

PK/PD FOR PREDICTION AND CONTAIN OF ANTIMICROBIAL RESISTANCE

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16.1. INTRODUCTION

In the present scenario, there is an alarming situation of losing treatment due to the increasing microbial resistance against the available antibiotics and the attitude of the pharmaceutical industry, which shows less interest in the production of new antibiotics based on the inadequate return on the investment. Due to the lack of new antibiotics and optimized dosage regimen, rational drug development and usage is becoming a valuable entity for bacterial killing and eradication [1]. The situation is further overwhelmed by the frequent use of antibiotics by the veterinarian, which increase the chances of resistant strains development [2]. Because of these situations, the pharmacokinetic/pharmacodynamic (PK/PD) indices are focused on where the associations between doses, concentrations, and effects (desired and undesired) are defined and quantitated [1].

Bacteria and their susceptibility to an antibacterial drug are usually defined in terms of breakpoints in the advanced microbiology laboratory practices. On the basis of testing technique (agar diffusion, broth dilution and agar dilution), it is either expressed in mg/litre or g/ml in case of concentration, or in mm in case of zone diameter [3]. These are actually biased concentrations which interpret the isolates as susceptible, intermediate or resistant. For setting and adjusting breakpoints, microbiological, pharmacological, clinical and pharmacodynamic approaches are used [4]. However, throughout the world, the established guidelines are used by laboratories for the interpretation of susceptibility tests irrespective of the testing technique. These established guidelines are produced by either European committee on antimicrobial susceptibility testing (EUCAST) or the clinical laboratory standards institute (CLSI). The CLSI guidelines are used in almost all countries outside the European Union, where EUCAST guidelines are followed [5].

Another important parameter for successful therapy is the dosage regimen of a drug, which is usually predicted by evaluating the pharmacodynamics and pharmacokinetic and toxicological data obtained in the preclinical trials. The three main possible approaches are dose titration, and PK/PD modelling and integration. Of these, PK/PD integration is very effective, useful and less expensive compared to the others. PK/PD integration is differentiated from PK/PD modelling on the basis that the former obtains collective data from separate PK and PD studies while the latter is based on the silico modelling of PK and PD data obtained from a single dose of the drug in a single investigation. PK/PD modelling works on the following two mining concepts for drug discovery and development [6]: (i) Has the best compound been selected as a candidate drug? (ii) Has not just an effective but the optimal dosage regimen been established?

It is dire need of the day to develop novel antibiotics, optimize the dosage regimen and guidelines in order to minimize the antimicrobial resistance and make the treatment successful. This review will look at the PK/PD indices, their role in breakpoint selection, optimization of the dosage regimen and how to minimize antimicrobial resistance.

16.2. PK/PD FOR PREDICTING THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

To avoid the emergence of resistance, the following three main strategies should be used.

The first strategy is based on the concept of changing the exposure time, use of combination therapy, sequential therapy and change in duration of treatment [7]. However, it is not suitable in veterinary medicine, particularly in treating animals for food, but could be used in pets and horses.

The second strategy generally focuses on how to adjust the dose interval in antimicrobial therapies by using the principles of PK/PD to minimize the overuse of antimicrobial agents and individual exposure, thus collectively reducing the chances of bacterial resistance. It is usually pathogen-specific, resulting in safer and more successful therapy with minimization of resistance [8]. In contrast to the first, this strategy could be used in highly valuable animals like horses but could not be used in human medicine because of its huge laboratory setup and knowledge.

The third strategy concentrates on calculation of the correct drug dose in order to overwhelm the amplification of less susceptible mutant bacterial species. This concept must be used in the development of new veterinary drugs. For the prediction of resistance in the bacterial population, a mutant selection window could be used [9]. A semi-mechanistic PK/PD model for the determination of bacterial resistance according to exposure to the antimicrobial agent over time is also useful. A previous study in which colistin methane sulfonate is used against *Pseudomonas aeruginosa* is a good example of this model [10]. Furthermore, this model could be used to study the range of bacterial outcomes, as it analyses pharmacokinetic variability via the population pharmacokinetic model; it is also feasible to study the selection of less susceptible or resistant subpopulations [11]. As it is already practised successfully in veterinary drugs, new drugs should be developed accordingly [12].

The commonly used antimicrobial classes include the β -lactams, aminoglycosides and fluoroquinolones. These agents are grouped on the basis of their involvement in either time-dependent or concentration-dependent killing of micro-organisms (Figure 1). To know the effective outcome for a

particular antimicrobial dosage regimen, the pharmacodynamic targets have been adjusted by combining the animal models, clinical data and in vitro studies [13]. Generally, the following PD parameters are used for predicting the efficacy of antibiotics; however, these PK/PD parameters are now used for reducing the development of resistance in micro-organisms [14].

16.2.1. For time-dependent agents

Previous investigations have reported that the bactericidal activity of the β -lactams is concentration-independent, and the maximum killing of microorganisms occurs at concentrations of three to four times the minimal inhibitory concentration (MIC). Any further increase in drug concentrations has almost no effect on microorganisms. The efficiency of these antibiotics is associated with the percentage of time that the drug concentration remains greater than the MIC ($\%t > \text{MIC}$). Previously it has been reported [15] that there is a direct relationship between the efficacy of β -lactam used against *P. Aeruginosa* and $\%t > \text{MIC}$. Using the neutropenic mouse model, the researchers reported that for high effectiveness of ticarcillin against *P. aeruginosa*, a $\%t > \text{MIC}$ value of nearly 100 % was required.

One study reported that the area under the curve (AUC)/MIC has a significant role in the emergence of linezolid resistance [16]. They also reported that there are chances of resistance development when the concentration of linezolid is maintained near the MIC value. It is also evident from previous work [17] that attaining concentrations of $T > \text{mutant prevention concentration (MPC)}$ for all dosing intervals is ideal for extreme bactericidal activity and for preventing the emergence of resistance. This is further supported by a study [18] in which $T > \text{MIC}$ is selected as a parameter for the evaluation of resistant mutation in *S. aureus*. The authors reported that $T > \text{MIC}$ values of 8.11 to 17.14 and 16.21 to 34.28 are the danger zones for induced resistant mutation in groups with $t_{1/2\beta}$ three hours after multiple dosages and in groups with $t_{1/2\beta}$ six hours after multiple dosages.

For the efficacy of time-dependent drugs, the responsible PK/PD parameters are the time and drug concentration above the MIC, which can be measured by the equation given below [19]:

$$T > \text{MIC} = \ln\left(\frac{D}{V_d \cdot \text{MIC}}\right) \cdot \frac{T_{1/2\beta}}{\ln 2} \cdot \frac{100}{t}.$$

16.2.2. For concentration-dependent agents

In contrast to β -lactams, the effectiveness of concentration-dependent agents is checked by using $C_{\max}$:MIC, which is a PD parameter. It is documented that as quicker the maximum concentration of a drug in blood or predilection site in the tissue is achieved more rapidly the pathogen will be removed. Generally, for the treatment and inhibition of resistance in gram negative and positive bacteria, a $C_{\max}$:MIC ratio of 8:10 is adopted [20,21]. Actually, this ratio has been accepted for the extreme killing of gram negative pathogens.

In case of $C_{\max}$:MIC failure, the area under the serum concentration-time curve AUC:MIC is used to check the effectiveness of a drug. It effectively describes the efficacy of ketolide, glycopeptide and fluoroquinolone [22]. In particular, the level of risk emergence of fluoroquinolone resistance is best described by this parameter. The reduced *Staphylococcus aureus* susceptibility or resistance to vancomycin is linked with the accessory gene regulator (*agr*) locus, particularly *agr* group II in *S. aureus*. Recent studies have reported that for calculating *S. aureus* exposure to vancomycin and the chances of resistance development, AUC/MIC ratio may be used [14].

Previously it has been reported [23] that the ratio of the area under the concentration-time curve from 0 to 24 h to the MIC (AUC_{0-24} :MIC) can be used as an important predictor of bacterial resistance ($P < 0.001$). For identification of those factors linked with the development of resistance in bacteria, the authors used the univariate screen and a classification and regression tree. They further explained that at an AUC_{0-24} :MIC ratio of less than 100, the chances of bacterial resistance increase significantly during the treatment.

In an *in vivo* *Mycoplasma Gallisepticum* infection model study, the concentrations of danofloxacin were analysed in lung tissues and plasma, followed by the determination of changes in antimicrobial susceptibility and counting of viable cells in air sac and lung tissues. Furthermore, for point mutation identification in *gyrB*, *gyrA*, *parE* and *parC*, polymerase chain reaction (PCR) amplification of quinolone resistance-determining regions (QRDRs) and sequencing DNA of selected resistant mutant strains were performed. While analysing the PK profile, it was noted that the danofloxacin concentration was greater in the lung tissue than in the plasma.

The ratios of AUC_{24} :MIC for $3 \log_{10}$ (CFU) and $2 \log_{10}$ (CFU) decrease were 97.98 and 31.97 Lh kg⁻¹, respectively. Replacements of Glu-87→Gly or Ser-83→Arg in *gyrA* and Glu-84→Lys in *parC* were noted in the resistant mutant strains of the dose group 1 and 2.5 mg kg⁻¹. MICs of levofloxacin, ofloxacin, gatifloxacin, norfloxacin, enrofloxacin and danofloxacin against the resistant mutant strains with a single mutation in position-83 were higher than in position-87. It was concluded that in the case of *M. gallisepticum*, infection in chicken's danofloxacin will be effective at a dosage of 5.5 mg kg⁻¹ once daily for three days [24].

It has also been reported in several previous works [25-28] that the optimal dosage for all those drugs, the effectiveness of which is linked to $AUC_{0-24}:MIC$, can be calculated by the equation given below, which can calculate the dose *per day* [2]:

$$\text{Dose} = \frac{(AUC_{24}/MIC) \cdot MIC \cdot CL}{f_u \cdot F},$$

where $AUC_{24}:MIC$ is the ratio used for optimal efficacy of routine treatment; MIC is the minimum inhibitory concentration; CL is drug clearance; f_u is free fraction and F is bioavailability of drug.

16.2.3. Mutant selection window (MSW) and MPC

The MSW concept has been established to define fluoroquinolone resistance. It was postulated to understand how drug exposures beneath the MPC produce circumstances for selecting resistant bacterial strains [22]. In MSW, it is assumed that the lowermost concentration is the lower boundary that applies selective pressure and inhibits bacterial colony formation by 99 % (MIC). On the basis of this hypothesis, a possible cause of clinical failure is the concentration of the drug falling within the MSW. One study [18] reported that when T_{MSW} reaches 36 % in groups with $t_{1/2\beta}$ three hours after multiple dosage or above 73 % in groups with $t_{1/2\beta}$ six hours after multiple dosages, Cefquinome will limit the resistant mutation.

It is the concentration which inhibits the first step mutants [29]. This is a new emerging hypothesis developed to reduce the emergence of resistance [30]. According to this concept, in antibacterial dosing that yields concentrations above the MPC, bacterial resistance will not occur during the dosing interval. It can be achieved for the compound with minute changes in b/w MPC and MIC by increasing the dose and reducing the dosing interval, which will ultimately decrease the time within the MSW [31]. A combined concept of MPC and MSW provides new ways for PK/PD to determine dosing guidelines. In a study conducted in aquaculture, the treatment time was increased, resulting in increased enrofloxacin concentration above MPC at the infection site; when these concentrations were in the MSW, the time was reduced. Therefore, $T > MPC$ was reported as a substantial parameter for designing the dosage regimen instead of $T > MIC$ for preventing mutant selection of antimicrobial drugs in aquaculture [32].

For selecting antimicrobial resistance, the ratio between MPC and AUC_{0-24} is a good predictor [33]. A related study [34] reported that $AUC_{0-24}:MPC$ above 25 h limits the attainment of resistance in *S. aureus* infection. Other studies (*in vitro* and *in vivo*) verified that a ratio of $AUC_{0-24}:MPC > 22$ h or > 20 h prevents resistance selection in the case of *Escherichia coli* infection [3,35,36]. It is therefore clear that $T > MPC$ and reduced time in MSW are suitable parameters for minimizing antibacterial resistance.

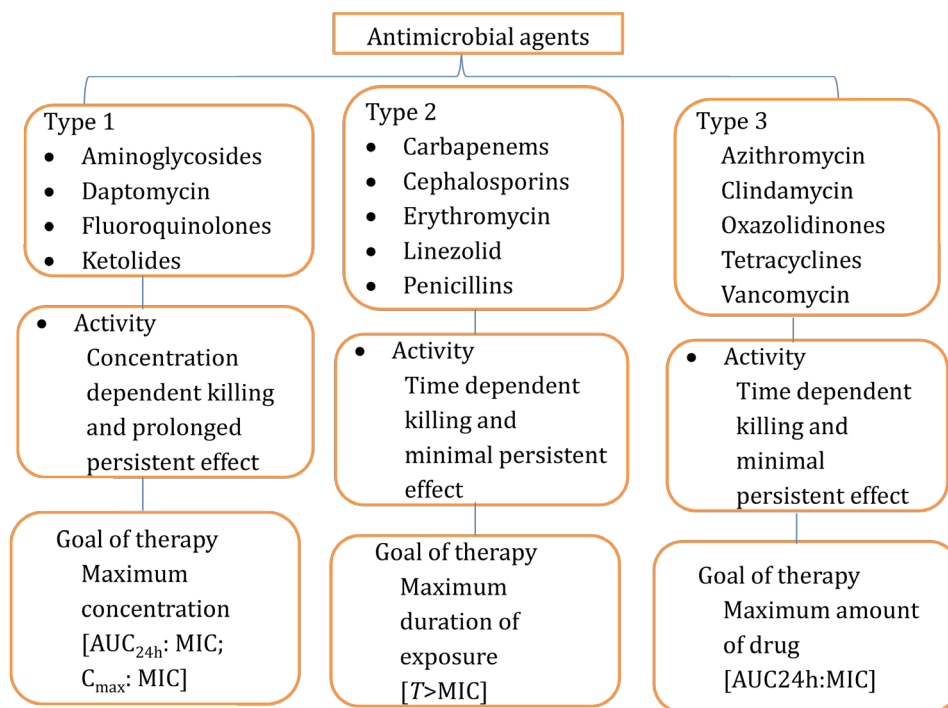


Figure 1. Classification of antibiotics on the basis of PK/PD parameters

16.3. PK/PD FOR ESTABLISHMENT OF ANTIMICROBIAL SUSCEPTIBILITY BREAKPOINTS

16.3.1. Definition of antimicrobial susceptibility breakpoints

Antimicrobial susceptibility breakpoint is defined as the antibiotic concentration (mg L^{-1}) upon which it is decided whether a bacterium is susceptible or resistant. Bacteria are considered susceptible to the antibiotic if the MIC is equal to or less than the susceptibility breakpoint. While defining the clinical, pharmacological and microbiological thresholds, the breakpoints usually generate confusion. To overcome this confusion, it has been suggested [3] that breakpoints should consider three cut-off values, including epidemiological cut-offs, PK/PD cut-offs, and clinical cut-offs.

The epidemiological cut-off (ECV) and wild-type cut-off (CO_{WT}) are measures of a drug's MIC distribution that separate bacterial populations into those representatives of a wild-type population and those with acquired or mutational resistance to the drug. A bacterium with a drug MIC that is greater than the ECV is likely to have an acquired form of resistance, whereas one with a drug MIC lower than or equal to the ECV is likely from the wild-type distribution of the bacterium for a particular drug. Principally, this is used to examine whether or not the clinical cut-offs and PK/PD fall below ECV and wild type cut-off and inside the wild-type MIC distribution. If so, then there will be problems in testing and understanding, because certain wild-type bacteria will be susceptible, while others will be either intermediate or resistant. This will further complicate the situation because, as the test results vary on a daily basis, so some bacteria could readily end up in any category. For wild-type distribution of breakpoints, no single solution is yet decided [3].

The PK/PD cut-off (CO_{PD}) originates from PK/PD modelling, which utilizes knowledge of the antimicrobial PK/PD parameters for the identification of MICs that accurately predict the probability of target achievement for specific bug-drug combinations [35]. In relation to the MIC distribution, it has been suggested [3] that its analysis should be the first step in determining the breakpoint for isolates collected worldwide. The authors further explain that the PK/PD cut-off applied to this collection yields the highest value in this condition by having (i) MIC as an in vitro measurement; (ii) the relevant PD parameter and its magnitude, predicting the in vivo effectiveness; and (iii) human PK and its inter-subject variation and the dosage regimen.

Clinical cut-offs (CO_{CL}) are based on the collection of isolates obtained during clinical effectiveness studies. They reflect the upper limit of the MIC values linked with a great probability of clinical achievement. The clinical cut-off is often used as a tool of authentication and validation for PK/PD cut-offs. These cut-offs gain weight when they fall below PK/PD cut-offs. In such cases, it is suggested that more PK/PD work should be done to understand the association between PD and its outcomes. Generally, variation in results is

observed when clinical versus PK/PD cutoffs are applied using different dosage regimens in clinical practice. The PK/PD cutoffs are usually applied to specific dosage regimens [3].

16.3.2. Examples of breakpoints development based on PK/PD cutoffs

The first example is the modification of the vancomycin breakpoint for methicillin resistant *S. aureus* (MRSA). Vancomycin was used in the treatment of MRSA infections until 2000 using the trough level $<10 \mu\text{g mL}^{-1}$, as it enhances toxicity [36]. Meanwhile, for a better clinical outcome, a trend of higher trough level was introduced by using high doses. This concept was grounded in part on PK/PD data, which suggest that attaining an $\text{AUC}:\text{MIC} \geq 400$ will result in better clinical outcomes [37]. The CLSI in 2006 decreased the clinical breakpoint to $\leq 2 \mu\text{g mL}^{-1}$ for MRSA by worrying about the development of hetero resistance, and aggravated clinical outcomes at higher vancomycin MIC values [38]. On the basis of these findings and reports, IDSA guidelines consequently suggest $15\text{--}20 \mu\text{g mL}^{-1}$ as targeting trough levels in case of severe infections caused by vancomycin-susceptible organisms [35].

The second example is the establishment of penicillin breakpoints for resistant *S. pneumoniae*. Initially, in 1970, the clinical breakpoints for penicillin were recognized in the treatment of meningitis caused by *S. pneumoniae*. Later on, in the 1990s, the ratio of penicillin-resistant *S. pneumoniae* increased in the United States; however, higher MIC values of penicillin worked very well in infections other than CNS [39]. Then, in 2008, the CLSI categorized the penicillin clinical breakpoints as non-meningitis (oral), meningitis (intravenous) and non-meningitis (intravenous). It was observed that in the case of meningitis, the pre-2008 cerebrospinal fluid (CSF) breakpoint values [$\leq 0.6 \mu\text{g mL}^{-1}$ (susceptible) and $\geq 0.12 \mu\text{g mL}^{-1}$ (resistant)] did not change, while the serum breakpoints [$\geq 8 \mu\text{g mL}^{-1}$ (resistant), $4 \mu\text{g mL}^{-1}$ (intermediate) and $\leq 2 \mu\text{g mL}^{-1}$ (susceptible)] were increased for non-meningitis infections. These clinical breakpoints for non-serum established a new model which promoted the intravenous use of penicillin for pneumococcal pneumonia and similar upper respiratory system infections in case of higher dose recommendation – *i.e.* at least 10 million units/day. Other PK/PD studies recommend that in case of pneumococcal isolates, higher doses of oral amoxicillin with higher penicillin MICs could be used [40].

The third example is the breakpoint of cefazolin for Enterobacteriaceae. In 2011, the CLSI again increased the susceptibility breakpoint for cefazolin from $1 \mu\text{g mL}^{-1}$ to $2 \mu\text{g mL}^{-1}$, which in 2010 was adjusted from 8 to $1 \mu\text{g mL}^{-1}$ against the Enterobacteriaceae. This increase from $1 \mu\text{g mL}^{-1}$ to $2 \mu\text{g mL}^{-1}$ was done because of a realization that the new breakpoint was too low and would unnecessarily eradicate the use of this drug against *Proteus mirabilis*, *Klebsiella spp* and *E. coli*. However, as the clinical laboratories are never

required to suggest the dosage, it remained unknown to the majority of clinicians. Similarly, The Food and Drug Administration (FDA) is using the old susceptibility breakpoint of $\leq 8 \mu\text{g mL}^{-1}$; therefore, several automated antimicrobial susceptibility testing (AST) panels are improved to test a cefazolin MIC of $2 \mu\text{g mL}^{-1}$. Hence, laboratories decide themselves how to test the susceptibility of cefazolin [35].

Other examples are breakpoints of β -lactam, trimethoprim-sulphamethoxazole and sulphafurazole for *Neisseria meningitides*. Using the PK/PD parameters, a study [41] was conducted to develop the break points for *N. meningitides*. The authors used time above the MIC for at least 50 % of the dosing interval for all beta-lactams, trimethoprim-sulphamethoxazole, chloramphenicol and sulphafurazole. An AUC:MIC ratio of greater than or equal to 25 and greater than or equal to 125 were used for tetracyclines and macrolides, and fluoroquinolones, respectively. A Monte Carlo simulation of 1000 was prepared (both serum and CSF) at MIC values of $0.03\text{--}64 \text{ mg L}^{-1}$ for each antimicrobial agent. Furthermore, the authors proposed that the PK/PD breakpoint would be the MIC, where the calculated target attainment would be greater than or equal to 95 %. Based on these assumptions, the suggested PK/PD breakpoints were 0.125 mg L^{-1} , 0.25 mg L^{-1} , 0.5 mg L^{-1} , 1 mg L^{-1} , 2 mg L^{-1} and 4 mg L^{-1} for azithromycin; doxycycline; cefotaxime, ciprofloxacin and levofloxacin; penicillin G, meropenem, rifampicin, tetracycline and minocycline; chloramphenicol and sulphafurazole and ampicillin, ceftriaxone; and trimethoprim-sulphamethoxazole. For CSF, the proposed PK/PD breakpoints were 0.06 mg L^{-1} , 0.125 mg L^{-1} , 0.25 mg L^{-1} , 0.5 mg L^{-1} and 1 mg L^{-1} for penicillin and cefotaxime; rifampicin; ceftriaxone, meropenem and trimethoprim-sulphamethoxazole; and ampicillin and chloramphenicol, respectively.

16.3.3. Comparison of breakpoints in CLSI and EUCAST

CLSI and EUCAST have recommended the establishment of breakpoints by PK/PD cut-offs. Over the last few decades, in various bacterial clinical pathogens, the emergence and spread of antibiotic resistance has been noted. One of the most popular guidelines used throughout the world is CLSI. Their cut-offs for various antibacterials depend on distributions of MIC, PK/PD properties and resistance mechanisms. Later on, in 1997, for the formation of the EUCAST, various national agencies in Europe harmonized for the selection of antibiotic interpretive breakpoints. Now most of the European countries have converted to EUCAST guidelines from CLSI. The clinical breakpoints of EUCAST are based on PK/PD properties and epidemiological MIC cut-offs [42]. The differences in their points of view on the breakpoints of antimicrobials are summarized in the following Tables 1 and 2.

Table 1. EUCAST and CLSI comparison of breakpoints and media selection for different microorganisms

S.No	Parameter		CLSI	EUCAST
1	Setting for Breakpoint		+Microbiological + PK/PD + Clinical Outcomes	+ PK/PD + Microbiological +Clinical Outcome
2	Media selection	<i>Streptococcus</i> spp.	MH+5 % sheep(disk) MH+2.25–5 % LH (BMD)	Mueller-Hinton F
		<i>Pasteurella multocida</i> (spp.)		
		<i>Campylobacter jejuni/coli</i>		
		<i>Haemophilus influenza</i> (+para)	Heamophilus test medium	
		<i>Listeria monocytogenes</i>	MH+2.25–5 % LH (BMD)	
		<i>Corynebacterium</i> spp.		
		<i>M. catarrhalis</i>	MHB & MHA	
		<i>N. gonorrhoeae</i>	GC agar + Suppl	(MIC method)
		<i>Helicobacter pylori</i>	MH + 5 % sheep aged (disk)	
		<i>N. meningitidis</i>	MH+5 % sheep(disk) MH+2.25–5 % LH (BMD)	
		<i>Anaerobes</i>	Brucella + Haemin + Vit K [agar Dilution, add LHB for BMD]	

Table 2. On the basis of EUCAST 2015 and CLSI 2015 guidelines, differences in the susceptibilities of *E. coli*, *P. aeruginosa* and *S. aureus* to various antibiotics: concordance and kappa statistics

S. No	Micro-organism	Antibiotic	CLSI (%); <i>n</i> = 532			EUCAST (%); <i>n</i> = 532			Concordance (%)	Kappa, κ (95 % CI)
			S	I	R	S	I	R		
			Amikicin	79.5	3.0	17.5	72.2	7.3	20.5	89.7
	Ceftazidime	70.9	4.7	24.4	70.90	0	29.1	95.3	0.89 (0.87;0.91)	
	Cefepime	72.6		22.7	72.6		27.4		0.886 (0.886;0.906)	
1	<i>P. aeruginosa</i>	Ciprofloxacin	71.8	5.3	22.9	66.2	5.6	28.2	89.1	0.762 (0.736; 0.788)
		Gentamicin	72.6	6.2	21.2	72.6	0	27.4	93.8	0.851 (0.829; 0.873)
2	<i>S. aureus</i>	Antibiotic	<u>CLSI (%): <i>n</i> = 1103</u>			<u>EUCAST (%): <i>n</i> = 1103</u>			Concordance (%)	Kappa, κ (95 % CI)
		S	I	R	S	I	R			
		Penicillin	10.6	0	89.4	10.6	0	89.4	100	1
		Levofloxacin	90.8	0.3	8.9	90.8	0.3	8.9		1
		Clindamycin	98		1.7	98	0.1	1.9	99.5	0.904 (0.826; 0.982)
		Gentamycin	96.3	0.5	3.2	91.5	0	8.5	99.6	0.537 (0.441; 0.633)
		Erythromycin	85.6		13.9	86		14	99.4	0.978 (0.960; 0.996)
3	<i>E. coli</i>	Antibiotic	<u>CLSI (%): <i>n</i> = 5165</u>			<u>EUCAST (%): <i>n</i> = 5165</u>			Concordance (%)	Kappa, κ (95 % CI)
		S	I	R	S	I	R			
		Amikacin	99.3	0.3	0.4	90.5	8.8	0.7	91.1	0.112 (0.079, 0.145)
		Gentamicin	78.5	0.2	21.3	78.1	0.4	21.5	99.5	0.979 (0.973, 0.985)
		Cefepime	80.5	10.0	9.5	72.9	9.8	17.3	84.9	0.600 (0.578, 0.622)
		Ceftazidime	76.3	0.9	22.8	71.5	4.8	23.7	93.7	0.859 (0.843, 0.85)
		Ampicillin	13.8	0.5	85.7	13.8	0	86.2	99.5	0.985 (0.979, 0.991)

16.4. PK/PD FOR OPTIMIZATION OF DOSE REGIMEN

The level of drug concentration in blood and its long-term maintenance close to a therapeutic value is very important for the treatment of many diseases. A dosage regimen which reduces under- and over-exposure to the target concentration increases the potency and safety, resulting in the successful recovery of the patient [43].

On the basis of the increased emergence of resistant organisms and their poor response to the existing antimicrobial agents and unpredictable pharmacokinetic changes in some patients, treatment of infectious diseases is becoming increasingly challenging. Therefore, there is an urgent need for novel strategies for dose optimization to reuse older and forgotten antibacterials and increase the efficacy of the existing one [44]. As has already been reported, bacterial exposure to sub-optimal concentration of an antimicrobial agent is an important factor in the emergence of resistance [45]; therefore, some strategies based on PK/PD parameters regarding the dosing regimen have been established (Figure 2) to help in minimizing the selection of antibiotic resistance [2].

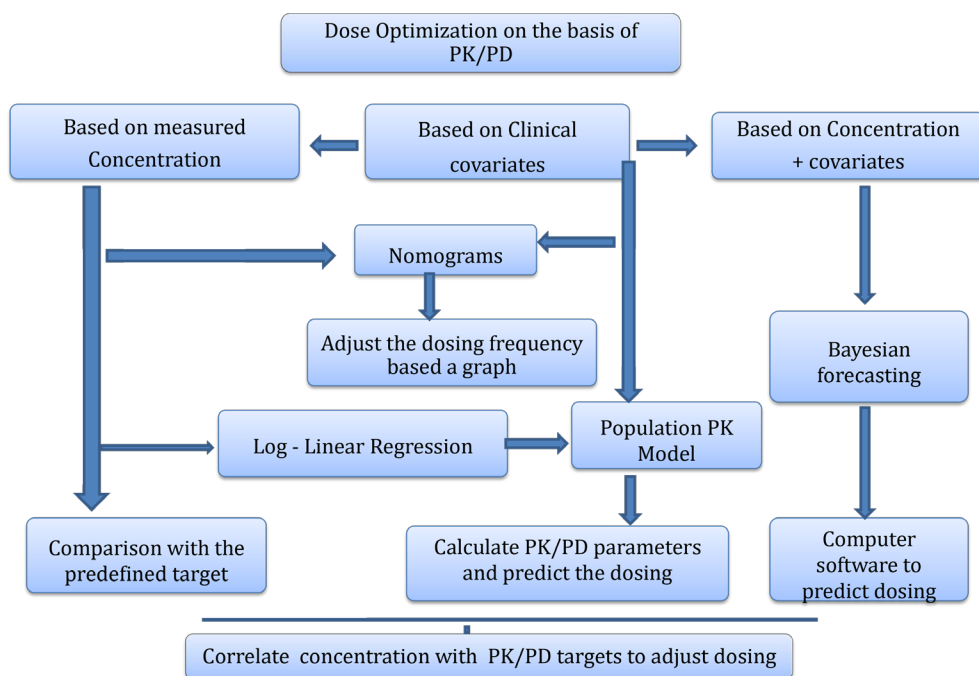


Figure 2. Different approaches used for dose optimization on basis of PK/PD parameters

A study conducted on PK/PD integration for optimization of the cefquinome dose against *S. aureus* [2] reported that for a time-dependent drug, dose determination is better than AUC:MIC and analysis of the number of viable bacteria after 24 h. This statement is supported by another study [46], which documented that PK/PD modelling is another important method for calculating the effectiveness of antimicrobials and predicted gentamicin as a successful treatment against *P. multocida*, with optimum daily dosage in buffalo calves being 2–2.5 mg kg⁻¹ (MIC 90 ≤ 1.0 µg mL⁻¹). However, in serious and difficult clinical cases caused by pathogens of MIC 90 ≤ 4.0 µg mL⁻¹, the authors recommended a dose of 7.5 mg kg⁻¹. They further suggested that in case of *P. multocida*, a low MPC of gentamicin means that there is a low selection pressure for amplification and resistance emergence in the subpopulation during the treatment.

A study conducted into the concept that PK/PD can be used in everyday clinical practice [47] reported that in antimicrobial therapy some obstacles have to be overcome. These obstacles include rapid and accurate isolation of the pathogen, which is generally used to minimize the time needed for measurement of MIC and plasma concentrations to know the individual patient's PK system, and final agreement on the PK/PD markers, including the relative breakpoints. However, these problems could be solved by using the population PK model, which provides many benefits and brings pharmaceutical care to a new level. Similarly, a study was conducted in veterinary medicine for optimization of the dosage regimen using PK/PD models [6]. The authors reported that instead of dose titration studies, the parameters obtained from PK/PD modelling may be used as an alternative for rational dosage regimen selection in clinical trials. PK/PD modelling is not in practice in the field of veterinary medicine because of limited studies and appreciation of PK/PD principles in the veterinary scientific community, its limited understanding and its absence from the guideline issued by the regulatory bodies. The factors which influence the design of a safe and effective dosage regimen are shown in the figure below (Figure 3).

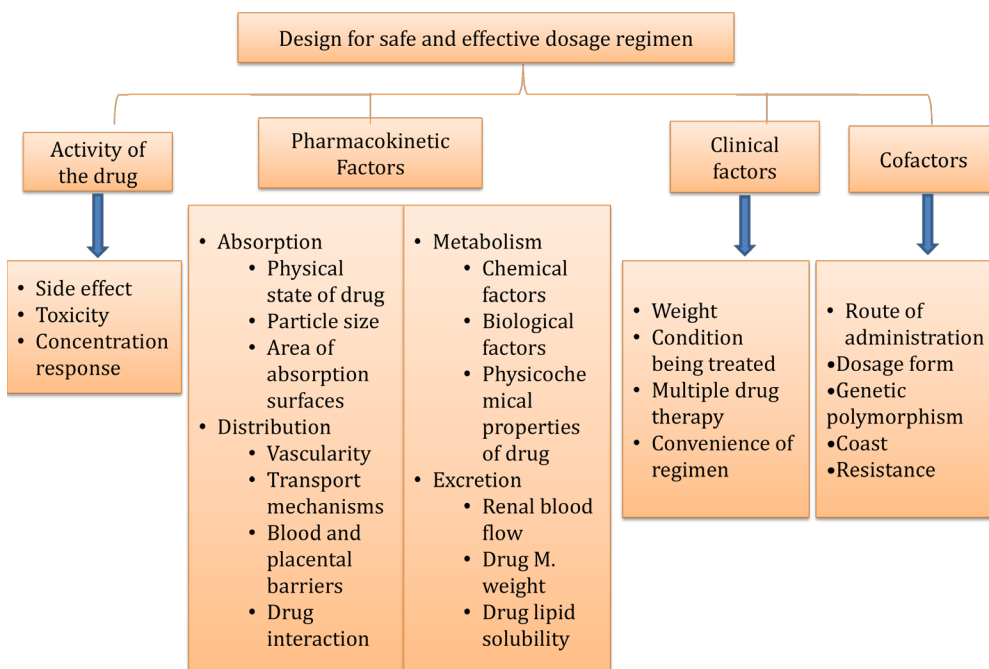


Figure 3. Factors which influence the design for safe and effective dosage regimen

16.5. CONCLUSION

PK/PD modelling is a technique that critically analyses quantitative data and establishes a relationship among dose, exposure and response to antibiotics. From this review, it is concluded that PK/PD indices/modelling have introduced and opened new doors for minimizing bacterial resistance and created new hope for clinicians in the sense of establishing an effective dosage regimen. On the basis of this set of tools, a mechanism on the basis of PK/PD modelling of an optimal dosage regimen can be developed for novel and established antibiotics with high efficacy and minimum chance of bacterial resistance development.

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