

A 30-years Review on Pharmacokinetics of Antibiotics: Is the Right Time for Pharmacogenetics?

Lorena Baietto^{1*}, Silvia Corcione^{1*}, Giovanni Pacini², Giovanni Di Perri¹, Antonio D'Avolio^{1#†} and Francesco Giuseppe De Rosa^{1†}

¹Department of Medical Sciences, University of Turin, Infectious Diseases, Amedeo di Savoia Hospital, Turin Italy; ²Novartis Farma SPA, Origgio, Varese, Italy

Abstract: Drug bioavailability may vary greatly amongst individuals, affecting both efficacy and toxicity: in humans, genetic variations account for a relevant proportion of such variability. In the last decade the use of pharmacogenetics in clinical practice, as a tool to individualize treatment, has shown a different degree of diffusion in various clinical fields.

In the field of infectious diseases, several studies identified a great number of associations between host genetic polymorphisms and responses to antiretroviral therapy. For example, in patients treated with abacavir the screening for HLA-B*5701 before starting treatment is routine clinical practice and standard of care for all patients; efavirenz plasma levels are influenced by single nucleotide polymorphism (SNP) *CYP2B6*-516G>T (rs3745274). Regarding antibiotics, many studies investigated drug transporters involved in antibiotic bioavailability, especially for fluoroquinolones, cephalosporins, and antituberculars. To date, few data are available about pharmacogenetics of recently developed antibiotics such as tigecycline, daptomycin or linezolid. Considering the effect of SNPs in gene coding for proteins involved in antibiotics bioavailability, few data have been published.

Increasing knowledge in the field of antibiotic pharmacogenetics could be useful to explain the high drug inter-patients variability and to individualize therapy. In this paper we reported an overview of pharmacokinetics, pharmacodynamics, and pharmacogenetics of antibiotics to underline the importance of an integrated approach in choosing the right dosage in clinical practice.

Keywords: Metabolism, pharmacology, pharmacogenomic, single nucleotide polymorphism (SNP), tailored therapy, therapeutic drug monitoring (TDM), transporter, treatment.

INTRODUCTION

Pharmacogenetics (PG), known as the study of inter-individual variation in DNA sequences related to pharmacokinetics/pharmacodynamics (PK/PD) of drugs, has rapidly evolved over the past decade and is increasingly recognized as a discipline with great potential for individualization, especially in critical care patients [1]. Important applications of PG include the identification of genetic mechanisms that may influence drugs exposure, toxicity and/or response to treatments [2]. Individual PK variability can also play a role in treatment failure, either directly through sub-therapeutic drug levels, or indirectly when toxic drug levels are associated with side effects.

PK variability of antibiotics depends on several factors, among which the most important are:

Drug–drug interactions: There are plenty of interactions involving antibiotic agents [3]. The more common interaction depends on co-administration of antibiotic with compounds that induce or inhibit the activity of metabolizing enzymes as cytochrome P450 (CYP P450) system or transporters such as P-glycoprotein (P-gp).

Drug–food interactions: Interactions between food and oral drugs can unintentionally reduce or increase the absorption and, indirectly, the effect of drug, resulting in therapeutic failure or increased toxicity. The majority of clinically relevant food-drug interactions are caused by food-induced changes in bioavailability of drug. For example, ciprofloxacin [4], doxycycline [5], norfloxacin

[6] oral absorption is reduced if administered with milk and the clinical effect observed is treatment failure.

Sex: Most reports of sex differences involve oral administration of low bioavailable drugs that undergo cytochrome 3A4 (CYP3A4) metabolism and P-gp transport. For example, greater inhibition of clarithromycin on intestinal metabolism was observed in women than in men [7]. Moreover body mass index and volume of distribution of drugs were influenced by sex.

Disease state (i.e. renal and hepatic function): Renal or hepatic impairment is associated with lower excretion of drugs that are excreted via these two ways. Accumulation of drugs in these compartments is often correlated with emergence of toxicity. For example meropenem, vancomycin, and daptomycin are mainly excreted through the kidneys and therefore a dosage adjustment is required for patients with renal impairment [8].

The hypothesis that genetic differences could play a role in influencing a patient's response was supported by reports showing that patients from distinct ethnic groups have significantly different clinical response [9, 10]. Genetic variability in drug metabolizing enzymes or drug transporters across ethnic groups, probably explains some of the differences between populations, although other factors such as body weight may also contribute. It should also be considered that while initial plasma concentrations may be unaffected by genetics, the inducibility of drug metabolizing enzymes by rifampicin or other co-administered drugs may vary according to the various polymorphisms affecting gene regulation such as promoter variation or nuclear factor.

In the last decade, PG has been used in clinical practice to individualize treatment. In some areas, such as in cardiovascular diseases or in cancer, PG testing is already applied for selecting or dosing a specific medication, while in other fields, such as in psychiatry, the PG approach has been mostly used for the identification, validation and development of new biomarkers.

*Address correspondence to this author at the Department of Medical Sciences, University of Turin, Infectious Diseases at Amedeo di Savoia Hospital, Corso Svizzera 164, 10149. Turin, Italy; Tel: +39.011.4393979; Fax: +39.011.4393882; E-mail: antonio.davolio@unito.it

†Last authors contributed equally.

#Both authors equally contributed to this work.

In the last years several single nucleotide polymorphisms (SNPs) that alter the expression of drug transporters proteins or metabolizing enzymes were found to influence drug PK. To date, SNPs in several genes coding for such proteins are known:

Multi-drug transporter genes. Drug transporters can be generally divided into two major classes: uptake and efflux transporters. Uptake transporters act by facilitating the translocation of drugs into cells or compartments. Efflux transporters act by exporting drugs from the intracellular to the extracellular compartment. For example, amongst uptake transporters, the organic anion transporting polypeptide 1B1 (OATP1B1), which plays a major role in the hepatic uptake of drugs, is coded by a polymorphic gene. The aplo-type OATP1B1*15 was found to be related with high plasma levels of pravastatin in Caucasians [11, 12]. The genetically polymorphic transporter P-gp or MDR1 is a well-known efflux transporter with ubiquitous expression coded in humans by *ABCB1* gene. The most famous SNP is 3435C>T (rs1045642). It was observed that subjects with 3435C>T mutation have higher levels of mutated P-gp in the duodenum and higher plasma area under the curve (AUC) of orally-administered digoxin than subjects with the wild type allele [13]. Many clinical studies investigated the influence of SNPs on *ABCB1* to clarify the clinical impact on the PK and PDs of various substrate drugs because of the relatively high frequency of this mutation and ethnic differences in the frequency (about 10% in African-Americans, 40–50% in Caucasians and Asians) [14].

Another genetically polymorphic efflux transporter is the breast cancer resistance protein (BCRP) coded by *ABCG* gene. The most important SNP is 421C>A (rs2231142). Since its frequency is relatively high, several clinical studies on this SNP have been carried out. 421C>A in *BCRP* gene was reported to cause the increase in the plasma concentrations of rosuvastatin and diflomotecan [15, 16]. Moreover, 24C>T (rs1717620) mutation in the gene coding for the multidrug resistance-associated protein 2 (MRP2) caused the increase in the steady-state plasma trough concentration of mycophenolic acid in transplanted patients [17] and the increase in the plasma AUC of methotrexate [18].

Cytochrome P450 Metabolizing Enzymes

To date, it is well established that the SNP 516C>T (rs3745274) in gene coding for CYP2B6 is associated with significantly greater efavirenz plasma exposure during HIV therapy [19, 20]. Among antifungals, voriconazole is extensively metabolized by the cytochrome P450 system and CYP2C19 is involved in the primary route of elimination. Several studies reported that SNPs in CYP2C19 coding gene are associated to voriconazole plasma levels in adult patients [21] and children [22].

The study of the association between drug plasma levels and SNPs in gene coding for protein involved in antibiotics absorption, distribution, metabolism, and elimination (ADME) processes may be useful to choose the right dosage especially at the beginning of treatment. We present a comprehensive review of the published literature to summarize the state of the art of PG and PK of antibiotics.

AMINOGLYCOSIDES

Aminoglycosides (AGAs) have been extensively used; streptomycin was the first aminoglycoside discovered and was isolated in 1943 from *Streptomyces griseus*. A second generation of AGAs, such as dibekacin (1971), amikacin (1972), arbekacin (1973), isepamicin (1975), and netilmicin (1976) were developed during the past decades [23].

Despite their nephrotoxicity and ototoxicity, AGAs are valuable in current clinical practice, since they retain good activity also against multidrug-resistant gram-negative pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter spp.*

Mechanism of action. Aminoglycosides act mostly as protein synthesis inhibitors, although their exact mechanism of action is not fully known: they interfere with the proofreading process, causing increased rate of error in synthesis with premature termination. Also, there is evidence of inhibition of ribosomal translocation where the peptidyl-tRNA moves from the A-site to the P-site. They can also disrupt the integrity of bacterial cell membrane.

PK-PD parameters predictive of efficacy. Time-kill studies have shown a concentration-dependent and partially concentration-dependent bacterial killing against gram-negative and gram-positive bacteria, respectively. PD data show that the administration by an extended-interval dosing scheme greatly enhances the potential of these agents, with the goal of achieving an AUC of 100 mg*h/L and a C_{max}/MIC ratio of 8–10. Aminoglycosides are characterized by a significant variability in the relationship between the dose administered and the resultant plasma levels in blood and therapeutic drug monitoring (TDM) is frequently necessary to obtain the correct dose.

ADME. Aminoglycosides can only be administered parenterally, except for intestinal infections or indication for decontamination. Protein binding is weak (0 to 30%) and the apparent elimination half-life is approximately 2h. Volume of distribution is low (<0.3 L/kg) thus aminoglycosides are mainly distributed in blood plasma. The major route of aminoglycoside elimination is renal excretion as only a small fraction was found to be eliminated through the bile (0.5-2% of the administered dose). The biotransformation is negligible (<10%); they are found almost entirely in the unchanged, biologically active form in the urine. The PK of elimination is independent of the dose and route of administration. Tissue diffusion is poor, but there is a good diffusion into peritoneal, pleural and pericardial fluid and synovial effusions, where the concentration attains 25 to 50% of levels in serum; the renal accumulation occurs particularly in the cortex [24].

PG data. To date, only one study was published about PG of aminoglycosides (Table 1). Oral absorption of some drugs is inhibited by P-gp which is involved in drug efflux in the brush border of intestinal mucosa. Banerjee *et al.* [25] found that P-gp is involved in tobramycin efflux. Therefore, P-gp inhibitors may have potential role to transport aminoglycosides, through gut, which is otherwise poorly absorbed after oral administration.

TETRACYCLINES

Tetracyclines, represent a large group of antibacterials, some of which were first introduced into clinical practice in the 1950s (tetracycline) while others have recently been approved (the glycylicline, tigecycline). The microbial spectrum includes gram-positive and gram-negative bacteria, intracellular *Chlamydiae*, *Mycoplasma*, *Rickettsiae* and several parasites such as malaria [26].

Mechanism of action. Tetracyclines are generally bacteriostatic. They reversibly bind to the 16S part of the 30S ribosomal subunit.

PK-PD parameters predictive of efficacy. Tetracyclines exhibit a predominantly time-dependent killing activity with a prolonged post-antibiotic effect. The PK parameter predictive of efficacy in these compounds is the AUC related to MIC (AUC/MIC). A target PK/PD breakpoint has still not been clearly identified.

ADME. Tetracycline is only available as a oral formulation, while doxycycline and minocycline can be given either orally or intravenously (iv not in Italy). The reported tissue distribution varies depending primarily upon the lipophilicity of the individual drugs. Protein binding is modest from 20% to 60%.

Oral absorption of tetracyclines occurs in the stomach and proximal small intestine. Oral bioavailability of these compounds is relatively high, ranging from 75% to 100%. Food can reduce the absorption of both tetracycline and doxycycline up to 50% [27]. Half-life of tetracyclines is relatively long, from 8 to 25 hours.

Table 1. Specific transporters of aminoglycosides, tetracyclines, macrolides, daptomycin, rifampicin and type of ADME processes involved.

Other antibiotics	Transporter	Coding gene	<i>In-vitro</i> model	ADME process involved	Reference
<i>Aminoglycosides</i>					
Tobramycin	P-gp	<i>ABCB1</i>	Mice	Oral delivery	Banerjee <i>et al.</i> 2000 [25]
<i>Tetracyclines</i>					
Minocycline	P-gp	<i>ABCB1</i>	Mice	BBB transport	Milane <i>et al.</i> 2007 [32]
Riluzole					
<i>Macrolides</i>					
Azithromycin	P-gp	<i>ABCB1</i>	Rats	Biliary and intestinal excretion	Sugie <i>et al.</i> 2004 [33]
Azytromycin	OATP1A5	<i>SLCO1A5</i>	MDCKII cells and rats	Intestinal absorption	Garver <i>et al.</i> 2008 [34]
Clarithromycin					
Daptomycin	P-gp	<i>ABCB1</i>	MDCKII cells and THP-1 macrophages	Intracellular activity against phagocytized <i>S. Aureus</i>	Lemaire <i>et al.</i> 2007 [35]
Rifampicin	P-gp	<i>ABCB1</i>	Mice	Intracellular accumulation	Schiuetz <i>et al.</i> 1996 [36]

ADME, absorption distribution metabolism elimination; P-gp, P-glycoprotein; OAT, organic anion transporter; ABC, ATP binding cassette; SLC, solute carrier; BBB, blood brain barrier.

These compounds are eliminated by both hepatic and renal mechanisms, they are filtered by the glomerulus but primarily reabsorbed because of their high lipid solubility. Tetracycline class are not effectively dialyzed, thus dose adjustment is not necessary in patients with renal impairment.

PG data. It was reported that minocycline exhibits anti-neurodegenerative properties [28-30] and that it is distributed to brain when administered by oral route [31]. Milane *et al.* investigated the interaction between riluzole, minocycline and P-gp at the blood-brain barrier (BBB). They found that minocycline and riluzole are both substrate of P-gp and that minocycline is also inhibitor of P-gp and increases the brain diffusion of riluzole. Therefore the study confirmed that minocycline and riluzole are transported by P-gp at the BBB level and that minocycline is involved in riluzole disposition into the brain through P-gp [32] (Table 1).

TIGECYCLINE

Tigecycline is an injectable antibacterial agent classified as a glycylcycline. It is the first member of this class that has been specifically developed to overcome the two major mechanisms of tetracycline resistance, ribosomal protection and efflux. *In vitro*, tigecycline is active against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

Mechanism of action. Tigecycline acts through inhibition of the bacterial protein translation by binding to the 30S ribosomal subunit and blocking the entry of amino-acyl tRNA molecules into the A site of the ribosome [37].

PK-PD parameters predictive of efficacy. Tigecycline exhibits time-dependent bactericidal activity not only against *Streptococcus pneumoniae*, but also against *Haemophilus influenzae* and *Neisseria gonorrhoeae* [38]. The AUC/MIC ratio is considered the most predictive index related to the clinical and microbiological efficacy [39]. To date no efficacy and toxicity breakpoints have been identified.

ADME. Tigecycline is available as a parenteral agent due to its limited oral bioavailability and it is administered i.v. as a 30-minute to 1h infusion, twice daily. Tigecycline has a large volume of dis-

tribution (7-10 L/kg) thus it is widely distributed in the body, with a half-life of 42 hours [39]. Tigecycline is moderately bound to human plasma proteins (71-89%) and it is eliminated by the liver via biliary excretion as unchanged drug and glucuronidation. Renal clearance is only a minor excretory way for tigecycline (approximately 10-15% of total systemic clearance) with less than 22% excreted unchanged in the urine. Tigecycline penetrates well into tissues and body fluids reaching higher concentrations compared to serum levels [40]. PK of tigecycline is not altered in patients with severe renal impairment as well as in patients with mild hepatic impairment. Therefore no dosage adjustment is required in these types of patients [39].

PG data. Eukaryotic efflux transporters can modulate the cellular concentration and the intracellular activity of antibiotics. Thus, Lemaire *et al.* investigated the role of P-gp and MRP1 in the modulation of the cellular accumulation and activity of tigecycline. In contrast with other antibiotics, where accumulation and intracellular activity are reduced by P-gp, tigecycline was found to be substrate of neither P-gp or MRP1 efflux transporters [41].

MACROLIDES

Macrolides, such as erythromycin, oleandomycin, spiramycin, roxithromycin, josamycin, midecamycin, clarithromycin, azithromycin and dirithromycin, are active against gram-positive staphylococci such as *Staphylococcus aureus*, coagulase-negative staphylococci, β -hemolytic streptococci, other streptococci species and some enterococci. Additional activity has been documented, especially for some agents, against *Haemophilus influenzae*, some pathogenic *Neisseria* species, *Bordetella*, *Corynebacterium*, *Chlamydia*, *Mycoplasma*, *Rickettsia* and *Legionella* species [42]. Azithromycin is considered one of the first choices to treat patients with peptic ulcer to eradicate *Helicobacter pylori* together with other antibacterial agents, such as amoxicillin and metronidazole.

Mechanism of action. Macrolides act by reversibly binding to the 23S ribosomal RNA (rRNA) in the 50S subunit of susceptible organisms, and inhibiting mRNA-directed protein synthesis. Moreover, they stimulate the dissociation of peptidyl-tRNA during translocation, suppressing RNA-dependent protein synthesis and

inhibiting bacterial growth. Resistance to macrolides in clinical isolates is most frequently due to post-transcriptional methylation of an adenine residue of 23S ribosomal RNA, which leads to cross-resistance to macrolides, lincosamides and streptogramins type B (the so-called MLSB phenotype) [43].

PK-PD parameters predictive of efficacy. Macrolides are generally bacteriostatic. Bactericidal activity may occur under certain conditions or against specific microorganisms. Macrolides are different from the other classes of antibacterial agents since they do not fall in a single category. $T > MIC$ is, indeed, the most important parameter for erythromycin. Optimal efficacy is obtained when $T > MIC$ is greater than 40% of the dosing interval [44].

However, experimental studies show that both $T > MIC$ and AUC/MIC influence the clinical efficacy of clarithromycin and azithromycin. For azythromycin AUC/MIC appears to be the most important parameter with the ratio exceeding 25 for optimal efficacy [43].

ADME. Macrolides tend to be characterized by high bioavailability. After oral administration they are readily absorbed from the gastrointestinal tract if not inactivated by gastric acid. They are characterized by a high volume of distribution (1–2.5 L/kg) that reflects the extensive tissue penetration.

They actually accumulate within many cells, including macrophages, in which they may be ≥ 20 times the plasma concentration. Macrolides tend to concentrate in the spleen, liver, kidneys, and particularly the lungs. They enter pleural and peritoneal fluids but not the cerebrospinal fluid (only 2–13% of plasma concentration unless the meninges are inflamed). They concentrate in the bile and milk. Up to 75% of the dose is bound to plasma proteins. Metabolic inactivation of the macrolides is usually extensive, but the relative proportion depends on the route of administration and the particular antibiotic. After oral administration, 80% of an erythromycin dose undergoes metabolic inactivation, whereas tylosin appears to be eliminated in an active form. Macrolide antibiotics and their metabolites are excreted mainly in bile (>60%) and often undergo enterohepatic cycling. Urinary clearance may be slow and variable (often <10%) but may represent a more significant route of elimination after parenteral administration [44].

PG data. According to “rule of 5” by Lipinski *et al.* [45], macrolide antibiotics azithromycin and clarithromycin are predicted to have poor permeation or absorption because of their large molecular weight and hydrogen binding potential; however, these macrolides show moderate to excellent oral exposure in preclinical species and humans [34]. One study reported that the biliary and intestinal excretion of azithromycin in rats is mediated by P-gp and MRP2 [33] (Table 1). The possible involvement of P-gp in azithromycin disposition is confirmed by the study described by He *et al.* [46]; they found that PK of azytromycin may be influenced by SNPs in *ABCB1* gene in healthy Chinese volunteers (Table 4). Garver *et al.* [34] found that the intestinal OATPs transporters are involved in the oral absorption of azithromycin and clarithromycin in the rat (Table 1).

OXAZOLIDINONES

Among oxazolidinones agents linezolid is the first and the only oxazolidinone approved for therapeutic use by FDA. It is active against gram-positive bacteria, including penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). It is used for the treatment of nosocomial pneumonia, uncomplicated and complicated skin and soft tissues infections caused by gram-positive bacteria [47]. Moreover, linezolid may be used in the treatment of multi-drug resistant tuberculosis, as second line agent.

Mechanism of action. It acts by binding to the 50S subunit of the bacterial ribosome producing an early inhibition of protein synthesis [48].

PK-PD parameters predictive of efficacy. Linezolid shows a time dependent killing. Data from literature reported that PK/PD parameters predictive of linezolid efficacy against staphylococci and enterococci are $AUC/MIC > 100$, $\%T_{MIC} > 85$, $C_{min} \geq 2$ mg/L and/or $AUC > 160-200$ mg·h/L for [49, 50]. Potential overexposure was defined as $C_{min} > 10$ mg/L and/or $AUC > 400$ mg·h/L [49, 51]. Linezolid is bacteriostatic with a significant post-antibiotic effect against the key pathogens.

ADME. Linezolid is available as intravenous formulation, film-coated tablets and oral suspension. The standard dose is 600 mg every 12 h and no dose adjustment is needed when switching from the intravenous to oral formulations or when there is moderate renal or hepatic impairment [52]. There are few data of linezolid PK in special situations such as ECMO [53]. Linezolid is well absorbed, with a bioavailability of approximately 100% in healthy volunteers. The level of plasma protein binding is 31% and the volume of distribution approximates to the total body water content of 40–50 L. Linezolid is metabolized to two inactive metabolites, an aminoethoxyacetic acid (metabolite A) and a hydroxyethyl glycine (metabolite B). It is excreted by non-renal (65%) and renal mechanisms. Renal tubular reabsorption may occur. A proportion of the dose is excreted unchanged in the urine [52].

PG data. The only published study dealing with linezolid PG was reported by Gebhart *et al.* These authors postulated that rifampicin may stimulate induction of P-gp expression, leading to increased clearance of linezolid. They found a significant reduction in linezolid plasma levels when a critically ill patient was treated with intravenous linezolid and rifampicin respect to linezolid alone. Thus, this research supports the hypothesis that P-gp expression plays a role in the potential interaction between linezolid and rifampicin [54].

FLUOROQUINOLONES

Fluoroquinolones are broad spectrum antimicrobials developed synthetically from the quinolone class of antimicrobials [55]. Ciprofloxacin exhibits activity against gram-negative and atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*) but lack potent *in vitro* activity against *Streptococcus pneumoniae*. Second and third generation fluoroquinolones such as levofloxacin and moxifloxacin, closed this coverage gap, providing enhanced bactericidal activity against gram-positive organisms [56].

Mechanism of action. Fluoroquinolones act by inhibiting two bacterial enzymes, DNA gyrase and topoisomerase IV, which have essential and distinct roles in DNA replication. Quinolones bind to the complex of each of these enzymes with DNA; the resulting complexes, including the drug, block progress of the DNA replication enzyme complex. Ultimately, this action results in damage to bacterial DNA and bacterial cell death [57].

PK-PD parameters predictive of efficacy. Fluoroquinolones exhibit concentration-dependent killing and a post-antibiotic effect [58]. Overall, the AUC/MIC has had the greatest correlation with outcome in either *in-vitro* or animal models of infection [59], but the greatest debate has focused on the magnitude of the AUC/MIC needed to maximize outcome or prevent emergence of resistance. Limited data from studies of human infections are available for the purpose of evaluating the PD thresholds necessary for maximizing therapeutic success. Attempts at “one-size- ts-all” cutoff values or thresholds have been problematic and have led to some pointed debate. While the best PK–PD targets to guide the use of fluoroquinolones may be unclear, the currently accepted target remains an AUC/MIC of ≥ 125 for gram-negative organisms [58].

ADME. After oral administration fluoroquinolones are rapidly absorbed from the intestine and widely distributed throughout the body [60, 61]. The major route of fluoroquinolone elimination is renal excretion as only a small fraction was found to be eliminated through the bile. Metabolism accounts for the hepatic elimination of

Table 2. PK data of fluoroquinolone compounds [60, 62, 63].

Fluoroquinolone Agent	Protein Binding (%)	Distribution Volume (L/kg)	GI Absorption (%)	Metabolism (%)	Excretion (%)	
					Renal	Hepatobiliary
Ciprofloxacin	20-40	-	70	-	40-50 (parent drug)	-
Levofloxacin	24-38	1.1	100	Limited by the liver	87 (parent drug)	-
Moxifloxacin	48	3.6	-	52% (N-sulfate and acyl glucuronide conjugates)	40 (parent drug and metabolites)	60 (parent drug and metabolites)
Ofloxacin	32	-	98	Limited by the liver	65-80 (parent drug)	4-8 in feces (parent drug)
Gemifloxacin	60-70	1.6-12.1	71	Limited by the liver	36% (parent drug and metabolites)	60 (parent drug and metabolites)

GI, gastrointestinal.

Table 3. Specific transporters of fluoroquinolones and ADME processes involved.

Fluoroquinolone Agent	Transporter	Coding gene	Model	ADME Process Involved	Ref.
Grepafloxacin	P-gp	<i>ABCB1</i>	Caco-2	Gastrointestinal secretion	Yamaguchi <i>et al.</i> 2000 [65]
Levofloxacin					
Levofloxacin	P-gp	<i>ABCB1</i>	LLC-PK1	Renal tubular secretion	Ito <i>et al.</i> 1997 [66]
Levofloxacin	MRP2, P-gp	<i>ABCC2</i> , <i>ABCB1</i>	Caco-2 and MDCK	Transepithelial secretion	Lowes <i>et al.</i> 2002 [67]
Levofloxacin	OATP1A2	<i>SLCO1A2</i>	<i>Xenopus</i> oocytes and Caco-2	Cellular uptake	Maeda <i>et al.</i> 2007 [68]
Ciprofloxacin					
Ciprofloxacin	BCRP	<i>ABCG2</i>	MDCK and mice	Milk secretion/oral availability	Merino <i>et al.</i> 2006 [69]
Ofloxacin					
Ciprofloxacin	BCRP	<i>ABCG2</i>	MDCK	Biliary excretion	Ando <i>et al.</i> 2007 [70]
Ofloxacin					
Ciprofloxacin	MRP4	<i>ABCC4</i>	Murine macrophages	Intracellular excretion	Marquez <i>et al.</i> 2009 [71]
Ciprofloxacin	OATP1A5	<i>SLCO1A5</i>	Rat enterocytes and <i>Xenopus</i> oocytes	Intestinal absorption	Arakawa <i>et al.</i> 2012 [72]
Ciprofloxacin	BCRP	<i>ABCG2</i>	MDCK, HEK 293 and Caco-2	Intestinal secretion	Haslam <i>et al.</i> 2011 [73]
Sparfloxacin	P-gp	<i>ABCB1</i>	LLC-PK1	BBB transport	de Lange <i>et al.</i> 2000 [74]
Sparfloxacin	P-gp	<i>ABCB1</i>	Caco-2	Intestinal elimination	Cormet-BoyaKa <i>et al.</i> 1998 [75]

ADME, Absorption distribution metabolism elimination; P-gp, P-glycoprotein; MRP, multidrug resistance-associated protein; OATP, organic anion transporting polypeptide; BCRP, breast cancer resistance protein; ABC, ATP binding cassette; SLCO, solute carrier organic anion transporter; BBB, blood brain barrier.

fluoroquinolones, and biliary excretion is usually a minor elimination pathway, except for moxifloxacin. Fluoroquinolone metabolic pathways include glucuronidation, N-oxidation and demethylation [62]. PK data regarding the most commonly used fluoroquinolones are reported in (Table 2).

PG data. Since these antibacterial agents are zwitterionic compounds, a passive diffusion mechanism may not fully explain their high intestinal absorption, selective tissue distribution and selective excretion. Accordingly, involvement of membrane transporters has been proposed. In the last years many studies investigated the involvement of several transporters in fluoroquinolone bioavailability. Notwithstanding that all these studies were performed *in-vitro*,

they could have important consequences in clinical practice for example in the field of drug-drug interactions. Moreover, for transporters coded by polymorphic genes the study of polymorphisms implicated in drug PK variability and response to treatment may be useful to improve outcome.

In Table 3 specific transporters involved in fluoroquinolone bioavailability are reported. The influence of SNPs on gene coding for transporters has been only investigated for moxifloxacin. In particular Weiner *et al.* [64] found that the SNP 3435C>T (rs1045642) in *ABCB1* gene coding for P-gp have no influence on moxifloxacin PK values in patients. Therefore P-gp seems not to be involved in moxifloxacin disposition (Table 4).

Table 4. PG studies regarding association among antibiotic PK and genotype of transporters and enzymes involved in ADME processes.

Antibiotic	Transporter/ Enzyme	Coding gene	SNP investigated	<i>In-vivo</i> effect	Model	Reference
<i>Macrolides</i>						
Azytromycin	P-pg	<i>ABCB1</i>	2677G>T	Lower C _{max} in patients with 2677TT/3435TT genotype, higher T _{max} in patients with 2677TT/3435TT genotype	Healthy Chinese volunteers, n=20	He <i>et al.</i> 2009 [46]
			3435C>T			
			1236C>T			
<i>Fluoroquinolones</i>						
Moxifloxacin	P-pg	<i>ABCB1</i>	3435C>T	SNP 3435C>T do not influence moxifloxacin plasma levels	Healthy volunteers, n=16	Weiner <i>et al.</i> 2007 [64]
<i>Beta-lactams</i>						
Dicloxacillin	P-pg	<i>ABCB1</i>	3435C>T	SNP 3435C>T do not influence dicloxacillin plasma levels, use of rifampicin increases dicloxacillin metabolism	Healthy volunteers, n=18	Putnam <i>et al.</i> 2005 [76]
Cloxacillin	P-pg	<i>ABCB1</i>	1236C>T	Lower C _{max} , AUC, and urinary excretion in subjects with 1236CC genotype	Healthy Chinese male volunteers, n=18	Yin <i>et al.</i> 2009 [77]
<i>Lipopeptides</i>						
Daptomycin	P-pg	<i>ABCB1</i>	3435C>T	Higher C _{max} in patients with 3435TT, 2677TT, and 1236TT genotype. Higher AUC in patients with 3435TT genotype and lower clearance	Caucasian patients, n=19	Baietto <i>et al.</i> 2012 [78]
<i>Sulfonamides</i>						
Sulphamethoxazole	CYP2C9	<i>CYP2C9</i>	CYP2C9*2, CYP2C9Arg144 to Cys	Subjects with homozygous mutate genotype for CYP2C9Arg144 to Cys and CYP2C9Ile359 to Leu showed decrease in the activity of CYP2C9	Human liver, n=26	Gill <i>et al.</i> 1999 [79]
			CYP2C9*3, CYP2C9Ile359 to Leu			
Sulphamethoxazole	GCLC	<i>GCLC</i>	rs761142T > G	rs761142 T > G influences sulphamethoxazole induced hypersensitivity	HIV patients, n= 171 and n=249	Wang <i>et al.</i> 2012 [80]
<i>Antituberculars</i>						
Rifampicin	OATP1B1	<i>SLCO1B1</i>	463C>A,521T>C,1463G>C,388A>G,11187G>A	Lower rifampicin exposure in patients with <i>SLCO1B1</i> 463CA genotype	Patients, n=72	Weiner <i>et al.</i> 2010 [81]
	OATP1B3	<i>SLCO1B3</i>	334T>G			
	P-pg	<i>ABCB1</i>	3435C>T			
Rifampicin	OATP1B1	<i>SLCO1B1</i>	463C>A, 521T>C, 388A>G	Lower rifampicin exposure in patients with <i>SLCO1B1</i> 463CA genotype	Healthy volunteers, n=11	Kwara <i>et al.</i> 2014 [82]
Rifampicin	CES2	<i>CES2</i>	2263A>G,	2263A>G may alter rifampicin metabolism by affecting expression of the gene	Korean patients, n=35	Song <i>et al.</i> 2013 [83]

Table (4) contd....

Antibiotic	Transporter/ Enzyme	Coding gene	SNP investigated	<i>In-vivo</i> effect	Model	Reference
Rifampicin	P-pg	<i>ABCB1</i>	3435C>T, 2677G>T, 1236C>T, rs3842	Patients heterozygous and homozygous for <i>SLCO1B1</i> rs4149032 polymorphism had low-level rifampin exposure	African patients, n=60	Chigutsa <i>et al.</i> 2011 [84]
	OATP1B1	<i>SLCO1B1</i>	521T>C, rs4149032, 463C>A			
	PXR	<i>PXR</i>	63396C>T, 44477T>C			
	CAR	<i>CAR</i>	rs2307424			
Isoniazid	NAT2	<i>NAT2</i>	NAT2*5, 341T>C	NAT2 genotype affects isoniazid plasma levels	Patients, n=60	Parkin <i>et al.</i> 1997 [85]
			NAT2*6, 590G>A			
			NAT2*7, 857G>A			
			NAT2*12, 803A>G			
			NAT2*13, 282C>T			
			NAT2*14, 434A>C			
Isoniazid	NAT2	<i>NAT2</i>	NAT2*5	NAT2 genotype affects isoniazid PK variability	Caucasian healthy volunteers, n=18	Kinzig-Schippers <i>et al.</i> 2005 [86]
			NAT2*6			
			NAT2*7			
Isoniazid	NAT2	<i>NAT2</i>		NAT2 genotype affects the EBA of isoniazid over a range of doses	African patients, n=87	Donald <i>et al.</i> 2004 [87]

ADME, absorption distribution metabolism elimination; P-gp, P-glycoprotein; OAT, organic anion transporter; ABC, ATP binding cassette; SLC, solute carrier; CES, Carboxylesterase-2; PXR, pregnane X receptor; CAR, constitutive androstane receptor; NAT, N-acetyltransferase; CYP, Cytochrome P450; GCLC, glutamate-cysteine ligase catalytic subunit. Rs number: *ABCB1* 2677G>T, rs2032582; *ABCB1* 3435C>T, rs1045642; *ABCB1* 1236C>T, rs1128503; *SLCO1B1* 463C>A, rs11045819; *SLCO1B1* 521T>C, rs4149056; *SLCO1B1* 1463G>C, rs59502379; *SLCO1B1* 388A>G, rs2306283; *SLCO1B1* 11187G>A, rs4149015; *SLCO1B3* 334 T>G, rs4149117; *SLCO1B1* 463G>A, rs11045819; *PXR* 63396C>T, rs2472677; *PXR* 44477T>C, rs1523130; *NAT2**5, 341C>T, rs 1801280; *NAT2**6, 590G>A, rs1799930; *NAT2**7, 857G>A, rs1799931; *NAT2**12, 803A>G, rs1208; *NAT2**13, 282C>T, rs1041983.

β-LACTAM ANTIBIOTICS

β-lactam antibiotics are a broad class of antibiotics characterized by having a β-lactam ring in their molecular structures. This class includes penicillin derivatives, cephalosporins, monobactams, and carbapenems. β-lactam antibiotics are administered for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. They are active against a wide variety of gram-positive and gram-negative bacteria, including anaerobes.

Mechanism of action. Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. β-lactams are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls.

PK-PD parameters predictive of efficacy. The PK/PD index that best describes efficacy for β-lactam agents is the time the free drug concentration remains above MIC ($f T > MIC$) [88]. However, the optimal $f T > MIC$ is controversial. Targeting trough concentration (4-5xMIC) may decrease the likelihood of suboptimal plasma concentrations. The higher concentration would enable enhanced distribution of drug into tissues with deranged microcirculation (e.g., septic shock) and improve impaired tissue β-lactam penetration [89-91]. In the absence of well conducted, prospective, clinical trials addressing the therapeutic benefit of currently recommended PK-PD targets, 100% $f T > MIC$ could be considered a prudent

PK/PD target for β-lactams in critically ill patients or immunocompromised. Non-critically ill and non-immunocompromised patients may only require minimal exposures of 40-70% $f T > MIC$ [92].

ADME. Penicillins. Penicillins have different values of protein binding; with the exception of piperacillin and clavulanic acid that are not orally absorbed, the gastrointestinal absorption is >50% for almost all drugs considered. They are minimally metabolized and the main route of elimination is renal excretion as parent drug. PK characteristics of penicillins are reported in Table 5.

ADME. Cephalosporins. Cephalosporins are a new class of broad-spectrum antibiotics that bind to plasma proteins in different degrees. Reported values for protein binding range from 6% for cephadrine to 92% for cefazolin [104]. Cephalosporins generally distribute well into the lung, kidney, urine, synovial, pleural, and pericardial fluids. Penetration into the CSF of some third generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) is adequate to effectively treat bacterial meningitis. Elimination is primarily via the kidneys, though a few exceptions include cefoperazone and ceftriaxone which have significant biliary elimination. Biliary excretion of cephalosporins is highly dependent on molecular weight in rats: less than 15% of the dose is excreted into the bile for cephalosporins with a molecular weight of less than 450, but those with a molecular weight of more than 450 exhibit 15 to 100% recovery in bile [105]. In addition, their elimination pathway is

Table 5. PK characteristics of penicillins.

Penicillins	Protein Binding (%)	Distribution Volume (L/kg) ^a	GI absorption (%)	Metabolism (%)	Excretion (%)	
					Renal	Hepatobiliary
Penicillin G	20-30	0.17-0.21	50	20	60 (parent drug)	
Cloxacillin [77, 93]	>90	na	37-60	22 (hydrolysis)	>90	
Dicloxacillin [94]	97	na	50	10	>90 (parent drug)	
Ampicillin [95-97]	28	0.32	80 ^b	10	65 (parent drug)	minimal
Amoxicillin [98]	20	0.43	75	<30	>70 (parent drug)	
Piperacillin [99-103]	30	0.23-0.27	no		56-73 (parent drug)	
Clavulanic Acid	25	-	no	55-75	-	
Sulbactam [95-97]	28	0.34	80 ^b	10	46 (parent drug)	minimal
Tazobactam [99, 100]	20-23	0.18-0.27	50		60	

GI, gastrointestinal.

a, value obtained considering a body weight of 70 kg

b, after administration of sulfaticillin (ampicillin + sulbactam)

Table 6. PK characteristics of carbapenems.

Carbapenems	Protein binding (%)	Distribution Volume (L/kg)	Metabolism (%)	Excretion (%)	
				Renal	Hepatobiliary
Imipenem [110]	20	0.20-0.23	-	70 (parent drug)	
Meropenem [111, 112]	2	0.18-0.30	19-27 (chemical hydrolysis, extrarenal metabolism, and renal metabolism via DHP-I)	70 (parent drug)	
Doripenem [113, 114]	9	0.24	no	97.2 (parent drug)	
Ertapenem [109, 115]	95-92	0.11-0.12 (total fraction)	minimal	~40 (parent drug)	10 (parent drug)

a, value obtained considering a body weight of 70 kg

mainly excretion into bile and/or urine with minimal metabolism in the body [106, 107].

ADME. Carbapenems. Plasma protein binding of imipenem, meropenem and doripenem is low (20, 2 and 9% respectively) and independent of plasma drug concentrations [108]. Ertapenem is highly bound to plasma protein, from ~95% at concentrations of 50 mg/L to ~92% at concentrations of 150 mg/L [109]. Carbapenems are not orally absorbed, therefore they are administered via infusion. PK characteristics of carbapenems are reported in Table 6.

PG data. As above reported β -lactam agents are primarily excreted by the kidneys and are poorly metabolized. From 1995 many studies, especially on cephalosporins, investigated transporters responsible of β -lactam bioavailability (Table 7). Uptake transporters as peptide transporter 1 and 2 (PEPT1, PEPT2) were found to be involved in intestinal and renal absorption of cephalosporins [116-118]. Moreover cephalosporins showed interaction with the organic anion transporters 1, 3, and 4 (OAT1, OAT3, OAT4) localized in the proximal tubule where they play a distinct role in the basolateral and apical uptake of cephalosporin antibiotics [119-121]. Recently, Kato *et al.* [122] found that weight-dependent biliary excretion of several cephalosporins including cefoperazone, cefbuperazone, cefpiramide, all of which are mainly excreted into bile, is mediated by MRP2 transporter. The involvement of P-gp on β -lactam disposition was only investigated for dicloxacillin and cloxacillin [77,

123]. The influence of SNPs in gene coding for transporters involved in β -lactam bioavailability was poorly studied. Putnam *et al.* [76] found that 3435C>T (rs1045642) variant of the *ABCB1* do not influence dicloxacillin plasma levels in 18 volunteers but the data suggested that rifampicin induces intestinal P-gp and increases dicloxacillin metabolism. Yin *et al.* [77] found that the 1236C>T (rs1128503) variant of *ABCB1* appeared to be an important contributor to inter-individual differences in plasma cloxacillin exposure in healthy Chinese male subjects. This effect depends most likely through an effect on oral absorption rather than on disposition (Table 4).

DAPTOMYCIN

Daptomycin is a lipopeptide antibiotic used for the treatment of complicated skin and soft-tissue infections, right-sided infective endocarditis due to *Staphylococcus aureus*, *S. aureus* bacteraemia when associated with right-sided infective endocarditis or with complicated skin and soft-tissue infections. It is active against gram-positive bacteria only [125].

Mechanism of action. Daptomycin is rapidly bactericidal. It acts by penetrating into the membrane of gram-positive bacteria and causing rapid membrane depolarization [126].

PK-PD parameters predictive of efficacy. Daptomycin has a concentration-dependent bactericidal activity *in-vitro* and *in-vivo*

Table 7. Specific transporters of cephalosporins and type of ADME processes involved.

Beta-lactams agents	Transporter	Coding gene	Model	ADME Process Involved	Ref.
Dicloxacillin	P-gp	<i>ABCB1</i>	MDCK	Renal clearance	Susanto <i>et al.</i> 2002 [123]
Ceftriaxone	MRP2	<i>ABCC2</i>		Biliary excretion	Kato <i>et al.</i> 2008 [122]
Cefoperazone					
Cefbuperazone					
Cefpiramide					
Cefaloridine	OAT3	<i>SLC22A8</i>	HEK293 cells	Renal secretion	Ueo <i>et al.</i> 2005 [119]
Cefdinir					
Cefotiam					
Cefaloridine	OAT1	<i>SLC22A6</i>	Xenopus laevis oocytes	Renal secretion	Jariyawat <i>et al.</i> 1999 [120]
Cefazolin	OAT1	<i>SLC22A6</i>	Xenopus laevis oocytes	Renal secretion	Uway <i>et al.</i> 2002 [121]
Cefotiam					
Cephalexin					
Cephalexin	PEPT2	<i>SLC15A2</i>	SKPT cells	Renal reabsorption	Luckner <i>et al.</i> 2004 [124]
Cefadroxil					
Cefaclor					
Cyclacillin					
Cephadrine					
Moxalactam					
Ceftibutene	PEPT1	<i>SLC15A1</i>	Caco-2 cells	Intestinal absorption	Matsumoto <i>et al.</i> 1994 [116]
Cephadrine					
Ceftibutene	PEPT1	<i>SLC15A1</i>	Xenopus oocytes	Intestinal and renal absorption	Saito <i>et al.</i> 1995 [117]
Cephadrine					
Ceftibutene	PEPT1	<i>SLC15A1</i>	LLC-PK1	Intestinal absorption	Terada <i>et al.</i> 1997 [118]
Cephadrine					

ADME, absorption distribution metabolism elimination; P-gp, P-glycoprotein; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; PEPT, peptide transporter; ABC, ATP binding cassette; SLC, solute carrier.

animal models. The PK/PD indices that best correlate with its activity are C_{max}/MIC or AUC/MIC . Optimal theoretical PK/PD determinants correlated with improved outcome and reduced toxicity are $C_{max} > 60$ mg/L [127] and $C_{min} < 24.3$ mg/L [128], respectively for infections sustained by microorganisms having $MIC < 1$ mg/L.

ADME. Animal studies showed that daptomycin is not absorbed to any significant extent after oral administration. The volume of distribution at steady state of daptomycin in healthy adult subjects was approximately 0.1 L/kg corresponding with a predominantly extracellular distribution and high protein binding [129]. In healthy volunteers and patients treated with daptomycin, protein binding averaged about 90% including subjects with renal impairment. The binding is reversible and concentration independent [125, 130]. Tissue distribution studies in rats showed that daptomycin appears to only minimally penetrate the BBB and the placental barrier following single and multiple doses. Daptomycin

is mainly excreted by the kidneys. In patients with severe or terminal renal insufficiency (creatinine $CL < 30$ ml/min) and in subjects undergoing hemodialysis or peritoneal dialysis daptomycin should be used cautiously because elimination half-life and AUC are increased by two- to three-fold [131]. In *in-vitro* studies, daptomycin was not metabolized by human liver microsomes with only minimal involvement of the CYP P450 isoenzymes [129]. 78% of the administered dose was recovered from the urine based on total radioactivity, whilst urinary recovery of unchanged daptomycin was approximately 50% of the dose. About 5% of the administered radiolabeled dose is excreted in the feces [125].

PG data. In a recent study conducted by Lemaire *et al.* [35] it was reported that daptomycin is subjected to efflux from THP-1 macrophages and MDCK cells by P-gp, which reduces its intracellular activity against phagocytized *Staphylococcus aureus* (Table 1). The influence of SNPs on *ABCB1* gene coding for P-gp on dap-

tomycin bioavailability was observed by Baietto L *et al.* [78]. They found that patients with homozygous mutate genotype (TT) for 3435C>T (rs1045642), 1236C>T (rs1128503) and 2677G>T (rs2032582) had significantly higher levels of daptomycin plasma levels and reduced clearance. These results highlight the importance of P-gp in understanding inter-individual variability of daptomycin PK (Table 4).

GLYCOPEPTIDES: VANCOMYCIN AND TEICOPLANIN

Glycopeptide antibiotics are a class of antibiotic drugs active against gram-positive bacteria. They are characterized by a narrow spectrum of action, and are active against staphylococci (including methicillin resistant strains), streptococci, enterococci and *Clostridium* spp. Tissue diffusion is not generally good, as into the cerebrospinal fluid, for example. Penetration can be influenced by inflammation and disease state.

Mechanism of action. They inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis. They bind to the aminoacids within the cell wall preventing the addition of new units to the peptidoglycan.

PK-PD parameters predictive of efficacy. Vancomycin and teicoplanin have a time dependent activity and vancomycin has clear dose-response correlations, since highly significant association between clinical cure and an AUC/MIC>400 was demonstrated [132]. Based on this study, current dosing guidelines propose target trough levels of 15–20 mg/L for a pathogen with an MIC of 1 mg/L to obtain the target AUC/MIC [133]. The dose-toxicity relationship remains to be established [134]. TDM of vancomycin is frequently employed especially in patients with impairment of renal function. Some authors suggested a specific role for continuous infusion to increase the likelihood of AUC/MIC>400 [135].

Teicoplanin acts in a time dependent manner: trough concentrations >10 mg/L have been recommended for most infections and >20 mg/L for endocarditis [136].

ADME. Vancomycin protein binding is low, a level of 50–55% is most often stated [137, 138]. Volume of distribution is around 0.4 L/Kg. Teicoplanin is characterized by a high protein binding of 90% and a volume of distribution of 1 L/kg [139]. Both vancomycin and teicoplanin are cleared unchanged renally, and doses should be reduced in patients with renal impairment.

PG data. To date, no data were published about PG of vancomycin and teicoplanin. As vancomycin induced kidney damage is determined via the tubular secretion [140], in the future, investigating the influence of SNPs in genes coding for proteins involved in renal transporters activity, as P-gp, OCT, and OAT, could be useful to further individualize therapy. Del Moral *et al.* [141] reported that P-gp is thought to be involved in the defense against cyclosporin nephrotoxicity. Considering these data, studying the influence of P-gp in vancomycin elimination could be useful to reduce the drug induced kidney damage.

POLYMXINS: COLISTIN AND POLYMXIN B

Colistin and polymixin B are old antibiotics which had fallen out of favour in the 1970s due to reports of nephrotoxicity and neurotoxicity [142]. In 1980s due to increased emergence of bacterial resistance and declining development of new antibiotics, colistin had to be used against multi drug resistant bacteria. We will focus on colistin, as an example of this class of antibiotics. Colistin is a cationic antimicrobial peptide available in two different forms: colistin sulphate and sodium colistin methanesulphonate (CMS). CMS is 'less toxic' than colistin when administered parenterally [143] and hence it is CMS that is present in all parenteral (and most inhalational) formulations. Colistin is used for the treatment of infections caused by gram-negative bacilli, including multidrug-

resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* [144].

Mechanism of action. Colistin is an amphipathic compound. Hydrophobic/hydrophilic regions interact with the cytoplasmic membrane like a detergent, solubilizing the membrane in an aqueous environment.

PK-PD parameters predictive of efficacy. Colistin has a concentration dependent activity. Recently it was revealed that CMS is an inactive pro-drug of colistin, therefore showing separate determination of CMS and formed colistin concentrations are essential to fully understand the pharmacology of CMS/colistin [145] and to optimize the outcome in clinical practice. In clinical practice the attainment of steady-state plasma colistin concentrations above the MIC breakpoint of 2 mg/L was found to be associated with improved outcome [146-148].

ADME. Both colistin sulfate and CMS are administered intravenously and colistin sulfate is also available as topical formulation for skin infections. Colistin is not absorbed from the gastrointestinal tract [149]. Following an intravenous bolus dose of colistin sulfate only 0.18 ± 0.14% of the total colistin dose is recovered in urine over 24 h [150]. Therefore this result suggested that colistin undergoes very extensive renal tubular reabsorption through a carrier-mediated process, and that it is cleared mainly via nonrenal pathway [151]. After administration of CMS, colistin appears rapidly in plasma [152]. PK analysis revealed that only approximately 7% of the administered dose of CMS was converted to colistin systemically. CMS is eliminated predominantly by the kidneys. After parenteral administration, approximately 60% of CMS is excreted in the urine during the first 24 h [152].

PG data. Given that one of the side effects associated with colistin treatment is neurotoxicity [153], and that colistin exhibits some of the characteristics possessed by known P-gp substrates [154], Jin *et al.* [155] investigated whether efflux by P-gp was also contributing to the low brain uptake of colistin. These studies suggested that P-gp does not contribute to the low brain up-take of colistin and that the brain uptake of colistin is significantly increased during systemic inflammation when BBB integrity is compromised.

SULFONAMIDES

Sulfonamides were the forerunner of the modern era of antibiotics after discovery of sulfamidochrysoidine in 1935.

The combination of adverse effects and bacterial resistance lead to a decrease in sulfonamides prescription, but their potential activity against parasitic infections revived the interests in these class of antibiotics. Since 1968, sulfonamides have been one of the components in combination with dihydrofolate reductase (DHFR) inhibitors, such as trimethoprim (co-trimoxazole; TMP-SMX).

Sulfonamides are classified in short or intermediate acting (sulfisoxazole, sulfamethoxazole, sulfadiazine; these compound can also be used in combination) and long-acting (sulfadoxine and sulfamethoxine).

They are active against *S.aureus*, including MRSA, streptococci, *E. faecalis*, *Corynebacterium diphtheriae*, *Nocardia* and *Actinomyces* as well as the majority of enteric gram negative bacteria. Combination of proguanil and certain sulfonamides are used in malaria due to *P. falciparum*. TMP-SMX has also activity against selected protozoa and it is approved for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis and treatment [156].

Mechanism of action. Sulfonamides act by inhibiting the formation of dihydropteroic acid by competing with para-aminobenzoic acid for condensation with 7,8-pterin pyrophosphate, a reaction cata-

lyzed by the enzyme dihydropteroate synthase (DHPS). Inhibition results in the cells becoming depleted of tetrahydrofolate [156].

PK-PD parameters predictive of efficacy. Sulfonamides are generally bacteriostatic, no PK-PD parameters predictive of efficacy or toxicity have been identified.

ADME. Sulfonamides are administered orally or parenterally (sulfadiazine) and they are well absorbed by gastrointestinal tract. Half life ranges from 10 to 150 hours, according to different compounds. They have a well distribution in CSF, pleural and peritoneal fluid as well as placental barrier. Protein binding is high (50 to 95%). The major route of sulfonamides metabolism is liver, where they were acetylated and glucuronidated, whilst elimination is act by glomerular filtration.

PG data. The majority of PG data available are focused on sulphamethoxazole. Sulphamethoxazole undergoes bioactivation to a hydroxylamine by CYP2C9 enzyme. In a study performed by Gill *et al.*, it was observed that CYP2C9*2 and CYP2C9*3 polymorphisms may have some influence on the bioactivation of sulphamethoxazole, particularly in individuals who are homozygous mutants, and this could act as a protective factor against sulphamethoxazole hypersensitivity [79].

Pirmohamed *et al.* investigated the influence of SNPs in gene coding for enzymes involved in co-trimoxazole metabolism in HIV-positive patients. They found that none of the SNPs investigated in CYP2C9, GSTM1, GSTT1, GSTP1 and NAT2 coding genes resulted major predisposing factors in determining individual susceptibility to co-trimoxazole hypersensitivity in HIV positive patients [157]. A study performed by Wang *et al.* showed that SNP in glutamate cysteine ligase catalytic subunit coding gene (GCLC) (SNP rs761142 T>G) was significantly associated with sulphamethoxazole -induced hypersensitivity and with reduced GCLC mRNA expression in HIV infected patients [80] (Table 4). Susanto *et al.* found that sulphamethoxazole is not a P-gp substrate [123].

FIRST LINE ANTITUBERCULARS

Antituberculars agents used as first line treatment are: isoniazid, rifampicin, ethambutol and pyrazinamide. They are used in the treatment of susceptible mycobacterium tuberculosis. The treatment consists in the combination of the four drugs during the first two months of therapy and of isoniazid and rifampicin for the remaining four months.

Mechanism of action. Isoniazid and ethambutol act by inhibiting mycobacterial cell wall lipid, and nucleic acid synthesis [158]. Rifampicin blocks transcription [158] while mode of action of pyrazinamide is poorly understood; it probably acts by disrupting membrane energetics and inhibiting membrane transport function in Mycobacterium tuberculosis [159].

PK-PD parameters predictive of efficacy. No precise TDM targets are available from human studies. Target plasma levels refer to findings in healthy volunteers. The following target ranges of peak plasma concentrations (2 hours post-dose) have been proposed by Peloquin *et al.* [160]: 3-6 mg/L for isoniazid 300 mg qd, 8-24 mg/L for rifampicin 600 mg qd, 2-6 mg/L for ethambutol 25 mg/kg qd and 20-50 mg/L for pyrazinamide 25 mg/kg qd. To date, no toxicity targets have been proposed.

ADME. Food reduces absorption of isoniazid, rifampicin and ethambutol; no effect on pyrazinamide oral bioavailability was observed [161]. Thus isoniazid, rifampicin, and ethambutol should be given in an empty stomach [160]. Isoniazide is metabolized in the liver to acetylisoniazid via N-acetyltransferase (NAT2) enzyme, following, acetylisoniazid is hydrolyzed to acetylhydrazine that is further hydrolyzed to hepatotoxic compounds by cytochrome P450

2E1 (CYP2E1). Among antituberculars, isoniazid is the main drug to induce hepatotoxicity [162]. Rifampicin is metabolized to 25-desacetyl rifampicin (it has 20% of microbiological activity that of the parent compound) by liver microsomes [163] and it is excreted via biliary and renal route [164]. Pyrazinamide is metabolized by the liver to pyrazinoic acid, 5-hydroxy-pyrazinamide, 5-hydroxy-pyrazinoic acid and pyrazinuric acid and excretion is via renal route. Ethambutol is metabolized by the liver, approximately 50% and 20% of the initial dose is excreted unchanged in the urine, and in the feces, respectively [165].

PG Data. Even if PG data regarding antituberculars were reported in a previous published review written by Ramachandran *et al.* [166], we have chosen to report all studies published until today in order to have a more clear and updated overview of antitubercular PG. Data are reported in Tables 4 and 8. Considering antituberculars PK, several studies investigated the influence of SNPs in SLCO1B1, ABCB1, CES2, PXR, CAR, NAT2 coding gene and antitubercular PK. In particular it was found that SLCO1B1 463 CA genotype (rs11045819) and SLOCO1B1 rs4149032 are associated to rifampicin plasma levels [81, 82, 84] (Table 4). The most common side effect associated to first line antituberculars is hepatitis [167]. In (Table 8) we reported previous published studies regarding the association among genotype of antitubercular transporters and metabolizing enzymes and toxicity. Several studies investigated the association between NAT2 genotype and emergence of drug induced hepatotoxicity [168-173]. NAT2 is coded by a highly polymorphic gene and variability in its expression can affect drug levels. NAT2 genotype resulted also associated to isoniazid plasma levels [85], to isoniazid PK variability [86], and to the early bactericidal activity (EBA) of isoniazid [87]. The association between CYP2E1 genotype and hepatotoxicity was also previously investigated. It was observed that patients with homozygous wild type genotype (CYP2E1 c1/c1) had higher risk of hepatotoxicity [162, 169, 171, 174]. GST are a group of enzymes involved in solubilization and elimination of isoniazid toxic metabolites. Two recently published studies reported that hepatotoxicity is also associated to GSTM1 and GSTT1 genotype [175, 176]. Kim *et al.* hypothesized that polymorphisms in tumor necrosis factor (*TNFA*) gene are associated with hepatitis and they found an influence of *TNFA* 308G>A (rs1800629) on anti-tuberculosis drug induced hepatitis [177]. The same authors found that SNPs in gene coding for P-gp, OATP1 and MRP2 were not associated to hepatitis induced by antituberculosis drugs in Korean patients [178].

CONCLUSIONS

In the last years the antibiotic resistance is increased and the research on new compounds has decreased. TDM and PG represent two new strategies to individualize therapy in an era of enhanced complexity of patients and treatments, to increase the likelihood of appropriate therapy. The optimization of the plasma and tissue concentrations of antibiotics is crucial especially in critically ill and immunocompromised patients. In this review we focused on describing PK of antibiotics and reporting PG studies to better understand the role of PG in improving treatment outcome. Regarding antituberculosis treatment, several studies showed that PG plays an important role especially in isoniazid metabolism. Considering the other antibiotics, most of the PG studies were mainly focused on drug transporters involved in drug elimination and distribution and data regarding the association between SNPs and clinical effect are still lacking.

P-gp resulted the most studied transporter probably because it has a ubiquitous expression, it is coded by a polymorphic gene, and because several SNPs in *ABCB1* gene are correlated with P-gp activity. As reported in this review, P-gp seems to have an influence

Table (8) contd....

Antibiotic administered	Transporter/ Enzyme	Coding gene	Alleles	SNP	In-vivo effect	Model	Reference
Isoniazid	TNF- α	TNF- α	-	308G>A	Higher number of patients with ATD-induced hepatitis had 308AG or 308AA genotypes compared with ATD-tolerant controls	Korean ATD-induced hepatitis patients, n=77, Korean ATD-tolerant control, n=229	Kim <i>et al.</i> 2011 [177]
Rifampicin							
Ethambutol							
Pyrazinamide							
Isoniazid	Pgp OATP1 MRP2	ABCB1 SLCO1B1 ABCC2	-	-	SNPs in gene coding for P-gp, OATP1, and MRP2 were not associated to hepatitis induced by anti-tuberculosis drugs	Korean patients, n=67	Kim <i>et al.</i> 2012 [178]
Rifampicin							
Ethambutol							
Pyrazinamide							

ADME, absorption distribution metabolism elimination; NAT, N-acetyltransferase; CYP, Cytochrome P450; Mn SOD, Manganese superoxide dismutase; NQO1, NAD (P) H Quinone oxidoreductase 1; GST, glutathione S-transferase; TNF, tumor necrosis factor; P-gp, P-glycoprotein; OAT, organic anion transporter; MRP, multidrug resistance-associated protein; ABC, ATP binding cassette; SLC, solute carrier. Rs number: NAT2*5, 481C>T, rs1799929; NAT2*6 590G>A, rs1799930; NAT2*7, 857G>A, rs1799931; NAT2*5, 341C>T, rs1801280; MnSOD 47C>T, rs4880; NQO1 609C>T, rs 1800566; TNF- α 308G>A, rs1800629.

on disposition of several antibiotics. P-gp is involved in transport of tobramycin, azithromycin and clarithromycin through the gut and it can potentially restrict intestinal absorption [25, 33, 179]. At the BBB level, P-gp was found to act as an efflux transporter for minocycline [32] and sparfloxacin [74]. P-gp is also involved in fluoroquinolone secretion at different compartments: gastrointestinal [65, 73, 75], renal [66], hepatic [70], transepithelial [67]. This efflux transporter is also important in PG because many drugs, as minocycline, are P-gp inhibitors. Minocycline, for example, was found to increase plasma levels of riluzole, and for this reason it is considered an antibiotic with anti-neurodegenerative properties [32]. β -lactams are substrate of uptake transporters as OAT and PEPT that mediate renal and intestinal absorption. To date, no SNPs in gene coding for these transporters have been identified. But, knowing the association between transporters and antibiotics could be useful both during drug development both in clinical practice when several drugs are co-administered.

Notwithstanding antibiotic therapy is shorter than antiretroviral therapy, improving research on identification of SNPs involved in antibiotic bioavailability could be useful to understand the importance of a PG approach in clinical practice. In this review we reported data regarding PK, PDs, and PG of antibiotics to underline the importance of an integrated approach to individualize therapy. We acknowledge that in the last years PK/PD indexes, predictive of efficacy and toxicity, have been identified for almost all antibiotics and the use of TDM in clinical practice is increasingly recognized as a tool to optimize treatment.

A new approach based on TDM and PG could be useful to further optimize therapy and perhaps to reduce costs associated to patients hospitalization. Further studies are needed to investigate new correlations among PG and drug bioavailability and to understand the full potential of this innovative approach.

CONFLICT OF INTEREST

SC received funding by Novartis for preparation of this manuscript. FDR and GDP were speaker for Novartis.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Lesko, L. J.; Schmidt, S. Individualization of drug therapy: history, present state, and opportunities for the future. *Clin. Pharmacol. Ther.*, **2012**, *92*(4), 458-466.
- [2] Cressey, T. R.; Lallemand, M. Pharmacogenetics of antiretroviral drugs for the treatment of HIV-infected patients: an update. *Infect. Genet. Evol.*, **2007**, *7*(2), 333-342.
- [3] Wright, J.; Paauw, D. S. Complications of antibiotic therapy. *Med Clin North Am.*, **2013**, *97*(4), 667-679, xi.
- [4] Neuvonen, P. J.; Kivisto, K. T.; Lehto, P. Interference of dairy products with the absorption of ciprofloxacin. *Clin. Pharmacol. Ther.*, **1991**, *50*(5) Pt 1, 498-502.
- [5] Meyer, F. P.; Specht, H.; Quednow, B.; Walther, H. Influence of milk on the bioavailability of doxycycline—new aspects. *Infection.*, **1989**, *17*(4), 245-246.
- [6] Minami, R.; Inotsume, N.; Nakano, M.; Sudo, Y.; Higashi, A.; Matsuda, I. Effect of milk on absorption of norfloxacin in healthy volunteers. *J. Clin. Pharmacol.*, **1993**, *33*(12), 1238-1240.
- [7] Gorski, J. C.; Jones, D. R.; Haehner-Daniels, B. D.; Hamman, M. A.; O'Mara, E. M., Jr.; Hall, S. D. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin. Pharmacol. Ther.*, **1998**, *64*(2), 133-143.
- [8] Nicolau, D. P. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin. Infect. Dis.*, **2008**, *47*(Suppl 1), S32-40.
- [9] Kim, K.; Johnson, J. A.; Derendorf, H. Differences in drug pharmacokinetics between East Asians and Caucasians and the role of genetic polymorphisms. *J. Clin. Pharmacol.*, **2004**, *44*(10), 1083-1105.
- [10] Matthews, H. W. Racial, ethnic and gender differences in response to medicines. *Drug. Metabol. Drug. Interact.*, **1995**, *12*(2), 77-91.
- [11] Mwinyi, J.; Johne, A.; Bauer, S.; Roots, I.; Gerloff, T. Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics. *Clin. Pharmacol. Ther.*, **2004**, *75*(5), 415-421.
- [12] Niemi, M.; Schaeffeler, E.; Lang, T.; Fromm, M. F.; Neuvonen, M.; Kyrklund, C.; Backman, J. T.; Kerb, R.; Schwab, M.; Neuvonen, P. J.; Eichelbaum, M.; Kivisto, K. T. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). *Pharmacogenetics*, **2004**, *14*(7), 429-440.
- [13] Hoffmeyer, S.; Burk, O.; von Richter, O.; Arnold, H. P.; Brockmoller, J.; Johne, A.; Cascorbi, I.; Gerloff, T.; Roots, I.; Eichelbaum, M.; Brinkmann, U. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and

- activity *in vivo*. *Proc. Natl. Acad. Sci. U S A.*, **2000**, 97(7), 3473-3478.
- [14] Maeda, K.; Sugiyama, Y. Impact of genetic polymorphisms of transporters on the pharmacokinetic, pharmacodynamic and toxicological properties of anionic drugs. *Drug. Metab. Pharmacokinet.*, **2008**, 23(4), 223-235.
- [15] Zhang, W.; Yu, B. N.; He, Y. J.; Fan, L.; Li, Q.; Liu, Z. Q.; Wang, A.; Liu, Y. L.; Tan, Z. R.; Fen, J.; Huang, Y. F.; Zhou, H. H. Role of BCRP 421C>A polymorphism on rosuvastatin pharmacokinetics in healthy Chinese males. *Clin. Chim. Acta.*, **2006**, 373(1-2), 99-103.
- [16] Sparreboom, A.; Gelderblom, H.; Marsh, S.; Ahluwalia, R.; Obach, R.; Principe, P.; Twelves, C.; Verweij, J.; McLeod, H. L. Diflomotecan pharmacokinetics in relation to ABCG2 421C>A genotype. *Clin. Pharmacol. Ther.*, **2004**, 76(1), 38-44.
- [17] Naesens, M.; Kuypers, D. R.; Verbeke, K.; Vanrenterghem, Y. Multidrug resistance protein 2 genetic polymorphisms influence mycophenolic acid exposure in renal allograft recipients. *Transplantation*, **2006**, 82(8), 1074-1084.
- [18] Rau, T.; Erney, B.; Gores, R.; Eschenhagen, T.; Beck, J.; Langer, T. High-dose methotrexate in pediatric acute lymphoblastic leukemia: impact of ABCG2 polymorphisms on plasma concentrations. *Clin. Pharmacol. Ther.*, **2006**, 80(5), 468-476.
- [19] Haas, D. W.; Ribaldo, H. J.; Kim, R. B.; Tierney, C.; Wilkinson, G. R.; Gulick, R. M.; Clifford, D. B.; Hulgand, T.; Marzolini, C.; Acosta, E. P. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*, **2004**, 18(18), 2391-2400.
- [20] Rodriguez-Novoa, S.; Barreiro, P.; Rendon, A.; Jimenez-Nacher, I.; Gonzalez-Lahoz, J.; Soriano, V. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin. Infect. Dis.*, **2005**, 40(9), 1358-1361.
- [21] Ikeda, Y.; Umemura, K.; Kondo, K.; Sekiguchi, K.; Miyoshi, S.; Nakashima, M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clin. Pharmacol. Ther.*, **2004**, 75(6), 587-588.
- [22] Narita, A.; Muramatsu, H.; Sakaguchi, H.; Doisaki, S.; Tanaka, M.; Hama, A.; Shimada, A.; Takahashi, Y.; Yoshida, N.; Matsumoto, K.; Kato, K.; Kudo, K.; Furukawa-Hibi, Y.; Yamada, K.; Kojima, S. Correlation of CYP2C19 phenotype with voriconazole plasma concentration in children. *J. Pediatr. Hematol. Oncol.*, **2013**, 35(5), e219-223.
- [23] Becker, B.; Cooper, M. A. Aminoglycoside antibiotics in the 21st century. *ACS. Chem. Biol.*, **2013**, 8(1), 105-115.
- [24] Briskier, A.; Veyssier, P., Aminocyclitol and aminoglycoside. In *Antimicrobial agents; antibacterials and antifungals*, Press, A., Ed. **2005**; pp 453-457.
- [25] Banerjee, S. K.; Jagannath, C.; Hunter, R. L.; Dasgupta, A. Bioavailability of tobramycin after oral delivery in FVB mice using CRL-1605 copolymer, an inhibitor of P-glycoprotein. *Life Sci.*, **2000**, 67(16), 2011-2016.
- [26] Briskier, A.; Veyssier, P., Tetracyclines. In *Antimicrobial agents; antibacterials and antifungals*, Press, A., Ed. **2005**; pp 642-649.
- [27] Agwuh, K. N.; MacGowan, A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylicylines. *J. Antimicrob. Chemother.*, **2006**, 58(2), 256-265.
- [28] Amin, A. R.; Attur, M. G.; Thakker, G. D.; Patel, P. D.; Vyas, P. R.; Patel, R. N.; Patel, I. R.; Abramson, S. B. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. *Proc. Natl. Acad. Sci. U S A.*, **1996**, 93(24), 14014-14019.
- [29] Gabler, W. L.; Creamer, H. R. Suppression of human neutrophil functions by tetracyclines. *J. Periodontol. Res.*, **1991**, 26(1), 52-58.
- [30] Whiteman, M.; Halliwell, B. Prevention of peroxynitrite-dependent tyrosine nitration and inactivation of alpha1-antitrypsinase by antibiotics. *Free Radic. Res.*, **1997**, 26(1), 49-56.
- [31] Colovic, M.; Caccia, S. Liquid chromatographic determination of minocycline in brain-to-plasma distribution studies in the rat. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.*, **2003**, 791(1-2), 337-343.
- [32] Milane, A.; Fernandez, C.; Vautier, S.; Bensimon, G.; Meininger, V.; Farinotti, R. Minocycline and riluzole brain disposition: interactions with p-glycoprotein at the blood-brain barrier. *J. Neurochem.*, **2007**, 103(1), 164-173.
- [33] Sugie, M.; Asakura, E.; Zhao, Y. L.; Torita, S.; Nadai, M.; Baba, K.; Kitaichi, K.; Takagi, K.; Hasegawa, T. Possible involvement of the drug transporters P glycoprotein and multidrug resistance-associated protein Mrp2 in disposition of azithromycin. *Antimicrob. Agents Chemother.*, **2004**, 48(3), 809-814.
- [34] Garver, E.; Hugger, E. D.; Shearn, S. P.; Rao, A.; Dawson, P. A.; Davis, C. B.; Han, C. Involvement of intestinal uptake transporters in the absorption of azithromycin and clarithromycin in the rat. *Drug Metab. Dispos.*, **2008**, 36(12), 2492-2498.
- [35] Lemaire, S.; Van Bambeke, F.; Mingeot-Leclercq, M. P.; Tulkens, P. M. Modulation of the cellular accumulation and intracellular activity of daptomycin towards phagocytized *Staphylococcus aureus* by the P-glycoprotein (MDR1) efflux transporter in human THP-1 macrophages and madin-darby canine kidney cells. *Antimicrob. Agents Chemother.*, **2007**, 51(8), 2748-2757.
- [36] Schuetz, E. G.; Schinkel, A. H.; Relling, M. V.; Schuetz, J. D. P-glycoprotein: a major determinant of rifampicin-inducible expression of cytochrome P4503A in mice and humans. *Proc. Natl. Acad. Sci. U. S. A.*, **1996**, 93(9), 4001-4005.
- [37] Giamarellou, H.; Poulakou, G. Pharmacokinetic and pharmacodynamic evaluation of tigecycline. *Expert Opin. Drug Metab. Toxicol.*, **2011**, 7(11), 1459-1470.
- [38] Petersen, P. J.; Jacobus, N. V.; Weiss, W. J.; Sum, P. E.; Testa, R. T. *In vitro* and *in vivo* antibacterial activities of a novel glycylicylcline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob. Agents Chemother.*, **1999**, 43(4), 738-744.
- [39] Meagher, A. K.; Ambrose, P. G.; Grasele, T. H.; Ellis-Grosse, E. J. Pharmacokinetic/pharmacodynamic profile for tigecycline-a new glycylicylcline antimicrobial agent. *Diagn. Microbiol. Infect. Dis.*, **2005**, 52(3), 165-171.
- [40] Zhanel, G. G.; Karlowsky, J. A.; Rubinstein, E.; Hoban, D. J. Tigecycline: a novel glycylicylcline antibiotic. *Expert Rev. Anti. Infect. Ther.*, **2006**, 4(1), 9-25.
- [41] Lemaire, S.; Van Bambeke, F.; Mingeot-Leclercq, M. P.; Tulkens, P. M. In: (P-glycoprotein) and MRP1 (multidrug resistance-related protein 1) eukaryotic efflux transporters do not affect the cellular accumulation and intracellular activity of tigecycline towards intraphagocytic *Staphylococcus aureus*, Proceedings of the 18th ECCMID, Barcelona, Spain, April 19-22, **2008**.
- [42] Carbon, C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clin. Infect. Dis.*, **1998**, 27(1), 28-32.
- [43] Van Bambeke, F.; Tulkens, P. M. Macrolides: pharmacokinetics and pharmacodynamics. *Int. J. Antimicrob. Agents*, **2001**, 18 Suppl 1, S17-23.
- [44] Nightingale, C. H.; Murakawa, T.; Ambrose, P. G., Macrolide, Azalide, and Ketolide Pharmacodynamics. In *Antimicrobial Pharmacodynamics in Theory and Clinical Practice*, AG, M. D., Ed. **2002**; pp 205-220.
- [45] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.*, **2001**, 46(1-3), 3-26.
- [46] He, X. J.; Zhao, L. M.; Qiu, F.; Sun, Y. X.; Li-Ling, J. Influence of ABCB1 gene polymorphisms on the pharmacokinetics of azithromycin among healthy Chinese Han ethnic subjects. *Pharmacol. Rep.*, **2009**, 61(5), 843-850.
- [47] Baietto, L.; D'Avolio, A.; Ariaudo, A.; Corcione, S.; Simiele, M.; Cusato, J.; Urbino, R.; Di Perri, G.; Ranieri, V. M.; De Rosa, F. G. Development and validation of a new UPLC-PDA method to quantify linezolid in plasma and in dried plasma spots. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.*, **2013**, 936, 42-47.
- [48] Rivera, A. M.; Boucher, H. W. Current concepts in antimicrobial therapy against select gram-positive organisms: methicillin-resistant *Staphylococcus aureus*, penicillin-resistant pneumococci, and vancomycin-resistant enterococci. *Mayo. Clin. Proc.*, **2011**, 86(12), 1230-1243.
- [49] Pea, F.; Furlanot, M.; Cojutti, P.; Cristini, F.; Zamparini, E.; Franceschi, L.; Viale, P. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. *Antimicrob. Agents Chemother.*, **2010**, 54(11), 4605-4610.
- [50] Rayner, C. R.; Forrest, A.; Meagher, A. K.; Birmingham, M. C.; Schentag, J. J. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. *Clin. Pharmacokinet.*, **2003**, 42(15), 1411-1423.
- [51] Canut, A.; Isla, A.; Betriu, C.; Gascon, A. R. Pharmacokinetic-pharmacodynamic evaluation of daptomycin, tigecycline, and

- linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. *Eur. J. Clin. Microbiol. Infect. Dis.*, **2012**, *31*(9), 2227-2235.
- [52] Dryden, M. S. Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. *J. Antimicrob. Chemother.*, **2011**, *66* Suppl 4, iv7-iv15.
- [53] De Rosa, F. G.; Corcione, S.; Baietto, L.; Ariaudo, A.; Di Perri, G.; Ranieri, V. M.; D'Avolio, A. Pharmacokinetics of linezolid during extracorporeal membrane oxygenation. *Int. J. Antimicrob. Agents*, **2013**, *41*(6), 590-591.
- [54] Gebhart, B. C.; Barker, B. C.; Markewitz, B. A. Decreased serum linezolid levels in a critically ill patient receiving concomitant linezolid and rifampin. *Pharmacotherapy*, **2007**, *27*(3), 476-479.
- [55] Andriole, V. T. The quinolones: past, present, and future. *Clin. Infect. Dis.*, **2005**, *41* Suppl 2, S113-119.
- [56] Labreche, M. J.; Frei, C. R. Declining susceptibilities of gram-negative bacteria to the fluoroquinolones: effects on pharmacokinetics, pharmacodynamics, and clinical outcomes. *Am. J. Health Syst. Pharm.*, **2012**, *69*(21), 1863-1870.
- [57] Drlaca, K.; Malik, M. Fluoroquinolones: action and resistance. *Curr. Top. Med. Chem.*, **2003**, *3*(3), 249-282.
- [58] Fish, D. N. Levofloxacin: update and perspectives on one of the original 'respiratory quinolones'. *Expert Rev. Anti Infect. Ther.*, **2003**, *1*(3), 371-387.
- [59] Ambrose, P. G.; Bhavnani, S. M.; Owens, R. C., Jr. Clinical pharmacodynamics of quinolones. *Infect. Dis. Clin. North Am.*, **2003**, *17*(3), 529-543.
- [60] Fish, D. N.; Chow, A. T. The clinical pharmacokinetics of levofloxacin. *Clin. Pharmacokinet.*, **1997**, *32*(2), 101-119.
- [61] Wolfson, J. S.; Hooper, D. C. Treatment of genitourinary tract infections with fluoroquinolones: activity *in vitro*, pharmacokinetics, and clinical efficacy in urinary tract infections and prostatitis. *Antimicrob. Agents Chemother.*, **1989**, *33*(10), 1655-1661.
- [62] Martinez, M.; McDermott, P.; Walker, R. Pharmacology of the fluoroquinolones: a perspective for the use in domestic animals. *Vet. J.*, **2006**, *172*(1), 10-28.
- [63] Nightingale, C. H. Moxifloxacin, a new antibiotic designed to treat community-acquired respiratory tract infections: a review of microbiologic and pharmacokinetic-pharmacodynamic characteristics. *Pharmacotherapy*, **2000**, *20*(3), 245-256.
- [64] Weiner, M.; Burman, W.; Luo, C. C.; Peloquin, C. A.; Engle, M.; Goldberg, S.; Agarwal, V.; Vernon, A. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob. Agents Chemother.*, **2007**, *51*(8), 2861-2866.
- [65] Yamaguchi, H.; Yano, I.; Hashimoto, Y.; Inui, K. I. Secretory mechanisms of grepafloxacin and levofloxacin in the human intestinal cell line caco-2. *J. Pharmacol. Exp. Ther.*, **2000**, *295*(1), 360-366.
- [66] Ito, T.; Yano, I.; Tanaka, K.; Inui, K. I. Transport of quinolone antibacterial drugs by human P-glycoprotein expressed in a kidney epithelial cell line, LLC-PK1. *J. Pharmacol. Exp. Ther.*, **1997**, *282*(2), 955-960.
- [67] Lowes, S.; Simmons, N. L. Multiple pathways for fluoroquinolone secretion by human intestinal epithelial (Caco-2) cells. *Br. J. Pharmacol.*, **2002**, *135*(5), 1263-1275.
- [68] Maeda, T.; Takahashi, K.; Ohtsu, N.; Oguma, T.; Ohnishi, T.; Atsumi, R.; Tamai, I. Identification of influx transporter for the quinolone antibacterial agent levofloxacin. *Mol. Pharm.*, **2007**, *4*(1), 85-94.
- [69] Merino, G.; Alvarez, A. I.; Pulido, M. M.; Molina, A. J.; Schinkel, A. H.; Prieto, J. G. Breast cancer resistance protein (BCRP/ABCG2) transports fluoroquinolone antibiotics and affects their oral availability, pharmacokinetics, and milk secretion. *Drug Metab. Dispos.*, **2006**, *34*(4), 690-695.
- [70] Ando, T.; Kusahara, H.; Merino, G.; Alvarez, A. I.; Schinkel, A. H.; Sugiyama, Y. Involvement of breast cancer resistance protein (ABCG2) in the biliary excretion mechanism of fluoroquinolones. *Drug Metab. Dispos.*, **2007**, *35*(10), 1873-1879.
- [71] Marquez, B.; Caceres, N. E.; Mingeot-Leclercq, M. P.; Tulkens, P. M.; Van Bambeke, F. Identification of the efflux transporter of the fluoroquinolone antibiotic ciprofloxacin in murine macrophages: studies with ciprofloxacin-resistant cells. *Antimicrob. Agents Chemother.*, **2009**, *53*(6), 2410-2416.
- [72] Arakawa, H.; Shirasaka, Y.; Haga, M.; Nakanishi, T.; Tamai, I. Active intestinal absorption of fluoroquinolone antibacterial agent ciprofloxacin by organic anion transporting polypeptide, Oatp1a5. *Biopharm. Drug Dispos.*, **2012**, *33*(6), 332-341.
- [73] Haslam, I. S.; Wright, J. A.; O'Reilly, D. A.; Sherlock, D. J.; Coleman, T.; Simmons, N. L. Intestinal ciprofloxacin efflux: the role of breast cancer resistance protein (ABCG2). *Drug Metab. Dispos.*, **2011**, *39*(12), 2321-2328.
- [74] de Lange, E. C.; Marchand, S.; van den Berg, D.; van der Sandt, I. C.; de Boer, A. G.; Delon, A.; Bouquet, S.; Couet, W. *In vitro* and *in vivo* investigations on fluoroquinolones; effects of the P-glycoprotein efflux transporter on brain distribution of sparfloxacin. *Eur. J. Pharm. Sci.*, **2000**, *12*(2), 85-93.
- [75] Cormet-Boyaka, E.; Huneau, J. F.; Mordrelle, A.; Boyaka, P. N.; Carbon, C.; Rubinstein, E.; Tome, D. Secretion of sparfloxacin from the human intestinal Caco-2 cell line is altered by P-glycoprotein inhibitors. *Antimicrob. Agents Chemother.*, **1998**, *42*(10), 2607-2611.
- [76] Putnam, W. S.; Woo, J. M.; Huang, Y.; Benet, L. Z. Effect of the MDR1 C3435T variant and P-glycoprotein induction on dicloxacillin pharmacokinetics. *J. Clin. Pharmacol.*, **2005**, *45*(4), 411-421.
- [77] Yin, O. Q.; Tomlinson, B.; Chow, M. S. Effect of multidrug resistance gene-1 (ABCB1) polymorphisms on the single-dose pharmacokinetics of cloxacillin in healthy adult Chinese men. *Clin. Ther.*, **2009**, *31*(5), 999-1006.
- [78] Baietto, L.; D'Avolio, A.; De Rosa, F. G.; Cusato, J.; Pace, S.; Calcagno, A.; Pagani, N.; Montrucchio, C.; Simiele, M.; Di Perri, G. In: *Single Nucleotide Polymorphisms of ABCB1 Gene Influence Daptomycin Pharmacokinetics in Adult Patients*, proceedings of the 52nd ICAAC, San Francisco, USA, September 9-12, **2012**.
- [79] Gill, H. J.; Tjia, J. F.; Kitteringham, N. R.; Pirmohamed, M.; Back, D. J.; Park, B. K. The effect of genetic polymorphisms in CYP2C9 on sulphamethoxazole N-hydroxylation. *Pharmacogenetics*, **1999**, *9*(1), 43-53.
- [80] Wang, D.; Curtis, A.; Papp, A. C.; Koletar, S. L.; Para, M. F. Polymorphism in glutamate cysteine ligase catalytic subunit (GCLC) is associated with sulfamethoxazole-induced hypersensitivity in HIV/AIDS patients. *BMC Med. Genomics*, **2012**, *5*, 32.
- [81] Weiner, M.; Peloquin, C.; Burman, W.; Luo, C. C.; Engle, M.; Prihoda, T. J.; Mac Kenzie, W. R.; Bliven-Sizemore, E.; Johnson, J. L.; Vernon, A. Effects of tuberculosis, race, and human gene SLCO1B1 polymorphisms on rifampin concentrations. *Antimicrob. Agents Chemother.*, **2010**, *54*(10), 4192-4200.
- [82] Kwara, A.; Cao, L.; Yang, H.; Poethke, P.; Kurpewski, J.; Tashima, K. T.; Mahjoub, B. D.; Court, M. H.; Peloquin, C. A. Factors Associated with Variability in Rifampin Plasma Pharmacokinetics and the Relationship between Rifampin Concentrations and Induction of Efavirenz Clearance. *Pharmacotherapy*, **2014**.
- [83] Song, S. H.; Chang, H. E.; Jun, S. H.; Park, K. U.; Lee, J. H.; Lee, E. M.; Song, Y. H.; Song, J. Relationship between CES2 genetic variations and rifampicin metabolism. *J. Antimicrob. Chemother.*, **2013**, *68*(6), 1281-1284.
- [84] Chigutsa, E.; Visser, M. E.; Swart, E. C.; Denti, P.; Pushpakom, S.; Egan, D.; Holford, N. H.; Smith, P. J.; Maartens, G.; Owen, A.; Mclleron, H. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: dosing implications. *Antimicrob. Agents Chemother.*, **2011**, *55*(9), 4122-4127.
- [85] Parkin, D. P.; Vandenplas, S.; Botha, F. J.; Vandenplas, M. L.; Seifart, H. I.; van Helden, P. D.; van der Walt, B. J.; Donald, P. R.; van Jaarsveld, P. P. Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. *Am. J. Respir. Crit. Care Med.*, **1997**, *155*(5), 1717-1722.
- [86] Kinzig-Schippers, M.; Tomalik-Scharte, D.; Jetter, A.; Scheidel, B.; Jakob, V.; Rodamer, M.; Cascorbi, I.; Doroshyenko, O.; Sorgel, F.; Fuhr, U. Should we use N-acetyltransferase type 2 genotyping to personalize isoniazid doses? *Antimicrob. Agents Chemother.*, **2005**, *49*(5), 1733-1738.
- [87] Donald, P. R.; Sirgel, F. A.; Venter, A.; Parkin, D. P.; Seifart, H. I.; van de Wal, B. W.; Werely, C.; van Helden, P. D.; Maritz, J. S. The influence of human N-acetyltransferase genotype on the early bactericidal activity of isoniazid. *Clin. Infect. Dis.*, **2004**, *39*(10), 1425-1430.
- [88] Craig, W. A. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-

- spectrum cephalosporins. *Diagn. Microbiol. Infect. Dis.*, **1995**, 22(1-2), 89-96.
- [89] Joukhadar, C.; Frossard, M.; Mayer, B. X.; Brunner, M.; Klein, N.; Siostrzonek, P.; Eichler, H. G.; Muller, M. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. *Crit. Care Med.*, **2001**, 29(2), 385-391.
- [90] Roberts, J. A.; Kirkpatrick, C. M.; Roberts, M. S.; Robertson, T. A.; Dalley, A. J.; Lipman, J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J. Antimicrob. Chemother.*, **2009**, 64(1), 142-150.
- [91] Roberts, J. A.; Roberts, M. S.; Robertson, T. A.; Dalley, A. J.; Lipman, J. Piperacillin penetration into tissue of critically ill patients with sepsis--bolus versus continuous administration? *Crit. Care Med.*, **2009**, 37(3), 926-933.
- [92] Sime, F. B.; Roberts, M. S.; Peake, S. L.; Lipman, J.; Roberts, J. A. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. *Ann. Intensive Care*, **2012**, 2(1), 35.
- [93] Paton, D. M. Comparative bioavailability and half-lives of cloxacillin and flucloxacillin. *Int. J. Clin. Pharmacol. Res.*, **1986**, 6, 5, 347-349.
- [94] DRUGBANK, Dicloxacillin. <http://www.drugbank.ca/drugs/DB00485> (accessed September 15, 2013).
- [95] Campoli-Richards, D. M.; Brogden, R. N. Sulbactam/ampicillin. A review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. *Drugs*, **1987**, 33(6), 577-609.
- [96] Nahata, M. C.; Vashi, V. I.; Swanson, R. N.; Messig, M. A.; Chung, M. Pharmacokinetics of ampicillin and sulbactam in pediatric patients. *Antimicrob. Agents Chemother.*, **1999**, 43(5), 1225-1229.
- [97] Betrosian, A. P.; Douzinas, E. E. Ampicillin-sulbactam: an update on the use of parenteral and oral forms in bacterial infections. *Expert Opin. Drug Metab. Toxicol.*, **2009**, 5(9), 1099-1112.
- [98] DRUGBANK Amoxicillin. <http://www.drugbank.ca/drugs/DB01060> (accessed September 15, 2013).
- [99] Sorgel, F.; Kinzig, M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J. Antimicrob. Chemother.*, **1993**, 31 Suppl A, 39-60.
- [100] Kinzig, M.; Sorgel, F.; Brismar, B.; Nord, C. E. Pharmacokinetics and tissue penetration of tazobactam and piperacillin in patients undergoing colorectal surgery. *Antimicrob. Agents Chemother.*, **1992**, 36, 9, 1997-2004.
- [101] Tjandramaga, T. B.; Mullie, A.; Verbesselt, R.; De Schepper, P. J.; Verbist, L. Piperacillin: human pharmacokinetics after intravenous and intramuscular administration. *Antimicrob. Agents Chemother.*, **1978**, 14(6), 829-837.
- [102] Hayashi, Y.; Roberts, J. A.; Paterson, D. L.; Lipman, J. Pharmacokinetic evaluation of piperacillin-tazobactam. *Expert Opin. Drug Metab. Toxicol.*, **2010**, 6(8), 1017-1031.
- [103] Ghibellini, G.; Bridges, A. S.; Generaux, C. N.; Brouwer, K. L. *In vitro* and *in vivo* determination of piperacillin metabolism in humans. *Drug Metab. Dispos.*, **2007**, 35(3), 345-349.
- [104] Singhvi, S. M.; Heald, A. F.; Schreiber, E. C. Pharmacokinetics of cephalosporin antibiotics: protein-binding considerations. *Chemotherapy*, **1978**, 24(3), 121-133.
- [105] Wright, W. E.; Line, V. D. Biliary excretion of cephalosporins in rats: influence of molecular weight. *Antimicrob. Agents Chemother.*, **1980**, 17(5), 842-846.
- [106] Tsuji, A.; Yoshikawa, T.; Nishide, K.; Minami, H.; Kimura, M.; Nakashima, E.; Terasaki, T.; Miyamoto, E.; Nightingale, C. H.; Yamana, T. Physiologically based pharmacokinetic model for beta-lactam antibiotics I: Tissue distribution and elimination in rats. *J. Pharm. Sci.*, **1983**, 72(11), 1239-1252.
- [107] Tsuji, A. Impact of transporter-mediated drug absorption, distribution, elimination and drug interactions in antimicrobial chemotherapy. *J. Infect. Chemother.*, **2006**, 12(5), 241-250.
- [108] Lister, P. D. Carbapenems in the USA: focus on doripenem. *Expert Rev. Anti. Infect. Ther.*, **2007**, 5(5), 793-809.
- [109] Majumdar, A. K.; Musson, D. G.; Birk, K. L.; Kitchen, C. J.; Holland, S.; McCrea, J.; Mistry, G.; Hesney, M.; Xi, L.; Li, S. X.; Haesen, R.; Blum, R. A.; Lins, R. L.; Greenberg, H.; Waldman, S.; Deutsch, P.; Rogers, J. D. Pharmacokinetics of ertapenem in healthy young volunteers. *Antimicrob. Agents Chemother.*, **2002**, 46(11), 3506-3511.
- [110] EUCAST. Imipenem: rationale for the EUCAST clinical breakpoints, version 1.3 **2009**.
- [111] Moon, Y. S.; Chung, K. C.; Gill, M. A. Pharmacokinetics of meropenem in animals, healthy volunteers, and patients. *Clin. Infect. Dis.*, **1997**, 24 Suppl 2, S249-255.
- [112] Mouton, J. W.; Touzw, D. J.; Horrevorts, A. M.; Vinks, A. A. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin. Pharmacokinet.*, **2000**, 39(3), 185-201.
- [113] Breilh, D.; Texier-Maugein, J.; Allaouchiche, B.; Saux, M. C.; Boselli, E. Carbapenems. *J. Chemother.*, **2013**, 25(1), 1-17.
- [114] Cirillo, I.; Mannens, G.; Janssen, C.; Vermeir, M.; Cuyckens, F.; Desai-Krieger, D.; Vaccaro, N.; Kao, L. M.; Devineni, D.; Redman, R.; Turner, K. Disposition, metabolism, and excretion of [14C]doripenem after a single 500-milligram intravenous infusion in healthy men. *Antimicrob. Agents Chemother.*, **2008**, 52(10), 3478-3483.
- [115] Nix, D. E.; Majumdar, A. K.; DiNubile, M. J. Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians. *J. Antimicrob. Chemother.*, **2004**, 53 Suppl 2, ii23-28.
- [116] Matsumoto, S.; Saito, H.; Inui, K. Transcellular transport of oral cephalosporins in human intestinal epithelial cells, Caco-2: interaction with dipeptide transport systems in apical and basolateral membranes. *J. Pharmacol. Exp. Ther.*, **1994**, 270(2), 498-504.
- [117] Saito, H.; Okuda, M.; Terada, T.; Sasaki, S.; Inui, K. Cloning and characterization of a rat H⁺/peptide cotransporter mediating absorption of beta-lactam antibiotics in the intestine and kidney. *J. Pharmacol. Exp. Ther.*, **1995**, 275(3), 1631-1637.
- [118] Terada, T.; Saito, H.; Mukai, M.; Inui, K. Characterization of stably transfected kidney epithelial cell line expressing rat H⁺/peptide cotransporter PEPT1: localization of PEPT1 and transport of beta-lactam antibiotics. *J. Pharmacol. Exp. Ther.*, **1997**, 281(3), 1415-1421.
- [119] Ueo, H.; Motohashi, H.; Katsura, T.; Inui, K. Human organic anion transporter hOAT3 is a potent transporter of cephalosporin antibiotics, in comparison with hOAT1. *Biochem. Pharmacol.*, **2005**, 70(7), 1104-1113.
- [120] Jariyawat, S.; Sekine, T.; Takeda, M.; Apiwatanakul, N.; Kanai, Y.; Sophasan, S.; Endou, H. The interaction and transport of beta-lactam antibiotics with the cloned rat renal organic anion transporter 1. *J. Pharmacol. Exp. Ther.*, **1999**, 290(2), 672-677.
- [121] Uwai, Y.; Saito, H.; Inui, K. Rat renal organic anion transporter rOAT1 mediates transport of urinary-excreted cephalosporins, but not of biliary-excreted cefoperazone. *Drug Metab. Pharmacokinet.*, **2002**, 17(2), 125-129.
- [122] Kato, S.; Ito, K.; Kato, Y.; Wakayama, T.; Kubo, Y.; Iseki, S.; Tsuji, A. Involvement of multidrug resistance-associated protein 1 in intestinal toxicity of methotrexate. *Pharm. Res.*, **2009**, 26(6), 1467-1476.
- [123] Susanto, M.; Benet, L. Z. Can the enhanced renal clearance of antibiotics in cystic fibrosis patients be explained by P-glycoprotein transport? *Pharm. Res.*, **2002**, 19(4), 457-462.
- [124] Luckner, P.; Brandsch, M. Interaction of 31 beta-lactam antibiotics with the H⁺/peptide symporter PEPT2: analysis of affinity constants and comparison with PEPT1. *Eur. J. Pharm. Biopharm.*, **2005**, 59(1), 17-24.
- [125] EMA; EUROPA Cubicin powder for concentrate for solution for injection or infusion. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000637/WC500036049.pdf (accessed September 25, 2013).
- [126] Silverman, J. A.; Perlmutter, N. G.; Shapiro, H. M. Correlation of daptomycin bactericidal activity and membrane depolarization in *Staphylococcus aureus*. *Antimicrob. Agents Chemother.*, **2003**, 47(8), 2538-2544.
- [127] Pea, F.; Cojutti, P.; Sbrojavacca, R.; Cadeo, B.; Cristini, F.; Bulfoni, A.; Furlanut, M. TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. *Ann. Pharmacother.*, **2011**, 45(7-8), e37.
- [128] Bhavnani, S. M.; Rubino, C. M.; Ambrose, P. G.; Drusano, G. L. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin. Infect. Dis.*, **2010**, 50(12), 1568-1574.
- [129] Woodworth, J. R.; Nyhart, E. H., Jr.; Brier, G. L.; Wolny, J. D.; Black, H. R. Single-dose pharmacokinetics and antibacterial

- activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob. Agents Chemother.*, **1992**, 36(2), 318-325.
- [130] Lee, B. L.; Sachdeva, M.; Chambers, H. F. Effect of protein binding of daptomycin on MIC and antibacterial activity. *Antimicrob. Agents Chemother.*, **1991**, 35(12), 2505-2508.
- [131] Sauerbann, R.; Rothenburger, M.; Graninger, W.; Joukhadar, C. Daptomycin: a review 4 years after first approval. *Pharmacology*, **2008**, 81(2), 79-91.
- [132] Moise-Broder, P. A.; Forrest, A.; Birmingham, M. C.; Schentag, J. J. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. *Clin. Pharmacokinet.*, **2004**, 43(13), 925-942.
- [133] ATS. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.*, **2005**, 171(4), 388-416.
- [134] Vandecasteele, S. J.; De Vriese, A. S.; Tacconelli, E. The pharmacokinetics and pharmacodynamics of vancomycin in clinical practice: evidence and uncertainties. *J. Antimicrob. Chemother.*, **2013**, 68(4), 743-748.
- [135] Pea, F.; Cojutti, P.; Petrosillo, N.; Furlan, M.; Entenza, J. M.; Veloso, T. R.; Vouillamoz, J.; Giddey, M.; Moreillon, P. Continuous infusion may improve the efficacy of vancomycin in treatment of experimental endocarditis due to heterogeneous vancomycin-intermediate Staphylococcus aureus. *Antimicrob. Agents Chemother.*, **2011**, 55(9), 4496; author reply 4496-4497.
- [136] Reeves, D. S. Therapeutic drug monitoring of aminoglycoside antibiotics. *Infection*, **1980**, 8 Suppl 3, S 313-320.
- [137] Ackerman, B. H.; Taylor, E. H.; Olsen, K. M.; Abdel-Malak, W.; Pappas, A. A. Vancomycin serum protein binding determination by ultrafiltration. *Drug Intell. Clin. Pharm.*, **1988**, 22(4), 300-303.
- [138] Albrecht, L. M.; Rybak, M. J.; Warbasse, L. H.; Edwards, D. J. Vancomycin protein binding in patients with infections caused by Staphylococcus aureus. *DICP*, **1991**, 25(7-8), 713-715.
- [139] Brogden, R. N.; Peters, D. H. Teicoplanin. A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*, **1994**, 47(5), 823-854.
- [140] Fanos, V.; Cataldi, L. Renal transport of antibiotics and nephrotoxicity: a review. *J. Chemother.*, **2001**, 13(5), 461-472.
- [141] del Moral, R. G.; Olmo, A.; Aguilar, M.; O'Valle, F. P. Glycoprotein: a new mechanism to control drug-induced nephrotoxicity. *Exp. Nephrol.*, **1998**, 6(2), 89-97.
- [142] Koch-Weser, J.; Sidel, V. W.; Federman, E. B.; Kanarek, P.; Finer, D. C.; Eaton, A. E. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann. Intern. Med.*, **1970**, 72(6), 857-868.
- [143] Beveridge, E. G.; Martin, A. J. Sodium sulphomethyl derivatives of polymyxins. *Br. J. Pharmacol. Chemother.*, **1967**, 29(2), 125-135.
- [144] Biswas, S.; Brunel, J. M.; Dubus, J. C.; Reynaud-Gaubert, M.; Rolain, J. M. Colistin: an update on the antibiotic of the 21st century. *Expert Rev. Anti. Infect. Ther.*, **2012**, 10(8), 917-934.
- [145] Bergen, P. J.; Li, J.; Rayner, C. R.; Nation, R. L. Colistin methanesulfonate is an inactive prodrug of colistin against *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.*, **2006**, 50(6), 1953-1958.
- [146] Garonzik, S. M.; Li, J.; Thamlikitkul, V.; Paterson, D. L.; Shoham, S.; Jacob, J.; Silveira, F. P.; Forrest, A.; Nation, R. L. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob. Agents Chemother.*, **2011**, 55(7), 3284-3294.
- [147] Mohamed, A. F.; Karaiskos, I.; Plachouras, D.; Karvanen, M.; Pontikis, K.; Jansson, B.; Papadomichelakis, E.; Antoniadou, A.; Giamarellou, H.; Armaganidis, A.; Cars, O.; Friberg, L. E. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. *Antimicrob. Agents Chemother.*, **2012**, 56(8), 4241-4249.
- [148] Plachouras, D.; Karvanen, M.; Friberg, L. E.; Papadomichelakis, E.; Antoniadou, A.; Tsangaris, I.; Karaiskos, I.; Poulakou, G.; Kontopidou, F.; Armaganidis, A.; Cars, O.; Giamarellou, H. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob. Agents Chemother.*, **2009**, 53(8), 3430-3436.
- [149] Conly, J.; Johnston, B. Colistin: the phoenix arises. *Can. J. Infect. Dis. Med. Microbiol.*, **2006**, 17(5), 267-269.
- [150] Li, J.; Milne, R. W.; Nation, R. L.; Turnidge, J. D.; Smeaton, T. C.; Coulthard, K. Use of high-performance liquid chromatography to study the pharmacokinetics of colistin sulfate in rats following intravenous administration. *Antimicrob. Agents Chemother.*, **2003**, 47(5), 1766-1770.
- [151] Bergen, P. J.; Landersdorfer, C. B.; Zhang, J.; Zhao, M.; Lee, H. J.; Nation, R. L.; Li, J. Pharmacokinetics and pharmacodynamics of 'old' polymyxins: what is new? *Diagn. Microbiol. Infect. Dis.*, **2012**, 74(3), 213-223.
- [152] Li, J.; Milne, R. W.; Nation, R. L.; Turnidge, J. D.; Smeaton, T. C.; Coulthard, K. Pharmacokinetics of colistin methanesulfonate and colistin in rats following an intravenous dose of colistin methanesulfonate. *J. Antimicrob. Chemother.*, **2004**, 53(5), 837-840.
- [153] Bosso, J. A.; Liptak, C. A.; Seilheimer, D. K.; Harrison, G. M. Toxicity of colistin in cystic fibrosis patients. *DICP*, **1991**, 25(11), 1168-1170.
- [154] Li, J.; Nation, R. L.; Milne, R. W.; Turnidge, J. D.; Coulthard, K. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. *Int. J. Antimicrob. Agents*, **2005**, 25(1), 11-25.
- [155] Jin, L.; Li, J.; Nation, R. L.; Nicolazzo, J. A. Impact of p-glycoprotein inhibition and lipopolysaccharide administration on blood-brain barrier transport of colistin in mice. *Antimicrob. Agents Chemother.*, **2011**, 55(2), 502-507.
- [156] Bryskier, A.; Dihydrofolate reductase inhibitors, nitroheterocycles (furans), and 8-Hydroxyquinolines. In *Antimicrobial Agents: Antibacterials and Antifungals*, Press, A., Ed. **2005**; pp 941-945.
- [157] Pirmohamed, M.; Alfirevic, A.; Vilar, J.; Stalford, A.; Wilkins, E. G.; Sim, E.; Park, B. K. Association analysis of drug metabolizing enzyme gene polymorphisms in HIV-positive patients with cotrimoxazole hypersensitivity. *Pharmacogenetics*, **2000**, 10(8), 705-713.
- [158] Telenti, A. Genetics and pulmonary medicine. 5. Genetics of drug resistant tuberculosis. *Thorax*, **1998**, 53(9), 793-797.
- [159] Zhang, Y.; Wade, M. M.; Scorpio, A.; Zhang, H.; Sun, Z. Mode of action of pyrazinamide: disruption of Mycobacterium tuberculosis membrane transport and energetics by pyrazinoic acid. *J. Antimicrob. Chemother.*, **2003**, 52(5), 790-795.
- [160] Peloquin, C. A. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs*, **2002**, 62(15), 2169-2183.
- [161] Lin, M. Y.; Lin, S. J.; Chan, L. C.; Lu, Y. C. Impact of food and antacids on the pharmacokinetics of anti-tuberculosis drugs: systematic review and meta-analysis. *Int. J. Tuberc Lung Dis.*, **2010**, 14(7), 806-818.
- [162] Huang, Y. S.; Chern, H. D.; Su, W. J.; Wu, J. C.; Chang, S. C.; Chiang, C. H.; Chang, F. Y.; Lee, S. D. Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology*, **2003**, 37(4), 924-930.
- [163] Jamis-Dow, C. A.; Katki, A. G.; Collins, J. M.; Klecker, R. W. Rifampin and rifabutin and their metabolism by human liver esterases. *Xenobiotica*, **1997**, 27(10), 1015-1024.
- [164] Donald, P. R.; Maritz, J. S.; Diacon, A. H. The pharmacokinetics and pharmacodynamics of rifampicin in adults and children in relation to the dosage recommended for children. *Tuberculosis (Edinb)*, **2011**, 91(3), 196-207.
- [165] DRUGBANK Ethambutol. <http://www.drugbank.ca/drugs/DB00330> (accessed February 13, 2014).
- [166] Ramachandran, G.; Swaminathan, S. Role of pharmacogenomics in the treatment of tuberculosis: a review. *Pharmacogenomics Pers. Med.*, **2012**, 5, 89-98.
- [167] Yee, D.; Valiquette, C.; Pelletier, M.; Parisien, I.; Rocher, I.; Menzies, D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am. J. Respir. Crit. Care Med.*, **2003**, 167(11), 1472-1477.
- [168] Ben Mahmoud, L.; Ghazzi, H.; Kamoun, A.; Hakim, A.; Hachicha, H.; Hammami, S.; Sahnoun, Z.; Zalila, N.; Makni, H.; Zeghal, K. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis. *Pathol. Biol. (Paris)*, **2011**, 60(5), 324-330.
- [169] Cho, H. J.; Koh, W. J.; Ryu, Y. J.; Ki, C. S.; Nam, M. H.; Kim, J. W.; Lee, S. Y. Genetic polymorphisms of NAT2 and CYP2E1 associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. *Tuberculosis (Edinb)*, **2007**, 87(6), 551-556.

- [170] Hiratsuka, M.; Kishikawa, Y.; Takekuma, Y.; Matsuura, M.; Narahara, K.; Inoue, T.; Hamdy, S. I.; Endo, N.; Goto, J.; Mizugaki, M. Genotyping of the N-acetyltransferase2 polymorphism in the prediction of adverse drug reactions to isoniazid in Japanese patients. *Drug Metab. Pharmacokinet.*, **2002**, *17*(4), 357-362.
- [171] Lee, S. W.; Chung, L. S.; Huang, H. H.; Chuang, T. Y.; Liou, Y. H.; Wu, L. S. NAT2 and CYP2E1 polymorphisms and susceptibility to first-line anti-tuberculosis drug-induced hepatitis. *Int. J. Tuberc. Lung Dis.*, **2010**, *14*(5), 622-626.
- [172] Ohno, M.; Yamaguchi, I.; Yamamoto, I.; Fukuda, T.; Yokota, S.; Maekura, R.; Ito, M.; Yamamoto, Y.; Ogura, T.; Maeda, K.; Komuta, K.; Igarashi, T.; Azuma, J. Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Int. J. Tuberc. Lung Dis.*, **2000**, *4*(3), 256-261.
- [173] Wang, P. Y.; Xie, S. Y.; Hao, Q.; Zhang, C.; Jiang, B. F. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int. J. Tuberc. Lung Dis.*, **2012**, *16*(5), 589-595.
- [174] Roy, B.; Ghosh, S. K.; Sutradhar, D.; Sikdar, N.; Mazumder, S.; Barman, S. Predisposition of antituberculosis drug induced hepatotoxicity by cytochrome P450 2E1 genotype and haplotype in pediatric patients. *J. Gastroenterol. Hepatol.*, **2006**, *21*(4), 784-786.
- [175] Gupta, V. H.; Singh, M.; Amarapurkar, D. N.; Sasi, P.; Joshi, J. M.; Bajjal, R.; H, R. P.; Amarapurkar, A. D.; Joshi, K.; Wangikar, P. P. Association of GST null genotypes with anti-tuberculosis drug induced hepatotoxicity in Western Indian population. *Ann. Hepatol.*, **2013**, *12*(6), 959-965.
- [176] Huang, Y. S.; Su, W. J.; Huang, Y. H.; Chen, C. Y.; Chang, F. Y.; Lin, H. C.; Lee, S. D. Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H:quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. *J. Hepatol.*, **2007**, *47*(1), 128-134.
- [177] Kim, S. H.; Yoon, H. J.; Shin, D. H.; Park, S. S.; Kim, Y. S.; Park, J. S.; Jee, Y. K. TNF-alpha genetic polymorphism -308G/A and antituberculosis drug-induced hepatitis. *Liver Int.*, **2011**, *32*(5), 809-814.
- [178] Kim, S. H.; Lee, J. H.; Lee, B. H.; Kim, Y. S.; Park, J. S.; Jee, Y. K. Polymorphisms in drug transporter genes (ABCB1, SLCO1B1 and ABCC2) and hepatitis induced by antituberculosis drugs. *Tuberculosis (Edinb)*, **2011**, *92*(1), 100-104.
- [179] Pachot, J. I.; Botham, R. P.; Haegele, K. D.; Hwang, K. Experimental estimation of the role of P-Glycoprotein in the pharmacokinetic behaviour of telithromycin, a novel ketolide, in comparison with roxithromycin and other macrolides using the Caco-2 cell model. *J. Pharm. Pharm. Sci.*, **2003**, *6*(1), 1-12.