Recent Updates on the Role of Pharmacokinetics-pharmacodynamics in Antimicrobial Susceptibility Testing as Applied to Clinical Practice

Matthew J. Labreche, Christopher J. Graber, and Hien M. Nguyen

Given current challenges in antimicrobial resistance and drug development, infectious diseases clinicians must rely on their own ingenuity to effectively treat infections while preserving the current antimicrobial armamentarium. An understanding of pharmacokinetics (PK), pharmacodynamics (PD), antimicrobial susceptibility testing (AST), and how these concepts relate, is essential to this task. In this review, we discuss how and why PK-PD impacts AST and the way infectious diseases are being treated, with a particular focus on vancomycin for methicillin-resistant Staphylococcus aureus, penicillin for Streptococcus pneumoniae, and an update on cephalosporins for Enterobacteriaceae. Finally, we address how new ideas to exploit PK-PD can promote innovative study design and bring about more rapid regulatory review of new antimicrobials.

Keywords. pharmacokinetics; pharmacodynamics; breakpoints; susceptibility testing.

OVERVIEW OF PK-PD

Pharmacokinetics (PK) describes drug concentrations over time in the host and at the site of action, whereas pharmacodynamics (PD) describes the effect of the drug on the targeted disease and the patient [1]. PK-PD describes the triangular relationship between the effect of the antimicrobial on the infecting organism, typically measured in vitro (PD), antimicrobial exposure to the infecting organism in vivo (PK), and clinical and microbiological outcomes in the host [2]. Bacterial killing is best described by indices that incorporate the antimicrobial’s PK and PD parameters and the minimum inhibitory concentration (MIC), the lowest concentration of an antimicrobial required to prevent the growth of the target organism. These indices include: duration of time the free drug concentration remains above the MIC (fT > MIC), the ratio of the peak free drug concentration to the MIC (fCmax:MIC), and the ratio of the area under the 24 hour free drug concentration time-curve to the MIC (fAUC:MIC) (Figure 1) [3, 4]. Antimicrobials are linked to PK-PD indices that best describe their antimicrobial effects: in particular, fT > MIC for ß-lactams, fAUC:MIC for vancomycin, fluoroquinolones, and aminoglycosides, of which fluoroquinolones and aminoglycosides have both also been linked with the fCmax:MIC index [5]. PK-PD indices can be further categorized as time-dependent (fT > MIC), concentration-dependent (fCmax:MIC), or some combination of the 2 (fAUC:MIC). These indices are evaluated both in vivo and in vitro, and through population modeling using Monte Carlo simulations (computer algorithms in which repeated random sampling is done to obtain a probability distribution) to predict the probability of target attainment at different index thresholds using different dosing regimens [6].

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Correspondence: Hien M. Nguyen, MD, 9900 SE Sunnydale Rd, Clackamas, OR 97015 (hien.m.nguyen@kp.org).
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HISTORY OF PK-PD

Harry Eagle is considered the founder of antimicrobial PK-PD through his investigations of the time-dependent killing of penicillin in the 1940s–1950s [7]. In the 1970s, Shah and colleagues introduced the concept of classifying the activity of an antimicrobial as time- or concentration-dependent [8]. Antimicrobial PK-PD underwent a renaissance in the mid-1970s when Craig and others discovered its potential for predicting therapeutic outcome in animal models [9]. From the 1990s to 2000s, Forrest, Drusano, and Ambrose evaluated clinical data from human subjects to characterize antimicrobial PK-PD relationships for efficacy [10–12]. These PK-PD targets for efficacy in humans were subsequently shown to be concordant with those based on animal data, thus, demonstrating the utility of preclinical PK-PD targets for efficacy [4]. Using such targets, together with population pharmacokinetics and Monte Carlo simulation, dosing regimens associated with high probabilities of PK-PD target attainment can be identified [6].

Meanwhile, clinicians identified the need for promotion of appropriate antimicrobial utilization to improve clinical outcomes and prevent adverse effects, including the development of antimicrobial resistance. The term “antimicrobial stewardship,” introduced by Dale Gerding and first appearing in Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (IDSA) guidelines in 1997 [13], is defined as “the optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome, for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance development” [8]. Modern-day antimicrobial stewardship aims to employ the clinical application of PK-PD principles while providing the narrowest coverage for the infection at hand.

ANTIMICROBIAL SUSCEPTIBILITY TESTING AND BREAKPOINTS

The primary concern of the prescribing clinician is that the selected antimicrobial will disable the offending organism, producing a good clinical outcome. It is often assumed that this will be the case when an organism is reported as “susceptible” to the chosen antimicrobial(s) and the converse when an organism is reported as “intermediate” or “resistant.” Antimicrobial susceptibility testing (AST), however, is often based on the response of the organism to an antimicrobial in testing media, and the S-I-R (susceptible, intermediate, and resistant) nomenclature does not necessarily convey exclusivity in categorizing predicted clinical response [14]. Some have proposed the “90–60 rule,” to describe the observation that a favorable therapeutic outcome is seen approximately 90% or 60% of time when an isolate is reported as susceptible or resistant, respectively [15]. The relationship between S-I-R and clinical outcome has become more predictable in recent years, largely due to better understanding and application of PK-PD to AST [16].

Susceptibility testing provides quantitative results (usually with MIC values). As described in examples later in this manuscript, these quantitative values may allow for greater individualization of antimicrobial therapy. However, these values are often presented in qualitative format as S, I, or R on the basis of interpretive criteria. Interpretive criteria for in vitro susceptibility testing, or “breakpoints,” have significantly changed in recent years, largely due to trends in bacterial resistance and advancements in the fields of microbiologic diagnostics and PK-PD. The term “breakpoints” often creates confusion because of its use to describe microbiologic, pharmacologic, and clinical thresholds. In an effort to provide clarity, Turnidge and Paterson have recommended that “breakpoints” be renamed and separated into 3 categories: “epidemiological cutoffs,” “PK-PD cutoffs,” and “clinical cutoffs” [3]. Epidemiological cutoffs separate the population of wild-type organisms without innate or acquired resistance mechanisms from those with such mechanisms. PK-PD cutoffs, derived from PK-PD modeling (ie, Monte Carlo simulations), utilize knowledge of antimicrobial PK and PD parameters to identify MICs that best predict the probability of target attainment for specific bug-drug combinations. Finally, clinical cutoffs...
identify the threshold MIC values that divide isolates with a high vs low likelihood of clinical success upon treatment with a particular antimicrobial agent. The authors recommend that the term “breakpoint” represent the final value selected to be applied in AST. Unfortunately, there is no single formula that can assist in the construction of breakpoints. An array of data is considered, including clinical outcome studies, microbiological outcome studies, epidemiologic studies, genotypic/phenotypic resistance studies, and other PK-PD studies. The paucity of PK-PD data in critically ill patients, who exhibit pathophysiologic changes not present in healthy volunteers, and clinical outcome data in patients with specific infecting organism MIC values, present major challenges to identifying threshold MIC values [17, 18].

**AGENCIES THAT DETERMINE ANTIMICROBIAL BREAKPOINTS**

In the United States, the Clinical and Laboratory Standards Institute (CLSI), formerly the National Committee for Clinical Laboratory Standards, and the Food and Drug Administration (FDA) are responsible for setting breakpoint standards. In Europe, the main agencies are the European Union Committee on Antimicrobial Susceptibility Testing (EUCAST) and the European Medicines Agency (EMA). Breakpoints developed by these agencies conflict at times and have caused confusion for clinical microbiologists, drug and equipment manufacturers, and practicing clinicians.

The 2 main, nongovernmental agencies, CLSI and EUCAST, differ in philosophy and approach toward setting antimicrobial breakpoints as well as in how they report to their respective governmental counterparts, the FDA and EMA (Table 1) [19]. By law, US manufacturers are required to follow FDA breakpoints for drug approval and for AST systems that interpret MIC data. All too often, CLSI and FDA breakpoints do not agree, as illustrated in Table 2 [16, 20–23]. In contrast, EUCAST operates as the breakpoint committee for the EMA.

EUCAST has employed 2 different MIC values: clinical breakpoints and epidemiologic cutoffs, the latter of which has greater sensitivity for detecting changes in antimicrobial susceptibility [24]. In contrast, CLSI only utilizes clinical breakpoints, which tend to be higher than those of EUCAST. Consequently, more resistant organisms may go undetected when CLSI breakpoints are applied [25]. When data do not clearly support a particular PK-PD target, EUCAST will prioritize epidemiologic cutoff values to avoid splitting the MIC distribution of the wild-type population, or they will not establish a clinical breakpoint. Hence, EUCAST clinical breakpoints are generally lower than those of CLSI. Part of the rationale for CLSI’s higher clinical breakpoints is CLSI’s use of the “intermediate” category. CLSI fundamentally defines the intermediate category as being associated with a lower response rate, but clinical efficacy can be obtained if adequate drug levels are achieved [26]. EUCAST, on the other hand, has largely done away with the intermediate category, perceiving it as a grey zone to prevent serious categorization errors with unpredictable therapeutic response. More recently, CLSI has modified the intermediate category to include susceptible dose-dependent (SDD) breakpoints for cefepime and the Enterobacteriaceae [27].

The realization that antimicrobial resistance is a global problem argues for harmonization of antimicrobial breakpoints across agencies. Much work is still required, particularly for CLSI and EUCAST clinical breakpoints established for older antimicrobials [28]. In response, the National Antimicrobial

### Table 1. Comparison of Clinical Laboratory Standard Institute and European Committee for Antimicrobial Susceptibility Testing

<table>
<thead>
<tr>
<th></th>
<th>CLSI</th>
<th>EUCAST</th>
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<tbody>
<tr>
<td><strong>Members</strong></td>
<td>Representatives from different fields and agencies</td>
<td>Representatives from different fields and agencies</td>
</tr>
<tr>
<td><strong>Role of government</strong></td>
<td>Recognized by FDA, but FDA still determines its own breakpoints. Breakpoints determined by FDA can be modified by CLSI after 2 yr</td>
<td>Functions as breakpoint committee for EMA</td>
</tr>
<tr>
<td><strong>Role of industry</strong></td>
<td>Part of decision process</td>
<td>Consultative role</td>
</tr>
<tr>
<td><strong>Decision making</strong></td>
<td>Consensus by group votes</td>
<td>Consensus of executive committee (no vote)</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td>Industry, government and sales of documents</td>
<td>ESCMID, ECDC, government</td>
</tr>
<tr>
<td><strong>Data and Rationale documents</strong></td>
<td>For sale <a href="http://www.clsi.org">www.clsi.org</a></td>
<td>Free <a href="http://www.eucast.org">www.eucast.org</a></td>
</tr>
<tr>
<td><strong>Meetings</strong></td>
<td>2 per year</td>
<td>5 per year</td>
</tr>
<tr>
<td><strong>Breakpoints</strong></td>
<td>Clinical breakpoints Retains intermediate category, expanding concept of SDD</td>
<td>Epidemiological cutoffs Clinical breakpoints Largely abandoned intermediate category</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLSI, Clinical Laboratory Standard Institute; ECDC, European Center for Disease Control and Prevention; EMA, European Medicines Agency; ESCMID, European Society Clinical Microbiology and Infectious Diseases; EUCAST, European Union Committee for Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; SDD, susceptible dose-dependent.
Susceptibility Testing Committee for the USA (USCAST; www.uscast.org) was created in 2013 as a national branch of EUCAST. The overarching goals of USCAST are to work closely with EUCAST, the FDA, and EMA to harmonize AST, to provide access to clinical breakpoints data and guidelines, to educate healthcare specialists, and to facilitate new drug development.

The following examples highlight the influence of PK-PD studies on breakpoint development as it applies to antimicrobial utilization. There are many other examples in which PK-PD studies have influenced the approach to antimicrobial therapy (eg, use of vancomycin loading doses, continuous infusion of piperacillin-tazobactam, once-daily aminoglycoside dosing, and therapeutic drug monitoring), but they are beyond the scope of this manuscript.

**RECENT IMPACT OF PK-PD ON BREAKPOINT DEVELOPMENT**

**Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin**

Until the early 2000s, when used in the treatment of staphylococcal infections, vancomycin was commonly dosed to avoid trough levels >10 µg/mL, which were thought to promote toxicity [29]. A trend toward more aggressive dosing to achieve higher trough levels subsequently emerged, based in part on PK-PD data suggesting that achieving an AUC/MIC ≥400 improved clinical outcomes in patients with *Staphylococcus aureus* pneumonia [30]. In 2006, CLSI also lowered the methicillin-resistant *Staphylococcus aureus* (MRSA) clinical breakpoint to ≤2 µg/mL over concern for heteroresistance and worsened clinical outcomes at higher vancomycin MIC values [31]. IDSA guidelines subsequently recommended targeting trough levels of 15–20 µg/mL for severe infections caused by organisms susceptible to vancomycin within this new susceptibility range, though there remains considerable controversy regarding the ability of a vancomycin MIC of 1.5 to 2.0 µg/mL to predict vancomycin failure and whether or not current dosing strategies can achieve the AUC/MIC target of ≥400 at these MICs [32–34].

**Penicillin-resistant *Streptococcus pneumoniae* and Penicillin**

Unlike the clinical breakpoints for many antimicrobials, which have been lowered out of concerns for evolving resistance, clinical breakpoints for penicillin against *Streptococcus pneumoniae* were raised in 2008 to encourage its use [35]. Penicillin clinical breakpoints for *S. pneumoniae* were established in the 1970s primarily to guide the treatment of meningitis. In the 1990s, there was a dramatic spike in penicillin-resistant *S. pneumoniae* in the United States; however, higher penicillin MIC values did not necessarily result in poor outcomes, particularly for infections outside the central nervous system [35]. In response, CLSI established three separate penicillin clinical breakpoint categories in 2008: meningitis (intravenous), non-meningitis (intravenous), and non-meningitis (oral). For meningitis, the pre-2008 CSF breakpoints did not change [≤0.06 µg/mL (susceptible) and ≥0.12 µg/mL (resistant)]. For non-meningitis infections, the serum breakpoints were increased to ≤2 µg/mL (susceptible), 4 µg/mL (intermediate) and ≥8 µg/mL (resistant). The introduction of these nonserum clinical breakpoints set a new precedent and increased the utility of IV penicillin for pneumococcal pneumonia and other upper respiratory infections when higher doses are given (ie, at least 10 million units per day). Further, PK-PD studies suggest the use of higher doses of oral amoxicillin (which has better bioavailability than oral penicillin) against pneumococcal isolates with higher penicillin MICs [35, 36].

**Cefazolin and Enterobacteriaceae**

Particular disharmony has been seen in cefazolin AST for Enterobacteriaceae. In 2010, CLSI lowered the cefazolin susceptibility

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**Table 2. ** *Clinical Laboratory Standards Institute, European Union Committee for Antimicrobial Susceptibility Testing, and US Food and Drug Administration Clinical Breakpoints for Enterobacteriaceae and Common Intravenous Cephalosporins*

<table>
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<tbody>
<tr>
<td>Cefazolin</td>
<td>≤8</td>
<td>≤1</td>
<td>≤2</td>
<td>. . .</td>
<td>≤16</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>≤8</td>
<td>≤8</td>
<td>≤8</td>
<td>≤8</td>
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</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤8</td>
<td>≤1</td>
<td>≤1</td>
<td>≤1</td>
<td>≤1</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>≤8</td>
<td>≤4</td>
<td>≤4</td>
<td>≤1</td>
<td>≤16</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤8</td>
<td>≤8</td>
<td>≤2, SDD (4–8)</td>
<td>≤1</td>
<td>≤8</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≤8</td>
<td>≤4</td>
<td>≤4</td>
<td>≤1</td>
<td>≤4</td>
</tr>
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</table>

Abbreviations: CLSI, Clinical Laboratory Standards Institute; EMA, European Medicines Agency; EUCAST, European Union Committee for Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; IV, intravenous; SDD, susceptible dose-dependent.
breakpoint against the Enterobacteriaceae from 8 to 1 µg/mL [20]. It was soon recognized that the new breakpoint was set too low and would needlessly eliminate the use of this drug against Escherichia coli, Klebsiella spp, and Proteus mirabilis. In 2011, CLSI increased the cefazolin susceptibility breakpoint to 2 µg/mL, contingent upon use of cefazolin dosage of 2 gm IV every 8 hours (based on PK-PD considerations) instead of the typical 1 gm IV every 8 hours [20]. However, clinical microbiology laboratories are not required to report dosage suggestions and this recommendation remained unknown to many clinicians. The FDA did not adopt the lower CLSI clinical breakpoints and still referred to the older susceptibility breakpoint of ≤8 µg/mL. As a result, FDA-endorsed automated AST systems were outdated in their clinical breakpoint recommendations. In addition, many automated AST panels could not be modified to test a cefazolin MIC of 2 µg/mL. Hence, labs were left on their own to decide how best to test for cefazolin susceptibility.

### Urinary Breakpoints for Cephalosporins vs Enterobacteriaceae

β-lactams and cephalosporins have long been considered inferior to other antimicrobial classes for the treatment of urinary tract infections (UTI) caused by Enterobacteriaceae [37]. In past CLSI guidelines, as recent as 2013, it was suggested that cephalothin susceptibility could predict that of cephalaxin, cefadroxil, loracarbef, and cefpodoxime for uncomplicated UTIs and breakpoints for many oral cephalosporins were not established [38]. However, as previously identified, cephalothin is a poor class representative of these oral cephalosporins [39].

The majority of clinical microbiology laboratories and clinicians in the United States rely on the susceptibility of cefazolin to predict the susceptibility of cephalaxin, a commonly used oral 1st generation cephalosporin [39]. However, the use of the current CLSI serum cefazolin susceptibility breakpoint of ≤2 µg/mL would overpredict cephalaxin resistance considering that cefazolin is more potent than cephalaxin [39]. Many microbiologists have lobbied for the development of separate urine breakpoints for oral antimicrobials, including oral cephalosporins, that concentrate 100–1000× higher in urine than serum [40]. From a PK-PD standpoint, these higher urinary concentrations translate into a greater $f_t$ > MIC against urinary pathogens, including those with higher MICs. In 2014, CLSI created a urine susceptibility breakpoint of ≤16 µg/mL for the use of cefazolin in uncomplicated UTIs due to E. coli, Klebsiella spp, and P. mirabilis. The cefazolin urine breakpoint can also be used to predict the susceptibility of 7 oral cephalosporins (cephalexin, cefaclor, cefprozil, cefdinir, cefuroxime, loracarbef, cefdinir, and cefpodoxime) [41]. Of note, cefazolin can overpredict cefdinir and cefpodoxime resistance; however, clinicians can request individual AST of these 3rd generation cephalosporins on a case-by-case basis. It must be stressed that clinicians should not apply the new urine cefazolin susceptibility breakpoint to the treatment of complicated UTIs and pyelonephritis, where the serum breakpoint (≤2 µg/mL) may be more appropriate given involvement of disease above the bladder.

### Extended-spectrum β-lactamase (ESBL) and Cephalosporins

Breakpoints for cephalosporins against Enterobacteriaceae (eg, E. coli, Klebsiella spp, P. mirabilis) were established in the 1980s based mostly on in vitro data; clinical outcome and PK-PD data were either not available at the time or largely not considered [16]. Rising cephalosporin MICs in the early 2000s aroused fear that CLSI and EUCAST clinical breakpoints could not fully detect Enterobacteriaceae that harbor extended-spectrum β-lactamases (ESBL), which hydrolyze most cephalosporins [27]. In the mid-2000s, CLSI and EUCAST implemented a temporary solution to detect ESBL producers that did not rely directly on MICs. This involved placing a ceftazidime or cefotaxime disk next to a clavulanate disk (an inhibitor of ESBLs) [42]. If clavulanate reverses ceftazidime/cefotaxime resistance, this phenotypic test is considered positive, and the isolate is reported as an ESBL producer, resistant to all cephalosporins (including cefepime) and aztreonam.

However, studies demonstrated that drug response in vivo was fundamentally similar between ESBL- and non-ESBL producing isolates and could be predicted based on the MIC [43]. In response, EUCAST and CLSI both lowered clinical breakpoints for most cephalosporins against E. coli, Klebsiella spp, and P. mirabilis (Table 2) [27]. ESBL phenotypic testing is no longer recommended for AST in the vast majority of clinical situations, with the dual benefit of eliminating a labor-intensive process and increasing the utility of cephalosporins (particularly cefepime and ceftazidime) as treatment options for ESBL producers [27]. Both CLSI and EUCAST recommend that the ESBL phenotypic test still be considered, but only for epidemiologic purposes.

### Cefepime and Susceptible Dose-dependent

Cefepime is a 4th generation cephalosporin with higher stability against some β-lactamases compared with earlier generation cephalosporins [44]. This stability against resistant organisms led CLSI to maintain the cefepime breakpoints while lowering those of other cephalosporins in 2010 [27]. However, new clinical data emerged suggesting that higher cefepime MIC values among Enterobacteriaceae were associated with worse outcomes despite susceptible MIC values ≤8 µg/mL [45]. For comparison, EUCAST has set the cefepime susceptibility breakpoint at ≤1 µg/mL dating back to at least 2009. In 2014, CLSI lowered cefepime’s clinical breakpoints to ≤2 µg/mL (susceptible) and >8 µg/mL (resistant). CLSI also created a new AST category for cefepime known as SDD with a MIC range of 4–8 µg/mL. The intention of this category is to promote the use of higher
doses of cefepime (2 gm every 12 hours or 1–2 gm every 8 hour) for elevated MICs to achieve the PK-PD index associated with efficacy ($f/T > \text{MIC}$) [27]. If this trend is successful, CLSI may apply the SDD category to other antimicrobials in the future.

**PK-PD AND DRUG DEVELOPMENT**

As described above, PK-PD has helped clinicians to make better use of currently available antimicrobials. However, PK-PD may play yet another important role in the development of new antimicrobial agents. Currently, there is a critical need to expedite the regulatory pathways for new drug development and approval [46]. Traditionally, new drugs are evaluated through noninferiority trials using historical controls to measure the magnitude of the treatment effect. However, regulatory uncertainty on clinical and surrogate endpoints and their ability to appropriately capture meaningful treatment effects has undermined noninferiority designs. A Bayesian pharmacometric-based approach utilizing PK-PD provides an alternative pathway to measure treatment effect and restore the statistical power of noninferiority studies [47]. This pharmacometric approach utilizes available clinical and microbiological response study data, PK-PD study data, and the appropriate PK-PD index (eg, $f/T > \text{MIC}$, $\text{fAUC: MIC}$, $f_{\text{Cmax}}: \text{MIC}$) to estimate the placebo-response rate (ie, when PK-PD index approaches zero). The treatment effect is the difference in likelihood of clinical (or microbiological) success between the maximal (intervention) and minimal (placebo) drug exposure according to the PK-PD index examined. According to Ambrose, this approach would involve 3 phases:[48, 49] in vitro and in vivo studies to evaluate antimicrobial activity and identify the best PK-PD index to describe antimicrobial activity; a randomized-controlled trial of patients infected with wild-type phenotype pathogens to collect PK-PD and clinical response data; and finally, a noncomparative trial involving only patients with pathogens having the resistant phenotype of interest to collect PK-PD and clinical response data. This pharmacometric approach would negate the need and difficulty of recruiting for a large randomized controlled trial in patients with resistant organisms.

**CONCLUSION**

Clinicians now practice in an age where a single susceptibility breakpoint may not accurately predict a favorable clinical outcome. Resistance mechanisms, site of infection and dosing regimen, among other variables, must be considered. Significant progress has been made in the fields of PK-PD and AST over the past few decades to inform these decisions. These developments come at an auspicious time given the current crisis of multidrug resistant organisms and the scarcity of effective and/or safe antimicrobials to treat the infections they cause. Clinicians must be educated to be stewards of antimicrobials while other invested parties—research, academia, industry, and government—must coordinate their efforts in order to combat antimicrobial resistance and facilitate the development of new antimicrobials and effective treatment strategies.

**Note**

*Potential conflicts of interest.* All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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