**The management of anti-infective agents in intensive care units: the potential role of a 'fast' pharmacology**

# THE MANAGEMENT OF ANTIINFECTIVE AGENTS IN INTENSIVE CARE UNITS: THE POTENTIAL ROLE OF A "FAST" PHARMACOLOGY

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**Abstract**

**Introduction**: Patients in intensive care units (ICU) are often develop severe infections in which are associated with significant mortality rates. A number of novel technologies for the rapid microbiological diagnosis of these infections have been developed, introducing the era of 'fast microbiology'. Treatment of bacterial and fungal infections in ICU is however complicated by alterations in the pharmacokinetics of antimicrobial agents.

**Areas covered**: We review novel pharmacologic tools that can be used to optimize anti-infective therapies and patient management in ICU. A MEDLINE Pubmed search for articles published from January 1995 to 2019 was completed matching the terms pharmacokinetics and pharmacology with antimicrobial agents and ICU or critically-ill patients. Moreover, additional studies were identified from the reference list of retrieved articles.

**Expert opinion**: Several tools are in development for the full automation of the analytical methods used for the quantification of antimicrobial concentrations within a few hours after sample collection. *Ad hoc* software with adaptive feedback is also available for appropriate dose adjustments based on both individual patient covariate data and therapeutic drug monitoring (TDM) data when available. The application of these technological improvements in the clinical practice should open the way to a "fast pharmacology" at the bedside.

Key words: Critically ill patients; anti-infective agents; fast pharmacology; drug management

## 1. Introduction

Patients in intensive care units (ICU) differ considerably from those in other hospital wards, having a higher level of sickness severity requiring tailored and aggressive medical interventions and often present with or contract severe infections. Multidrug-resistant (MDR) organisms are also common in this setting [1]. As a result, these patients have substantial mortality rates (40-65%), particularly if they have a high severity of illness score, sepsis and septic shock [2,3].

Given this background, immediate and appropriate anti-infective therapy – defined in terms of timely commencement of pharmacologic treatment with appropriate spectrum for the pathogen(s) – is mandatory to improve the clinical outcome of ICU patients [4]. Anti-infective therapy for ICU patients is initially empirical but revised when the results of the microbiological tests become available, previously 48-96 hours after collection of specimens. However, in recent years a number of novel technologies for the microbiological diagnosis of infections that provide results in a shorter time frame when compared with conventional diagnostic approaches have been developed [5,6]. These technological improvements have opened the era of fast microbiology (also referred as fast-track microbiology).

It must be recognised, however, that microbiology represents only one of the key disciplines in this setting. In fact, successful treatment of severe infections in ICU is based on a proper antimicrobial stewardship program [7]. This includes the selection of the most appropriate antimicrobial agent(s) and ensuring adequate exposure whilst taking into consideration both the pathophysiologic changes of ICU patients and the physicochemical properties of the antimicrobial agent(s) administered to reach optimal pharmacokinetic/pharmacodynamic (PK/PD) targets [8-10]. This task may be accomplished by multidisciplinary teams involving all caregivers (i.e. clinical pharmacologists, pharmacists, microbiologists, physicians, nurses, etc.).

In this review, we firstly review the clinical and pharmacokinetic issues of anti-infective agents in ICU. The second section of the manuscript covers the novel pharmacologic tools that can be used to

optimize anti-infective therapies and patient management in ICU which, when combined with microbiological tools, should open the way to “fast pharmacology” at the bedside.

### 2.1 Clinical issues: Infections in the ICU patient

A high prevalence of infections has been described from both medical and surgical ICU. A recent European multicentre study reported that the proportion of infected patients in ICUs can be as high as 50%; and most of these are healthcare associated [11]. Indeed, ICU patients are at greater risk of developing health care-associated infections (HCAI) (from 9 to 37% compared with 5–15% of the all hospitalized patients) [12] for several reasons such as co-morbidities (i.e. diabetes, chronic lung diseases, etc.), longer stay, impaired host defences, immunosuppressive therapies, older age, colonization by pathogenic or potentially pathogenic microorganisms which are likely to exhibit multi-drug resistance, and invasive diagnostic and monitoring procedures (i.e. endotracheal intubation, central venous catheterization, urinary tract catheters, or mechanical ventilation) [13-15].

The most commonly reported site of infections in the ICU patient is the respiratory tract [13,16,17]. Although the development of nosocomial pneumonia is associated with similar risk factors to other nosocomial infections, there are some predisposing factors that are specific to pulmonary infections: these include endotracheal intubation, mechanical ventilation and micro-aspiration of oropharyngeal secretions. Endotracheal intubation with mechanical ventilation increases the risk of nosocomial pneumonia by 6 to 21 times as it bypasses local defences such as coughing, sneezing, and muco-ciliary clearance. Urinary tract infections, generally associated with the presence of a urinary catheter, are the second most common site of nosocomial infection accounting for 8–35% of infections [13]; the consequences of these infections are usually less severe than for other types of HCAI [13]. The main causes of ICU-acquired bacteraemia are intravascular catheters (29.2%) followed by lower respiratory tract (18.0%) and digestive tract (13.6%) infections; however, the source of ICU-acquired bacteraemia cannot be determined in approximately 25% of cases [18].

The most common organisms causing community-acquired infections resulting in ICU admission are *S.pneumoniae* and *S. aureus* (Gram positive organisms) and *E. coli* (Gram negative organisms). Available beta-lactam antibiotics active against these bacteria did not change in the past decade; however, extended spectrum beta-lactamase-producing *E. coli* and community acquired methicillin-resistant *S. aureus* (MRSA) are increasingly reported. In the majority of studies, Gram-negative bacteria have been reported as the most common cause of ICU-acquired infections.

Among the different pathogens, 16%–20% include MDR phenotypes: MRSA, vancomycin-resistant *E. faecium*, carbapenem-resistant *P. aeruginosa*, extended-spectrum cephalosporin-resistant *K. pneumoniae, K. oxytoca, E. coli,* and *Enterobacter species*, and carbapenem-resistant *P. aeruginosa, K. pneumoniae/ K. oxytoca, E. coli, Enterobacter species,* and *A. baumannii* [19,20] The burden of antimicrobial resistance in ICU is increasing as the severity of patient illness increases, variation in infection control practices and inappropriate antibiotic selection can exert selective pressure on the normal antimicrobial flora resulting in endogenous colonisation with potentially pathogenic organisms [21]. Conversely exogenous colonisation arises from cross-transmission via direct contact, droplet, or aerosol spread from patients, staff, visitors or inanimate objects. For example, direct contact can include spread from the hands of health-care workers or visitors and from contaminated equipment and infusions [13].

Infections in ICU increase morbidity, mortality and length of hospital stay and increase health resource utilization and health care costs [22-24]. Management of these infections includes implementation of antimicrobial stewardship protocols, targeted active microbiology surveillance but above all a rapid etiologic microbiological diagnosis and early use of appropriate antimicrobial therapy.

**2.2 Pharmacokinetic issues**

A basic understanding of pharmacokinetics is important for clinicians when prescribing drugs. This is particularly true for anti-infective agents because under-dosing may result in treatment failure and

increase the likelihood of the development of antimicrobial resistance [9,25]. The achievement of optimal antimicrobial exposure is difficult in clinical practice because most of these drugs are administered according to standard dosing regimens which do not take into account pathophysiologic and/or iatrogenic factors that are likely to affect the pharmacokinetics in ICU patients. This makes the management of antimicrobial therapy in these patients extremely challenging [9,10,25]. The effects of altered pathophysiology in ICU patients on the pharmacokinetics of antimicrobial agents have been recently reviewed [10,26-31] and are briefly summarized below (Table 1).

The most frequently altered pharmacokinetic parameter in ICU patients is the volume of distribution. Infections result in a significant increase in the production of endogenous mediators which can cause endothelial damage, increased capillary permeability and capillary leakage resulting in a shift of the fluids from the intravascular compartment to the interstitial space (third spacing); This is usually treated with fluid resuscitation and catecholamines which, in turn, can cause a significant expansion of the extracellular fluid volumes and, therefore, the apparent volume of distribution of several drugs, including antimicrobial agents. These events cause a significant "dilution" of the systemic concentrations of antibiotics characterized by a low volume of distribution (i.e. less than 20 L such as beta-lactams, aminoglycosides) resulting in suboptimal drug exposure [32]. Conversely, drugs with a large volume of distribution, such as azithromycin, tigecycline, clarithromycin and fluoroquinolones, would be expected to be minimally affected [32].

Approximately 35-40% of ICU patients are severely hypoalbuminemic (serum albumin concentrations < 2 g/dL) [33,34]. This needs to be taken into account when these patients are treated with highly bound antimicrobial agents (those with a drug protein binding >80%), especially if these drugs have some degree of renal elimination. The reduced concentration of albumin is likely to increase the free drug fraction available for elimination through the kidneys resulting in sub-therapeutic drug concentrations. It has been reported that the clearance of highly protein bound

antibiotics such as ertapenem, daptomycin, flucloxacillin, ceftriaxone, can be increased up to 100-500% in hypoalbuminemic ICU patients [33,34].

Another important clinical condition that needs to be carefully considered in ICU is altered renal function, especially when hydrophilic antimicrobials are administered. Acute kidney injury results in reduced drug excretion whilst augmented renal clearance (usually defined by a creatinine clearance >130 mL/min) is associated with a 2-to-8-fold increase in the clearance of renally excreted drugs such as the beta-lactam antibiotics [26,27]. The attending physician must be aware of the creatinine clearance and make the appropriate dose adjustments as renal function changes over time.

Even more complicated is the selection of the optimal antimicrobial dose in patients with extracorporeal clearance (i.e. renal replacement therapy and/or ECMO). For many recently approved antimicrobial agents there is data on their pharmacokinetics in the intermittent hemodialysis patient. However, approximately 5% of ICU patients are treated with continuous renal replacement therapies, such as continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD) or continuous veno-venous hemodiafiltration (CVVHDF) instead of intermittent hemodialysis to better maintain hemodynamic stability [35]. However, pharmacokinetic data of many antimicrobial agents in continuous renal replacement therapy (CRRT) is largely lacking. The same is unfortunately true also for ECMO, an invasive intervention that is increasingly used in ICU to assist critically ill patients with severe lung and/or heart dysfunction. The scanty data available for older drugs have shown that the variable characteristics of ECMO procedures result in large intra- and inter-individual drug pharmacokinetics [36,37].

Finally, drugs metabolized by the hepatic route may be affected in ICU patients with acute or chronic forms of hepatic dysfunction caused by infection associated with hepatocellular injury, ischemia, hemolysis or direct damage from drug-related hepatotoxicity [38].

### 2.3 Drug-drug interaction issues in ICU

Patients admitted to the ICU are at high risk for drug-drug interactions (DDIs) due to the significant number of drugs prescribed and the complexity of drug regimens in this clinical setting [39]. As a consequence, an analysis of risk factors for adverse events in ICU patients reported that an increasing number of medications and DDIs was associated with a higher risk of injury [40].

With regard to DDIs specifically involving anti-infective agents, according to available literature a significant number of patients experienced at least one DDI during their ICU admission, with the antifungal drug fluconazole ranking in the top-ten DDIs, followed by aminoglycosides and macrolides [39,41,42]. More recently, Kusku et al [43] analyzed data from 5 different hospitals and reported that DDIs with antimicrobial agents represented 26% of all interactions, with 42% and 38% of them "contraindicated" and "major", respectively according to the Micromedex online reference system. Notably, apart from the azoles, quinolones, metronidazole, linezolid, and clarithromycin were responsible for 92% of the reported DDIs. In multivariate analysis, the number of prescribed antimicrobial agents (odds ratio: 2.3), the number of prescribed drugs (odds ratio: 1.2), and hospitalization in a university hospital (odds ratio: 1.8) were independent risk factors for developing DDIs. Similarly, Mehralian and co-workers in their cross-sectional prospective study found that 60% of ICU patients had at least one DDI [41]; nearly 87% of them, involving mainly antibiotics, were scored as harmful. Of particular relevance, DDIs involving metronidazole, azoles, azithromycin and quinolones have been associated with QT prolongation. [44,45].

It is clear that the implementation of appropriate programs and interventions aimed to reduce the frequency of DDIs in ICU is critical. An additional important role of a "fast" clinical pharmacology would be the correct and prompt identification of clinically relevant DDIs, taking advantage from both the availability of dedicated drug interaction software [46] and the therapeutic drug monitoring (TDM) of anti-infective and non-anti-infective medications when available [47]. Indeed, preliminary but consistent evidence is now available showing that a combination of the evaluation of potential DDIs by clinical pharmacy/pharmacology services and the monitoring of critically ill

patients is an effective strategy that can be used as complementary tool for safety assessments and the prevention of drug-related adverse events in ICU patients [39,46].

### 3. The fast microbiology: an example to follow

A disadvantage of traditional bacteriological culture techniques has always been the time taken between inoculation of the agar plates and the growth and identification of the pathogenic organisms. In other areas of microbiology such as virology the problem was even greater as routine laboratories were unable to culture viruses and many viruses were difficult to grow even in tissue culture systems. Therefore, rapid diagnostics were not possible and microbiology remained relatively unchanged for many decades. Recently there has been a remarkable effort to develop novel technologies for faster microbiological diagnosis and antimicrobial susceptibility testing, enabling information on pathogen identification and, in some cases, antimicrobial resistance profiles in a shorter timeframe when compared with the conventional diagnostic workflow which involves subculture followed by identification and antimicrobial susceptibility testing carried out from isolated bacterial or fungal colonies. A result could be available within hours, as opposed to the 72 hours required by conventional methods.

The concept of fast microbiology was first introduced by Mulatero *et al* in 2011 [6] who proposed the following definition: fast microbiology is based on a premise of faster results, reducing the time needed for a result, to allow earlier and optimized patient management. There is no universal consensus on the definition of 'fast', but it is reasonable to describe it as obtaining the result within a working day shift (i.e. 8 h) [48].

In recent years a number of novel technologies for the microbiological diagnosis of bacterial infections have been developed that return result in a shorter timeframe when compared with conventional diagnostic approaches. Rapid methods that do not use culture or cultivation of serological processes have gained popularity because they can expedite diagnosis and aid antimicrobial stewardship by reducing the time to appropriate antimicrobial chemotherapy. Rapid

microbial identification and antimicrobial susceptibility testing techniques have been recently reviewed and their detailed description is beyond the scope of the present analysis [5,49,50]. They include multiplex polymerase chain reaction (PCR), matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and lateral flow assays or immuno-chromatographic methods. Novel technologies for rapid diagnosis may still require positive blood cultures or, in selected cases, can work directly from blood specimens. Among these techniques, the implementation of MALDI-TOF MS has increased significantly in the last 10 years and it is now considered a robust technique for rapid microbial identification [50]. This is achieved by searching databases containing mass spectra of peptides and proteins extracted from microorganisms of interest, using scoring algorithms to match analysed spectra with reference spectra to identify an organism.

Irrespective of the technology adopted, a critical component of success is the expertise of the clinical microbiologist. Although the way in which microbiological testing is performed may change, the expert interpretation of test results and the proposal of targeted treatments will remain. Moreover, it must be stressed that the utility of fast microbiology for guidance in the choice of antibiotic therapy should be interpreted in the context of how well physicians choose empiric therapy when facing a challenging clinical situation. Nevertheless, we believe that fast microbiology is a good example of how the optimization of antibiotic therapy can be based on laboratory data matched with specific expertise in the field, providing the rationale for the potential implementation of a fast pharmacology, as detailed in the next sections.

## 4. The potential role of a fast pharmacology in ICU: definitions

A PUBMED search of the term “fast pharmacology” retrieved no results. In the following sections we propose fast pharmacology as a branch of clinical pharmacology by direct analogy with what has been achieved in microbiology and enabled by improvements in analytical techniques. The concept of fast pharmacology facilitates the application of the pharmacologic concepts at the

bedside with the goal of improving the safety and efficacy of antimicrobial therapy for ICU patients.

### 4.1 Therapeutic drug monitoring of anti-infective agents: analytical aspects

TDM is the clinical practice of measuring drugs to optimise individual dosage regimens. This approach is usually adopted in patients treated with narrow therapeutic index drugs such as the aminoglycoside antibiotics. However, it is increasingly recognized that there is a role for TDM for drugs with a wide therapeutic index especially in the ICU setting [51]. However, for TDM to be clinically useful, validated bioanalytical assays with a rapid turnaround time to be used for the quantification of anti-infective drugs in biological matrices are essential.

#### ***4.1.1. Commercial kits available for the quantification of antibiotics***

Historically, the analytical approach to TDM in serum or plasma utilised gas chromatography or high performance liquid chromatography usually coupled with ultraviolet (UV), photo-dyode array (PDA) or fluorescence detector. 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 antimicrobial drugs (Table 2). Even with this limitation, the use of immunoassays in automated chemistry labs for specific assays can offer adequate accuracy and precision and appropriate turnaround times for the critical decision making point.

As shown in Table 2, commercial kits are available for the quantification of antimicrobial agents using liquid-chromatography coupled to mass spectrometry (LC-MS/MS); however, the setting-up of the analytical methods is time-consuming and requires expertise in the field and dedicated personnel. In addition, these kits cover a limited range of available antimicrobial agents. The only option for the application of TDM for all the other anti-infective drugs not included in Table 2, is

through the development and proper validation of in-house methods, taking advantage of technological innovations detailed below.

### ***4.1.2. The improvements in LC-MS/MS***

The use of LC-MS-MS has been expanding rapidly over the last 10 years. The need for ever-increasing productivity in the laboratory and decreasing the time to perform an assay are part of the driving force behind the development of a new field of separation science: the Ultra High Pressure Liquid Chromatography (UHPLC). Coupling UHPLC instruments with tandem mass spectrometry detectors offers superior specificity, higher throughput, better sensitivity and resolution and the ability to undertake qualitative and quantitative analysis on multiple assays within in a single sample analysis. The run times on these assays can very between 5 and 10 minutes depending on many factors such as physical and chemical properties of the analytes, the number of analyses being monitored simultaneously, sample clean up and chromatography and sensitivity of MS detector.

A new liquid-chromatography column technology offers a novel approach to fast chromatography using "Active Flow Technology". This unique design offers up to 5-times higher flow rates through the column, with the ability to perform a radial split of the flow at the column outlet, thus still having the appropriate flow rate being delivered to the MS without compromising the ion source, with the remaining flow diverted to waste. The Active Flow Technology column is designed for ultra-high-throughput assays, enabling reductions of up to 80% in run-time and the ability to overcome well known challenges and limitations of the interface between LC and MS detector. This technology has been developed by Thermo Scientific in partnership with Western Sydney University, Australia and is in process of being commercialised.

To take full advantage of LC-MS/MS as an analytical technique in the clinical setting, it has traditionally been necessary to employ highly skilled scientists to operate the instruments making it an expensive method. The use of automation or simplified techniques to reduce costs is thus desirable.

### *4.1.3 The improvements in pre-analytical step*

Some laboratories are attempting to overall turnaround times by automating the pre-analytical component of a TDM assay with the use of robotics and/or liquid handling instrument. This non-integrated approach still offers improvements in speed, elimination of human error and less operator involvement, as well as the ability to mix-and-match sample preparation devices with LC and MS equipment from different vendors. There are a large number of robots available from multiple vendors, accommodating numerous applications. The selection of appropriate automation is depended on the technique (i.e. protein precipitation, liquid-liquid extraction, solid-phase extraction, etc.) used for the sample preparation and the flow of the laboratory and thus will be specific for the needs of the individual laboratory.

Liquid handling instruments from Tecan® and Hamilton® are designed as flexible, programmable and modular systems that can perform a range of pipetting functions to and from all sample containers typically used in the TDM laboratory including primary tubes, vials and well-plates that can be placed directly into the HPLC autosampler. These systems can greatly accelerate sample preparation steps through the use of multi-channel flow-paths simultaneously processing multiple samples, are flexible to more challenging analytes and allow for the use of (washable) re-usable or disposable pipette tips to control sample carryover.

Tecan® market a range of liquid-handling systems with the Freedom EVO® Clinical system specifically geared towards the workflow and regulatory needs of TDM laboratories. Products with similar capabilities, but marked as Research Use Only, are sold by Hamilton, Gilson and Beckman Coulter Life Sciences division. The benefit of these systems is the range of sample preparation techniques that can be automated, as well as a much larger sample capacity than fully-LCMS-integrated systems described below.

### *4.1.4. Towards automated clinical analysers for LC-MS/MS*

To further improve turnaround times and minimize of the need for highly trained scientists, some vendors have worked towards the development of fully automated clinical analysers incorporating robotic sample preparation and a full LC-MS/MS system in a single unit. These analysers offer the benefits of traditional immunoassay-based automated analysers with minimal sample preparation and involvement required from the operator as well as the specificity offered by mass spectrometry detection. Currently two vendors offer these type of analysers; the CLAM (Clinical Laboratory Automated Module) from Shimadzu and the Thermo Fisher Scientific Cascadion SM Clinical Analyser.

The CLAM 2000 is based on precipitation and filtration analyser technology and can analyse a range of different biological matrices such as blood, plasma, serum and urine. This instrument is labeled as “For Research Use Only” and “Not for use in diagnostic procedures”; however fully automated methods can be validated as in-house in vitro diagnostics (IVDs). Technical notes and application methods for this system are available from the Shimadzu website.

The limitations of this analyser are the ability to couple only Shimadzu MS instruments (8040; 8045; 8050; 8060) to CLAM and the sample capacity of 60. This is not a problem during the day when the autosampler can be continuously replenished but it is not an ideal solution for overnight runs due to the limited capacity.

Based on the same principles the Cascadion SM Clinical Analyser is all-in-one clinical analyser with LC-MS/MS technology designed to meet the needs of routine clinical laboratories. The Cascadion can support the analysis of serum, plasma and whole blood and has the capacity of 60 positions for samples and 60 positions for reagents and controls. The mass spectrometry component is integrated into the unit and is designed to be operated by any user in the laboratory. The Product is IVD/CE-marked but not 510(k) cleared and not available for sale in the U.S. As for the CLAM-2000 system, the Cascadian limits laboratories to a single choice of LC-MS vendor and the limited sample capacity is not suited to overnight or otherwise unattended running, particularly for rapid methods.

### *4.1.5 Towards eliminating the separation step*

While not yet commercially available, mass spectrometry vendor SCIEX, along with their academic and commercial partners, has recently demonstrated some novel and revolutionary approaches to fast analysis by removing the rate-limiting step of the chromatographic separation. A device referred to as the "Open Port Probe" allows for open-access introduction of samples into the mass spectrometer source via a constant stream of carrier liquid. Gómez-Ríos *et al.* [52] used Solid Phase Micro-Extraction (SPME) to capture and concentrate clinically-relevant analytes from urine with subsequent introduction into a Quadrupole-Linear-Ion-Trap mass spectrometer equipped with a Differential Mobility Spectrometry device via the open-port-probe. Loss of specificity resulting from removal of the chromatographic separation was demonstrated to have been circumvented by the use of differential mobility separation or multistage fragmentation, with acceptable quantitative accuracy and precision from analyses requiring only 10-15sec.

More recently, scientists from Labcyte Inc. have demonstrated the use of acoustic liquid handling, where nanoliter-sized droplets can be ejected with accuracy and precision from liquid samples contained in a standard well-plate coupled to mass spectrometry (Acoustic Injection Mass Spectrometry) for ultra-high throughput bioanalysis. While still early in the development cycle, the coupling of acoustic sampling to the open port probe (OPP) shows promise to greatly reduce the need for extensive sample preparation and liquid chromatography separation before tandem-MS analysis with potential throughput of up to three samples per second [53].

## 4.2 Therapeutic drug monitoring of anti-infective agents: an update of therapeutic ranges

The issue of TDM of anti-infective agents in critically ill patients has been recently reviewed by Jager et al [51]. Here, we briefly summarise and update the available evidence on this topic.

### *4.2.1 TDM and antimicrobial toxicity*

The TDM of antimicrobial agents has been clearly proven to be of great clinical relevance for the management and prevention of drug-related toxicity. Indeed, extensive evidence is available demonstrating that aminoglycoside-associated nephrotoxicity or ototoxicity and vancomycin-associated nephrotoxicity are dependent on the absolute drug concentrations and the duration of exposure, providing a solid rationale for the adoption of trough-based TDM as mandatory tool to optimize the use of these antibiotics in clinical practice (reviewed in [51]). Recent studies have also identified trough concentrations predictive of colistin-related nephrotoxicity [54] and teicoplanin-associated neutropenia [55].

Beta-lactam antibiotics are usually well tolerated. Drug-related toxicity is generally ascribed to hypersensitivity reactions, independent from 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 [56]. Similarly, consistent and significant associations have been reported between high cefepime trough concentrations and drug-related toxicity [57-59] although there appears to be heterogeneity in the upper therapeutic threshold to be adopted to prevent cefepime-induced neurological complications.

The oxazolidinone antibiotic linezolid is associated with severe adverse effects including thrombocytopenia, peripheral neuropathy, lactic acidosis and optic neuropathy. Without careful 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 (reviewed in [60]). The potential relationship between linezolid exposure and toxicity is less clearly defined for other adverse effects such as neuropathy and lactic acidosis.

With respect to antifungal agents, solid and consistent evidence is available demonstrating a significant association between voriconazole trough concentrations and drug-related neurological and hepatic adverse events. Two recently published meta-analyses have indeed shown that the likelihood of toxicity associated with supratherapeutic voriconazole trough concentrations (that is trough>4 or trough >6 mg/L according to the meta-analysis considered) was 3-to-4-fold that of therapeutic concentrations [61,62].

A proposal for upper threshold values for drug concentrations that should not be exceeded to limit antimicrobial toxicity is outlined in Table 3.

#### ***4.2.2 TDM and antimicrobial efficacy***

The relationship between absolute drug concentrations and antimicrobial efficacy is more controversial. For some drugs such as teicoplanin, rifampicin, linezolid and voriconazole, concentrations-based minimum therapeutic thresholds targets have been proposed for drug efficacy [51] (Table 3). A meta-analysis of more than 20 studies has recently demonstrated that patients with therapeutic voriconazole blood concentrations (that is trough >1 mg/L) were more likely to have successful outcomes when compared with those with subtherapeutic drug concentrations (odd ratio: 2.3) [61].

Nevertheless, this approach can no longer be considered adequate because it does not take into account the different degree of sensitivity/resistance of a pathogen for a given drug, as exemplified in Figure 1. More correctly, the definition of therapeutic efficacy thresholds, at least for antibiotics, should rely on PK/PD targets (see section 5 for a detailed discussion on this topic). This is less evident for antifungal agents probably due to the difficulties to obtain susceptibility testing and/or minimum inhibitory concentration (MIC) values for these drugs.

## 5. Matching fast microbiology with fast pharmacology: new timings of PK/PD assessments at the bedside

In the previous sections we have emphasized how in the critically ill patient there are significant variations in the processes of distribution and elimination of drugs and how the TDM can help to quantify the individual variations. However, the PK of antimicrobial agents 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 MIC which is defined as the minimum antimicrobial concentration that prevents growth of the pathogen *in vitro*. When a MIC is not available international breakpoints can be used as surrogates for the actual MIC [63]. However, it must be remembered that the MIC value simply reflects the potency of the given antimicrobial and provides no information regarding the time-course of antimicrobial effect nor whether the rate of bacterial killing may be altered *in vivo* by inadequate drug exposure [25]. Accordingly, the best way to categorize an antibiotic or an antifungal drug is through the combination of the PK/PD characteristics as it defines the individualized drug exposure necessary to ensure the optimal drug effectiveness for a given pathogen. In the past, this was considered merely a theoretical concept; however, thanks to the identification of clinically relevant PK/PD targets measurable in hospital laboratories, individualized dosing strategies have been recently proposed [51,64].

Antimicrobial agents can be classified according to the 3 pharmacodyamic properties of antibiotics that best describe killing activity: time-dependence, concentration-dependence, and persistent effects such as post-antibiotic effect which is defined as the persistent suppression of bacterial growth following antibiotic exposure. Time dependent antibiotics, where the rate of killing is determined by the length of time necessary to kill, include the beta-lactam agents. Concentration-dependent antibiotics, where killing is dependent on increasing concentrations of the drug, include aminoglycosides, daptomycin and fluoroquinolones. Some antimicrobial agents such as azithromycin, clindamycin, vancomycin, oxazolidinones and tetracycline exhibit mixedtime-

dependent and concentration-dependent properties. The optimal PK/PD parameter for time, concentration and mixed dependence is T>MIC, Cmax/MIC and 24 hr AUC/MIC respectively. For example, for beta-lactams antimicrobial agents, increments in the blood concentrations have minimal effects on bacterial killing, whereas maintaining drug concentrations above the MIC of the pathogen for a portion of the dosing interval has been shown to best predict microbiologic efficacy [25,51,64]. The PK/PD characteristics of time-dependent antibiotics is theoretically optimized by increased frequency of drug administration or through prolonged or continuous infusion regimens. Despite these promising findings, conflicting results have been noted in more recent studies [65,66], leading to ambiguity regarding the role of this dosing strategy in critically ill patients.

The concentration-dependent antimicrobial agents include "pure" concentration-dependent drugs such as aminoglycosides, daptomycin, and echinocandins which are best characterized by peak-to-MIC ratio ($C_{max}$/MIC) for which strategies aimed at maximizing the magnitude of drug concentrations should be pursued. Mixed concentration-dependent drugs with time-dependency such as fluoroquinolones, glycopeptides, oxazolidinones or antifungal triazoles are best characterized by area under the curve-to-MIC ratio (AUC/MIC), for which strategies aimed at maximizing drug exposure should be adopted. The PK/PD targets for these 3 classes of antimicrobial agents is summarised in Table 3.

A growing body of literature has been published in the last 2-3 years showing that licensed standard doses of antimicrobial agents are often insufficient to achieve PK/PD targets in ICU patients. This has been demonstrated for linezolid [67,68], meropenem [69], ceftriaxone [70], piperacillin-tazobactam [71], daptomycin [72] and antifungal agents [73,74]. Patients at risk of not attaining these targets would benefit from drug dose intensification, with significant improvements in the clinical cure rates. Indeed, Ruiz *et al* have recently demonstrated that an amikacin $C_{max}$/MIC ratio >6 was directly related to the response to treatment and the lack of selection of resistant bacteria in critically ill patients [75]. Similarly, Xu and co-workers prospectively compared standard (50 mg twice daily) versus high doses (100 mg twice daily) of tigecycline for the treatment of pneumonia

caused by MDR bacteria and demonstrated that an AUC/MIC ratio >10 was associated with a higher frequency of clinical cure rate in ICU patients [76]. Similar findings have been reported for other antimicrobial agents as reviewed in [28,29].

These concepts are likely to become even more important in the management of infections in ICU patients considering the new definitions of intermediate (I) microorganisms recently revised by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Intermediate microorganisms are now categorized as "Susceptible, increased exposure" when there is a high likelihood of therapeutic success if exposure to the agent is increased by adjusting the dosing regimen or the concentration at the site of infection; within this definition, exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection. In other words, this new definition emphasizes the importance of optimizing antimicrobial exposure through the application of the above mentioned PK/PD targets.

## 6. Conclusions

The current scenario of persisting poor outcomes for ICU patients with infection, as well as the documented association between suboptimal antimicrobial exposure and treatment failure, call for the urgent and rapid optimization of drug dosing in this clinical setting. A fast pharmacology could help to address this issue by providing TDM results with a short turnaround time and by guiding physicians in the rational adjustment of antibiotic and/or antifungal doses by proper identification and weight of the clinical variables eventually affecting drug pharmacokinetics in ICU through the use of nomograms or dedicated dosing software (reviewed in [77-79]).

Prospective clinical trials are, however, required to determine whether a fast pharmacology-based approach (ideally combined with a fast microbiology to reach PK/PD targets) can significantly improve the treatment of infections in ICU patients.

## 7. Expert Opinion

Actual challenges for the widespread application of a fast-track pharmacology for antimicrobial agents relate to the availability of bioanalytic assays for routine TDM analysis. Only a limited number of commercial kits are actually available for the quantification of antimicrobial agents, primarily the beta-lactam antibiotics and the azole antifungal agents. However, several tools are in development for the full automation of LC-MS/MS methods that could favor the widespread diffusion of these analytical techniques into hospital laboratories, allowing the quantification of drug concentrations in a few hours after sample collection for virtually all antimicrobial agents.

Other concerns include the lack of clear-cut definition of therapeutic ranges for all antimicrobial agents, disagreement on which drug concentrations to be measured (total versus free fraction) and which biological matrix should to be considered (plasma taken as surrogate marker of systemic drug availability versus tissue drug concentrations), as well as lack of data on the pharmacokinetics of these drugs in ICU patients undergoing complex dialysis procedures or ECMO in terms of implementation for each antibiotic of a "standardized" Sieving coefficient and "easy equation" to enable the correct loading and maintenance dose. Growing literature is now available demonstrating that the application of TDM in the routine clinical management of antimicrobial agents (mainly glicopeptides, aminoglycosides, beta-lactams, linezolid and voriconazole) can quantify the contribution of dialysis procedures on drug disposition. However, in the clinical practice, dose adjustments based on TDM results remains largely empiric. This can be significantly improved using drug dosing software with adaptive feedback [64,79]. Indeed, when software packages are implemented in the patient electronic folder or in management software for intensive therapies, they can provide customized software-driven recommendations for dose adjustments based on both individual patient covariate data and TDM data when available [79,80]. Available computerized programs, which generally utilize the Bayesian estimation procedures to optimize antibiotic dosing therapy especially in ICU setting have been recently reviewed [79,81].

The importance of matching pharmacokinetic/TDM data with microbiological data with the goal of reaching the PK/PD targets associated with optimal response to antimicrobial therapy has been emphasized in the text. It must be considered, however, that such PK/PD targets usually rely on the measurement of single MIC determinations which are imprecise measurements [82,83]. Mouton *et al* have suggested ways to further improve the validity of MIC results. In particular, they showed that only repeated measurements of MICs for individual strains within one laboratory may provide an indication of differences in susceptibility between strains [82]. Moreover, they also suggested interpretation of the MIC for target attainment under various conditions, taking into account the MIC found, the number of dilution used, the laboratory proficiency and the extent of the WT distribution [83].

Novel surrogate PD markers of antimicrobial responses as alternative to MIC have been recently proposed [84]. Wilson *et al* have demonstrated that the area under the concentration-time curve required to produce half maximal response (AUC:EC50) can be a useful PK-PD index which reflects both host and bacterial response to ceftriaxone *in vivo*. Preliminary results are encouraging but proper clinical validation in real-life settings is required.

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**References**

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


1. Kollef MH, Bassetti M, Francois B, et al. The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship. Intensive Care Med. 2017;43:1187-1197.

2. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:775-787.

3. Law AC, Stevens JP, Walkey AJ. National Trends in Timing of Death Among Patients With Septic Shock, 1994-2014.Crit Care Med. 2019 [Epub ahead of print].

4. MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis. 2004;38:284-288.

5. Özenci V, Rossolini GM. Rapid microbial identification and antimicrobial susceptibility testing to drive better patient care: an evolving scenario. J Antimicrob Chemother. 2019;74(Supplement_1):i2-i5.

   *** This report provides an excellent review on the rapid microbiological tests available on the market**

6. Mulatero F, Bonnardel V, Micolaud C. The way forward for fast microbiology. Clin Microbiol Infect. 2011;17:661-667.

7. De Waele JJ, Dhaese S. Antibiotic stewardship in sepsis management: toward a balanced use of antibiotics for the severely ill patient. Expert Rev Anti Infect Ther. 2019;17:89-97.

8. Leone M, Roberts JA, Bassetti M, et al. Update in antibiotic therapy in intensive care unit: report from the 2019 Nîmes International Symposium. Anaesth Crit Care Pain Med. 2019;38:647-656.

9. Sumi CD, Heffernan AJ, Lipman J, et al. What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review. Clin Pharmacokinet. 2019;58:1407-1443.

10. Heffernan AJ, Sime FB, Taccone FS, et al. How to optimize antibiotic pharmacokinetic/pharmacodynamics for Gram-negative infections in critically ill patients. Curr Opin Infect Dis. 2018;31:555-565.

11. Zarb P, Coignard B, Griskeviciene J, et al. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Eurosurveillance. 2012;17:4–19

12. Timsit JF, Soubirou JF, Voiriot G, et al. Treatment of bloodstream infections in ICUs. BMC Infect Dis. 2014;14:489.

13. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet. 2003;361:2068–2077.

14. Salgado CD, Sepkowitz KA, John JF, et al. Copper Surfaces Reduce the Rate of Healthcare-Acquired Infections in the Intensive Care Unit. Infect Control Hosp Epidemiol. 2013;34:479–86.

15. Viderman D, Khamzina Y, Kaligozhin Z, et al. An observational case study of hospital associated infections in a critical care unit in Astana, Kazakhstan. Antimicrob Resist Infect Control. 2018;7:1–9.

16. Vincent JL, Bihari D, Suter P, et al. The prevalence of nosocomial infection in intensive care units in Europe. EPIC study J Am MedAssoc 1995;274:639e44.

17. Haque M, Sartelli M, McKimm J, et al. Health care-associated infections - an overview. Infect Drug Resist. 2018;11:2321–2333.

18. Timsit JF, L'Heriteau F, Lepape A, et al. A multicentre analysis of catheter-related infection based on a hierarchical model. Intensive Care Med 2012;38:1662–1672.

19. Edwardson S, Cairns C. Nosocomial infections in the ICU. Anaesthesia & Intensive Care Medicine, 2018; 20:14-18.

20. Haque M, Sartelli M, McKimm J, et al. Health care-associated infections - an overview. Infect Drug Resist. 2018;11:2321–2333.

21. Otter JA, Mutters NT, Tacconelli E, et al. Controversies in guidelines for the control of multidrug-resistant Gram-negative bacteria in EU countries. Clin Microbiol Infect. 2015;21:1057–1066.

22. Ylipalosaari P, Ala-Kokko TI, Laurila J, et al. Intensive care acquired infection is an independent risk factor for hospital mortality: a prospective cohort study. Crit Care. 2006;10:R6.

23. Puchter L, Chaberny IF, Schwab F, et al. Economic burden of nosocomial infections caused by vancomycin-resistant enterococci. Antimicrob Resist Infect Control. 2018;7:7-11.

24. Zimlichman E, Henderson D, Tamir O, et al. Health Care-Associated Infections A Meta-analysis of Costs and Financial Impact on the US Health Care System. JAMA Intern Med. 2013;173:2039–2046.

*** This study provides a well balanced pharmacoeconomic analysis of the costs associated with health care associated infections**

25. Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin Ther. 2016;38:1930-1047.

26. Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. Pharmacotherapy. 2015;35:1063-1075.

27. Udy AA, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol. 2011;7:539-543.

28. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. Crit Care. 2018;22:233-237.

29. Heavner MS, Claeys KC, Masich AM, et al. Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients. Curr Infect Dis Rep. 2018;20:10-16.

30. Zamoner W, de Freitas FM, Garms DS, et al. Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients. Pharmacol Res Perspect. 2016;4:e00280.

31. Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care. 2015;21:412-420.

32. Pea F. Intracellular Pharmacokinetics of Antibacterials and Their Clinical Implications. Clin Pharmacokinet. 2018;57:177-189.
***This report provides an updated review on the intracellular pharmacology of antibacterials**

33. Roberts JA, Pea F, Lipman J. The clinical relevance of plasma protein binding changes. Clin Pharmacokinet. 2013;52:1-8.

34. Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50:99-110.

35. Heung M, Yessayan L. Renal Replacement Therapy in Acute Kidney Injury: Controversies and Consensus. Crit Care Clin. 2017;33:365-378.

36. Honore PM, Jacobs R, De Waele E, et al. Applying pharmacokinetic/pharmacodynamic principles for optimizing antimicrobial therapy during continuous renal replacement therapy. Anaesthesiol Intensive Ther. 2017;49:412-418.

37. Kuang D, Verbine A, Ronco C. Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. Clin Nephrol. 2007;67:267-284.

38. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014;77:3-11.

39. Fitzmaurice MG, Wong A, Akerberg H, et al. Evaluation of Potential Drug-Drug Interactions in Adults in the Intensive Care Unit: A Systematic Review and Meta-Analysis. Drug Saf. 2019;42:1035-1044.

40. Kane-Gill SL, Kirisci L, Verrico MM, et al. Analysis of risk factors for adverse drug events in critically ill patients. Crit Care Med. 2012;40:823-828.

41. Mehralian HA, Moghaddasi J, Rafiei H. The prevalence of potentially beneficial and harmful drug-drug interactions in intensive care units. Drug Metab Pers Ther. 2019 [Epub ahead of print].

42. Łój P, Olender A, Ślęzak W, et al. Pharmacokinetic drug-drug interactions in the intensive care unit - single-centre experience and literature review. Anaesthesiol Intensive Ther. 2017;49:259-267.

43. Kuscu F, Ulu A, Inal AS, et al. Potential Drug-Drug Interactions with Antimicrobials in Hospitalized Patients: A Multicenter Point-Prevalence Study. Med Sci Monit. 2018;24:4240-4247.

44. Armahizer MJ, Seybert AL, Smithburger PL, et al. Drug-drug interactions contributing to QT prolongation in cardiac intensive care units. J Crit Care. 2013;28:243-249.

45. Smithburger PL, Seybert AL, Armahizer MJ, et al. QT prolongation in the intensive care unit: commonly used medications and the impact of drug-drug interactions. Expert Opin Drug Saf. 2010;9:699-712.

46. Reis AM, Cassiani SH. Evaluation of three brands of drug interaction software for use in intensive care units. Pharm World Sci. 2010;32:822-828.

47. Gervasoni C, Formenti T, Cattaneo D. Management of Polypharmacy and Drug-Drug Interactions in HIV Patients: A 2-year Experience of a Multidisciplinary Outpatient Clinic. AIDS Rev. 2019;21:40-49.

48. Buehler SS, Madison B, Snyder SR, et al. Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis. Clin Microbiol Rev. 2016;29:59-103.

49. Narayanan M. New technologies in microbiology and their potential impact on paediatric practice. Arch Dis Child. 2019;104:513-517.

50. Jang KS, Kim YH. Rapid and robust MALDI-TOF MS techniques for microbial identification: a brief overview of their diverse applications. J Microbiol. 2018;56:209-216.

51. Jager NG, van Hest RM, Lipman J, et al. Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol. 2016;9:961-79.

52. Gómez-Ríos GA, Liu C, Tascon M, et al. Open Port Probe Sampling Interface for the Direct Coupling of Biocompatible Solid-Phase Microextraction to Atmospheric Pressure Ionization Mass Spectrometry. Anal Chem. 2017;89:3805-3809.

53. Sinclair I, Bachman M, Addison D, et al. Acoustic Mist Ionization Platform for Direct and Contactless Ultrahigh-Throughput Mass Spectrometry Analysis of Liquid Samples. Anal Chem. 2019;91:3790-3794.

54. Sorlí L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, Alvarez-Lerma F, Knobel H, Benito N, Horcajada JP. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis. 2013;13:380-387.

55. Kim SH, Kang CI, Huh K, et al. Evaluating the optimal dose of teicoplanin with therapeutic drug monitoring: not too high for adverse event, not too low for treatment efficacy. Eur J Clin Microbiol Infect Dis. 2019;38:2113-2120.

56. Imani S, Buscher H, Marriott D, et al. Too much of a good thing: a retrospective study of β-lactam concentration-toxicity relationships. J Antimicrob Chemother. 2017;72:2891-2897.

57. Lau C, Marriott D, Gould M, Andresen D, Reuter SE, Penm J. A retrospective study to determine the cefepime-induced neurotoxicity threshold in hospitalized patients. J Antimicrob Chemother. 2019 [Epub ahead of print].

58. Boschung-Pasquier L, Atkinson A, Kastner LK, et al. Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study. Clin Microbiol Infect. 2019. [Epub ahead of print].

59. Huwyler T, Lenggenhager L, Abbas M, et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect. 2017;23:454-459.

60. Rao GG, Konicki R, Cattaneo D, et al. Therapeutic Drug Monitoring Can Improve Linezolid Dosing Regimens in Current Clinical Practice: A Review of Linezolid Pharmacokinetics and Pharmacodynamics. Ther Drug Monit. 2019 [Epub ahead of print].

61. Luong ML, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother. 2016;71:1786-99.

62. Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. J Antimicrob Chemother. 2016;71:1772-1785.

63. Mouton JW, Brown DF, Apfalter P, et al. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clin Microbiol Infect. 2012;18:E37-E45.

64. Roberts JA, Kumar A, Lipman J. Right Dose, Right Now: Customized Drug Dosing in the Critically Ill. Crit Care Med. 2017;45:331-336.

65. Abdul-Aziz, H. Sulaiman, M.B. Mat-Nor, V, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent β-lactam infusion in critically ill patients with severe sepsis Intensive Care Med 2016;42:1535-1545.

66. Dulhunty JM, J.A. Roberts JA, J.S. Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis Am J Respir Crit Care Med 2015;192:1298-1305.

67. Taubert M, Zoller M, Maier B, et al. Predictors of Inadequate Linezolid Concentrations after Standard Dosing in Critically Ill Patients. Antimicrob Agents Chemother. 2016;60:5254-5261.

68. Minichmayr IK, Schaeftlein A, Kuti JL, et al. Clinical Determinants of Target Non-Attainment of Linezolid in Plasma and Interstitial Space Fluid: A Pooled Population

Pharmacokinetic Analysis with Focus on Critically Ill Patients. Clin Pharmacokinet. 2017;56:617-633.

69. Ehmann L, Zoller M, Minichmayr IK, et al. Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study. Crit Care. 2017;21:263-267.

70. Ollivier J, Carrié C, d'Houdain N, et al. Are Standard Dosing Regimens of Ceftriaxone Adapted for Critically Ill Patients with Augmented Creatinine Clearance? Antimicrob Agents Chemother. 2019;63: e02134-18.

71. Carrié C, Legeron R, Petit L, et al. Higher than standard dosing regimen are needed to achieve optimal antibiotic exposure in critically ill patients with augmented renal clearance receiving piperacillin-tazobactam administered by continuous infusion. J Crit Care. 2018;48:66-71.

72. Soraluce A, Asín-Prieto E, Rodríguez-Gascón A, et al. Population pharmacokinetics of daptomycin in critically ill patients. Int J Antimicrob Agents. 2018;52:158-165.

73. Pérez-Pitarch A, Ferriols-Lisart R, Aguilar G, et al. Dosing of caspofungin based on a pharmacokinetic/pharmacodynamic index for the treatment of invasive fungal infections in critically ill patients on continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2018;51:115-121.

74. Aoyama T, Hirata K, Hirata R, et al. Population pharmacokinetics of fluconazole after administration of fosfluconazole and fluconazole in critically ill patients. J Clin Pharm Ther. 2012;37:356-363.

75. Ruiz J, Ramirez P, Company MJ, et al. Impact of amikacin pharmacokinetic/pharmacodynamic index on treatment response in critically ill patients. J Glob Antimicrob Resist. 2018;12:90-95.

76. Xu Y, Jin L, Liu N, et al. Evaluation of the ratio of the estimated area under the concentration-time curve to minimum inhibitory concentration (estimated AUIC) as a predictor of the outcome for tigecycline treatment for pneumonia due to multidrug-resistant bacteria in an intensive care unit. Int J Infect Dis. 2019;82:79-85.

77. Röhrig R, Beuteführ H, Hartmann B, et al. Summative software evaluation of a therapeutic guideline assistance system for empiric antimicrobial therapy in ICU. J Clin Monit Comput. 2007;21:203-210.

78. Williams P, Beall G, Cotta MO, et al. Antimicrobial dosing in Critical Care: A pragmatic adult dosing nomogram. Int J Antimicrob Agents. 2019 [Epub Ahead of Print].

79. Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14:498-509.
****This reports provides a complete review on the PK/PD changes of antibiotics in critically ill patients**

80. Fuchs A, Csajka C, Thoma Y, et al. Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin Pharmacokinet. 2013;52:9-22.

81. Avent ML, Rogers BA. Optimising antimicrobial therapy through the use of Bayesian dosing programs. Int J Clin Pharm. 2019;41:1121-1130.

82. Mouton JW, Meletiadis J, Voss A, et al. Variation of MIC measurements: the contribution of strain and laboratory variability to measurement precision. J Antimicrob Chemother. 2018;73:2374-2379.

***This review deals with the main limitation of single MIC assessments**

83. Mouton JW, Muller AE, Canton R, et al. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother. 2018;73:564-568.

84. Wilson R, Farkas A, Rawson TM, et al. A prospective study investigating the prediction of beta-lactam pharmacodynamics using AUC:EC50. 29th ECCMID Congress, Amsterdam, April 13-16, 2019 [Abstract 00825].

## Legend to the Figures

*Figure 1*

The upper panel depicts the time-course blood concentrations of an oral antimicrobial (dashed lines represent different MIC values). The table describes the probability to reach a pre-specified PK/PD cutoff according to different MIC values but at equal drug trough concentrations.