Pharmacokinetic and Pharmacodynamic Issues for Antimicrobial Therapy in Patients With Cancer

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In patients battling cancer, many aspects of antimicrobial treatment become more complex, and standard antimicrobial regimens may be inadequate. Various pathophysiological changes in critically ill patients with cancer significantly affect the pharmacokinetics (PK) of antimicrobials. In an unacceptably high percentage of these patients, variability of relevant PK parameters results in inadequate antimicrobial drug exposure across all drug classes. The pathogen, with its susceptibility to an antibacterial agent (ie, pharmacodynamics [PD]), is a given; however, drug exposure (ie, PK) can be influenced by adjusting the dosage regimen. Dosage optimization strategies to improve the probability of attaining the PK/PD target and, thus, achieve clinical success are a key area of current translational research. An intensified focus on dosage regimens targeted at bacterial killing of both the fully susceptible bacterial population and resistant mutants may prevent emergence of resistance while also better meeting the needs of this substantial patient population.

In patients with nonhematological malignant processes who are not on chemotherapy, the causative microorganisms are commonly associated with the site of the tumor. Infections in patients with hematological malignant processes are usually caused by pathogens that are influenced by the malignancy and therapy-specific immune deficiencies [1–3]. Among the common bacterial pathogens in neutropenic patients, staphylococci, enterococci, a range of enterobacteria (eg, Escherichia coli, Klebsiella, Enterobacter), and nonfermenters (eg, Pseudomonas, Acinetobacter, Stenotrophomonas) have the highest rate of multidrug resistance and are the most difficult to treat. Effective antibacterial treatment of these infections requires informed management of antibacterial treatment options. Beyond the selection of a suitable antibiotic, the administration of an appropriate dosing regimen (dose and schedule) influences the probability for clinical success [4]. Most guidelines for the use of antimicrobial agents in patients with cancer do not elaborate on specific dosing requirements in this vulnerable patient group, nor do approved labels provide specific information to support oncologists in their decision-making process.

During the last decade, considerable progress has been made in understanding pharmacokinetics (PK) and pharmacodynamics (PD) relationships to identify an appropriate dosage regimen. In order to determine the optimal dose, drug exposure (ie, PK) is correlated to the antimicrobial effect (ie, PD), thus linking PK and PD to form the predictive PK/PD index [5] (Figure 1). The most commonly employed PK/PD indices are the ratio of free drug area under the curve (AUC) over 24 hours to minimum inhibitory concentration (MIC) (fAUC₀–₂₄/MIC), the percentage of the dosing interval in which the free concentration of the antibiotic exceeds the MIC (% f_t>MIC), and the ratio of free maximal concentration to MIC (fCmax/MIC) [4]. Studies confirm that the magnitude of the PK/PD index predicts the microbiological effect for a given drug class.
and a given pathogen group, as measured by inhibition (static effect) or by reduction of the bacterial load by 1, 2, 3, or more \( \log_{10} \) steps. The discriminative power of the magnitude of PK/PD indices in differentiating outcomes has been shown in vitro and in animals as well as in human patients [4, 6].

The escalating drug-resistance crisis highlights the problem of selection and overgrowth of less-susceptible subpopulations as a result of inadequate drug exposure. In tackling these concerns, 3 potentially conflicting objectives regarding dosing must be reconciled: maximizing antibacterial effect, minimizing emergence of resistance, and limiting toxicity.

THE PK FACTOR

Because PK and PD are strongly connected, changes in either of these factors affect clinical outcome. Pharmacokinetics varies from patient to patient depending on numerous variables. However, if assessed carefully, PK variation can be accounted for by adjusting the dosage because drug exposure (drug concentration over time) is a direct result of the dosage regimen in the individual patient. The dosage regimen is a key factor that clinicians can fine tune to improve the probability of a favorable outcome [7].

Although approved antibiotic dosage regimens are based on PK data that were obtained from healthy volunteers or less severely ill patients, information is now available from specific patient groups with severe illnesses, including oncology patients. Pharmacokinetics data from severely ill patients, whether from defined groups of patients with cancer or intensive care unit (ICU) or compassionate-use patient cohorts, show similar PK changes as well as consistently high interpatient variability [1, 8, 9]. Deviations of PK parameter values are primarily relevant to clearance and volume of distribution (Vd). Similar to other severely ill patients, oncology patients represent a very diverse group with various pathophysiological conditions and treatment concepts, producing high variability in PK parameters that cannot be attributed to any single variable. Even in relatively homogenous groups of patients with cancer (eg, febrile patients with severe neutropenia who have undergone aggressive chemotherapy for acute myeloid leukemia), highly variable PK parameters are observed [10, 11]. Not only interpatient but also intraindividual PK variability over the treatment course puts this severely ill patient group at high risk of failing to achieve adequate drug exposure [12, 13].

Although solid or hematogenous malignant processes does not by themselves affect the PK of antimicrobials, various pathophysiological changes induced by these malignant processes at different times do affect the PK. Cachexia, hypalbuminemia, and effusions are common conditions in patients with cancer that may lead to increased drug Vd and enhanced renal clearance accompanied by reduced exposure of hydrophilic antibacterial agents, including \( \beta \)-lactams, aminoglycosides, glycopeptides, daptomycin, and colistin [5, 14, 15].

As commonly described in patients with cancer, effusions with high protein content can bind antibiotics with high protein binding (eg, daptomycin, telavancin, oxacillin, ceftriaxone, and ertapenem), resulting in slow back distribution into the systemic circulation, thus reducing the peak concentration and prolonging overall elimination half-life [16, 17]. Hypoalbuminemia, a frequent condition in patients with terminal cancer, severe sepsis, or cancer resection surgery [18], increases the unbound fraction of highly protein-bound antibiotics, enabling both more rapid distribution and enhanced renal clearance, resulting in lower antibacterial exposures. There is increasing recognition that inflammation associated with advanced cancer, and frailty, as well as age-related physiological changes, may have a considerable impact on PK and thus drug exposure [19]. Additionally, severe infections themselves often cause physiological changes. During the initial phase of severe sepsis and septic shock, increased Vd from fluid overload and transcapillary movement of fluid into peripheral tissues results in lower serum concentrations [20]. Besides Vd, PK variation due to end-organ dysfunction, especially acute renal failure and the confounding use of dialysis, is frequently encountered, and doses must be adjusted to account for these PK changes [12, 21].

Infections occur not only in the blood but also at other infection sites. Therefore, drug concentration at the site of infection is critical, especially in tissues protected by barriers to drug penetration [22, 23]. However, it is often difficult to determine the concentration of a drug at the site of infection, so drug concentration values in serum are commonly.

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**Figure 1.** Variability and relationship between dosing, drug exposure (pharmacokinetics), minimum inhibitory concentration (pharmacodynamics), and microbiological effect that predicts the probability of clinical cure. Abbreviations: MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics.
used as surrogates [22]. Although unbound concentrations in blood typically correlate with those in the interstitial fluid of tissues, aberrations do occur, especially in severely ill patients. As has been shown in antibacterial drugs, such as linezolid and piperacillin, in these patients adequate serum concentrations might not guarantee adequate concentrations at other sites of infection [24, 25].

**THE PD FACTOR**

Despite several shortcomings, MIC determinations remain commonly used as a simple static surrogate for antimicrobial activity. In cases with an identified pathogen and where susceptibility testing is performed in individual patients, knowing the MIC value provides important information about the safety margin in relation to the break point. In case of a patient with cancer who is at risk of disease-related unfavorable PK, a low MIC (several dilutions below the break point) will balance the PK/PD ratio without requiring dosage modification. However, hospitalized severely ill patients with cancer with multiple recent antibiotic exposures are at higher risk for pathogens with elevated MICs. Although these strains may remain designated as susceptible by accepted MIC break points, such elevated MIC values may compound a potentially impaired PK situation and shift the desired PK/PD ratio to higher necessary drug-exposure values than are achievable due to drug-toxicity limits. For drugs with relatively high MICs in wild-type populations that cluster around the break point (eg, linezolid), fluctuations in PK create variable drug-exposure conditions, potentially resulting in failure to reach the PK/PD target.

**THE PATIENT FACTOR**

Antibacterial therapy aims to reduce the number of bacteria but, in most cases, relies on the immune system to eliminate them completely. Granulocytes are able to phagocytose bacteria only up to a certain load that marks the saturation of the system [26]. Infections, such as ventilator-associated pneumonia (VAP), with a high bacterial burden that is above the limit of saturation (approximately 7 × 10^5–10^7 colony-forming units [CFUs]/g) require antibiotics that quickly generate a bacterial cell kill of 2–3 log_10 CFUs/mL [27]. In malignancy-associated neutropenia, even a very low bacterial burden may overwhelm the system. Based on the neutropenic mouse thigh model, profound neutropenia increases the required magnitude of the PK/PD index by 50%–100% (ie, 1.5–2.0-fold) [28]. Although it complements data from animal models, the sparse information available from clinical studies indicates that a higher PK/PD target may be required in immunosuppressed patients with cancer. In the febrile neutropenic population, the relationship between the PK/PD index and clinical outcome, as well as the required higher magnitude of the PK/PD index, has been established for meropenem. This retrospective clinical study identified an average of 83% t > MIC for the 42 clinical responders compared with 59% t > MIC for the 18 nonresponders [29]. More research into other commonly used antibacterial drug classes is needed to validate the optimal magnitude of PK/PD indices and the minimum threshold of bacterial load reduction in patients with profound neutropenia.

Although randomized comparative trials proofing the clinical superiority of a fast bactericidal over bacteriostatic activity are not available, in vitro and experimental in vivo data, as well as scattered clinical reports, indicate that bactericidal agents may be critical in neutropenic patients. Most antibacterial agents used in this patient group have a pronounced bactericidal mode of action, with a reduction of >3 log_10 CFUs/mL in <8 hours in vitro. Linezolid, a bacteriostatic agent, is an exception with considerable off-label usage in febrile neutropenic patients. The only comparative study in neutropenic patients versus vancomycin [30] failed to clarify the clinical question of the appropriateness of using bacteriostatic agents in neutropenic patients because the dosage regimen of the comparator vancomycin may not have been optimal. Based on experimental results, most experts agree that bactericidal agents continue to be preferred to bacteriostatic agents for the treatment of life-threatening infections in neutropenic patients [31, 32]. Clinical studies to support this claim are warranted.

**PK/PD AND DOSING OPTIMIZATION**

Potentially useful patient-specific information (ie, MIC of infecting bacteria and individual PK data) to support immediate treatment decisions is usually not available in the clinical setting. As previously discussed, high interpatient PK variability in the cohort of severely ill patients with cancer, as well as the MIC distribution of presumed pathogens, complicates appropriate empiric antibiotic dosing in individual patients. To aid in the evaluation and selection of antibacterial dosing regimens in a selected patient population, human population PK modeling combined with Monte Carlo simulation remains the preferred method for modeling broad variability in PK parameters that is interpreted using the distribution of MIC values typically seen in this clinical environment. This method calculates the probability of achieving a defined PK/PD target resulting from a specific drug dose expressed as probability of target attainment (PTA). Table 1 provides relevant examples showing model-derived probabilities of attaining a defined PK/PD target based on currently recommended dosages in severely ill patients with cancer or ICU patients. The low PTAs shown in this table
undertake the urgent need to optimize dosage regimens by using current and evolving PK/PD knowledge for individual patients with cancer.

For β-lactam antibiotics, Figure 2 [45] illustrates the influence of different dosage regimens and infusion times on the PTA for a specific MIC value. This meropenem example demonstrates the power of population PK and Monte Carlo simulation for guiding an optimized β-lactam dosing regimen. Prolonging the infusion time or using continuous infusion of antibiotics with time-dependent activity increases the PTA, thus improving the likelihood of a favorable clinical outcome [33, 46–48]. It is important to note that the benefit of these optimized dosage regimens is primarily seen in patients infected with less-susceptible organisms. However, even when undertaking these optimization measures, therapeutic drug monitoring (TDM) may be required in selected cases to assure an appropriate drug exposure in an individual patient. Similar to β-lactam antibiotics, other hydrophilic antibacterial drugs, such as aminoglycosides and vancomycin, also have lower drug concentrations in severely ill patients with cancer and may require higher-than-usual dosing regimens [13, 49]. Both of these drug classes have a narrow therapeutic window that requires delicately balancing therapeutic benefit with toxic effect, as shown for aminoglycosides (Figure 3) [13, 35, 50]. Knowing the MIC value rather than simply the interpretive category can usefully guide the dosing decision. Aminoglycosides and vancomycin are typical examples of antibacterial drugs that may not reach required PK/PD targets in a majority of patients with cancer. Thus, adequate initial dosing regimens

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Table 1. Pharmacokinetic-Pharmacodynamic (PK/PD) Index Predictive of Outcome, Magnitude of PK/PD Index, Probability of Target Attainment, and Dosing Strategies

<table>
<thead>
<tr>
<th>Antibacterial Class</th>
<th>PK/PD Index Predictive of Outcome</th>
<th>Required Magnitude of PK/PD Index to Optimize Activity</th>
<th>PTA in Severely Ill Patients With Cancer or ICU Patients (Selected Examples)</th>
<th>Dosing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam antibiotics</td>
<td>% ft&gt;MIC: 40%–70%; 80%–100% in immunocompromised patients</td>
<td>% ft&gt;MIC: 40%–70%; 80%–100% in immunocompromised patients</td>
<td>53% with imipenem 500 mg every 4 h at MIC 1 mg/L (100 mL/min GFR) [34]</td>
<td>Intravenous: prolonged infusion, continuous infusion; oral: more frequent dosing per day</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>AUC0–24/MIC and Cmax/MIC</td>
<td>AUC0–24/MIC: &gt;150 [35]</td>
<td>55% with tobramycin 5 mg/kg at MIC 1 mg/L [36]</td>
<td>Once-daily administration, duration of therapy for &gt;5–7 days, TDM</td>
</tr>
<tr>
<td>Glycopeptides: vancomycin</td>
<td>AUC0–24/MIC</td>
<td>AUC0–24/MIC: &gt;400 (total drug, protein binding 50%) [37]</td>
<td>50% with vancomycin 2 g/d at MIC 2 mg/L (Clrenal 60–120 mL/min) [11]</td>
<td>Dosing according to TDM [38]</td>
</tr>
<tr>
<td>Lipopeptides: daptomycin</td>
<td>AUC0–24/MIC and Cmax/MIC</td>
<td>AUC0–24/MIC: &gt;800 (total drug, protein binding 90%) [39]</td>
<td>77% with daptomycin 6 mg/kg/d at MIC 1 mg/L [40]</td>
<td>High once-daily dosing, TDM would be beneficial, not enough clinical data</td>
</tr>
<tr>
<td>Oxazolidinones: linezolid</td>
<td>% ft&gt;MIC</td>
<td>AUC0–24/MIC: &gt;100 and % t &gt; MIC: &gt; 85% (total drug, protein binding 30%) [41]</td>
<td>70% with linezolid 600 mg every 12 h at MIC 2 mg/L [42]</td>
<td>Dosing according to TDM to avoid treatment failure and dose-dependent toxicity [42]</td>
</tr>
<tr>
<td>Quinolones</td>
<td>AUC0–24/MIC</td>
<td>AUC0–24/MIC: 70–90 and &gt;250 for maximal effect [6, 43]</td>
<td>77% with ciprofloxacin 400 mg every 8 h at MIC 0.25 mg/L [44]</td>
<td>High dosages, TDM may be beneficial</td>
</tr>
</tbody>
</table>

Abbreviations: % ft>MIC, percentage of dosing interval in which free concentration of antibiotic exceeds minimum inhibitory concentration (MIC); Clrenal, renal clearance; Cmax, maximal concentration; AUC0–24/MIC, the ratio of free drug area under the curve (AUC) over 24 hours to MIC; Cmax/MIC, the ratio of free Cmax to MIC; GFR, glomerular filtration rate; ICU, intensive care unit; PTA, probability of target attainment; TDM, therapeutic drug monitoring.

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Figure 2. Example of the probability of target attainment of a chosen pharmacokinetic-pharmacodynamic target (percentage of dosing interval in which free concentration of antibiotic exceeds minimum inhibitory concentration [% ft>MIC], 80%) with 3 dosage regimens of meropenem in relation to minimum inhibitory concentration values. Reproduced with permission [45]. Abbreviations: MIC, minimum inhibitory concentration; PTA, probability of target attainment.
and subsequent TDM is critical to ensuring appropriate drug exposure in the individual patient while minimizing toxicity [7, 36, 37].

Dosing challenges in patients with cancer are not limited to hydrophilic drugs. For instance, the lipophilic antibiotic linezolid is well known for the substantial interpatient and intraindividual variability of its PK parameters Vd and clearance in severely ill patients (Figure 4) [24, 51]. Faced with high PK variability, a wild-type population of Staphylococcus aureus close to the clinical break point and exposure-dependent platelet decreases [52], results of PTAs, reveal that the risk of clinical failure in critically ill patients could be increased when the MICs of linezolid are >1 mg/L. Therefore, TDM and individualized dosing is strongly recommended because the benefits of optimal antibacterial activity must be balanced against the risks of toxicity [42]. Similar issues are encountered with the class of the quinolones. Higher dosages for pathogens found in critically ill patients, as well as TDM, have been suggested [53].

**PK/PD AND RESISTANCE**

Emergence of resistance caused by selection of preexistent resistant bacterial cells or by de novo resistance mutations has been recently demonstrated in individual ICU patients with VAP [54] and in hematological patients with ciprofloxacin prophylaxis [55]. In this later study, ciprofloxacin resistance could be attributed on a patient level to selection pressure, and thus drug exposure in about 40% of patients [55]. Until recently, it has not been common practice to consider the potential for selection of resistance when evaluating antibacterial drug exposure and the impact of antibiotic regimens or duration of therapy. For example, when first revived as a last-resort antibiotic against multidrug-resistant Gram-negative bacteria, colistin’s PK and PD characteristics had not been well defined, and dosage regimens currently in use fail to suppress the emergence of resistance despite recent progress in describing this issue. Indeed, escalating reports of colistin resistance clearly illustrate the urgency of determining comprehensive PK/PD information and deepening our understanding of the evolution in antibacterial resistance.

Accumulating evidence confirms that dosage regimens focused only on reducing the susceptible bacterial population are clearly associated with a risk of selecting preexisting or newly formed mutants and allow complete replacement of the susceptible population with a resistant bacterial population [56]. An alternate PK/PD index and its magnitude for suppression of resistance is not usually considered when calculating PTAs, as listed in Table 1. Especially in high-risk situations, such as infections with high bacterial burden (eg, VAP), the higher drug exposure required to suppress emergence of resistance might not be feasible in the clinical situation due to toxicity limits. In these cases, well-defined combinations might still be capable of suppressing less-susceptible subpopulations as shown in vitro and in animal models [57, 58]. Recent debate regarding the use of combination therapy in severely ill patients to prevent emergence of resistance continues because available trials of combination therapy versus monotherapy were not designed to study the emergence of resistance.

Because clinical evidence is lacking, it is not yet clear whether dosing strategies aimed at improving efficacy actually favor emergence of resistance. For example, continuous infusion of vancomycin or linezolid might, in fact, promote selection of resistance if the drug stays in the susceptible bacterial population for longer durations.
resistant subpopulations as shown in in vitro models [59, 60]. However, clinical data are not conclusive.

Emergence of resistance is also correlated to the duration of therapy. The longer the therapy continues, the more intense the drug exposure needs to be to maintain suppression of the less-susceptible subpopulation [61]. In the course of therapy, the PK/PD index and its magnitude may change depending on the duration of the therapy and the parameter of outcome [62]. This is clearly an area of research that may lead to flexible dosing in the course of the therapy. Indeed, the formerly common practice of reducing dosage with clinical improvement and continuing treatment with low dosages has most likely contributed to emergence of resistance.

**FUTURE AGENDA REGARDING ANTIBACTERIAL PK/PD IN PATIENTS WITH CANCER**

Despite progress in recent years, a number of areas urgently require intensified research as well as translation into clinical practice:

- The unpredictable variation of PK in defined groups of high-risk patients should be determined systematically and incorporated into PK/PD modeling.
- Profound neutropenia increases the required magnitude of the PK/PD index, resulting in higher required drug exposure, although little clinical information is available.
- The results of these studies might fuel discussions regarding applicability of current break points to these patient groups and refined reporting of microbiological test results in selected cases where the actual MIC is important.
- Therapeutic drug monitoring strategies should be expanded to all patient groups with a low probability of reaching the PK/PD target or at an elevated risk of toxicity with increased dosage.
- Deeper knowledge is needed to identify drug exposures that allow suppression of resistant subpopulations while providing maximal bacterial killing at an acceptable toxicity level.
- If the PK/PD target is beyond clinically achievable drug exposure, appropriate drug combinations need to be defined and validated in clinical studies.
- Duration of therapy and, thus, overall drug exposure are strong factors in resistance development. Our knowledge in this regard remains insufficient.
- The PK/PD indices and/or the magnitude of the index may change in the course of longer-duration therapy. This is clearly an area of research that may lead to flexible dosing during the course of a therapy.
- The PK/PD modeling so far refers to monomicrobial infections. The complex nature of polymicrobial infections requires active research.

**CONCLUSIONS**

As our understanding of the variability of drug exposure in critically ill patients with cancer deepens, it has become apparent that, when treated with approved dosage regimens, many of these patients fail to reach PK/PD targets that are predictive of clinical success. Wide PK variability in severely ill patients with cancer is apparent with all antibacterial classes and must be compensated for by appropriate dosing unless there is limiting toxicity. Optimized dosing regimens have been developed and clinically validated for β-lactam (prolonged infusion) and aminoglycoside (once daily) antibiotics. A growing body of evidence indicates that, for other common antibacterial classes, such as vancomycin, linezolid, daptomycin, and quinolones, individualized higher dosages based on TDM may be required. To guide the dosing decision process in severely ill patients with cancer, PTAs based on the predictive PK/PD index, population PK, and local MIC distribution are becoming essential clinically validated tools. Selection of less-susceptible subpopulations and, thus, resistance development during therapy as a result of suboptimal dosage regimens particular to patients with cancer occur commonly and require increased attention. Although progress has been made recently, more data and translational studies are needed to individualize and optimize antibiotic dosing regimens in critically ill patients with cancer.

**Note**

*Potential conflicts of interest.* Author certifies no potential conflicts of interest.

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**References**