The role of the clinical pharmacokinetics service on the battle against pathogens

C. Sanches-Giraud[1,2], **C.V. Silva Jr**[1], **D.S. Gomez**[3] and **S.R.C.J. Santos**[1]

[1] Clinical Pharmacokinetics Research Group, School of Pharmaceutical Sciences, University of Sao Paulo – Sao Paulo/SP, Brazil
[2] Federal Universityof São João del Rei, Campus Centro Oeste – Divinópolis/MG, Brazil
[3] Plastic Surgery and Burns Division, Hospital das Clinicas/Medical School, University of Sao Paulo – Sao Paulo/SP, Brazil

Antimicrobial resistance occurs as a function of several factor´s including the lack of laboratory support to the clinical team related to Therapeutic Drug Monitoring (TDM) Service. In addition, improvements on antimicrobial prescriptions an important tool to optimize the treatment of critical patients in sepsis, once dosing regimens optimized are required to avoid sub-optimal dosing. PK/PD analysis is the main tool available actually to guarantee antimicrobial effectiveness by severe infections control in critically ill patients. This task can be performed by several hospital's team efforts from the central laboratory including microbiology service linked to the clinical pharmacokinetics´ service, known also by TDM service. Thus, this chapter will focus on three steps of clinical pharmacokinetic service: blood sample´s collection (pre-analysis), purification of biological matrices followed by the quantification of the analyte in serum or plasma (analytical procedure) and the interpretation of drug analysis by PK study (in vivo data) plus PD parameter (in vitro data based on the minimum inhibitory concentration/MIC).

Keywords: Clinical pharmacokinetics, PK/PD correlation, Antimicrobials, drug plasma monitoring

1. Introduction

Microbial drug resistance is a worldwide concern with different actions fronts needed to minimize its occurrence and damage. The first action, and the most important, is prevention and control; as examples promoting hygiene, sanitation, access to potable water, vaccination and prophylaxis in surgery. The second action is to promote research and development of new classes of antimicrobials. The use of advanced therapies is the third action required and includes the use of new medical products as genes, cell's therapy or tissue engineering. Finally, the last, but not the least action is to optimize the use of available antibiotics [1,2].

Improvements on antimicrobial usage are essential once resistance partially induced by misuse or abuse of them. Dosing regimen optimization is required to avoid both sub-optimal dosing with consequent drug resistance emergent, poor clinical outcomes and high exposures with increased incidence of side effects, treatment drop and consequently clinical failure [1,3-5]. The main tool actually available is the PK/PD analysis concentrating two main specialties of the hospital team and clinical laboratory: clinical pharmacokinetic (also known as therapeutic drug monitoring service) plus microbiology services.

During drug development, estimation of PK parameters and establishment of dosing regimens are based on clinical trials conducted in healthy volunteers. However, in clinical practice, as reported in patients critically ill with severe infections, the infection host isn't in a health state and consequently, with a different PK profile and the outcome becomes unpredictable [1,3].

In other chapters, more information is provided about microbiology services; thus, this chapter will focus on clinical pharmacokinetic services based on the subsequent steps: pre-analytical at the first step, analytical procedure for drug plasma measurements at the second step and finally, at the last step, patient data interpretation. It is important to highlight that PK/PD analysis have being considered a valuable tool to improve the patient' outcome and be cost-saving, reducing the length of the patient' ICU staying, and to avoid microbial drug resistance. Therefore, the aim of this chapter is to review drug monitoring practices focusing in PK/PD analysis.

2. Clinical Pharmacokinetics Services

One of basic pharmacokinetics principle is kinetic homogeneity; postulating that plasma drug concentrations reflect receptor drug concentration. Otherwise, this assumption is wrong when the sampling is performed at inappropriate times, a delayed absorption is present, a hypoalbuminemia are happening. In these cases dose adjustment could be an inappropriate decision. Thus, to guarantee a confident dosing and, as a consequence, the effectiveness of antimicrobial therapy it is important standardizing procedures from the pharmacokinetics' services focusing in best practice [6]. Finally, table 1 summarize the requirements of therapeutic drug monitoring in routine clinical practice.

Table 1 Requirements for antimicrobials therapeutic drug monitoring [7].

Antimicrobial	Patients eligible for TDM	Sampling Time	Assay	Dose Adjustment strategies
β-lactams	Sepsis or septic shock	Trough at steady state	-Determination of unbound concentration - Liquid Chromatography	calculating the individual patient's drug clearance
Aminoglycosides	Burns, septic shock and hemodynamic and/or renal function.	Two samples: -30 min post completion of the drug infusion - 6–22 hours post administration	immunoassay	Calculate individual AUC and dosage adjustment using dosing software
Vancomycin	-In patients with high doses; during therapy with other nephrotoxic or ototoxic agents; -In patients with unstable renal function, -Receiving prolonged therapy (>3 to 5 days), during renal replacement therapy -In hemodynamically unstable critically ill septic patients	Trough concentrations at steady state	immunoassay	-Proportionally increasing or decreasing the dose relative to the ratio of the measured and the target concentration. -Real time Bayesian forecasting coupled with TDM is thought to be most accurate.
Linezolid	- Critically ill patients with sepsis, burns, pleural and peritoneal effusions, organ failure; - Multidrug resistant bacteria; - Pharmacokinetic interactions; -Long term linezolid therapy	Trough concentrations at steady state	HPLC in plasma, dried plasma spots or oral fluid.	- Increasing or decreasing the dose proportionally relative to the ratio of the measured and the target concentration.
Fluoroquinolones	TDM is not recommended	At least two samples at the steady state.	HPLC in plasma or dried blood spots; capillary electrophoresis or immunoassay.	No validated approach.

3. Pre-analytical management

3.1 Information from dataset form

The main information required from patient records are:

- Patient information at admission in the Intensive Care Unit: sex, age, BW, height, an admission narrative, current medical history, presumed diagnoses, co-morbidities and previous medical history
- Information related to the suspected or documented infection including fluids and secretions collected for cultures, microbiology data, and the target of infection
- Antimicrobial therapy: first choice agents recommended to the initial therapy
- Daily dose of the antimicrobial chosen and dose regimen including D0
- Time of the last dose administered
- Daily routine laboratory data including specific biomarkers'
- Complete electronic drug prescription
- Last medical evaluation reports and image exams of clinical relevance

It's important to highlight the exact actual time when the last dose was administered to the patient, as well as the exact actual time of blood sampling for TDM contributes to dose adjustment for optimization of antimicrobial therapy, once a delay of 0.5 to 1-hour result in unacceptable error for drug plasma measurements.

Additional information is from microbiology data, previous infections and hospitalization reports, concomitant medicines prescribed (vasoactive drugs, another's antimicrobial, and drug interaction) and co-morbidities of the patient.

Finally, accuracy of information collected is essential. Thus, double checking from the patient drug sheet a nursing chart is essential to minimize potential errors, especially from timing [8].

3.2 Biological matrix and sampling

For antimicrobial PK/PD analysis it is important to guarantee steady-state concentrations achievements. If a dose adjustment is performed based on drug concentrations while the accumulating process is still occurring, disastrous results can occur. Additionally, this time period of five half-lives should also be respected after a dose adjustment is performed. An important exception occurs in prophylaxis treatments, where in a unique dose or in a small dosing interval, the therapeutic concentration should be achieved. Thus, the loading dose should guarantee the coverage of the PK/PD index proposed.

Set' blood sample follows a specific standardization procedure on the basis of the bioanalytical method chosen for drug measurements (whole blood, serum or plasma), blood sampling from the venous catheter to vacuum-tubes with or without anticoagulant agents; and finally if stabilizer solution must be added prior to the storage of samples for drug analysis.

Concerning sampling schedule, the appropriate timing should be carefully planned to represent the goal. The trough is usually the elect time in general TDM analysis; otherwise, in PK/PD analysis will depend of the antimicrobial profile. For example, for a concentration dependent antimicrobial, the sampling should be strategically programmed to represent the peak plasma drug concentration.

Serum or heparinized plasma is the preferred specimen. The site of the blood sample collection's site should also be a concern. Some reports, shown that plasma concentrations obtained from central venous access devices are higher than peripheral catheters [9]. Additionally, there is evidence that samples collected at gel separators interfere in drug measurements in an unpredictable manner [10].

The timing also is an important point of discussion and should be carefully designed and should be a focus of education [11]. For example, for many years, drug plasma concentrations of vancomycin were performed by sampling Peak and Trough; but the evidence of the peak concentration measurements are weak, and trough concentrations are sufficient to predict efficacy and safety of vancomycin [12].

3.3 Purification of biological matrices

For antimicrobial analysis, three main information are required: only unbound antibiotics concentrations are responsible for the effect at the target site; concentrations of the free fraction is always lower than the total plasma concentration; hypoalbuminemia is a common condition in critical ill patients and albumin serum concentrations are inversely proportional to free drug concentrations. Thus, the measurements of free tissue concentrations of antibiotics are essential [13]. Several techniques are available to measure the free fraction as:

- Microdyalisis: evaluate the tissue perfusion by the drug diffusion between interstitial fluid and dialysis solution. This technique has been applied in animal models to evaluate drug permeability. But, in clinical practice, there is no evidence supporting its application since it is an uncomfortable technique with the need of high trained support personnel with any evidence of better outcomes [14].
- Ultrafiltration: molecular weight cut-off. The main disadvantage of this technic is the high cost to perform procedure [15].
- Estimation of free drug plasma concentration: has been applied for albumin drug binding studies by the equation bellow (Eq.1), but the lack of accuracy has been pointed [13]:

$$\text{Free concentration} = (\text{drug plasma concentration})/(1 + (n\text{Ka} \times \text{serum albumin})) \quad \text{Eq. (1)}$$

Where: n (the number of drug binding sites per albumin molecule) and Ka (association constant). Finally, for zero order kinetics drugs with a high extent protein binding, as phenytoin, the bellow equations are described [16]:

$$C^{SS}_{trough}\ (\text{Normal Salb}) = \text{Total } C^{SS}_{trough}/[0.9 \times (\text{serum albumin}/4{,}4) + 0.1] \quad \text{Eq. (2)}$$

4. Analytical procedure

Other critical step in the clinical pharmacokinetic service is to guarantee the specificity and accuracy of the assays used. Actually, a large variability of analytical methods of sample quantification is available, from radioimmunoassay to high performance liquid chromatography procedures. The most common methods in clinical practice are the immunoassays: fluorescence polarization immunoassay (FPIA), enzyme multiplied immunoassay technique (EMIT) and enzyme-linked immunosorbent assay (ELISA). The main disadvantage of the immunoassay is specificity; cross-reaction with metabolites or drug-like substances is common and results in untrue concentrations [17,18]. Additionally, the presence of interferences (bilirubin, haemoglobin, lipids) should always be considered when quantifying.

5. Interpretation of drug analysis

5.1 Pharmacokinetic study (in vivo data)

Pharmacokinetics (PK) is known as the study of the time course of drug by absorption, distribution, metabolism and excretion in the body by measuring the evolution of the drug's concentration in different fluids. All these process conditions the pharmacokinetics of the drug and undergo different concentration-time profile according each individual physiologic characteristic. The main PK parameters are described on table 2.

Table 2 Pharmacokinetics parameters presentations [18].

PK parameter	Abbreviation	Unit	Definition
Peak	C^{ss}_{max}	mg/L	Maximum concentration at steady state
Trough	C^{ss}_{min}	mg/L	Minimum concentration at steady state
Area Unter the Curve	AUC^{ss}	mg.h/L	Area under the plasma concentration at steady state over time dosing curve. It´s the measurement of the bioavailability of drugs.
Clearance	CL	L/h.kg	Describes the removal of the drug from a volume of plasma in a given amount of time (drug loss from the body)
Volume of distribution	Vd	L/kg	Indicates the extent of drug distribution by the body.
Half-life	$t_{1/2}$	h	The time necessary for the drug plasma concentration to decrease by half.

An important concept that should always be kept in mind in therapeutic drug monitoring is the accumulation and steady state levels, with exception to surgical prophylaxis. Since antimicrobial treatment is a succession of dose administration of a drug a body drug accumulation is observed. After approximately five half-lives equilibrium (steady state) will be reached. For more information see Book 4 [18].

5.2 Pharmacodynamic parameter (in vitro data) and clinical's breakpoints

Pharmacodynamic is known as the relationship between drug concentration at the site of action and the resultant effect. In infection treatment the expected effect is microbial killing ability. The parameters indicating this effect is the minimum inhibitory concentration (MIC), defined as the lowest concentration that completely inhibits the visible growth of the organism in standards techniques [01, 18]. Several methodologies for MIC estimation are available in the microbiology service as disk diffusion, microdilution, macrodilution and E-test [1,4]. Sample collection for MIC determination (catheter, fluids, sounds, secretions, etc.) should always be collected before antimicrobial therapy beginning. Once the MIC's quantification, the desirable drug plasma concentration may be predicted by the PK/PD correlation.

The main limitation of MIC determination is estimating a bacterium killing from static antimicrobial concentrations, since antimicrobial concentrations in vivo is constantly floating in the human body fluids. Therefore, in vitro time-kill kinetic studies provides a closer approach since it is possible to study the effect of different dosing regimens, clearance, sites of infection, protein binding and other variables. Unfortunately, due to costs and complexity, time-kill curves are applied only in drug development [1].

A clinical breakpoint, also known as susceptibility, is based on the probability of an antimicrobial therapy propitious response against the strain. It serves as interpretative criteria and guides the antimicrobial prescription, selection or discard in clinical practice. Categorizing bacterial strains as susceptible, intermediate or resistant [1]. On the other hand, PK/PD breakpoints plus clinical data are of huge interest and necessary to establish effective breakpoints and will be discussed ahead.

PK/PD breakpoints are dependent mainly of drug regimen, despite the microbial species; thus, different breakpoints can be obtained for the same drug. This is the breakpoint used by some committees as European Committee on Antimicrobial Susceptibility Testing (EUCAST) and clinical and Laboratory Standards Institute (CLSI). PK/PD breakpoints are estimated as the highest MIC value the highest probability of target attainment (PTA), higher than 90% (PTA>90%). Obviously, the discrepancies are shown and MIC isolation is the most confident data; however, when laboratorial MIC data aren't available, these breakpoints are resorted [1].

5.3 PK/PD principles

The PK/PD index represents the quantitative correlation between both the pharmacokinetic and the pharmacodynamic parameters. It is composed mainly by three indices used to predict drug effectiveness as follows [18]:

- The percentage of time unbound drug concentration is above the MIC (%fT>MIC) – antimicrobial activity exhibits concentration dependent killing and no or small persistent effects. Only the unbound fraction is considered. This index is considered for the β-lactams (penicillin´s, cephalosporin's, carbapenems and monobactams), erythromycin, clarithromycin and lincosamide.

- The 24 hours free drug area under the concentration-time curve and MIC ratio (AUC0-24/MIC) – antimicrobial activity exhibits concentration dependent killing with prolonged persistent effects; examples are tetracycline's, tigecycline, macrolides, azithromycin, clindamycin, linezolid and other oxazolidinones, chloramphenicol, trimethoprim, sulfonamides or vancomycin.
- The free drug peak concentration and MIC ratio (Cmax/MIC) – antimicrobial activity exhibits concentration dependent killing with prolonged persistent effects. Some of the antimicrobial with this activity also present the AUC/MIC index. Examples are aminoglycosides, fluoroquinolones, polymyxins, daptomycin or metronidazole.

Magnitude of the index is different for each antimicrobial and should always be considered as a marker of efficacy as described in Table 3.

Table 3 Antimicrobial PK/PD index [1,13,19,20].

Antimicrobial	PK/PD index
Amynoglicosides	Cmax/MIC>8
Azithromycin	fAUC$_{0\text{-}24}$/MIC>25
Carbapenem	40-75%fT>MIC
Cephalosporins	60-100%fT>MIC
Clarithromycin	fAUC$_{0\text{-}24}$/MIC>25
Colistin	fAUC$_{0\text{-}24}$/MIC>7-23
Daptomycin	AUC$_{0\text{-}24}$/MIC>200
Linezolid	fAUC$_{0\text{-}24}$/MIC>85
Penicillins	50-60%fT>MIC
Quinolones	fAUC$_{0\text{-}24}$/MIC>30-250
Teiclopramine	No validated targets
Tetracycline	AUC$_{0\text{-}24}$/MIC>25
Tigecycline	AUC$_{0\text{-}24}$/MIC>18
Vancomycin	AUC$_{0\text{-}24}$/MIC>400

Abbreviations: f: unbound fraction; AUC0–24/MIC: ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. Cmax/MIC=ratio of maximum concentration of antibiotic to minimum inhibitory concentration. %fT>MIC: percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration.

5.5 Populational PK/PD estimation

In daily routine uncertainty is always present, a classical example is the initial dose with no knowledge of individual PK parameters. This data, in general, comes from population studies. Once therapeutic drug monitoring for individual dose adjustment is not available for many antimicrobials in the routine of clinical setting, population PK estimation presents itself as an important tool to determine an antimicrobial optimal dose regimen, presenting a maximum probability to attain the PK/PD target and considering a population as similar as possible of the individual. Most often in PK/PD analysis, a simple approach of population a data as means or medians are not accurate and seems to be a poor efficacy predictor. Thus, simulation based approaches are needed and the Bayesian estimation by Monte Carlo simulation is commonly used. The main advantage is allowing expansion of sample size considering, in this case, the variability of both PK and PD parameters to predict the PK/PD index [1,19].

To perform a population simulation, by the nonlinear mixed effect, the main requirements are [21]:

- Population PK parameters; Inter-individual variability and analyze the influence of individual characteristic on the PK-parameters
- Pharmacodynamic model
- PK/PD index already validated

Population PK/PD analysis, the probability of target attainment (PTA) represents the percentage of simulated patients with PK/PD index estimated equal to or higher than the efficacy value of the antibiotic against a certain MIC from a pathogen. Commonly PTA above 90% is desirable. The MIC´ cut-off is the pharmacodynamic target (PDT) [1].

On the other hand, on clinical practice, when diagnose has been made, in many times the microorganism susceptibility has not been determined. In these situations, the cumulative fraction of response (CFR) is used to determine the population PTA at a dosing regimen, given a population of microorganisms. It expresses the probability of a dosing regimen to access success against a microorganism in the absence of MIC value. Thus, the MIC population distribution is used. It is important highlighting that MIC population distribution selection is always critical once a large variability is present between countries, regions or health centers. Additionally, the susceptibility testing should always be performed with the PK/PD approach; non-observance of this can lead to misleading results and treatment failure.

Nevertheless, five steps required to select the optimal dosing regimens in antimicrobial therapy were proposed [1]:

- 1st step: To obtain PK-population data for a specific group of patients that requires changes on dose regimen
- 2nd step: To determine PK/PD index and its magnitude
- 3rd step: To simulate a dosing regimen based on the PK-population data for each specific group of patients
- 4th step: To determine the PTA on the basis of the PK/PD index
- 5th step: Dosing regimen is chosen, if PTA > 90%; but if PTA bellows 90% a new simulation must be performed to select the best dosing regimen.

Actually, different software's available combines individual data from each individual patient to the PK-population model estimated by Bayesian approach; these combinations can offer an appropriate dose to achieve the PK/PD index. It is important to test each program available to the drug target that contains interfaces, costs, etc., illustrated as follows [21].

5.6 Selection of the drug infusion

The appliance of PK/PD index has been applied to elucidate the infusion role in drug effectiveness. In time-dependent antibiotics, it has been demonstrated that continuous infusion, mainly form β-lactams guarantee better target achievements than the short infusion. On the other way, for concentration-dependent antibiotics once a day dosing instead of lower doses more times a day also has been evaluated [14,19].

For β-lactams antibiotics an extensive change on PK parameter has been shown subtherapeutical concentrations. Thus, therapeutic drug monitoring became an indispensable tool for drug effectiveness measurement. It has been proposed that higher concentrations of four to five times the MIC (%fT>4xMIC) would provide better tissue penetration, especially in life-threatening infections. Additionally, to guarantee this target, continuous infusion, more frequent dosing and extended infusions have been proposed, but till the moment, there is conflicting evidence of the benefits in patient's outcome [14,22,23]. Based on a meta-analysis approach, an important improvement related to the successful of antimicrobial therapy was registered; a reduction on patients' mortality was also found concerning to the systemic administration of antimicrobials by comparison of prolonged drug infusion against the intermittent boluses. It was suggested by the authors, a serial of limitations related to drug administration by the infusion in clinical practice as described below [24]:

- Low stability of some antimicrobials at room temperature;
- Low number of pumps available and infusion devices;
- Limited intravenous access in critically ill patients;
- Incompatibilities with co-medications
- Patients' mobility limitation.

6. Antimicrobial dose individualisation in specific populations

6.1 Critically ill patients

In critically ill patients, a large inter and intra individual variability are seem, once changes on pathophysiology and intensive care procedures patients undergoes are in constant changes and, consequently, are the PK. Thus, the empiric antibiotic protocols to treat infectious diseases aren't recommended. Additionally, microorganisms with reduced susceptibility are found in the ICU contributing to the variability, more specific the PD variability (Fig. 1) [1,4,5,19,25,26].

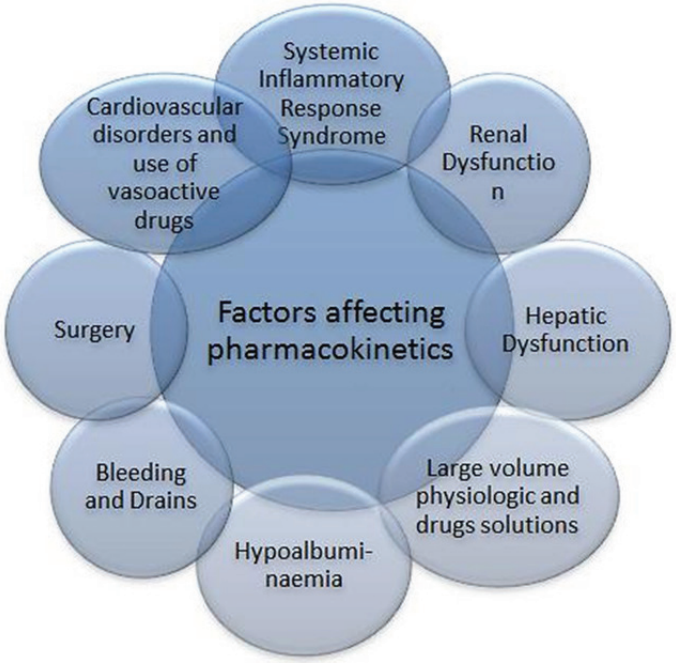

Fig. 1 Factors affecting Pharmacokinetics [1,4,5,19,25,26].

PK changes of many drugs are expected in critically ill patients, once increases or decreases on the volume of distribution, or in total body clearance and reduction or increases on protein drug plasma binding occur. Then, critically ill patients, including higher surgeries, polythrauma and burns with severe infection (sepsis, pneumonia, and bacteremia) have the Systemic Inflammatory Response Syndrome (SIRS) associated. The SIRS indicates that infection is systemic and it is characterized by hypothermia, leucopenia or leukocytosis, tachycardia, hypotension, tachypnea and produces the sepsis' syndrome. These changes are responsible for the large population' variability and makes unpredictable drug plasma level as reported by Carlier et al, 2014. Consequently, the probability to achieve the target is reduced in these patients; thus the antimicrobial dose regimen individualization is emergent by TDM (therapeutic drug monitoring) and a combination of anti-infective agents is recommended. PK-population data estimated by Monte Carlo Simulation program is an alternative to dose adjustment; but the specificity of the population should be considered as presented below [04, 05, 19, 27, 28](Fig.02).

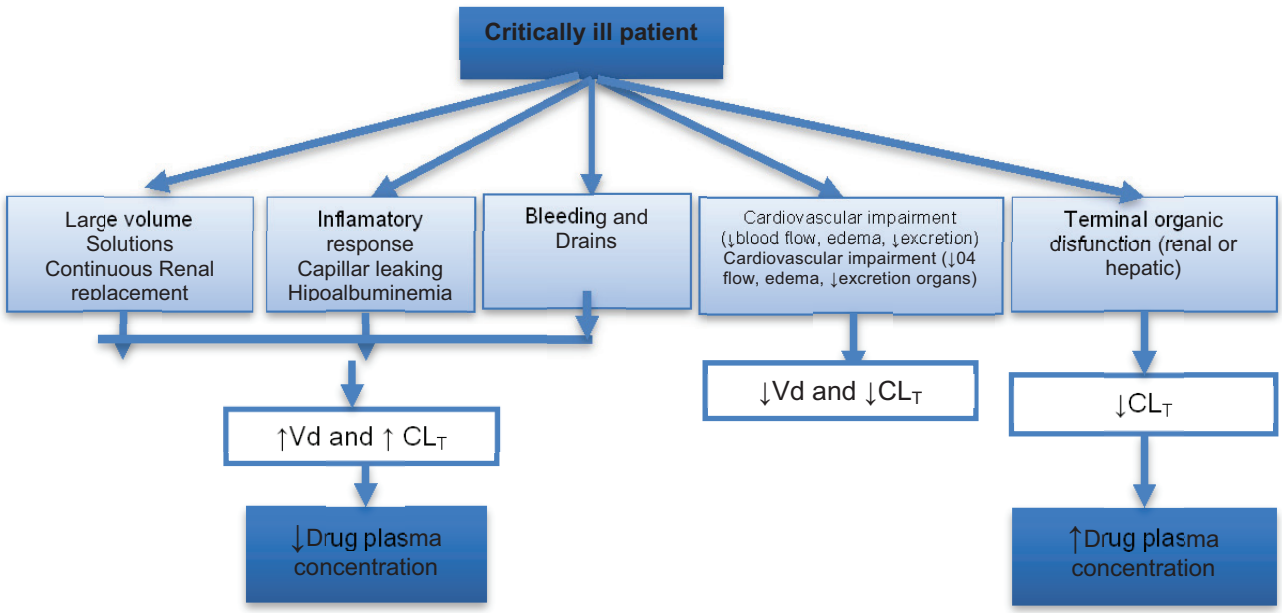

Fig. 2 Pharmacokinetics changes in critical ill patients [4,13,14,29].

6.2 Aging

Many changes are reported in the physiology of the body by aging and PK change also occurs in the same extent (Fig. 3). Consequently, caution should be taken during dosing adaptation to pediatrics or elderly populations, as long as occurred in drug development at the pre-clinical phase, since the initial dosing schedule and applied models were performed at phase 1 in healthy adults or at phase 2 in patients under disease's chronic treatment.

In elderly, dose adjustment requirements of fluoroquinolones and linezolid were reported as a consequence of physiological changes. On the other side, in pediatrics' dosing is also a challenge, since dosing adjustment based mainly on weight isn't enough to guarantee PK/PD index. Thus, considering these both populations, it's imperative to develop PK/PD analysis for dosing optimization. Pharmacokinetics changes according aging are described in the figure bellow [1].

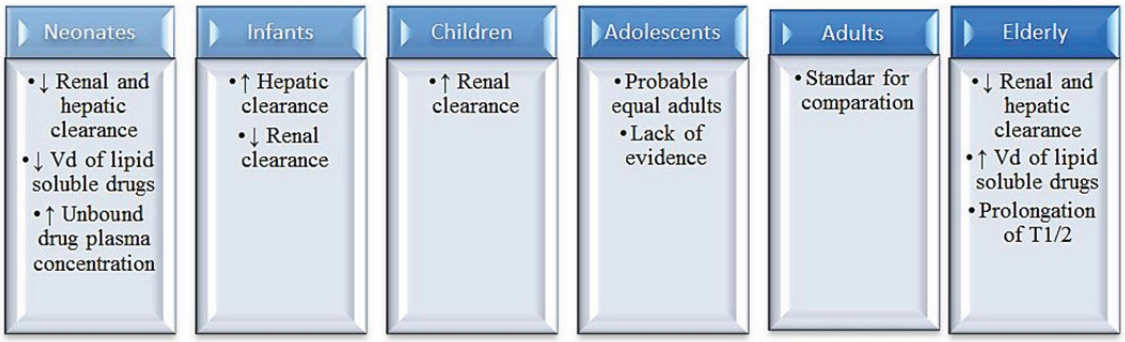

Fig. 3 Pharmacokinetics changes according aging [1,30-32].

6.3 Obesity

PK-parameters are commonly altered in obese patients, and mainly for antimicrobial agents, once treatment failure related to obesity was reported. Changes mainly on the volume of distributions and plasma clearance have been reported; thus dose adjustment on guidelines or based on population PK-data aren't available or conflicting. Therefore, additional studies are required to improve the information required to those patients as well as the proportionality on dose requirements to obese patients and its relationship according to body mass index [1]

6.4 Renail impairment

In general, the antimicrobial plasma clearance decreases and the risk of toxicity is increased, as a consequence of renal impairment. On the other hand, increases on the volume of distribution in septic patients can compensate drug plasma concentrations in the earlier stages of the kidney impairment. Thus, dose reductions are not always recommended [4].

An acute kidney injury may occur as a consequence of hemorrhagic, septic or cardiogenic causes. The impact of the injury on drug plasma concentrations depends mainly on the extent of kidney impairment. Dosing and regimen adjustment are different according antimicrobial PK/PD characteristics [4]:

- Concentration-dependent – dosing interval should be prolonged and the dose amount should be maintained to guarantee peak concentrations and PK/PD index achievement.
- Time-dependent – dose amount reduction and dosing interval maintenance to maximize PK/PD index.

Despite the expected higher concentrations of drug plasma in patients with renal impairment, under continue renal replacement therapy, therapeutic drug concentrations at the trough wasn't achieved after the empirical dosing recommended. Renal replacement therapies are efficient in extracting hydrophilic drugs, especially those with high unbound extend drug. In those cases, therapeutic drug monitoring is recommended to guarantee antimicrobial effectiveness [1,4,5].

6.5 Hepatic impairment

Hepatic impairment leads to increases in drug plasma levels, just for mainly of antimicrobials biotransformed by the liver, since the hepatic clearance decreases. The variability on drug plasma levels is due to the extent of drug metabolism and changes in hepatic blood flow. CYP enzymes´ isoforms, responsible for the phase 1 oxi-reduction reactions, are affected by several liver diseases as alcoholic cirrhosis, hepatitis, negligence tropical diseases or even in the hepatorenal end-stage patients; while the phase 2 - conjugation reactions, mainly the glucoronidation has been less affected. The severity of liver function impairment can be measured by the score called Child-Pug as guidance for dose adjustment. Nevertheless, this score semi-quantitative has some limitation, since it has not been validated in critically ill patients and does not have shown the sensitivity to drug metabolism. Additionally, hypoalbuminemia is a clinical consequence of the liver impairment and its consequences on drugs pharmacokinetic have been previously discussed in

this chapter. Additionally, it is recommended to avoid the antimicrobials eliminated by drug metabolism in the liver [4,33].

6.6 Infection site dependence

As already discussed, PK/PD analysis predicts antibiotic concentrations that are effective in plasma; on the other hand, tissue concentrations may not be the required to overmatch the infection. Meanwhile, cerebral, bone, ocular and respiratory infections are a challenge. The effectiveness of antimicrobials has been postulated by a local administration to guarantee the target attainment, however, the feasibility for the local administration will depend on patient's clinical status, antimicrobial characteristics and the infection [1].

HIV-critically ill patients with meningitis by *Cryptococcus neoformans*, for instance, the transfer of amphotericin B thought the haematoencephalic barrier is very low, once a very low CSF/plasma ratio was reported. Thus, the plasma PK/PD analysis might overestimate the effectiveness and cerebrospinal fluid should be also collected [34].

7. Prophylaxis and continuous treatment with antimicrobials

The prophylactic use of antibiotics aimed to prevent surgical site infections during the post-operative period. The choice of antibiotics should take into account [1,35,36]:

- Pathogens susceptibility according infection site – broad spectrum antibiotic that covers susceptive anaerobic and aerobic bacteria
- Antimicrobial kinetic profile and distribution into the surgical wound – target concentrations should be achieved in plasma and interstitial tissue throughout the surgery until the end of the procedure. Unbound drug plasma concentration above the highest possible MIC recommended should be guaranteed during the surgical intervention and, in some cases until the first 24 hours of the postoperative period [1]. Thus, the accumulation and steady state aren't achieved in many antimicrobials during prophylaxis, needing higher doses.

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