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Review

All Roads Lead to Rome: Enhancing the Probability of Target Attainment with Different Pharmacokinetic/Pharmacodynamic Modelling Approaches

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Abstract: In light of rising antimicrobial resistance and a decreasing number of antibiotics with novel modes of action, it is of utmost importance to accelerate development of novel treatment options. One aspect of acceleration is to understand pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and to assess the probability of target attainment (PTA). Several in vitro and in vivo methods are deployed to determine these parameters, such as time-kill-curves, hollow-fiber infection models or animal models. However, to date the use of in silico methods to predict PK/PD and PTA is increasing. Since there is not just one way to perform the in silico analysis, we embarked on reviewing for which indications and how PK and PK/PD models as well as PTA analysis has been used to contribute to the understanding of the PK and PD of a drug. Therefore, we examined four recent examples in more detail, namely ceftazidime-avibactam, omadacycline, gepotidacin and zoliflodacin as well as cefiderocol. Whereas the first two compound classes mainly relied on the 'classical' development path and PK/PD was only deployed after approval, cefiderocol highly profited from in silico techniques that led to its approval. Finally, this review shall highlight current developments and possibilities to accelerate drug development, especially for anti-infectives.

Keywords: target attainment; PK/PD; modelling; cefiderocol; ceftazidime; avibactam; gepotidacin; zoliflodacin; omadacycline

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1. Introduction

The COVID-19 pandemic, which is currently moving towards the endemic phase in some parts of the world, has received great attention since 2020. However, out of the spotlight of COVID-19, the 'silent pandemic' of antimicrobial resistance (AMR) is still on-going and growing [1]. Back in 2014, the World Health Organization (WHO) already tried to put the spotlight on potential pathogens and defined a pathogen priority list [2]. Among the pathogens listed were the so-called *ESKAPE* pathogens [3], the *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species [4].

The research landscape has remained relatively unchanged despite the priority list being in place for nearly a decade. The reason for this is that the majority of antibiotic research is still being conducted by small and medium-sized companies and in academia [5]. As a result, the outlook for human health appears grim, with recent estimates showing a likelihood of over 10 million deaths due to AMR by 2050 [6–8]. Although the number of novel antimicrobials has increased recently, most of these novel drugs do not harbor novel modes of action [5,9,10]. The persistent lack of innovation has led to fewer newly approved antibiotics in the pipeline than cancer drugs [11]. Certainly, incentives have to be developed to foster and enable development in this area [12,13]. Moreover, a recent report by the FDA

has highlighted a number of key areas, including speeding up the development of new FDA-regulated products, reducing costs associated with assessing them, and improving health outcomes [14]. Thus, novel approaches will facilitate a faster transition from bench to bedside.

Once drugs enter the preclinical stage and, later, the clinical stage, pharmacokinetic (PK) and pharmacodynamic (PD) effects are investigated. However, this process is time consuming and expensive, in particular when entering clinical trials [5,12]. Therefore, it is of the utmost importance to understand PK/PD correlations and to estimate the probability of target attainment (PTA) in relevant compartments early in development. Traditionally, PK/PD considerations were based on the assumption that plasma concentrations are the best predictors of efficacy. This is certainly true and relevant in case of, e.g., bloodstream infections, but might have limitations for urinary tract infections, soft-tissue infections, or lung infections [15–17]. Recently, authorities have also attempted to demonstrate relevant concentrations in target tissues. Whereas the measurement of homogenized tissue concentrations neglects the compartmentalization of the tissue itself [18], approaches such as microdialysis or the determination of epithelial lining fluid (ELF) concentrations are more appropriate, but still have some restrictions, as the sampling of ELF in humans can be technically challenging [17,19–25]. The next step is to determine efficacy, i.e., the PD effect. Typically, this is performed using in vitro models, such as the minimal inhibitory concentration (MIC) [26], compartmental models [27], the determination of intracellularly active bacteria [28,29], time–kill curves in and without the presence of serum, and/or the hollow fiber infection model (HFIM) [30,31]; otherwise, it is performed using in vivo models, such as the neutropenic thigh, lung, sepsis, and urinary tract infection models [32–38]. These model systems serve to determine the so-called PK/PD index, a measure of efficacy depending on a certain PK parameter that is translatable from in vitro/preclinical species to humans. Most antibiotics fall into one of the three most clearly established categories: such as fC_{max}/MIC, fAUC/MIC, or $fT_{>MIC}$ [39]. Novel methods are needed to determine these PK/PD indices, in order to accelerate the process of demonstrating the target attainment of a drug. These novel methods can consist of deploying in silico methods to support or replace classical PK/PD determinations as performed with the currently available in vitro and in vivo systems [40–45].

The distinctiveness of the novel in silico methods lies in their diverse construction methods; this makes them a powerful tool capable of predicting target achievement. There are several options for constructing PK and PK/PD models [46,47]. Depending on the requirements and input data, rather simplistic compartmental models or more complex models, such as physiologically-based pharmacokinetic (PBPK) models, can be constructed [45,48–52]. The latter kind relies on the incorporation of physiological parameters and an organ-based substructure including sub-compartments. This enables the use of PBPK models inter alia for cross-species extrapolation and age-specific predictions of PK behavior [47,53]. Both types of model can then be linked to PD data, enabling to predict the probability of target attainment (PTA), i.e., a measure of how realistic a PD effect will be attained in vivo [54–57].

With this review, we aim to show how target attainment has been demonstrated by drugs that have been recently (less than five years) approved or drugs that are currently under late-stage clinical investigation. We selected drugs with different modes of action to highlight how PK/PD correlations and target attainment were determined in preclinical and clinical studies using different modelling techniques; we also investigated the lessons that can be learned for the development of novel anti-infectives. Our search criteria included the compound name, such as 'tigecycline, omadacycline, ceftazidime, avibactam, gepotidacin, zoliflodacin and cefiderocol', and the combined search terms 'PK/PD', 'PK model', 'PK modeling', 'PK modelling', and 'PTA'.

2. Development of Ceftazidime/Avibactam: Using Modelling to Determine the PK/PD Target

Ceftazidime (CAZ) is a cephalosporin that is active against *P. aeruginosa*; together with avibactam (AVI), a non-ß-lactam ß-lactamase-inhibitor inhibiting enzymes belonging to Ambler classes A and C and selected class D beta-lactamases [58], it extends the spectrum against *Enterobacteriaceae* and several multi-drug resistant (MDR) *Pseudomonas* isolates [59–61]. In the last five years, novel beta-lactamase inhibitors, such as taniborbactam combined with a cephalosporin [62,63], as well as reports on the resistance of ceftazidime-avibactam (CAZ-AVI), have emerged [64,65]; however, we would like to highlight how the PK/PD targets were determined for AVI alone and how target attainment was achieved for the combination using PK/PD modelling. CAZ-AVI has been studied extensively in preclinical in vitro and in vivo models, as summarized elsewhere [66]. In the following section, we want to highlight some PK/PD modelling studies that contribute to a better understanding and prediction of PK/PD targets as well as PTA. A non-exhaustive list of those studies can be found in Table 1.

Determining a PK/PD target for a beta-lactamase inhibitor, such as AVI, can be quite challenging, as it does not harbor intrinsic bacterial activity. Thus, several studies deploy PK/PD modelling based on in vitro data and/or on in vivo data. A study by Sy et al. investigated the PK/PD correlations of CAZ-AVI by developing a mathematical model incorporating the bacterial killing and degradation of CAZ, in the case of absence of AVI and in the case of restoration of CAZ activity in presence of AVI [67]. This semi-mechanistic model was constructed for and reflected the PK/PD relationships of three different MDR *P. aeruginosa* isolates. Although only based on time–kill kinetic studies, i.e., studies under static conditions, it correctly predicted results from in vitro HFIM, i.e., studies under dynamic conditions, for several strains, similarly to previously published models [54,55,68,69]. Moreover, this model also correctly predicted $\log_{10}$ cfu reductions in neutropenic thigh and lung infection models conducted with more than 25 strains. This showed a successful validation of this model. Additionally, it demonstrated the power of properly validated PK/PD models: having a PK/PD model in place to predict PK/PD relationships for different strains in in vivo standard pharmacodynamics models helps to reduce animal experimentation and is completely in line with 3R. Impressively, the model produced by Sy and colleagues also predicted the $\log_{10}$ cfu change in patients for doses of 2 g CAZ and 0.5 g AVI as a 2 h infusion correctly [67]. Using this model, the same group was able to predict the PK/PD index for AVI as $fT_{>MIC}$ [70] as it had previously been observed from experimental data [71,72]. Similarly to the predictions from Sy et al. [67,70], Kristoffersen et al. constructed a semi-mechanistic model for *Enterobacteriaceae*, incorporating the scenarios and interplays of an actively growing susceptible bacterial population, a non-growing drug-insusceptible resting state, and a pre-existing mutant population [73]. In contrast to the models developed by Sy et al., this model incorporated a drug effect for AVI that had been observed in the initial stages of the time–kill curves. Thus, it described the effects of CAZ and AVI alone, as well as the 'enhancer effect' of AVI on CAZ. Again using simulated human dosing, the utility of the model was demonstrated. This suggests that, if properly validated, PK/PD models could also serve as an option for conducting clinical trials virtually in future, as observed in fields other than anti-infective research [74–77]; consequently, they may accelerate drug development.

Table 1. PK/PD models used for ceftazidime-avibactam.

Type of Model	Purpose	Reference
Compartmental PK/PD model	Prediction of PTA in vivo and in humans for *P. aeruginosa* and *Enterobacteriaceae*	[67,69,70,73]
Compartmental population PK/PD model	Estimation of PTA in adults for different indications	[78–84]

Nevertheless, there is another dimension to consider when using PK/PD models for reaching target attainment, especially in clinical practice. Whereas the aforementioned PK/PD models offer a perspective on which doses are needed to achieve a PD effect in a 'standard' human being, for clinical PK/PD models, covariates are explored, reflecting the characteristics of different populations, such as pediatric populations or populations in certain disease states, as frequently observed in infectious diseases. For this purpose, population PK/PD models were developed (PopPK/PD). In the PopPK/PD model constructed and validated by Li et al., the model aimed to assess certain factors, known as covariates, that influence the success of therapy, i.e., to calculate the PTA [80]. They constructed a two-compartment PopPK/PD model for adult populations in the indications of complicated intra-abdominal (cIAI) and complicated urinary tract infections (cUTI). They used nonlinear mixed-effects modelling (NONMEM) for healthy populations and patients from cIAI and cUTI phase III clinical trials and set the joint target for CAZ as 50% $fT > 8$ mg/L and for AVI as 50% $fT > 1$ mg/L, as described previously [72]. As both CAZ and AVI are mainly excreted via the kidneys, creatinine clearance was found to be one of the most predominant covariates, warranting dose adjustments in instances of creatinine clearance values lower than 50 mL/min. Thus, this study highlighted that, across indications (not only limited to cIAI and cUTI, but also including nosocomial pneumonia), the MIC breakpoint of 8 mg/L was sufficient to reach a PTA > 90% against *Enterobacteriaceae* and *P.aeruginosa*. Moreover, it gave guidance for dose adjustments in the case of renal insufficiency [80]. In addition to this study in adults, Franzese et al. addressed the question of PTA in pediatric patients older than three months [84]. They calculated the PTA based on the dosing regimens used in pediatric populations in previous clinical trials [85,86] and proved that the doses were sufficient to reach PTA in pediatric populations with normal renal function or mild renal impairment. Thus, the modelling results supported the current dosing scheme in clinical practice [84].

Another PopPK/PD model aimed to describe ELF concentrations, as ELF is the target compartment for pneumonia. Modelling ELF concentrations is useful, as the sampling of ELF concentrations is technically challenging. Therefore, Dimelow and colleagues constructed two- and three-compartment PK models to fit plasma concentration data and to be able to compare ELF levels to plasma PK/PD targets [79]. The study used ELF data from a previous phase I study [87] to build the models. It showed that the ELF:plasma ratios for CAZ and AVI were higher, especially at lower plasma concentrations. Thus, the study concluded that the ELF penetration was greater than that calculated previously using non-compartmental AUC methods. It demonstrated that, in instances of nonlinear drug penetration into the lung, as has been observed for CAZ and AVI, compartmental PopPK models can be useful and have broad applicability for drugs penetrating the lungs [79].

In conclusion, PK/PD modelling for CAZ-AVI did prove to be helpful in preclinical as well as clinical settings. To date, many of the studies involving CAZ-AVI have shown that, especially in the clinical context, modelling is of utmost importance and can be a tool for reducing the number of clinical trials needed to explore dosage regimens for specific populations and indications [78,88].

3. The Case of Omadacycline: PK/PD Modelling Data Still Scarce

Omadacycline (OMC) is an aminomethylcycline antibiotic, first approved in 2018 by the United States Food and Drug Administration (FDA). It belongs to the group of third-generation tetracyclines and, in contrast to tigecycline or eravacycline, it allows for intravenous as well as oral step-down therapy [89]. Like other tetracyclines, it binds to the 16S rRNA component of the 30S subunit and effectively blocks the aminoacyl-tRNA to the acceptor side of the ribosome in a reversible manner [90]. It has been demonstrated that, compared to other tetracyclines, OMC retains its activity in the instance of resistance mechanisms involving efflux pumps or ribosomal protection proteins [91,92]. However, recent studies suggest that cross-resistance might occur between OMC and, e.g., tigecycline [93].

In contrast to CAZ-AVI, there are scarce PK/PD modelling data for OMC to support current dosing regimens: only two PopPK models have been published so far [94,95]. This might be attributed to the fact that OMC was only approved recently (<five years).

A study by Lakota et al. used a three-compartment model with first-order absorption and a transit compartment accounting for an absorption delay as a result of peroral administration and first-order elimination, as well as a three-compartment model with zero-order intravenous input; they gave the best fits upon validation with healthy subjects as well as with patients enrolled in phase 1b and phase 3 studies [94]. To enable the study of ELF levels, ELF concentrations were modelled as a sub-compartment of the first peripheral compartment. In that study, the model was constructed in such a way that OMC was distributed between the central (i.e., plasma) compartment and the first peripheral compartment. Moreover, ELF concentrations were estimated as a fraction of concentration in this first peripheral compartment. Using phase 3 patient data for external validation, population and individual plasma exposures were effectively captured. The timing of food consumption was considered an important factor, relative to dosing, for bioavailability. In the final model, this was parameterized as a function of the absolute time of food consumption relative to dosing by deploying a Hill-type function. Moreover, the assessment of patient-specific covariates showed the effect of sex was not of high importance, as C_{max} decreased only by 9%, C_{min} increased by 25%, and CL decreased by ~16% for females relative to males. In summary, the PopPK model described by Lakota et al. can serve as a good basis and starting point for subsequent PK/PD and PK/PD target attainment analysis [94].

It was surprising that only a few PK/PD models were available for OMC. A glance at the other third-generation tetracyclines shows that, for tigecycline, for example, only a few PK/PD modelling studies have been published to date [96–98]. As adjusted doses of tigecycline have been suggested for patients with severe hepatic functions [98], the only factor found in PK models for OMC affecting PK was the timing of food consumption. Future research might elucidate whether there are further covariates that should be considered for therapy with OMC, especially in critically ill patients.

4. Gepotidacin and Zoliflodacin: Novel Bacterial Topoisomerase II Inhibitors under Clinical Development

Zoliflodacin (ZOL) was mainly developed to treat infections caused by *Neisseria gonorrhoeae* [99,100], although it is also active against *S. aureus* [99]. Gepotidacin (GEP) recently proved to be effective against *S. aureus*, *Streptococcus pneumoniae* and *Escherichia coli* [101–103], as well as a plethora of Gram-positive and Gram-negative anaerobes [104]. Additionally, both ZOL and GEP harbor novel chemical scaffolds as spiropyrimidinetriones and triazaacenaphthylenes, respectively. Due to their unique mechanism of action, ZOL and GEP have been assigned a new drug category, as "Novel Bacterial Topoisomerase Inhibitors" (NBTI). They are currently under phase 3 clinical investigation for uncomplicated gonorrhea (ZOL) and uncomplicated UTIs (GEP) [100,105].

Compared to fluoroquinolones that induce double-stranded DNA breaks, GEP induces breaks in single-stranded DNA [106], whereas ZOL binds to the GyrB subunit and inhibits DNA synthesis by the accumulation of double-stranded cleavages via the stabilization of the cleaved DNA [107]. Thus, both GEP and ZOL exhibit modes of action distinct from those of conventional fluoroquinolones, such as moxifloxacin, and thereby open up new areas for further investigation. Interestingly, the preclinical data indicate that GEP might not exert the same side-effects as conventional fluoroquinolones with respect to negative effects on skeletal development [108].

In contrast to OMC, several studies deployed PK/PD modelling. A list of those studies can be found in Table 2. However, in the following section, the techniques or specific outcomes of selected studies will be highlighted.

Table 2. PK and PK/PD models used for gepotidacin and zoliflodacin.

Type of Model	Purpose	Reference
PBPK	Prediction of GEP dosages in renally impaired patients	[109]
PBPK and PopPK	Prediction of GEP dose needed to treat pediatrics in case of plaque	[110]
PopPK	Prediction of dose and dose selection for GEP for a phase 3 study of the treatment of uncomplicated urogenital gonorrhea	[111]
Compartmental PK/PD model	Prediction of efficacious dose for ZOL that also suppresses resistance selection	[112,113]

In a recent study that aimed to analyze the PK/PD relationships of ZOL in cases of suboptimal dosing and (partially) resistant strains of *N. gonorrhoeae*, a PopPK/PD model with three outputs, i.e., the concentration of ZOL, the total *N. gonorrhoeae* burden, and the burden of *N. gonorrhoeae* with lower susceptibility/resistance to ZOL, was developed [113]. Microbiological and in vitro PK/PD data for the *N. gonorrhoeae* strains upon treatment with different concentrations of ZOL were determined using an HFIM. Based on these in vitro data, the study aimed to predict the dosages to be used for therapy in humans that would enable eradication in a clinical setting. The results revealed that a single oral dose of 3 or 4 g eradicated a ZOL-susceptible *N. gonorrhoeae* strain and suppressed the amplification of selected mutants with increased ZOL MIC and *gyrB* resistance mutations. In contrast, 0.5, 1, and 2 g doses failed to eradicate it, resulting in selection for GyrB D429N-resistant populations. Moreover, the simulations revealed that ZOL double mutants (GyrB S467N plus the D429N substitution) might not be effectively treated, even with oral doses of 2–6 or 4–8 g q12h. Moreover, pre-existing ZOL-target GyrB S467N substitution was predisposed to develop resistance and the subsequent need for treatment with ZOL doses > 3 g. In conclusion, this study emphasized that rapid point-of-care testing might be necessary to detect possible *gyrB* mutations, as these have a high influence on the choice of ZOL dosing to assure successful therapy [113]. In a similar manner, Jacobsson and colleagues studied different WHO reference strains of *N. gonorrhoeae* in HFIM, using the same PopPK/PD model with three outputs [112]. Using this modelling, they were able to determine that the activity of ZOL was mainly concentration- rather than time-dependent. This finding was of particular importance for the design of subsequent clinical trials to enable the optimization of dosing compared to previous trials [114]. Moreover, they were able to demonstrate that the dosing frequency became less important for doses > 2 g of ZOL, as the kill rate *N. gonorrhoeae* approached a maximum and, consequently, supported the use of a single oral dose of 3 g of ZOL [112].

Likewise, several modelling studies have been conducted for GEP. Bulik and colleagues first conducted dose fractionation studies to determine the PK/PD index of GEP to inform clinical trials [39,115]. For GEP, *f*AUC/MIC best described the correlation of PK and PD. For the treatment of acute bacterial skin and skin structure infection (ABSSSI), a target *f*AUC/MIC ratio of 13.4 for *S. aureus* and of 14 for *S. pneumoniae* was identified; this was then implemented for the design of clinical trials [116]. Moreover, the study also assessed a post-antibiotic effect (PAE). The clinical utility of a PAE determined in vivo has been demonstrated previously [117]. Bulik and colleagues observed a PAE ranging from 3 to 12.5 h for *S. aureus* and from 5.25 to ~8.5 h for *S. pneumoniae* [115], which was comparable to fluoroquinolones [118]. As this effect was not dose dependent, the authors concluded that, in the case of GEP, the PAE was a predictable characteristic for informing decisions regarding clinical dosing intervals [115].

Hossain et al. developed a PBPK model to evaluate PK after the administration of different doses of GEP in populations without and with moderate or severe renal impairment [109]. Thereby, moderate renal impairment was defined with a GFR of 30 to 60 mL/min and severe renal impairment with a GFR of 15 to <30 mL/min. The rationale for choosing a PBPK model was that the researchers wanted to simulate GEP concentrations not only in plasma, but also in target compartments such as urine. Moreover, they also simulated concentrations in saliva, as the sampling of saliva might be more feasible when

invasive blood sampling is not possible, e.g., in pediatrics. The PBPK model was verified with virtual healthy white and Japanese populations against available clinical PK data. They demonstrated that the C_{max} values increased while clearance decreased, with a higher severity degree of renal impairment. Saliva concentrations were linear to the observed plasma concentrations. However, the geometric mean AUC_{0-t} was elevated to a higher extent than plasma in all patient groups with renal impairment. Hemodialysis was not able to remove significant amounts of the drug from the system. Urine drug levels remained high, although a decrease was observed with decreasing renal function. The authors highlighted this fact as the urine concentrations were still in the target range for efficacy and, thus, important for the treatment of urinary tract infections. In summary, this study demonstrated the utility of PBPK modelling for GEP as it predicted not only plasma and urine concentrations, but also saliva concentrations with potential utility for sampling.

In a similar manner, Nguyen et al. aimed to assess whether a PopPK or a PBPK model was best suited for predicting PK in pediatrics [110]. Both the PopPK and PBPK models were based on previously published models developed for adult populations. The PBPK model developed for adults was then used with similar parameters, but with pediatric physiology, including enzyme maturation. In contrast, the PopPK model was built using growth charts and tables for children that provided data for pediatrics aged from 2 to 20 years with the corresponding median body weights. Moreover, a second dataset from ModelRisk® was used, accounting for the age and weight span for pediatrics from 0.01 to 12 years of age. Additionally, allometric exponents were used to account for size-related changes to clearance, as well as a maturation function accounting for size- and age-related changes to total clearance. Both models, the PopPK as well as the PBPK model, provided good predictions for GEP in pediatric populations. However, the authors concluded that the performance of the PopPK model in children aged three months and younger was suboptimal as a result of differences in the maturation characterization of the drug-metabolizing enzymes involved in clearance, which are unrelated to body weight in adults. Thus, this study showed the utility of PBPK modelling, as it might better account for special populations and also for disease populations because it has a mechanistic understanding of drug disposition.

In summary, modelling studies for ZOL and GEP were used to describe PK rather than to conduct PTA analysis. In contrast to, e.g. OMC, PBPK models were also used to better describe the distribution of drugs to different sub-compartments.

5. New Routes with Cefiderocol: From In Silico Studies to Market

In the face of rising carbapenem resistance [7], cefiderocol (CEF), a siderophore-conjugated cephalosporin, has recently emerged as a novel antibiotic with an unprecedented mode of action [119]. CEF was granted FDA approval in November 2019 and is used to treat cUTIs [120]. Unlike the structurally similar antibiotics ceftazidime and cefepime, CEF carries a chlorocatechol group on the end of the C-3 side chain, conferring siderophore activity [121–123]. With its siderophore properties [124,125], the drug enters the periplasm of bacteria, as it relies on active iron transport and maintains stability against ß-lactamases, thereby killing bacteria in a more efficient way [126,127].

Due to the fact that CEF was developed under the FDA streamline development program [128], which aims to minimize the number of clinical trials and instead relies primarily on preclinical evaluations of antimicrobial effectiveness, it is pertinent to focus on in silico strategies, such as PK/PD modelling. This section, therefore, outlines modelling studies conducted with regard to CEF to illustrate the innovative strategies being employed; we highlight their ability to help replenish the antibiotic pipeline in a more sustainable fashion (Table 3).

Table 3. PK/PD models used for cefiderocol.

Type of Model	Purpose	Reference
Compartmental PopPK/PD model	Prediction for PTA in renally impaired patients and patients in different disease states	[129–131]
Compartmental PK	Prediction of exposure in ELF; prediction of total and unbound concentrations in critically ill patients	[132,133]

Kawaguchi and colleagues performed a series of studies on CEF utilizing compartmental modeling [129–132,134], with the most recent study utilizing an intrapulmonary PK model that adequately described the concentrations of the drug in ELF [132]. Data from 20 healthy subjects and 7 patients with pneumonia requiring mechanical ventilation were used to develop the model. They showed that the PTA values for both 75% $fT_{>MIC,\ ELF}$ and 100% $fT_{>MIC,\ ELF}$ were >90% against MICs $\leq$ 4 μg/mL in renally impaired patients and $\geq$87.0% in patients with normal renal function. Moreover, the delayed absorption and/or elimination of CEF in ELF was observed in patients with pneumonia but was not seen in healthy subjects, showing a difference in distribution towards ELF which might be attributed to the different physiological conditions in the lung, such as inflammation [25]. The authors concluded that the intrapulmonary PK modelling and PTA prediction were useful tools to support dosing recommendations in nosocomial pneumonia.

In a similar manner, Kawaguchi et al. aimed to conduct PTA analysis for different disease states, such as pneumonia, blood stream infection (BSI), sepsis, or cUTIs. Therefore, they built a PopPK/PD model to evaluate the impact of potential covariates on PK [131]. The PopPK model was constructed as a three-compartment model which accounted inter alia for the effects of creatinine clearance (CrCL), the effects of infection sites on total clearance (CL), the effect of body weight on the volume of distributions in the central and peripheral compartments, and albumin concentration. This more advanced PopPK model was built based on previous PopPK models for dose adjustment based on renal function [129] and on models evaluated with patient data from cUTI and acute uncomplicated pyelonephritis [130]. In this PopPK model, the estimated glomerular filtration rate (eGFR) adjusted by body surface area (BSA), absolute eGFR, and CrCL was used to calculate the plasma concentrations of CEF in PopPK [130]. Significant covariates in the final model were identified as the disease status (with or without infection) and body weight, although the effects of body weight were not considered to be clinically significant. The constructed model was able to effectively describe the plasma concentrations. Clear relationships between CL and all renal function markers were observed. Patients with infection had a 26% higher CL than those without infection. Notably, the authors found that CEF exposure in patients with infection was lower than in healthy subjects. However, in all patients with test regimens (2 g q8h as standard), the $fT_{>MIC}$ values were higher than 75% (and, in most patients, 100%), suggesting sufficient exposure to CEF [130]. In the subsequent model, which included more disease states, such as BSI, pneumonia, and cUTI, they showed that CrCL was the dominant covariate [131]. The CL in patients with pneumonia, BSI, and cUTI was comparable to that of healthy subjects. Furthermore, they observed that C_{max} and AUC overlapped among infection sites and that they were similar in pneumonia patients with and without mechanical ventilation. With respect to PK/PD relationships, no clear correlation was found for any of the outcomes or the vital status, which might be attributed to the fact that the $\%fT_{>MIC}$ was 100% in most of the patients. Nevertheless, they calculated the 75% $fT_{>MIC,}$ as well as the 100% $fT_{>MIC,}$ for the simulated patients with different infection sites and renal functions. The PTA for 75% $fT_{>MIC}$ was shown to be >95% against MICs < 4 μg/mL. This was independent of infection sites and renal function. In contrast, a difference was observed for PTA for 100% $fT_{>MIC}$: here, the PTA was >90% against MICs < 4 μg/mL for all infection sites and renal function groups, except for normal renal function in BSI. In conclusion, this model demonstrated that, even with augmented renal clearance, PTA can be achieved with the recommended dosing regimens and adjusted

regimens based on renal function in patients with pneumonia, BSI/sepsis, and cUTI caused by Gram-negative pathogens.

In summary, extensive modelling studies have been performed for CEF using different disease states and scenarios with respect to, e.g., the renal clearance. These studies demonstrate the power of PK/PD modelling as it helped to minimize clinical testing and to accelerate the development of CEF.

6. Discussion

We have discussed which specific models have been deployed for CAZ-AVI, OMC, GEP, ZOL, and CEF, and how they contribute to a better understanding of PK and PTA.

For CAZ-AVI several models, compartmental as well as PopPK models were only developed after approval; however, they still contribute to a better understanding of PK and PD and of dosing. It was especially surprising and encouraging how well predictions with respect to in vivo efficacy in animal models were made [69]. Moreover, in the case of CAZ-AVI, the PK/PD models helped to explain PK/PD indices for AVI and to estimate the dosages of AVI needed in combination with CAZ [73].

Surprisingly, published PK/PD modelling data for supporting dosing decisions and PTA are very scarce for OMC as well as tigecycline. Only PopPK models have been used; these require a fairly complex structure to capture all the characteristics of OMC after different routes of administration [94]. It is possible that, for OMC, this can be attributed to the fact that Lakota and colleagues only identified food consumption as an important covariate, but identified none of the conventional covariates, such as liver or renal function. Future studies for OMC might explain whether no other covariates influence PK.

In case of ZOL and GEP, compartmental, population and PBPK models were used. For the indications envisaged for ZOL and GEP, PBPK models are of particular interest as they enable researchers to model compound concentrations in target compartments and allow for a more complex structure. As shown here, the PBPK model enabled the prediction of saliva concentrations, which can be correlated with compound concentrations in other fluids; they therefore serve as a non-technically challenging sampling alternative [109]. The example of ZOL and GEP demonstrates that, dependent on the research question, either PopPK or PBPK models or both can be suitable [110].

Finally, several PopPK models of CEF demonstrated the power of validated PK/PD models. They served to predict PTA in different disease states and, adding slightly more complexity, for different degrees of renal function [129–132]. Notably, they did not deploy PBPK models, although this might have also enabled the prediction of compound concentrations in different target compartments, such as the lung or kidney. However, it seems that compartmental population models sufficed for prediction, meaning that there was no need for more complex models. The case of CEF demonstrates how modelling can help to determine dosages for different disease states and alterations in physiological functions in order to provide PTA and success of treatment.

7. Conclusions

In conclusion, recently approved drugs as well as drugs in the later stages of development profit from PK/PD modelling, as it helps to elucidate PK, PK/PD, and which dose is needed for each disease to achieve a high PTA. Out of the drugs with the four different mechanisms of action presented in this review, CEF constitutes a prime example for accelerated development using PK/PD modelling, whereas the opposite seems to be true for OMC, at least with respect to the published modelling data. Finally, PK/PD modelling can help to reduce preclinical experimentation as well as clinical trials in the event that virtual clinical trials are conducted. These techniques are already frequently deployed in other disciplines, so that there is hope that they can also be used for the acceleration of antibiotic development to bring novel treatment options to patients and, ultimately, to help combat AMR.

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