Determination of antibiotic dosage adjustments in patients with renal impairment: elements for success

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This report reviews a contemporary methodology for determining antibiotic dosage modifications among patients with renal impairment. Historically, the approach to identifying renal dosage adjustments has focused on achieving comparable concentration–time profiles between patients with renal impairment and those with normal kidney function. While this approach is intuitive, it fails to incorporate the relationship between antibiotic exposure and effect in the renal dose selection process. A candidate renal dosing scheme that is worthy of incorporation into clinical practice should balance the probability of achieving the exposure target associated with success against the risks of toxicity and the emergence of resistance. This review describes a methodology for optimally identifying dosage adjustments in patients with impaired renal function using extended-infusion piperacillin/tazobactam as an illustrative example.

Keywords: optimal dosing strategies, special populations, kidney dysfunction

Introduction

Patients requiring antibiotic therapy often have some degree of renal impairment. Since many commonly used antibiotics are primarily cleared by the kidneys, it is often necessary to alter the dosing schedule in patients with impaired renal function.1,2 Historically, the approach to identifying renal dosage adjustments has focused on achieving concentration–time profiles in patients with renal impairment that are comparable to antibiotic exposure profiles observed in patients with normal kidney function. Specifically, previous investigations have primarily compared pharmacokinetic parameters (e.g. elimination half-life, clearance etc.) between healthy volunteers and those with renal impairment; these data are then used to select a renal dose adjustment scheme that achieves a similar antibiotic concentration–time profile.3–11

Although these traditional renal dose adjustment methods are intuitive, they lack both rigor and precision. The most problematic aspect of previously employed renal dose adjustment methods is the heavy emphasis on matching pharmacokinetic profiles between healthy volunteers and patients with renal impairment. While it is important to match overall exposure profiles, these methods fail to incorporate the relationship between antibiotic exposure and effect or toxicity in the renal dose selection process. Identification of optimal dosage adjustments among patients with compromised renal function requires careful consideration of the relationships between antibiotic exposure and efficacy, toxicity, and the potential for antibiotic resistance. Over the past 25 years there has been considerable progress in our understanding of the relationship between antibiotic exposure and effect.12–15 For many antibiotics, the pharmacodynamic target or minimal exposure threshold associated with maximal response has been identified. Furthermore, advances in mathematical modelling now make it possible to apply antimicrobial pharmacodynamics in clinical practice. Specifically, population pharmacokinetic modelling and Monte Carlo simulation can be used to design empirical dosing regimens that ensure the greatest probability of achieving the pharmacodynamic targets associated with maximal antimicrobial response.13–15 These modelling techniques have an array of other utilities14 and can be used to design antibiotic dosing regimens that ensure a high probability of success with a minimal likelihood of toxicity among patients with impaired renal function.

This report systematically reviews the hierarchy of information required to optimize antibiotic dosing schemes for patients with compromised renal function. The paper also delineates the methods involved in optimal renal dose selection. The review concludes with an illustrative example employing one of the most commonly used antibiotics, piperacillin/tazobactam.

Considerations in designing antibiotic dosing regimens in patients with renal impairment

Prior to determining optimal renal dosage adjustments, a hierarchy of information is required. First, knowledge of the
pharmacokinetic parameters of a given antibiotic in patients with varying degrees of renal function is essential. Although this may seem intuitive, one must understand how these parameters change as a function of renal impairment before dose alteration schemes can be considered. Second, the pharmacodynamic index (% $fT_{\text{MIC}}$, $\text{AUC/MIC}$ ratio, $f_{\text{Cmax}}$/MIC ratio etc.) associated with the antimicrobial effect needs to be known; it will serve as the primary exposure target in the renal dose selection process. Third, one should understand the relationship between antibiotic exposure and toxicity. Fourth, although not critical, the pharmacodynamic parameter associated with the emergence of antibiotic resistance is desirable.

The pharmacodynamic indices linked to effect (e.g. efficacy, toxicity and emergence of resistance) can be presented as dichotomous (i.e. 50% $fT_{\text{MIC}}$ or continuous variables (AUC/MIC). These exposure–effect relationships are often presented as dichotomous variables. However, expression of the exposure–effect relationship as an ‘all-or-none’ phenomenon does not fully capture this association. For instance, if the pharmacodynamic endpoint associated with toxicity for a given antibiotic is a cumulative AUC of 1000 mg·L⁻¹·h, patients with a cumulative AUC of 950 mg·L⁻¹·h will not be considered at risk for toxicity. Thus, it may be preferable to express the pharmacodynamically linked variables as a continuous or logit function to fully capture the exposure–effect relationship. This is especially true for exposure–toxicity relationships, because the risk of toxicity typically increases over a continuum rather than at one critical threshold exposure.

On the other hand, it is not as imperative to evaluate the relationship between exposure and response as a continuous function. For exposure–response relationships, the drug exposure profile is customarily evaluated in relation to the MIC value (e.g. % $fT_{\text{MIC}}$, AUC/MIC, $C_{\text{max}}$/MIC etc.). Although MIC values are available along a continuum, they are typically presented as fixed values (e.g. log₂ dilutions, Etest incremental values) and the distribution of response profiles (e.g. % $fT_{\text{MIC}}$, AUC/MIC ratios) at each respective MIC value are reported. Like any other mathematical expression, the denominator (e.g. MIC value) drives these exposure–response relationships; the ability of a given antibiotic regimen to achieve the critical exposure threshold is a function of the MIC value more than the exposure profile within each MIC value. Typically, the ability of a given antibiotic regimen to achieve the critical exposure at a given MIC value will not vary considerably if the target is examined as a continuous or dichotomous function. Thus, it is reasonable to use either continuous or dichotomous functions when examining exposure–response relationships. Opinions vary regarding whether to express the pharmacodynamically linked index as a dichotomous or continuous variable. While the logit function is more informative, its interpretation is not as straightforward. If possible, evaluate the index as both a binary and continuous variable in the renal dose selection process.

Based on the hierarchy of information available on a given antibiotic, several potential candidate renal dose schemes can be formulated. While largely exploratory, the process is guided by the data available on exposure–effect relationships for a given drug. The pharmacodynamic index associated with maximal response will serve as the primary exposure target in the renal dose selection process. The initial goal is to identify candidate renal dose adjustment regimens that provide a probability of target attainment (PTA) profile comparable to the parent regimen in patients with normal renal function.

Criteria for initial selection of potential candidate renal dose adjusted regimens

When selecting potential candidate renal dose regimens, the first consideration is the creatinine clearance (CLCR) dose adjustment threshold. There are no steadfast rules for determining the critical CLCR value. Rather, the selection should be based on how the antibiotic is cleared in patients with renal dysfunction, and multiple CLCR dose adjustment thresholds should be evaluated. In our previous evaluations of ceftobiprole and piperacillin tazobactam, we examined dose alterations in ascending CLCR values from 20 to 50 mL/min in increments of 10 mL/min. We selected this CLCR range for several reasons. First, this range is where drug accumulation is typically observed. Second, robust pharmacokinetic data were available in patients within this distribution of CLCR values, whereas pharmacokinetic data were limited among patients with CLCR values <20 mL/min. Lastly, this CLCR range is consistent with current CLCR dose adjustment thresholds for most drugs.

Another consideration in selecting potential candidate renal dose adjustment regimens is the dose alteration scheme; the options are to either decrease the dose or lengthen the dosing schedule at a given CLCR threshold. This decision primarily depends on the nature of the pharmacodynamic parameter associated with efficacy. For β-lactam antibiotics, $fT_{\text{MIC}}$ is the main pharmacodynamic index associated with efficacy. Since elongating the dosing interval increases the duration of time that antibiotic concentrations need to exceed the MIC, it is prudent to first consider decreasing the dose. Please note that this is not an absolute rule. In our previous evaluation of ceftobiprole, both schedule elongation and dose reduction were found to produce comparable PTA profiles.

Compared with β-lactam antibiotics, the selection of candidate dose alteration strategies for AUC-driven drugs is more complex. Since the goal of most AUC-driven antibiotics is to maximize exposure, it intuitively, it does not make a difference if one extends the interval or decreases the dose as long as the cumulative antibiotic exposure profile or AUC is comparable to the parent regimen. However, the extent or duration of the post-antibiotic effect (PAE) needs to be considered when deciding between extending the interval and decreasing the dose. If one extends the dosing interval beyond the PAE period, this may result in a sub-optimal antibiotic exposure profile and microbiological response. In other words, if the interval is too long, persistent effect may be lost and the ability to kill the bacteria will be diminished. Bacterial regrowth may also occur. This is an important consideration for antibiotics that are dosed once daily in patients with normal renal function, since the dosing intervals are typically lengthened to 48–72 h among patients with compromised renal function.

Mathematical modelling techniques used in the renal dose selection process

Population pharmacokinetic modelling

After gathering the appropriate background information and selecting potential candidate dose alteration schemes, the next step is to model the pharmacokinetic data. The mathematical techniques used in the renal dose selection process are similar to those used in other pharmacokinetic modelling studies.
The structural model used to determine the optimal renal dose adjustment for a given antibiotic will be consistent with previous evaluations of the antibiotic.\textsuperscript{13,14,18} For most antibiotics, the standard two-compartment open model with zero-order infusion and first-order elimination (central compartment) and intercompartmental transfer rate constants will be employed.

The primary difference in the structural models used for determining renal dose adjustments is the parameterization of overall clearance.\textsuperscript{16,17} To properly evaluate candidate renal dose adjustment schemes, it is necessary to incorporate a measure of the patient’s renal function in the pharmacokinetic model and estimate the contribution of renal function to total clearance. By incorporating a measure of renal function as a covariate in the population pharmacokinetic analysis, one is able to examine the impact of different degrees of renal impairment on the associated concentration–time profile for a given antibiotic regimen.

While any method to estimate a patient’s renal function can be included as a covariate, the Cockcroft–Gault creatinine clearance (CL\textsubscript{CR}) equation is preferred, since most antibiotics have renal dosage adjustments based on this formula.\textsuperscript{19} The measure of a patient’s renal function is incorporated into the model by making clearance from the central compartment proportional to the estimated renal function. In our previous evaluation of ceftobiprole, this was accomplished by making ceftobiprole clearance proportional to CL\textsubscript{CR} as follows: (clearance slope \times estimated CL\textsubscript{CR}) + clearance intercept.\textsuperscript{17} For this example, the clearance slope multiplied by estimated CL\textsubscript{CR} reflects the renal clearance, and the clearance intercept term reflects non-renal clearance. For instance, in our previous study, the clearance of ceftobiprole had an intercept term of 2.35 L/h and a slope term of 0.51, indicating that for a patient with an estimated CL\textsubscript{CR} of 4.8 L/h (80 mL/min), the renal clearance would be 2.45 L/h, giving an overall clearance of 4.8 L/h. Restated mathematically: 4.8 L/h = (0.51 \times 4.8 L/h) + 2.35 L/h.\textsuperscript{17}

Once the structural pharmacokinetic model is determined, the next step is to select a program to model the data, and estimate the pharmacokinetic parameters and their associated dispersions. There are multiple population pharmacokinetic modeling programs available. The strengths and weaknesses of these various programs are discussed elsewhere.\textsuperscript{16,17,20} For our previous evaluations, we used the Big Non-Parametric Adaptive Grid with adaptive $\gamma$ (BigNPAG) program by Leary et al., and BIGNPOD (non-parametric optimal design).\textsuperscript{16,17,20}

**Monte Carlo simulation**

The parameter estimates and their associated dispersions (variance and covariance) from the best-fit model in the population pharmacokinetic analysis are embedded into the Monte Carlo simulation program. The Monte Carlo simulation methods used in the renal dose selection process are similar to previous PTA analyses.\textsuperscript{15,18} The major distinction is in the handling of clearance. In most pharmacodynamic profiling studies, pharmacokinetic parameters, including clearance, are randomly selected from a multivariate distribution. These data are used to simulate the dispersion or full spread of concentration–time profiles (e.g. peak concentration, AUC) that would be seen in a large population after administration of a specific dosing regimen. From this information, one can determine the probability that the given antibiotic dosing regimen achieves the desired pharmacodynamic target (e.g. 50% $T_{\geq \text{MIC}}$, AUC/MIC $>125$) against the range of pathogens encountered clinically in the patient population of interest.

In contrast, CL\textsubscript{CR} is fixed at a predetermined level (e.g. 50 mL/min, 30 mL/min) for a given antibiotic regimen in the Monte Carlo simulation renal dose selection analysis.\textsuperscript{16,17} By fixing CL\textsubscript{CR}, the distribution in concentration–time profiles for a given antibiotic regimen is estimated at the specified CL\textsubscript{CR} level, rather than across a potential continuum for the entire population. Similar to traditional pharmacodynamic profiling studies, this information can then be used to determine the probability that an antibiotic dosing regimen at a specified CL\textsubscript{CR} level achieves the pharmacodynamic index associated with maximal response. Knowledge of both the PTA and concentration–time profiles of candidate renal dose regimens at specified CL\textsubscript{CR} thresholds is critical to the renal dose selection process. Specifically, it allows one to determine the impact of the candidate renal dose adjustment schemes on the PTA as well as the degree of exposure just prior to the point of dose adjustment. This information can then be used to find a CL\textsubscript{CR} breakpoint and dose adjustment that would leave the PTA substantially unaltered, yet not produce excessive accumulation or exposure.

**Selection of optimal renal dose adjustment scheme**

After completing Monte Carlo simulation for the parent and candidate dosing regimens, a decision must be made about which candidate regimen to adopt. An ideal candidate dosing scheme will maximize the exposure–response relationship, minimize the risk of dose-related toxicity and suppress the emergence of antibiotic resistance.

Careful examination of the PTA for the renal dose alteration scheme at the CL\textsubscript{CR} threshold immediately following dose modification is critical to ensure that the antibiotic exposure profile will not be altered to such an extent that the PTA is unacceptably low for MIC values of interest. Optimal candidate dosing schemes should preserve the high PTA that would have been observed with the parent regimen in patients with normal renal function. For instance, in our ceftobiprole study, we compared the probability of achieving 50% $T_{\geq \text{MIC}}$ between the two candidate regimens at the CL\textsubscript{CR} dose adjustment threshold (500 mg of ceftobiprole intravenously every 12 h over a 2 h infusion at a CL\textsubscript{CR} of 50 mL/min and 250 mg of ceftobiprole in- intravenously every 8 h over a 2 h infusion at a CL\textsubscript{CR} of 30 mL/min) and 500 mg of ceftobiprole intravenously every 8 h (2 h infusion) in patients with normal renal function (CL\textsubscript{CR} of 100 mL/min).\textsuperscript{17}

Conversely, it is also important to consider the extent of toxicity that would occur in a patient receiving the parent dosing scheme at a CL\textsubscript{CR} threshold immediately prior to the candidate dose adjustment scheme. For most antibiotics, a defined exposure–toxicity relationship does not always exist. In these scenarios, one must make an empirical decision about how much accumulation (AUC$_{\text{24h}}$), and thus the theoretical amount of toxicity, is acceptable. Accumulation should be assessed at the CL\textsubscript{CR} level immediately prior to the dose adjustment threshold, because this is the point of maximum accumulation for the parent antibiotic regimen. For drugs with known
dose-related toxicities, lower accumulation or exposure ratios are desirable, whereas for relatively non-toxic agents, a higher accumulation or exposure ratio may be more acceptable. For instance, while an explicit concentration–toxicity relationship does not currently exist for cefotiboprole, the target maximal exposure was ≤2-fold, because studies have demonstrated the tolerability of cefotiboprole at 1 g every 8 h.17

Lastly, the candidate dosing scheme should be assessed for its ability to achieve pharmacodynamic exposures that are associated with the suppression of antibiotic resistance. However, this information is unknown for many agents.

Application of principles to identify the optimal dosage adjustment for extended-infusion piperacillin/tazobactam

Background

Extended-infusion piperacillin/tazobactam will serve as an example to describe the contemporary renal dosage selection process. Using the aforementioned principles and methods, we identified a renal dose adjustment scheme for an extended-infusion piperacillin/tazobactam regimen (3.375 g intravenously every 8 h via 4 h infusion) used at the Albany Medical Center, a 651 bed teaching hospital in Albany, New York, USA.16 The first step was to gather piperacillin/tazobactam pharmacokinetic data in patients with varying degrees of renal function.16 We were only interested in examining piperacillin, since current doses of tazobactam in the piperacillin/tazobactam formulation have been shown to be sufficient for an antibacterial effect when the target is 50% \( f_{\text{T>MIC}} \).12,13,16 Piperacillin pharmacokinetic data were obtained from 105 hospitalized patients with varying estimates of \( \text{CL} \text{CR} \).16 Of the 105 hospitalized patients, plasma concentration–time data were obtained from 93 hospitalized patients participating in four open-label studies evaluating the pharmacokinetics of piperacillin/tazobactam (two single-dose studies and two multiple-dose studies of hospitalized patients with a presumed infection requiring piperacillin/tazobactam therapy for abdominal or thoracic surgery, colorectal surgery, or hospitalization with neutropenia and bacterial infection).18 The remaining 12 patients who provided plasma samples were obtained from a prospective pharmacokinetic study that was conducted at the Albany Medical Center Hospital.16 This study included hospitalized patients receiving 3.375 g of piperacillin/tazobactam intravenously every 8 h over a 4 h infusion period.

The next step was to collect data on the relationship between piperacillin exposure and effect. We selected 50% \( f_{\text{T>MIC}} \) as the pharmacodynamic target based on previously published studies.12,13 We also sought information on the relationships between piperacillin exposure and both toxicity and emergence of antibiotic resistance. However, we were unable to find any reports demonstrating a clear association between piperacillin exposure and these effects. While an explicit concentration–toxicity relationship currently does not exist for piperacillin, the target maximal exposure was ≤4-fold, since previous studies have not demonstrated the safety of piperacillin beyond this exposure threshold.21,22

Methods for renal dosage adjustment analysis

We analysed all pharmacokinetic data using the BigNPAG program developed by Leary et al. The pharmacokinetic model was parameterized as a standard two-compartment model with zero-order infusion and first-order intercompartmental transfer. Elimination from the central compartment was also modelled as a first-order process. To assess the impact of renal function on total clearance, piperacillin clearance was made proportional to the estimated \( \text{CL} \text{CR} \) as follows: total piperacillin clearance = \( \text{CL} \text{CR} \times \text{est} \text{CL} \text{CR} \) + clearance intercept.16

A 9999 subject Monte Carlo simulation (ADAPT II),23 without process noise, was performed for the following candidate renal dose adjustment regimens: (i) 3.375 g intravenously every 12 h (4 h infusion) at a \( \text{CL} \text{CR} \) of 40 mL/min; and (ii) 3.375 g intravenously every 12 h (4 h infusion) at a \( \text{CL} \text{CR} \) of 20 mL/min.16 We selected these regimens for several reasons. First, we did not want to deviate from the approved package inserts’ renal dose adjustment schemes.24,25 Second, a crude assessment of piperacillin clearance in patients with renal impairment indicated the optimal dose adjustment was somewhere between 20 and 40 mL/min. Third, we did not have robust pharmacokinetic data in patients with a \( \text{CL} \text{CR} \) of <20 mL/min. Fourth, we opted to lengthen the interval rather than decrease the dose to ensure the same parent dose (3.375 g) was used in all patients, regardless of renal function in clinical practice.

For all regimens examined, the fraction of simulated subjects who achieved 50% \( f_{\text{T>MIC}} \) was calculated for the range of piperacillin MIC values (in the presence of tazobactam) from 0.25 to 32 mg/L.16 The degree of exposure was determined by taking the ratio of the distribution of AUC24SS for 3.375 g of piperacillin/tazobactam intravenously every 8 h when the \( \text{CL} \text{CR} \) was fixed at 40 and 20 mL/min (\( \text{CL} \text{CR} \) dose adjustment threshold and maximum accumulation points) relative to the AUC24SS distribution for the original regimen (3.375 g intravenously every 8 h) when the \( \text{CL} \text{CR} \) was fixed at 100 mL/min.16

Results of renal dose selection analysis

The pharmacokinetic parameter estimates and associated dispersions from the population pharmacokinetic analysis are displayed in Table 1. Model fit was highly acceptable for both the mean and the median after the Bayesian step. The median parameter estimates were selected as the measures of central tendency for the Monte Carlo simulation analyses for several

Table 1. Piperacillin population pharmacokinetic parameter estimates for hospitalized patients16

<table>
<thead>
<tr>
<th>Model</th>
<th>( V_I )</th>
<th>( \text{CL}_{\text{int}} )</th>
<th>( \text{CL}_{\text{slope}} )</th>
<th>( K_{\text{SP}} )</th>
<th>( K_{\text{PC}} )</th>
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<tr>
<td>Mean</td>
<td>13.32</td>
<td>3.76</td>
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<td>2.02</td>
<td>4.47</td>
</tr>
<tr>
<td>Median</td>
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<td>0.098</td>
<td>0.62</td>
<td>1.33</td>
</tr>
<tr>
<td>SD</td>
<td>5.72</td>
<td>2.66</td>
<td>0.057</td>
<td>3.07</td>
<td>6.37</td>
</tr>
</tbody>
</table>

\( K_{\text{SP}} \) transfer rate constant from the central compartment to the peripheral compartment (h\(^{-1}\)); \( K_{\text{PC}} \) transfer rate constant from the peripheral compartment to the central compartment (h\(^{-1}\)); \( V_I \), volume of the central compartment (L); \( \text{CL}_{\text{slope}} \), fraction of piperacillin clearance due to creatinine clearance (L/h); \( \text{CL}_{\text{int}} \), clearance due to non-renal means (L/h).
reasons: the slightly higher $r^2$; the lower bias-adjusted mean weighted square error; and the smaller intercept term in the observed–predicted plot.\textsuperscript{16}

Results of the PTA analysis are displayed in Table 2.\textsuperscript{16} The PTA was favourable for the parent regimen (3.375 g intravenously every 8 h over 4 h infusion at a CL\textsubscript{CR} of 100 mL/min) for MIC values $\leq 16$ mg/L. Both renal dose candidate regimens had $\geq 90\%$ PTA for MIC values $\leq 4$ mg/L. However, the renal dose candidate regimen adjusted at a CL\textsubscript{CR} of 40 mL/min had a suboptimal PTA profile for MIC values $>4$ mg/L. Similar to the parent regimen, the candidate regimen adjusted at a CL\textsubscript{CR} of 20 mL/min had a favourable PTA for MIC values $<16$ mg/L.\textsuperscript{16}

The cost of the more favourable PTA in the candidate renal dose regimen adjusted at a CL\textsubscript{CR} of 20 mL/min was a higher mean exposure ratio (Table 3) and a more positively skewed distribution of exposure ratios (Figures 1 and 2).\textsuperscript{16} However, distribution of exposure ratios observed for the candidate dose regimen modified at a CL\textsubscript{CR} of 20 mL/min was acceptable as per our a priori maximal exposure ratio of 4.\textsuperscript{16} The mean (standard deviation) was 2.0 (0.6) and the majority of the exposure ratios were $<3$. Based on the more favourable PTA and acceptable exposure ratio profile, 3.375 g of piperacillin/tazobactam intravenously every 12 h (4 h infusion) adjusted at a CL\textsubscript{CR} of 20 mL/min was selected as the optimal regimen for renal dosage adjustment.\textsuperscript{16}

**Summary**

Historically, the methodologies to determine optimal renal dosage adjustments for antibiotics have lacked precision and accuracy.
The majority of adjustments have focused primarily on achieving pharmacokinetic exposures in patients with compromised renal function that are similar to pharmacokinetic exposures in patients without renal compromise. While it is important to match overall exposure profiles, these methods fail to consider antibiotic exposure–effect relationships in the renal dose selection process.

A candidate dosing scheme that is worthy of incorporation into clinical practice as an optimal renal dose adjustment should balance the probability of achieving the exposure target associated with success against the risks of toxicity and the emergence of resistance. The concepts described in this review allow one to identify renal dosage adjustments for antibiotics with a high degree of precision and rigor. Throughout this report we review the steps for optimally identifying dosage adjustments in patients with impaired renal function. Adherence to these methods provides a systematic way to balance the risks of toxicity and antibiotic resistance against the probability of efficacy when selecting optimal renal dosing schemes. Ideally, pharmacokinetic/pharmacodynamic-optimized renal dosing regimens should first be tested in the clinical trial arena. In the absence of clinical trials, the use of pre-clinical infection models should be used to validate proposed renal dosing schemes before implementing in clinical practice. Pre-clinical infection models also afford the ability to study the emergence of resistance, which is often difficult in clinical practice.

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