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

Lorena Baietto[1]*, Silvia Corcione[1]*, Giovanni Pacini[2],
Giovanni Di Perri[1], Antonio D'Avolio[1#] and Francesco Giuseppe De Rosa[1#].

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

*both authors equally contributed to this work.
#last authors contributed equally

Corresponding Author:
Antonio D'Avolio, (BSc, MSc, SM)
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;

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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 is 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.

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], doxicycline [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.

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 aplotype 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 ubiquitary 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 (rs717620) 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 aminoglycosides 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 aminoglycosides 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 glycylcycline, 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 doxycicline and minocycline can be given either orally or intravenously (iv not in Italy). The reported tissue distribution varies depending primarily upon the liphophilicity 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. 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, mynocycline and P-gp at the blood-brain barrier (BBB). They found that mynocycline and riluzole are both substrate of P-gp and that mynocycline is also inhibitor of P-gp and increases the brain diffusion of riluzole. Therefore the study confirmed that mynocycline and riluzole are transported by P-gp at the BBB level and that minocycline is involved in riluzole disposition into the brain trough P-gp [32] (Table 1).

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

Table 1. Specific transporters of aminoglycosides, tetracyclines, macrolides, daptomycin, rifampicin and type of ADME processes involved. ADME, absorption distribution metabolism elimination; P-gp, P-glycoprotein; OAT, organic anion transporter; ABC, ATP binding cassette; SLC, solute carrier; BBB, blood brain barrier.

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 distribution (7-10 L/kg) thus it is widely distributed in the body, with an 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 type 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-pg, tigecycline was found to be substrate of neither P-pg 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*, coagulates-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 a adenine residue of 23S ribosomal RNA, which leads to co-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 gastro intestinal 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-fits-all” cutoff values or thresholds have been problematic and have lead 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 fluoroquinolones, and biliary excretion is usually a minor elimination pathway, except for moxifloxacin. Fluoroquinolone metabolic pathways include glucuronidation, N-oxidation and desmethylation [62]. PK data regarding the most commonly used fluroquinolones are reported in Table 2.

Fluoroquinolone Agent	Protein Binding (%)	Distibution 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)

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

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 gene 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).

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

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

Antibiotic	Transporter/ Enzyme	Coding gene	SNP investigated	in-vivo effect	Model	Reference
Macrolides						
Azytromycin	P-pg	*ABCB1*	2677G>T 3435C>T 1236C>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 et al. 2009 [46]
Fluoroquinolones						
Moxifloxacin	P-pg	*ABCB1*	3435C>T	SNP 3435C>T do not influence moxifloxacin plasma levels	Healthy volunteers, n=16	Weiner et al. 2007 [64]
Beta-lactams						
Dicloxacillin	P-pg	*ABCB1*	3435C>T	SNP 3435C>T do not influence dicloxacillin plasma levels, use of rifampicin increases dicloxacillin metabolism	Healthy volunteers, n=18	Putnam et al. 2005 [76]
Cloxacillin	P-pg	*ABCB1*	1236C>T	Lower C_{max}, AUC, and urinary excretion in subjects with 1236CC genotype	Healthy Chinese male volunteers, n=18	Yin et al. 2009 [77]
Lipopeptides						
Daptomycin	P-pg	*ABCB1*	3435C>T	Higher Cmax in patients with 3435TT, 2677TT, and 1236TT genotype. Higher AUC in patients with 3435TT genotype and lower clearance	Caucasian patients, n=19	Baietto et al. 2012 [78]
Sulfonamides						
Sulphamethoxazole	CYP2C9	*CYP2C9*	CYP2C9*2, CYP2C9Arg144 to Cys CYP2C9*3, CYP2C9Ile359 to Leu	Subjetcs with homozygous mutate genotype for CYP2C9Arg144 to Cys and CYP2C9Ile359 to Leu showed decrease in the activity of CYP2C9	Human liver, n=26	Gill et al. 1999 [79]
Sulphamethoxazole	GCLC	*GCLC*	rs761142T > G	rs761142 T > G influences sulphametoxazole induced hypersensitivity	HIV patients, n= 171 and n=249	Wang et al. 2012 [80]

Table 4. Continued.

Antibiotic	Transporter/ Enzyme	Coding gene	SNP investigated	in-vivo effect	Model	Reference
Antituberculars						
Rifampicin	OATP1B1	*SLCO1B1*	463C>A,521T> C,1463G>C, 388A>G,11187G>A	Lower rifampicin exposure in patients with SLCO1B1 463CA genotype	Patients, n=72	Weiner et al. 2010 [81]
	OATP1B3	*SLCO1B3*	334T>G			
	P-pg	*ABCB1*	3435C>T			
Rifampicin	OATP1B1	*SLCO1B1*	463C>A, 521T> C, 388A>G	Lower rifampicin exposure in patients with SLCO1B1 463CA genotype	Healthy volunteers, n=11	Kwara et al. 2014 [82]
Rifampicin	CES2	*CES2*	2263A>G,	2263A>G may alter rifampicin metabolism by affecting expression of the gene	Korean patients, n=35	Song et al. 2013 [83]
Rifampicin	P-pg	*ABCB1*	3435C>T, 2677G>T, 1236C>T, rs3842	Patients heterozygous and homozygous for SLCO1B1 rs4149032 polymorphism had low-level rifampin exposure	African patients, n=60	Chigutsa et al. 2011 [84]
	OATP1B1	*SLCO1B1*	521T>C, rs4149032, 463C>A			
	PXR	*PXR*	63396C>T, 44477T>C			
	CAR	*CAR*	rs2307424			
Isoniazid	NAT2	*NAT2*	NAT2*5, 341T>C NAT2*6, 590G>A NAT2*7, 857G>A NAT2*12, 803A>G NAT2*13, 282C>T NAT2*14, 434A>C	NAT2 genotype affects isoniazid plasma levels	Patients, n=60	Parkin et al. 1997 [85]

Table 4. Continued.

Antibiotic	Transporter/ Enzyme	Coding gene	SNP investigated	in-vivo effect	Model	Reference
Isoniazid	NAT2	*NAT2*	NAT2*5 NAT2*6 NAT2*7	NAT2 genotype affects isoniazid PK variability	Caucasian healthy volunteers, n=18	Kinzig-Schippers et al. 2005 [86]
Isoniazid	NAT2	*NAT2*		NAT2 genotype affects the EBA of isoniazid over a range of doses	African patients, n=87	Donald et al. 2004 [87]

Table 4. PG studies regarding association among antibiotic PK and genotype of transporters and enzymes involved in ADME processes. 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; SLCO1B111187G>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. Penicilins. 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.

Penicillins	Protein Binding (%)	Distibution 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	

a, value obtained considering a body weight of 70 kg

b, after administration of sulfaticillin (ampicillin + sulbactam)

Table 5. PK characteristics of penicillins. GI, gastrointestinal.

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 cephradine 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 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.

Carbapenems	**Protein binding (%)**	**Distibution 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

Table 6. PK characteristics of carbapenems.

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 tranporters 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).

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

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

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* 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 indipendent [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 daptomycin 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.

Polymixins: Colistin and polymixin 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/hydrophillic 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 antibiotis 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 diphteriae*, *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 catalyzed by the enzyme dihydropteroate synthase (DHPS). Inihibition results in the cells becoming depleted of thetrahydrofolate [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 hypersensivity and with reduced GCLC mRNA expression in HIV infected patients [80] (Table 4). Susanto et al. found that sulphametoxazole 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. Targets plasma levels refers 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 biovailability 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 hydrolized 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]. Rifampycin 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 SLO1B1 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 isoniazide plasma levels [85], to isoniazide 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 (*TNFα*) gene are associated with hepatitis and they found an influence of *TNFα* 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].

Antibiotic administered	Transporter/ Enzyme	Coding gene	Alleles	SNP	in-vivo effect	Model	Reference
Isoniazid, Rifampicin	NAT2	*NAT2*	NAT2*5 NAT2*6 NAT2*7	481C>T 590G>A 857G>A	NAT2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity	Japanese patients, n=77	Ohno et al. 2000 [172]
Isoniazid	NAT2	*NAT2*	NAT2*5 NAT2*6 NAT2*7	341T>C 590G>A 857G>A	NAT2 genotype is associated to adverse drug reactions induced by isoniazid	Japanese patients, n=102	Hiratsuka et al. 2002 [170]
Isoniazid	NAT2 CYP2E1	*NAT2* *CYP2E1*	NAT2*5 NAT2*6 NAT2*7 c1,c2	- - - -	NAT2 genotype affects the incidence of isoniazid induced hepatotoxicity	Korean patients, n=132	Cho et al. 2007 [169]
Isoniazid Rifampicin	NAT2 CYP2E1	*NAT2* *CYP2E1*	NAT2*5 NAT2*6 NAT2*7 c1,c2	- - - -	NAT2 and CYP2E1 genotype affects the incidence of ATDH	Taiwanese patients, n=34	Lee et al. 2010 [171]
Isoniazid	NAT2	*NAT2*	NAT2*5 NAT2*6 NAT2*7	481C>T 590G>A 857G>A	NAT2 genotype affects the incidence of isoniazid induced hepatotoxicity	Tunisian patients, n=66	Ben Mahmoud et al. 2012 [168]
Isoniazid	NAT2	*NAT2*	-	-	NAT2 genotype affects the incidence of ATDH	474 cases, 1446 controls	Wang et al. 2012 [173]

Table 8. Continued.

Antibiotic administered	Transporter/ Enzyme	Coding gene	Alleles	SNP	in-vivo effect	Model	Reference
Isoniazid Rifampicin Ethambutol Pyrazinamide	CYP2E1	*CYP2E1*	c1,c2	-	Patients with homozygous wild genotype CYP2E1c1/c1 had a higher risk of hepatotoxicity.	Indian pediatric patients, n= 111	Roy et al. 2006 [174]
Isoniazid Rifampicin Etambutol Pyrazinamide	MnSOD NQO1 GST	*MnSOD* *NQO1* *GSTM1*, *GSTT1*	-	47C>T 609C>T -	MnSOD and GSTM1 genotypes affect the incidence drug-induced liver injury (DILI) . Patients with MnSOD CC genotype and with GSTM1 null genotype are at increased risk to have DILI.	Taiwanese patients, n=115	Huang et al. 2007 [176]
Isoniazid Rifampicin Etambutol Pyrazinamide	GST	*GSTM1*, *GSTT1*	-	-	GSTM1 and GSTT1 genotypes affect the incidence of ATDH	Indian patients, 50 cases, 246 controls	Gupta et al. 2013 [175]
Isoniazid Rifampicin Ethambutol Pyrazinamide	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 et al. 2011 [177]
Isoniazid Rifampicin Ethambutol Pyrazinamide	Pgp OATP1 MRP2	*ABCB1* *SLCO1B1* *ABCC2*	-	-	SNPs in gene coding for P-gp, OATP1, and MRP2 were not associated to hepatitis induced by antituberculosis drugs	Korean patients, n=67	Kim et al. 2012 [178]

Table 8. PG studies regarding association among first line antituberculars associated toxicity and genotype of transporters and enzymes involved in ADME processes. 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.

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 ubiquitary 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 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.

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