Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

REVIEW
Bilingual edition English/Spanish

Personalized antimicrobial therapy in critical and elderly patients

Terapia antimicrobiana personalizada en pacientes críticos y en edad avanzada

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Received 13 June 2021;
Accepted 13 August 2021.
DOI: 10.7399/fh.11760

How to cite this paper
Grau S, De Antonio-Cuscó M, Ortonobes-Roig S, Los-Arcos I, Jiménez MJ, Soy D. Personalized antimicrobial therapy in critical and elderly patients. Farm Hosp. 2021;45(Suppl 1):S64-76

Abstract

Objective: Personalized therapy in the treatment of infections is essential to ensure optimization of antimicrobial drug levels. This strategy, together with an understanding of the activity of these drugs, decreases the risk of bacterial resistance and improves the drugs' safety profile. Alternative routes of administration, such as inhalation, and the information provided by pharmacokinetic models, are essential given the limitation of antimicrobial activity allowed by the new antimicrobials.
Method: A non-systematic review of the literature is presented as a way of tackling and finding solutions to the problem. A search for high-quality articles on the research topic was conducted.
Results: A total of 370 articles were detected, which were subjected to a further selection to discard low quality papers by a team of five clinical pharmacists and an intensivist. Finally, 153 articles were included in the review.
Conclusions: The geriatric and the critical care patient population require the administration of antimicrobials with close monitoring. The routes of administration recommended for the first group are discouraged for the second. The inhaled route often results in high plasma concentrations in patients with respiratory infections. Pharmacokinetic models are a valuable tool in the treatment of geriatric patients, who are often excluded from clinical trials.

KEYWORDS
Geriatrics; Critically ill patient; Antimicrobials; Pharmacokinetics-pharmacodynamics; Inhaled route.

Resumen

Objetivo: La terapia personalizada en el tratamiento de las infecciones es esencial para garantizar la optimización de los niveles de fármaco alcanzados en el paciente tratado. Adicionalmente, esta estrategia, juntamente con el conocimiento de la actividad antimicrobiana de estos fármacos, disminuye la posibilidad de desarrollar resistencias bacterianas y mejora el perfil de seguridad de estos fármacos. Las terapias por vías alternativas, como la inhalada, y el soporte de la información facilitada por modelos farmacocinéticos son esenciales debido a la limitación de la actividad aportada por los nuevos antimicrobianos.
Método: Se presenta una revisión no sistemática de la literatura como medida de orientación de la problemática y soluciones a lo expuesto anteriormente. Se ha efectuado una búsqueda de artículos de alta calidad sobre el tópico planteado.
Resultados: Se detectaron 231 artículos que sufrieron una selección posterior, en base a la calidad de los trabajos valorada por un equipo de cinco farmacéuticos clínicos y un médico intensivista. Finalmente, se incluyeron 153 artículos que soportan la revisión que se ha desarrollado.
Conclusiones: La población geriátrica y la integrada por pacientes críticos presenta la necesidad de utilización de los antimicrobianos con una estrecha monitorización. Vías de administración recomendadas en la primera, están desaconsejadas en la segunda. La vía inhalada es una vía que suele relacionarse con elevadas concentraciones en pacientes con infecciones respiratorias. Los modelos farmacocinéticos son un soporte de gran valor para poblaciones como la geriátrica debido a que es mayoritariamente excluida de los ensayos clínicos.

PALABRAS CLAVE
Geriatría; Paciente crítico; Antimicrobianos; Farmacocinética-farmacodinamia; Vía inhalada.

Introduction

The need for personalized therapy in the field of infectious diseases stems from the fact that, historically, many clinical trials of antimicrobials have been carried out in wide-ranging populations with different characteristics, often overlooking those patients that require greater precision in the prescription of these drugs[1]. The CORDIS programs are the main source of European Union funding for these purposes since 1990. These currently include the development of the program "Training towards personalized antibiotic treatment (TIPAT)", furnished with a total amount of almost €4M and having 2024 as its completion date[1]. The aim of the program is to combat the threat from increased bacterial resistance, especially in the context of severe infections. The goal is to increase the efficacy of these therapies while minimizing the risk of resistance, and gaining knowledge about the interrelations between patients, pathogens and drugs within the action framework of TIPAT. It includes an interdisciplinary network with wide experience in the field and is designed to integrate the biological and pharmacological data associated with pathogen-patient interaction on the basis of personalized therapies. These programs attempt to integrate clinical pharmacology, immunology and microbiology with a view to producing innovative methodologies that allow for the personalization of antimicrobial therapy. The TIPAT is aimed at hospitals, the pharmaceutical industry and regulatory agencies, and is also designed to include scientific innovation that helps to control and reduce bacterial resistance by optimizing the use of antimicrobial agents.

Numerous factors, including patient status, microbiological etiology and infection site, are essential for the personalization of antimicrobial therapy[2]. Furthermore, personalized therapy using the latest antimicrobial agents is limited, making it necessary to resort to alternative administration routes when using these drugs.

The aim of the present review is to describe the most relevant information on personalized antimicrobial therapy in critical and older patients, as well as to gain knowledge regarding its application with the latest available antimicrobial agents.

Methods

The search of the literature included papers published on Medline from January 2000 to May 2021. This was a non-systematic review carried out by five hospital pharmacists and one intensive care specialist. The search identified 370 articles, of which 153 (41.4%) were selected after excluding studies that were not directly related to our review's objective.

Geriatric population

How to address the increasing average age of the population is, without a doubt, one of the challenges facing the Spanish health system. Estimates tell us that by 2050 one fourth of the world population will be made up of people of over 60 years of age[3]. The use of antibiotics in geriatric care is widespread[4] and a balance between efficacy, safety and tolerability is not easy to guarantee[5]. If we focus on prescription of antimicrobials, it is thus necessary to be familiar with the pharmacokinetic and pharmacodynamic (pK/pD) alterations these agents undergo in association with old age, as well as their main pharmacological interactions and most common side effects[6].

The principal barriers preventing proper therapeutic management of infections in the geriatric population are shown in Table 1.

Table 1. Challenges of antimicrobial therapy in geriatric patients

Challenge	Pathophysiology and impact	Antimicrobial examples
Diagnostic difficulties	Atypical presentation of infectious diseases Immunosenescence	– Inappropriate or unnecessary antimicrobial therapies
Pharmacokinetic and pharmacodynamic changes	Absorption: decreased gastric depletion, lower gastric motility, decreased gastric flow and pH alterations.	– Reduced bioavailability (azithromycin, itraconazole)
	Distribution: increased fatty tissue, decreased body water, sarcopenia, malnutrition, hypoalbuminemia	– Increased distribution volume of lipophilic antimicrobials (rifampicin, quinolones, macrolides, oxazolidinones) – Decreased distribution volume of hydrophilic antimicrobials (beta-lactams, aminoglycosides, glycopeptides) – Decreased plasma protein binding rate (ceftriaxone)
	Metabolism: decreased phase 1 metabolizing enzymes (cytochrome P450); no alterations of phase 2 metabolism	– Increased half-life of hepatically metabolized antimicrobials (macrolides, quinolones, antifungals, azoles, antiretrovirals)
	Elimination: decreased renal function	– Accumulation of renally eliminated antimicrobials (beta-lactams, glycopeptides, aminoglycosides, daptomycin, ciprofloxacin, levofloxacin, cotrimoxazole)
Practical aspects of drug administration	Parenteral administration (endovenous, intramuscular, subcutaneous)	– Alternative subcutaneous administration (ceftriaxone, cefepime, ertapenem)
	Enteral administration (oral, tubes)	– Incompatibilities with enteral nutrition (quinolones)
Prevention of adverse effects	Enhancement resulting from polypharmacy and comorbidities Increased risk of hospitalization	– Cardiotoxicity: macrolides, quinolones – Hematological toxicity: linezolid – Nephrotoxicity: vancomycin, colistin, aminoglycosides – Neurotoxicity: beta-lactams, quinolones, carbapenems – Gastrointestinal toxicity (*Clostridioides difficile* infection)
Pharmacological interactions	Polypharmacy: competition for cytochrome P450 Increased risk of adverse effects	– Myopathies: statins and macrolides – Digitalis intoxication: digoxin and macrolides – Hyperpotassemia: ACE inhibitors or ARBs and cotrimoxazole – Hypoglycemia: sulfonylureas and quinolones

ACE: angiotensin-converting enzime inhibitors; ARBs: angiotensin receptor bloquers.

Diagnostic difficulties

Different factors lead to alterations in the way infectious diseases present themselves in the elderly. These patients are normally afflicted with reduced integrity of physical barriers like the skin or the connective tissue. Immunosuppression is also frequent, and the general immune response to face new infections is of little effect[7]. As people age, immunosenescence increases the risk of morbimortality following infectious diseases[6], due to alterations in cell function and systemic cytokine levels which negatively affect the immune system[8]. This all leads to nonspecific symptoms such as general disorientation, fatigue, falls or loss of weight, making it difficult to diagnose infections. This atypical presentation of disease has been recently associated with increased mortality[9].

Changes in pK/pD

In the context of ageing, the pK/pD behavior of antibiotics is mostly affected by kidney function deterioration and patient frailty[4]. The main alterations take place in each of the pharmacokinetic (pK) stages of the drugs for the reasons described below.

Absorption: In the elderly, gastric depletion and motility are usually decreased, as is gastrointestinal blood flow, and the digestive pH suffers alterations[10]. This alters drug absorption, thus affecting antibiotic bioavailability. The incidence of achlorhydria in geriatric patients is high, reducing bioavailability levels of different antimicrobial agents[11]. Lower drug availability is made worse by the frequent use of acidity suppressants or calcium salts[12]. In addition, the decreased function of intestinal transporter glycoprotein-P can affect the bioavailability of some antibiotics[10].

Distribution: Ageing increases the body's content in fat and reduces body water[4,6]. Drugs that are soluble in fat, such as rifampicin, quinolones, macrolides, oxazolidinones, tetracyclines, amphotericin B and most imidazole antifungals, have their half-life extended due to an increased volume of distribution (Vd). In some chronic pathologies, like chronic heart failure or ascites due to cirrhosis of the liver, the amount of water in the body is increased, favoring the distribution of hydrophilic drugs like aminoglycosides, beta-lactam antibiotics and glycopeptides[13]. Loading doses of hydrophilic antibiotics are recommended in cases of severe infection in patients with increased body water[13].

Variations in plasma protein levels in geriatric patients also affect drug distribution. Malnutrition and decreased albumin can also increase the free fraction of antibiotics[13], which is especially important in drugs with high plasma protein binding (PPB) rates, such as ceftriaxone[14]. In contrast, the elderly usually exhibit higher concentrations of alpha-1-acid glycoprotein, which reduces the free fraction of basic antimicrobials like macrolides.

Metabolism: Older patients have a decreased blood flow and lower metabolic rates in the liver, which can increase the half-life of hepatically metabolized drugs[15]. Such is the case with macrolides, quinolones, antifungals and azoles, whose hepatic extraction fractions are high[10,15].

The metabolic activity of the liver depends on phase 1 and 2 metabolizing enzymes. As regards phase 1 enzymes, cytochrome P450 oxidases are decreased in older people, causing a slower metabolization rate of drugs that are CYP3A4 substrates[16]. However, phase 2 enzymes, such as transferases, are well preserved in the elderly, thus guaranteeing the biotransformation of drugs in the body, although it has been suggested that frailty may decrease phase 2 metabolism[18].

Elimination: Clearance of antimicrobial agents is lower in geriatric patients because of the reduced excretory function of the lungs or the gastrointestinal system, although kidney function is the mainly affected one in this respect[19]. Comorbidities like high blood pressure, diabetes or cardiovascular disorders can aggravate kidney failure[20].

An impaired kidney function increases serum concentrations of drugs, creating a higher risk of toxicity from hydrophilic antibiotics, which are mostly excreted through the kidney[4]. When using antibiotics that have limited therapeutic margins or are dosed by body weight, it is very important to adjust the dosing with great precision, especially in the case of hydrophilic agents.

Different formulas are available to estimate renal clearance. The most widely used of these is the equation of Cockroft and Gault, who in 1976 had already shown that a linear inverse correlation existed between kidney function and age[21]. The Cockroft-Gault equation is the recommended formula in geriatric populations, together with the CKD-EPI equation, which was validated in 2009[22].

Practical aspects of drug administration

The skin of older patients is thinner and more susceptible to bruising. This, together with the highly prevalent use of anticoagulants in geriatric populations, can complicate the safe placement of endovenous catheters in these patients[23]. Nonetheless, parenteral administration is widely used in extreme situations in which the patient's life is at risk[6].

Intramuscular delivery is an alternative to endovenous administration, but it is not the method of choice in geriatric patients since it causes pain and is associated with a high risk of bruising. Because of this, subcutaneous administration is another parenteral approach that is widely used in geriatrics[24]. This form of delivery has a lower risk of causing thrombosis and catheter related infections[25]. The subcutaneous approach, which is not contraindicated in decoagulated patients[24] and is less painful than intramuscular administration, is of greater comfort and convenience to geriatric patients and may be used at home.

Following subcutaneous delivery, the drug must diffuse into the intravascular space, a step that reduces maximum concentration and delays maximum time as compared to endovenous delivery, although the area under the curve is usually similar. The subcutaneous route prolongs exposure to the drug, thereby optimizing the pK/pD parameters of time-dependent antibiotics like beta-lactam agents. Therefore, the most frequently used subcutaneous drugs are: ceftriaxone, cefepime, ceftazidime, ertapenem and –among glycopeptides– teicoplanin. Subcutaneous administration is not recommended for concentration-dependent antimicrobials like aminoglycosides or quinolones[24].

Disadvantages of subcutaneous delivery include the potential for causing edema or swelling, although these effects are infrequent (< 5%). Even so, it is not the approach of choice in emergency settings, since it does not allow for the administration of hyperosmolar solutions, and drug absorption depends on factors like perfusion and vascularization. Finally, it is not indicated in the presence of malnutrition or cachexia, which limits its use in geriatrics[24,26,27].

It should be added, in the case of oral administration, that dysphagia can impede drug delivery[28]. This may be addressed by using pharmaceutical solutions or suspensions. Pharmacists can recommend the most appropriate form of preparation in the geriatric population, especially in patients who bear (naso)gastric tubes.

Prevention of adverse effects

Age-related pK changes increase the risk of adverse effects associated with polypharmacy[29]. In addition, some antibiotics may be directly associated with severe adverse effects in the geriatric population, especially when underlying conditions or interactions exist[5,30]. A clear example of this is the presence of cardiovascular disease, which makes older people more vulnerable to the adverse effects of some antibiotics, like macrolides, that increase coronary-related mortality, while agents like quinolones prolong the QT interval and are associated with a higher risk of arrhythmia and a higher incidence of aortic aneurysms. The same family of drugs has been linked to increased levels of creatine kinase, having the potential for causing muscle toxicity in geriatric populations[31].

These populations are especially susceptible to *Clostridioides difficile* infection[32].

Pharmacological interactions

The efficacy of an antibiotic may be impaired because of concomitant administration of other drugs[14]. Proton pump inhibitors or histamine type 2 receptor antagonists reduce stomach acidity and interfere with the proper absorption of some antimicrobials like rilpivirine or posaconazole[33]. Most pharmacological interactions, however, take place through cytochrome P450[34].

Frail geriatric patients are polymedicated and this increases their risk of adverse effects and pharmacological interactions[35] in situations requiring, for example, the concomitant prescription of macrolides and statins, which can cause rhabdomyolysis and acute kidney damage[36]. A higher

risk of hospitalization for digitalis intoxication has also been reported in patients treated with digoxin and macrolides, and to a lesser extent with azithromycin[37]. In the case of patients treated with ACE inhibitors or ARBs, potassium levels must be monitored when administering cotrimoxazole, since there is a greater risk of hyperpotassemia[38]. Severe hypoglycemic episodes are also frequent in older patients when certain macrolides and quinolones are administered together with sulphonylureas[39]. Finally, the prescription of antibiotics like ciprofloxacin or cotrimoxazole together with anticoagulant vitamin K antagonists can cause severe bleeding in elderly patients[40].

New antimicrobials in older patients

There are few studies on the use of the newly available antimicrobial agents (ceftazidime-avibactam, ceftolozane/tazobactam, meropenem/vaborbactam or isavuconazole) in geriatric patients. However, isolated cases of patients treated with these antimicrobials have been described. Coinfections with carbapenemase producing *Klebsiella pneumoniae* and the SARS-CoV-2 virus worsen the prognosis, especially in older patients, with high mortality rates in spite of the use of ceftazidime-avibactam[41]. In contrast, a single case of a geriatric patient suffering from meningitis who was successfully treated with this antibiotic has been reported[42].

Given its antimicrobial spectrum and its safety and efficacy profile, ceftolozane/tazobactam has been proposed as an alternative in geriatric patients with skin and soft tissue infections or osteomyelitis[43]. Although only 11% of patients in the pivotal ceftolozane/tazobactam studies were older than 75, a higher incidence of adverse effects was noted, and correct dose adjustment in accordance with the patient's kidney function is recommended[44,45].

In the case of the new antifungal agents, a phase 1 trial has been carried out to determine the pharmacokinetic profile of isavuconazole after a single oral dose in 48 healthy individuals, of which 24 were over 65 years of age. The study concluded that dose adjustment for age or sex is not required[46].

Critical patients in the adult population

Epidemiology of infections in intensive care units

Infections are one of the leading causes of morbimortality in intensive care units (ICUs), with mortality rates in excess of 50%[47]. An estimated 51% of patients admitted to ICUs present active infection, while 71% receive antimicrobial treatment, at a cost accounting for up to 40% of total ICU expenditure[47].

ICU infections are usually the result or the consequence of the patient's critical illness[48]. This population is particularly vulnerable to infection because of the disruption of the physical barriers of the body (invasive devices, surgery, trauma, etc.) and the alterations in both the innate and adaptative immune systems. As a result, these patients present with exacerbated inflammation, hyporesponsiveness and/or circulating neutrophils with decreased chemotaxis[48,49]. Such imbalanced inflammatory and adaptative responses lead to tissue damage, sepsis, Acute Respiratory Distress Syndrome (ARDS) and/or multiorgan failure[50].

It should be noted that certain drugs commonly used in ICUs are associated with complications such as pneumonia infection followed by the reduction of cough and swallowing reflexes derived from neuromuscular blockade and sedoanalgesia[51].

Of the pathogens isolated in critical care units, 67% are gram-negative microorganisms, while 37% and 16% are gram-positive microbes and fungi, respectively[52].

Nosocomial infections are diagnosed in up to 32% of ICU patients and lead to a significant increase in mortality rates, especially in the presence of multi-resistant and extremely resistant microorganisms (MDRs/XDRs)[53] whose presence is mainly due to inappropriate use of antimicrobials, severity of illness, the insertion of central venous catheters and prolonged periods of hospitalisation[54].

The main barriers to adequate therapeutic management of infections in the adult ICU population are described in Table 2.

pK/pD alterations

Pharmacokinetic alterations

The efficacy of antimicrobial therapy is crucial for the survival of critically ill patients[47], the optimization of antimicrobial therapy should be a priority in the management of this population.

Absorption: Intravenous administration is the delivery route of choice in acute conditions, since the critically ill often suffer from enteric malabsorption[55]. This results from mesenteric hypoperfusion caused by the redistribution of the blood flow towards the outside of the gastrointestinal tract in order to regulate cardiovascular homeostasis in the presence of shock[55]. Such regional hypoperfusion may be enhanced by the action of vasopressors[56]. The use of subcutaneous and intramuscular antibiotics must therefore be avoided in these patients, in contrast to what applies in other populations.

In such settings, brief periods of enteral fasting may result in atrophy of the intestinal mucosa and loss of integrity of the tight junctions[57]. Other factors affecting absorption may include gastrointestinal dysmotility enhanced by sedoanalgesia due to slowing of gastric emptying[58] alkalization of gastric pH due to prophylactic treatment of stress ulcers, preventing the passage of drugs of an acidic nature through the membranes; and/or loss of bioavailability of drugs when they are administered using a nasogastric tube[59].

Distribution: Volume of distribution (Vd) is increased during septic processes due to capillary permeability caused by epithelial damage resulting from stimulation of different endogenous mediators by bacterial endotoxins[60]. All this has an effect on hydrophilic drugs because of their extracellular distribution, resulting in potentially suboptimal concentrations that may affect therapeutic efficacy[60] and pose a risk for the development of resistance[61]. Other factors that are common in critical patients, such as mechanical ventilation, extracorporeal circuits, ascites and pancreatitis, may also increase the Vd of drugs[62].

The presence of hypoalbuminemia in 40-50% of critical patients[63] can have an influence on both Vd and clearance of antibiotics with high plasma protein binding (PPB) rates[64].

Increased clearance can also take place in the context of hyperbilirubinemia[65] or elevated alpha-1-glycoprotein values[65] because of displaced albumin.

Metabolism: Inflammation and immunosuppression associated with critical illness can alter the metabolizing enzymes of drugs, carriers and plasma proteins[66].

Elimination: Between 20% and 60% of critical patients can present with higher rates of renal clearance due to increased cardiac output and vasodilation resulting from Systemic Inflammatory Response Syndrome (SIRS)[67]. Risk factors associated with the development of this condition include sepsis, surgery, trauma or burns[68]. Renal hyperfiltration has a strong impact on the standard dosing regimens of drugs that are eliminated through the kidneys, leading to subtherapeutic concentrations and clinical failure[68].

At the other end of the spectrum, 78% of critical patients can suffer from acute kidney failure[69], making it necessary to reduce doses of drugs that are cleared through the kidneys in order to avoid toxic concentrations of antimicrobial agents.

An additional consideration is the impact of potential liver failure, which alters the rate of excretion of drugs that are subject to biliary elimination.

Extracorporeal techniques like extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) may also have a significant impact on the elimination of certain antimicrobials, depending on the properties of the drugs themselves and on the techniques employed.

PK/PD optimization of the main families of ICU antimicrobials

Strategies for pK/pD optimization of the most common families of ICU antimicrobial agents are described below.

Aminoglycosides: Because of their hydrophilic nature, the Vd of these products is increased, leading to decreased maximum concentration (Cmax) levels. Since their efficacy depends on concentration, one strategy is to optimize the length of dosing intervals to allow higher Cmax values while reducing the risk of nephrotoxicity[70]. Plasma monitoring of the drug's concentration and knowledge of its MIC value with reference to the pathogen are indispensable for adequate follow-up in these cases[70].

Table 2. Challenges of antimicrobial therapy in critical care patients

Challenge	Pathophysiology and impact	Observations and antimicrobial examples
Pharmacokinetic and pharmacodynamic changes	Absorption: malabsorption, decreased/ increased gastric emptying, decreased/ increased intestinal motility	– Decreased bioavailability: first pass effect (penicillin G, remdesivir), gastric pH alkalization resulting from prophylactic treatment of stress ulcers (ketoconazole, itraconazole), manipulation of the pharmaceutical presentation to administer by tube, interaction with enteral nutrition (quinolones), ion chelation (tetracyclines, ciprofloxacin) – Increased bioavailability: decreased gastric emptying (doxycycline, isoniazid, minocycline, sulphonamides), interaction with enteral nutrition (itraconazole, nitrofurantoin) – Gastrointestinal dysmotility induced by sedoanalgesics – Increased gastrointestinal motility resulting from the use of prokinetic agents – Increased regional hypoperfusion caused by vasopressors – Atrophy of the intestinal mucosa resulting from prolonged fasting
	Distribution: increased capillary permeability, hypoalbuminemia, malnutrition, mechanical ventilation, extracorporeal circuits (renal replacement therapy, cardiopulmonary bypass, ECMO, drainage), ascites, pancreatitis, burn patients, hydric overload, hyperbilirubinemia	– Increased Vd of hydrophilic antimicrobials (beta-lactams, aminoglycosides, glycopeptides, linezolid, colistin) – The Vd of lipophilic antimicrobials (fluoroquinolones, macrolides, lincosamides, tigecycline) – Decreased PPB rates (ceftriaxone, daptomycin, ertapenem)
	Metabolism: inflammation and immunosuppression, alterations in drug metabolising enzymes, plasma carriers and proteins	
	Elimination: hyperfiltration (sepsis, surgery, trauma, burn patients), kidney failure, CRRT, ECMO, alterations in hepatic excretion (bile duct obstruction, cholestasis, cirrhosis)	– Drugs that are eliminated through the kidneys: beta-lactams, glycopeptides, aminoglycosides, daptomycin, ciprofloxacin, levofloxacin, cotrimoxazole, ganciclovir – Drugs that are eliminated through the liver: tigecycline, caspofungin – Drugs with high rates of extraction when using CRRT y ECMO (see Table 3)
Practical aspects of administration	Parenteral administration (endovenous, intramuscular, subcutaneous)	– Choice: intravenous route (bioavailability = 100%) – Avoid intramuscular and subcutaneous route, which are associated with erratic absorption in the presence of tissue hypoperfusion – Risk of extravasation
	Enteral administration (oral, tubes)	– Pharmaceutic formula not suited to grinding or and/or partitioning – Incompatibilities with enteral nutrition (quinolones) – Increased bioavailability with enteral nutrition (itraconazole, nitrofurantoin) – Chelation from ion interaction (tetracyclines, ciprofloxacin)
	Inhaled / nebulized administration	– Increased epithelial lining fluid (ELF) concentrations together with decreased systemic exposure (amikacin, colistin, tobramycin, vancomycin) – Risk of bronchospasm (pH and hyperosmolarity). The possibility of administering bronchodilators previously should be considered – Variable drug deposition: type of nebulizer; proper technique in mecanically ventilated patients; MV and nebulizer position in the circuit
	Intrathecal / epidural / intraventricular	– Strategy for severe cases. Risk/benefit assessment – Increased CSF concentrations together with decreased systemic exposure (amikacin, liposomal amphotericin B and amphotericin B deoxycholate, caspofungin, colistin, daptomycin, gentamicin, teicoplanin, tigecycline, tobramycin, vancomycin) – Dosing depends on drain aperture – Requirements: sterile and apyrogenous; free from solid particles (0.22 micron filter); isosmotic (292-297 mOsm/L); pH value approaching 7.32; preservative free; glucose serum contraindicated; volume, 2-5 mL
Prevention of adverse effects	Enhanced by polypharmacy and comorbidities Increased ICU and hospital stays	– Cardiotoxicity (QT interval prolongation): amphotericin B, atazanavir, azoles, chloroquine, macrolides, quinolones – Hemotoxicity: cotrimoxazole, ganciclovir, linezolid – Nephrotoxicity: aminoglycosides, acyclovir, colistin, vancomycin – Neurotoxicity: beta-lactams, carbapenems, quinolones – Gastrotoxicity (*Clostridioides difficile* infection)

Table 2 *(cont.).* Challenges of antimicrobial therapy in critical care patients

Challenge	Pathophysiology and impact	Observations and antimicrobial examples
Pharmacological interactions	Polypharmacy: competition for cytochrome P450 Increased risk of adverse effects	– Myopathies: statins and macrolides or daptomycin – Enhanced action of neuromuscular blockers: clindamycin, colistin, doxycycline, vancomycin – Digitalis intoxication: digoxin and macrolides – Increased risk of QT interval prolongation: amiodarone and voriconazole, haloperidol and azithromycin, methadone and levofloxacin – Hyperpotassemia: ACE inhibitors or ARBs and cotrimoxazole – Enhanced sedation: itraconazole and morphine, voriconazole y fentanyl – Decreased sedation: rifampicin and morphine, rifampicin and thiopental – Serotonin syndrome: linezolid and serotonin reuptake inhibitors – Drug-pathology interactions: myasthenia gravis and amikacin, cotrimoxazole and glucose-6-phosphate dehydrogenase deficiency
Development of multiresistances. PROA	Presence of risk factors that increase infections caused by multiresistant microorganisms Need for PROA programmes in ICUs	– Limited therapeutic armamentarium for multi-resistant bacteria – Antimicrobial pK/pD optimization depending on the drug's nature and pattern of antimicrobial activity

ACE: angiotensin-converting inhibitors; ARBs: angiotensin receptor bloquers; CFS: cerebrospinal fluid; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; iCU: intensive care unit; MV: mechanical ventilation; pD: pharmacodynamics; pK: pharmacokinetics; PPB: plasma protein binding; PROA: programmes for optimising the use of antibiotics; Vd: distribution volumen.

Beta-lactam agents: These highly hydrophilic drugs have an increased Vd which reduces their concentration levels considerably. It has been shown that prolonged administration and loading doses of these drugs makes it possible to achieve pK/pD goals, and thus achieve free concentrations four times higher than the MIC for 100% of the dosing interval (100% fT ≥ 4 x MIC)[71]. In cases of severe infection, in the absence of kidney failure, pneumonia or actual or suspected pathogens with lower sensitivity levels, the above should therefore be the strategy of choice[72].

Fluoroquinolones: Due to their lipophilic nature, these drugs have a high distribution reaching optimal concentrations both at intracellular and extracellular levels and in neutrophils and lymphocytes[73]. The pK of these antibiotics has a low impact on critical ilness. However, based on previous experience in the presence of hyperfiltration and high MICs, doses of levofloxacin and ciprofloxacin might require being increased to 750 mg/24 h[74] and 400 mg/8 h[75] respectively. When dosing has to be adjusted it is preferable to lengthen the dosing intervals, since the activity of these agents is concentration dependent.

Glycopeptides (vancomycin): The drugs in this group are relatively hydrophilic antibiotics[64]. Continuous infusion of vancomycin has shown to be superior to intermittent infusion: minimization of maximum plasma concentrations results in a 2.6 higher likelihood of reaching the pharmacokinetic goal, while reducing nephrotoxicity by 53%[76].

Lipopeptide (daptomycin): As a result of its high rate of PPB (%), clearance of the therapeutically active free fraction of this drug may be increased in conditions of hypoalbuminemia, hyperbilirubinemia and/or elevated alpha-1-glycoprotein[63]. Therefore, achieving optimal efficacy parameters in critical populations usually requires doses reaching AUC/MIC values of up to 400 and 800 respectively for bacteriostatic or bactericidal action to have effect[77].

Oxazolidinones (linezolid): It has been observed[78] that 30 to 40% of patients treated with linezolid do not reach optimal pK/pD concentrations, which in the case of critical patients have been set at values of 80-120 for AUC/MIC[79] and a T > MIC of 100%[80]. To achieve this, it could be necessary to prolong perfusion time and/or increase the dose in cases of obesity[81] or hyperfiltration[82] or in patients receiving CRRT[83], especially in individuals whose isolates exhibit high MIC values. Patients with kidney failure[84], or who are older[85], underweight or cirrhotic, can reach high plasma concentrations of the drug and develop linezolid induced thrombocytopenia as a result[86].

Table 3 shows ICU application of individualized new antimicrobial therapies.

Inhaled antimicrobial therapy as a strategy to improve respiratory drug concentrations

The use of nebulized antimicrobials maximizes drug concentration levels in the airways and the parenchyma of the lungs while minimizing systemic exposure and toxicity[107]. The effectiveness of inhaled antimicrobials correlates with the amount of drug deposited in the lungs, which in turn depends on three main parameters: airway anatomy, patient ventilation and characteristics of drug delivery aerosols[108]. The characteristics of the inhaled aerosol particles are the most easily adjustable factor and the one with greatest impact on the amount of drug that deposited in the airways and the parenchyma of the lungs. A nebulized drug that penetrates the alveolidense peripheral regions of the lungs with an efficacy of 90% should be made up of particles whose mass median aerodynamic diameter (MMAD) is between 1 and 5 µm in size[109].

Nebulized antimicrobial treatment can be of use in different clinical scenarios, such as maintenance treatment to prevent respiratory exacerbations in patients with bronchiectasis (with or without cystic fibrosis) or patients with different respiratory infections like ventilator-associated pneumonia (VAP)[108]. However, the effectiveness of nebulized antibiotics in the treatment of mechanical VAP continues to be controversial. The 2016 clinical guide of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) puts forward the weak recommendation (based on very poor quality evidence) that VAP caused by gram-negative bacilli, which are only sensitive to aminoglycosides or polymyxins, should be treated with both nebulized and systemic antibiotics[110]. Subsequently, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggested the avoidance of nebulized treatment in these cases because of the poor quality of the evidence[111]. Finally, a meta-analysis including two new clinical trials in addition to the nine studies in the IDSA/

ATS 2016 clinical guidelines suggested a benefit from nebulized antibiotics in the complementary treatment of VAP[112]. This benefit is mainly observed in infections caused by multi-resistant gram-negative bacilli with few therapeutic options.

The most important data on nebulized antimicrobial agents are described below.

Antibiotics

Aminoglycosides

Tobramycin is the most widely used aminoglycoside in nebulized form. One meta-analysis showed that nebulized tobramycin afforded the greatest benefit in long-term treatment for *Pseudomonas aeruginosa* infection in cystic

Table 3. Individualization of new intensive care units antimicrobial therapies

Antimicrobial	Antimicrobial properties	Optimal pK/pD index	Dose optimization strategy	Dosing adjustments	Dosing in extracorporeal techniques
Ceftazidime/ avibactam Standard dose: 2 g/0.5 g every 8 hours via 2 hour perfusion[87]	CAZ: Hydrophilic (log P = –1.6)[134] MP = 456.5 Da[134] PPB < 10%[134] Vd = 0.21-0.28 L/kg[134] Renal excretion: 85% unmodified[88] Biliary excretion < 1%[88] AVI: Hydrophilic (log P = –3,6) [134]. MP = 265.25 Da[134] PPB = 5.7-8.2%[134] Vd = 0.3 L/kg[134] Renal excretion: 95% unnmodified[88]	CAZ: %100 fT > 4 x MIC[89] AVI: %fT > CT	Administration of loading dose followed by prolonged or continuous perfusion[90]: Based on ceftazidime data: 15 mg/kg + 6 g on continuous infusion (CrCl < 60 mL/min)[91]	Renal impairment: depending on perfusion: Prolonged over 2 h: – CrCl 31-50: 1 g/0.25 g every 8 hours[87] – CrCl 16-30 mL/min: 0.7 g/0.1875 g every 12 hours[87] – CrCl 6-15 mL/min: 0,7 g/0.1875 g every 24 hours[87] Continuous (based on ceftazidime data): The loading dose should not be adjusted – CrCl 31-50 mL/min: 4 g/1 g on continuous perfusion pump in 24 hours[91] – CrCl 11-29 mL/min: 2 g/0.5 g on continuous perfusion pump in 24 hours[92] Hepatic impairment: not required[87]	IHD (dialyses 80%[88]): 1 g/0.25 every 24 hours (after dialysis[88]) CVVHF: 1 g/0.25 g every 8 hours[93] CVVHD: 2 g/0.5 g every 8 hours[194] Clearance depends significantly on the dialysate rate. AVI clearance is rapid, especially at high dialysate rates[95] CVVHDF: 2 g/0.5 g every 8 hours at dialysate rates of 1.5 L/g[88] ECMO: data not available for CAZ-AVI. For CAZ the literature suggests little impact[96], although prolonged therapies could be associated with increased plasma concentration levels of the drug
Ceftolozane/ tazobactam Standard dose: 1 g/0.5 g-2 g/1 g every 8 hours via 1 hour perfusion[97]	CEF: Hydrophilic (log P ceftolozane = –6,2)[134] MP = 666.7 Da[134] PPB = 30%[134] Vd = 0.2 L/kg[134] Renal excretion: 95% unmodified[88] TAZ: Hydrophilic (log P tazobactam = –1.4)[134] MP = 300.29 Da[134] PPB = 16-21%[134] Vd = 0.3 L/kg[134] Renal excretion: 70% unmodified[88]	CEF: %100 fT > 4 x MIC[89] TAZ: % fT > CT	Administration of loading dose followed by prolonged or continuous perfusion[98]	Renal impairment: – CrCl > 50 mL/min: IAI and UTI: 1 g/0.5 g every 8 hours[97] VAP and HAP: 2 g/1 g every 8 hours[97] – CrCl 30-50 mL/min: IAI and UTI: 0.5 g/0.25 g every 8 hours[129] VAP and HAP: 1 g/0.5 every 12-8 hours, 0.5 g/0.25 g every 8 hours[97] – CrCl 15-29 mL/min: IAI and UTI: 250 mg/125 mg every 8 hours[97] VAP and HAP: 500 mg/25 mg every 8 hours[97] – CrCl < 15 mL/min: 1 g/0.5 g every 24 hours IAI and UTI: 500 mg/250 mg loading dose followed by 100 mg/50 mg every 8 hours[91] VAP and HAP: 1.5/0.75 g loading dose followed by 300 mg/150 mg every 8 hours[91] Hepatic impairment: not required[97]	IHD (dialyses 60%[88]): IAI and UTI: 500 mg/250 mg loading dose followed by 100 mg/50 mg every 8 hours (after dialysis) [97] VAP and HAP: 1.5/0.75 g loading dose followed by 300 mg/150 mg every 8 hours (after dialysis) [97] Alternative: 1 g/0.5 g loading dose 3 days per week after dialysis[88] CVVHF and CVVHD: 1 g/0.5 g every 8 hours[88,99] CVVHDF: 2 g/1 g every 8 hours[88] ECMO: increased Vd[91]; minimum CS[91]. Decrease of 37% in tazobactam clearance[88]. No adjustment is required[88]

Table 3 *(cont.).* Individualization of new intensive care units antimicrobial therapies

Antimicrobial	Antimicrobial properties	Optimal pK/pD index	Dose optimization strategy	Dosing adjustments	Dosing in extracorporeal techniques
Meropenem/ vaborbactam Standard dose: 2 g/2 g every 8 hours via 3 hour perfusion[100]	MER: Hydrophilic (log P = –0.6) [134] MP = 383.5 Da[134] PPB = 2%[134] Vd = 0.25 L/kg[134] Renal excretion: 70% unmodified[88] Biliary excretion: minimal[88] VAB: Hydrophilic (log P = 1.02)[134] MP = 297.14 Da[134] PPB = 33%[134] Vd = 0,3 L/kg[134] Renal excretion: 80-90% unmodified[88]	%100 fT > 4 x MIC[89] % fT > CT	Administration in prolonged, 3 hour perfusion[100] Based on meropenem data: 2 g/2 g every 8 hours on continuous infusion[91]	Renal impairment: – CrCl 39-20 mL/min: 2 g/2 g every 8 hours[101] – CrCl 19-10 mL/min: 1 g/1 g every 12 hours[101] – CrCl<10 mL/min: 0.5 g/0.5 g every 12 hours[101] Hepatic impairment: not required[101] Continuous (based on meropenem data): The loading dose should not be adjusted – CrCl 30-49 mL/min: 1 g/1 g every 8 hours on continuous infusion[91] – CrCl 10-29 mL/min: 1 g/1 g every 12 hours on continuous infusion[91]	IHD (dialyses < 50%[88]): 0.5 g/0,5 g every 12 hours after dialysis[88] CVVHF: 0.5 g/0.5 g every 8 hours for a flow rate of 1-2 L/h or 1 g/1 g every 8 hours for a flow rate of 3-4 L/h[88] CVVHD: no data available for MER-VAB CVVHDF: no data available for MER-VAB. For MER: 1 g-2 g/8 h[88] ECMO: no data available for MER-VAB; however, the literature suggests very little impact from MER (increased Vd, minimal CS)[91]
Isavuconazole Standard iv/oral dose: 200 mg every 8 hours for 48 hours + 200 mg every 24 hours (12 hours or 24 hours after the loading dose)[102]	Highly lipophilic (log P = 4.14) [134] MP = 437.5 Da[134] PPB > 99%[134] Vd = 5 L/kg[134] Renal excretion 40% inactive metabolites and < 1% like isavuconazole[88]	f AUC/MIC = 25-50[103]	Loading dose: 200 mg every 8 h x 6 doses (48 hrs)[88] Maintenance dose: 200 mg daily (beginning 12-24 hrs after last loading dose)[88]	Renal impairment: no adjustment required, even in terminal kidney failure cases[102] Hepatic impairment: in Child-Pugh class C cases it might be necessary to reduce the dose by 50%. This should be avoided if possible[104]	The characteristics of isavuconazole might cause it to exhibit plasma concentration alterations in the presence of extracorporeal techniques. Monitoring of the drug's concentration levels is recommended It does not dialyse, and therefore does not require adjustments during dialysis[102]. In one case of a patient on sustained low efficiency dialysis a reduction of 42% in ISA concentrations was reported[105] ECMO: one case was reported of high sequestration and deposition of isavuconazole on the circuit. Doubling of the standard dose could be required[106]

AVI: avibactam; CAZ: ceftazdidime; CEF: ceftolozane; CrCl: creatinine clearance; CRRT: continuous renal replacement therapy; CS: circuit sequestration; CVVHD: continuous venovenous hemodialysis; CVVHDF: continuous venovenous hemodiafiltration; CVVHF: continuous venovenous hemofiltration; fAUC/MIC: area under the unbound drug concentration-time curve; fCMI > MIC: percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; HAP: pulmonary hypertension arterial; IHD: intermittent hemodialysis; ISA: isavuconazole; MER: meropenem; MP: molecular weight; PPB: plasma protein binding; PPB: plasmatic protein binding; TAZ: Tazobactam; VAB: vaborbactam; VAP: ventilator associated pneumonia; Vd: distribution volume.

fibrosis patients[113]. The high doses required and the need for prolonged use, however, create some concern regarding its potential renal toxicity, which has been described in some specific cases[114,115].

Another drug of this group that is used in nebulized form is amikacin. The risk of systemic absorption with the standard formulation is similar to that of endovenous amikacin and can cause potential side effects[108]. Nebulized liposomal amikacin, a newly developed formulation, increases local concentration of the drug while reducing its systemic absorption. Its use in patients with cystic fibrosis was well tolerated, but did not show to be superior to conventional nebulized tobramycin[116]. In one clinical trial, nebulized liposomal amikacin produced a higher negativization rate of germ cultures when it was added to standard treatment of pulmonary infections with *Mycobacterium avium* complex that were resistant to conventional treatment[117]. It has thus become a promising new drug in the treatment regimen of respiratory infections caused by nontuberculous mycobacteria.

Colistin

Nebulized colistin is formulated as colistimethate sodium, which subsequently becomes colistin sulfate *in vivo*[108]. It is, so far, the most frequently used nebulized antibiotic in the treatment of respiratory infections caused by multi-resistant gram-negative bacilli. A variety of doses is used in

VAP patients, ranging from 1 million IUs every 12 hours to 5 million IUs every 8 hours[108], making it difficult to compare the data. Although one meta-analysis showed a lower mortality rate when nebulized colistin was added to endovenous colistin to treat VAP[118], the usefulness of nebulized antimicrobials in the context of VAP, as pointed out before, continues to be controversial, as are the adequate dosing levels of colistin in its nebulized form. Given that systemic absorption of nebulized colistimethate sodium is practically null, no nephrotoxicity associated to nebulized treatment has been described[115].

Aztreonam

Aztreonam lysine is a nebulized drug formulation that has been approved for the treatment of *P. aeruginosa* infection in patients diagnosed with cystic fibrosis[107]. However, it has not been shown to have a similar benefit in clinical trials including patients with non-cystic fibrosis bronchiectasis[119].

Fluoroquinolones

Among the antibiotics in this group, nebulized ciprofloxacin has been given the most frequent use. Specifically, a liposomal ciprofloxacin formulation was used in phase 3 clinical trials in patients with non-cystic fibrosis bronchiectasis. The results of the two clinical trials that were conducted turned out to be contradictory: one of them showed a benefit, over time, in preventing respiratory exacerbations, while the other did not confirm this finding[120]. Further studies are, therefore, needed to determine the potential benefits of this nebulized drug in daily clinical practice.

Antifungals

Nebulized amphotericin B

Nebulized amphotericin B, especially in it liposomal formulation, has been widely used for antifungal prophylaxis in lung transplant patients[121]. Although no clinical trials are available for this population, the data published in different studies are favorable in terms of drug's long-term effectiveness, tolerability and influence on respiratory function tests[122,123]. On the basis of accumulated experience in prophylaxis, it has also been used for antifungal therapy, but studies are limited to case descriptions[124].

Azoles

Experience with nebulized azoles is more limited, but some studies have shown that the physico-chemical characteristics of both posaconazole and voriconazole are well suited to nebulisation[125]. Cases of lung transplant patients with invasive fungal infections, treated adequately with these nebulized azoles have already been reported[125,126].

Echinocandins

The physico-chemical characteristics of micafungin and anidulafungin have been described as appropriate for nebulisation[127]. Two cases were recently reported of lung transplant patients with tracheobronchitis from *Scopulariopsis* spp. who were treated successfully with nebulized micafungin[128]. These drugs could, therefore, be potentially used on an individualized basis in these infections, which are difficult to treat and exhibit resistance to most antifungal agents.

Personalization of antimicrobial therapy using pK/pD models

An essential strategy in personalizing antimicrobial therapy consists in developing pK/pD models. Optimization of antimicrobial treatment requires knowledge of the pK/pD behavior of drugs following the administration of a given dose. The inherent variability of life (intraindividual, interindividual, in LADME processes and in terms of efficacy and/or toxicity regarding results) makes such optimization difficult. Measuring this variability, as well as identifying and quantifying the different factors that contribute to it, will help in the task of optimizing dosing regimens with adequate precision[129,130].

Antibiotic therapy and population models. Studies of pK/pD in different populations make it possible to: (i) quantify pK parameter alterations of a drug in a given group of patients and determine intra- and interindividual variability; (ii) individualize/optimize dosing regimens on the basis of administered doses and blood concentration levels of the drug and population pK parameters; (iii) make recommendations on how to estimate optimal initial doses using clinical variables that are easily available at no further cost[130,131].

The goal is to reach biophase concentration levels of the antibiotic that can eradicate the microorganism without causing toxic effects. The use, in clinical practice, of mathematical-statistical models based on pK/pD concepts makes it easier to predict therapeutic results and to design optimal dosing regimens[131].

The information provided by the pK/pD population models is the basis for individualization after dosing. Knowledge of the drug's individual pK parameters (and individual concentration-time profiles) is required in order to relate them to the pharmacodynamic value associated to effect and toxicity. In the case of antimicrobials, the most widely accepted pD variable is the drug's MIC for the microorganism that is causing the infection.

The creation in antibiotic therapy of population pK/pD models for a given patient population provides information about the individuals included in the study and makes it possible to extrapolate to new patients within the same population in real time, using optimized initial and maintenance doses on the basis of the previously described pK/pD values.

The inclusion of covariables in the model allows for refinement and optimization of dosing regimens in special situations, such as: kidney failure, extreme old age, biochemical alterations, etc.[132,133]. The model also incorporates pK/pD process variability at different levels[134,135].

These models are clearly an ideal tool for application and use in patient populations that are not included in clinical trials and for whom information on antimicrobial dosing and side effects may be contradictory, limited or even unknown. The models, however, can never serve as replacements for clinical trials in patients.

Table 4 shows the main advantages and drawbacks of pK/pD models[134,135].

Population modelling. The application of pK in clinical practice requires the definition of specific mathematical-statistical models describing the evolution of drug concentrations over time. Such models are defined by mathematical equations that include the pK parameters associated with the drug's characteristic behavior and make it possible to predict what the concentration-time values will be following the administration of known doses of a given drug[136].

The most common methods currently employed for estimating pK parameters can be divided into two main groups: (i) individual pK estimation methods and (ii) population pK estimation methods. The former ones assess the pK of a drug in an individual without considering the variability of pK parameters of other individuals. The latter aim at identifying and quantifying drug concentration variability among individuals belonging to a given population after receiving standard doses of a drug[136].

Individualization of antibiotic dosing regimens is a good example of personalized therapy. Therapeutic monitoring of drug's blood concentration levels following a known dose of the antimicrobial agent is the tool employed to this end. PK monitoring, which is highly advisable in clinical practice, requires certain indispensable data for interpretation purposes (Table 5). After obtaining blood samples of an antimicrobial agent following the administration of a known dose of the drug, individual pK parameters (profile of concentration-time values) can be estimated, and

Table 4. Advantages and inconvenients of pK/pD models

Advantages	Inconvenients
Rapid access to data and results as compared to clinical trials	Need for prior premises and assumptions that must be as rigorous, precise and accurate as possible
Cost savings	The model's robustness must be fully guaranteed
	The mathematical-statistical techniques used for model validation can be complex and slow to run

Table 5. pK monitoring in clinical practice[137]

Required data
– One or more serum concentrations of the antibiotic (pK)
– Population pK parameters (estimated in advance)
– Software application (Bayesian method)
– Therapeutic target: pK/pD index

pD: pharmacodynamic; pK: pharmacokinetic .

the ideal pK/pD relationship for the antimicrobial type or family can be defined. This information is the basis for dosing regimen optimization. The calculation is performed using nonlinear regression mathematical-statistical analysis and the Bayesian method, since it is possible to estimate individual pK parameters on the basis of information regarding the drug's pK behavior within a given population (*a priori* data). Integration of populational pK data and local or regional MIC values for a given microorganism or antibiotic makes it possible to evaluate, by means of Monte Carlo simulations, the model's predictive capacity in terms of optimizing the pK/pD values of different dosing regimens of the antibiotic. These approaches help to make recommendations regarding initial antimicrobial dosing regimens, with a view to optimizing therapy from the very beginning of the treatment period on the basis of the covariables that have an influence on its variability.

PK models with the new antimicrobial agents. In the case of the new antibiotics, there is one study in patients with cystic fibrosis (CF) and infectious exacerbations caused by *P. aeruginosa*[138]. In this populational pK/pD model, the study's authors showed that the plasma clearance of ceftolozane/tazobactam was comparable to that of adult patients without CF. In contrast, a decreased central Vd was observed in patients with CF. On the basis of these data, the probability of reaching the therapeutic goal ($fT_{>MIC}$: 60%) was assessed using Monte Carlo simulations, suggesting that a dose of 1.5 g/8 h, infused for 60 minutes, would reach the therapeutic target in 39%, 60% and 100% of cases for MIC values of 8, 4 and 2 mg/L, respectively. It was also shown that for a dose of 3 g/8 h, these same percentages optimized the therapeutic goal for MIC values of 16, 8 and 4 mg/L, respectively. These data will contribute to the optimization of dosing regimens in future CF patients.

Isavuconazole is a new antifungal for the treatment of invasive aspergillosis and mucormycosis. A pK population model was used to assess dose adjustment needs in patients with hepatic impairment[139]. The drug's clearance was found to decrease as a function of the degree of hepatic involvement, while the Vd was influenced by the patient's body mass index. These data made it possible to simulate the pK profiles of patients with varying degrees of hepatic impairment and to show that, in such patients, the average concentrations of isavuconazole in static balance exceed by less than twice the minimum concentration observed in healthy individuals, and that no side effects occur. In these conditions it was determined that isavuconazole did not require dose adjustment in patients with moderate liver failure.

Funding

No funding.

Conflict of interest

No conflicts of interests.

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