an urgent need for establishing new sets of recommendations corroborated by large-scale prospective clinical studies conducted in homogenous patient populations treated according to the uniform RRT procedures. Because until then we are a bit left to wander in the dark, we hope to shed some light on this complex and important topic.

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ARTYKUŁ POGLĄDOWY

Dawkowanie antybiotyków u chorych w stanie krytycznym – czy jesteśmy wciąż skazani na błądzenie w ciemności?

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antybiotyki, krytycznie chorzy, sepsa, terapia nerkozastępcza

STRESZCZENIE

U chorych w stanie krytycznym często obserwuje się ostrą niewydolność nerek powiązaną z niewydolnością innych układów i narządów. Sepsa jest podstawową przyczyną zespołu dysfunkcji wielonarządowej w tej grupie chorych, stąd skuteczna antybiotykoterapia ma tu ogromne znaczenie. Jednakże leczenie to jest wyjątkowo trudne, co wynika ze zmienionej u tych chorych farmakokinetyki leków, dynamicznych zmian stanu ogólnego oraz – w wielu przypadkach – z konieczności stosowania leczenia nerkozastępczego (*renal replacement therapy* – RRT). Dostępne wytyczne dotyczące dawkowania antybiotyków w tej populacji są mało wiarygodne, gdyż opierają się na badaniach niewielkich i heterogennych grup pacjentów, często leczonych za pomocą różnych technik RRT. W artykule przedstawiono podstawowe parametry farmakokinetyczne, farmakodynamiczne i inne czynniki, które należy uwzględnić przy ustalaniu odpowiedniego planu leczenia w tej grupie chorych.

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