Tab. 1. *Factors that could potentially alter the pharmacokinetics and clinical response of antibiotics in intensive care unit patients*

Changes	Effect on drug pharmacokinetics
Impaired drug absorption	Reduced bioavailability of orally administered antibiotics (not frequent in critically ill patients)
Hypoalbuminemia	Increased drug clearance and higher risk to fail PK/PD target attainment (most relevant for renally excreted antibiotics with protein binding > 80%)
Obesity	Changes in the Vd, hepatic drug metabolism and renal excretion for hydrophilic antibiotics (i.e. beta-lactams, vancomycin)
Renal insufficiency	Reduced clearance of hydrophilic drugs with increased risk to reach supra-therapeutic plasma concentrations and to develop drug-related toxicity (i.e. beta-lactams, aminoglycosides; glycopeptides)
Hepatic insufficiency	Increased risk of accumulation of antibiotics with high hepatic extraction rate. For the remaining, the effects on drug pharmacokinetics are less predictable
Augmented renal clearance (acute hyperdynamic phase)	Increased clearance of hydrophilic antibiotics with increased risk of sub-therapeutic plasma concentrations (i.e. beta-lactams, linezolid)
Altered fluid balance (increased capillary permeability)	Expansion of extracellular fluid volume leading to increased drug Vd and lower plasma drug concentrations. This effect is particularly relevant for hydrophilic antibiotics with low Vd (i.e. aminoglycosides, beta-lactams)
Extracorporeal clearance for organ support (RRT, ECMO)	increased Vd and clearance of hydrophilic antimicrobials with increased risk of drug underexposure
PK-driven drug-drug interactions	Increased risk of suboptimal exposure of antibiotics when co-administered with drugs affecting the ADME phases

Vd: volume of distribution; RRT: renal replacement therapy; ECMO: extra corporeal membrane oxygenation; ADME: absoption, distribution, metabolism, elimination.

usually coupled with ultraviolet (UV), photo--dyode array (PDA) or fluorescence detector (Table 2). This approach further evolved towards immunoassay analysis to accommodate minimal sample preparation and faster turnaround times. However, the immunoassay technique is only available for a restricted range of antibiotics. Recently, commercial kits for the quantification of antibiotics using LC coupled with mass spectrometry (MS/MS) have been developed (11). These kits may overcome previous limitations on the widespread use of LC-MS/MS methods in hospital laboratories, such as the need for dedicated personnel with expertise in the field.

Tab. 2. *Available analytical techniques for the TDM of antibiotics*

Separation techniques	■ Gas chromatography (GC) ■ High performance liquid chromatography (HPLC, LC) ■ Ultra-high performance liquid chromatography (UPLC/UHPLC) ■ Capillary electrophoresis (CE)
Identification/quantification techniques	■ Mass spectrometry (MS) ■ Mass spectrometry, single quadrupole (SIM, SRM, MS) ■ Mass spectrometry, multiple quadrupoles (MS/MS) ■ High resolution mass spektrometry (HRMS)
Combined technologies	■ LC-MS/MS ■ GC-MS/MS ■ LC-HR-MS/MS ■ CE-MS/MS ■ CE-HR-MS/MS
Immunoassays (FPIA, MELA, EIA, etc)	

Therapeutic drug monitoring to limit antibiotic toxicity

The TDM of antimicrobial agents has been clearly proven to be of clinical relevance for the management and prevention of drug-related toxicity. Indeed, extensive evidence is available demonstrating that aminoglycoside-associated nephrotoxicity or ototoxicity, vancomycin-associated nephrotoxicity, colistin-related nephrotoxicity and teicoplanin--associated neutropenia are dependent on the absolute drug concentrations and the duration of exposure. This provides a solid rationale for the adoption of trough-based TDM as mandatory tool to optimize the use of these antibiotics in clinical practice (12).

Beta-lactam antibiotics are usually well tolerated. Drug-related toxicity is generally ascribed to hypersensitivity reactions, regardless of drug dose or drug overexposure. However, a retrospective analysis by Imani et al. documented significant associations between toxic concentrations of piperacillin, meropenem, flucloxacillin and drug-related neurotoxic/nephrotoxic effects (13). Similarly, consistent and significant associations have been reported between high cefepime trough concentrations and drug-related toxicity (14).

The oxazolidinone antibiotic linezolid is associated with severe adverse effects, including thrombocytopenia, peripheral neuropathy, lactic acidosis and optic neuropathy. Without accurate management, the toxicity of linezolid may outweigh the benefits of continuing treatment for extended periods of time, as the risk of adverse effects increases with exposure and duration of treatment. Monitoring trough concentrations is used to prevent linezolid toxicity. Decreasing the linezolid dose and/or frequency, whenever trough concentrations exceed a pre-established toxicity threshold (usually set at 8 mg/L), can decrease the risk of toxicity, primarily thrombocytopenia (15).

Matching fast-track microbiology with fast-track pharmacology: new timings of PK/PD assessments at the bedside

The significant variations in the PK of antibiotics in critically ill patients and how the TDM can help to quantify the individual variations have been reported in the previous sections. Nevertheless, the PK of antibiotics may have limited clinical consequences if not adequately matched with their PD, which reflects the relationship between the drug concentrations and the antimicrobial effect. The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC) that prevents the pathogen growth *in vitro*. When the MIC is not available, international breakpoints can be used as surrogates for the actual MIC. However, it is important to highlight that the MIC value simply reflects