Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and Aztreonam

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Widespread resistance in Enterobacteriaceae and *Pseudomonas aeruginosa* to cephalosporin and monobactam antibiotics due to extended-spectrum \(\beta\)-lactamases (ESBLs) has resulted in the need for reassessment of the interpretative criteria (breakpoints) established for these agents more than 2 decades ago. Following extensive evaluation, the Clinical and Laboratory Standards Institute recently adopted and published new breakpoints for these agents for use in clinical laboratories and provided updated recommendations for use of the ESBL screening test. This paper summarizes the background and supportive rationale for new interpretative criteria for cephalosporins and aztreonam for testing Enterobacteriaceae.

**Keywords.** breakpoints; Enterobacteriaceae; cephalosporins; *Pseudomonas*; CLSI.

\(\beta\)-Lactam antimicrobial agents are highly useful for treating infections caused by Enterobacteriaceae. New generations of agents, including methoxyimino cephalosporins and monobactams, with great stability to these enzymes were developed in the 1980s; however, the dissemination of extended-spectrum \(\beta\)-lactamases (ESBLs) that hydrolyze these agents as well earlier-generation \(\beta\)-lactams have changed the potency of these drugs against most Enterobacteriaceae. Early observations on the response to cephalosporins in infections due to ESBLs among Enterobacteriaceae suggested reduced clinical efficacy, particularly when the drugs were used at lower doses [1, 2].

In addition, there have been advances in the understanding of the relationship between the minimum inhibitory concentration (MIC), drug resistance, and drug exposure (pharmacokinetics/pharmacodynamics [PK-PD]) and outcomes in nonclinical models of infection and clinical trials for \(\beta\)-lactam antibiotics [3]. This understanding has been applied in setting in vitro susceptibility criteria (breakpoints) for antimicrobial agents [4].

The data and approach used to set the original breakpoints for cefotaxime vs Enterobacteriaceae served as a basis for setting breakpoints for other extended-spectrum cephalosporins. Analysis of the data available at the time these breakpoints were established showed that the data supporting a susceptible breakpoint value of \(\leq 8\) mg/L were inadequate compared to current approaches for establishing susceptibility breakpoints. In the only large surveillance database available at the time, >95% of gram-negative isolates had MICs
≤1 mg/L [5]. In the cefotaxime clinical trial database, clinical response rates declined slightly for cefotaxime MICs ≥32 compared to lower values; however, most organisms had MICs <8 mg/L, consistent with the surveillance data. Organisms with higher MICs were limited to Acinetobacter species and Pseudomonas aeruginosa. Thus, it appears that the best support for the original cefotaxime breakpoints came from studies of patients with Acinetobacter infections, in which the bacteriologic eradication rates were 98%, 89%, and 50% for strains with MICs of ≤8, 16, and ≥32, respectively [5]. In addition to data from cefotaxime clinical trials, pharmacologic and PK-PD data were also considered but limited to assessment of peak drug concentrations (based on the rarely used 2-g dose) related to the MICs; more modern concepts of $fT > MIC$ (percentage of a dosing interval in which free-drug concentrations exceed the MIC) being important for β-lactam antibiotics had not been developed at the time. Thus, the original cefotaxime breakpoints for Enterobacteriaceae were based upon rudimentary PK-PD considerations, and observations on clinical or microbiological responses in infections due to P. aeruginosa and Acinetobacter, as they were the only organisms with MICs in the higher range in the era prior to dissemination of ESBLs. The breakpoints selected from this analysis then served as a basis for assigning breakpoints to subsequent cephalosporins and aztreonam, regardless of their pharmacokinetics or dosage regimen.

**Extended-Spectrum β-Lactamases**

Although many ESBL-producing Enterobacteriaceae have cephalosporins and aztreonam MICs far in excess of the original Clinical and Laboratory Standards Institute (CLSI) and Food and Drug Administration (FDA) resistance breakpoints, many clinical isolates have MICs that fell within the existing “susceptible” category. The identification of this “gap,” as well as uncertainty concerning the clinical response in infections due to these strains, led to the development of ESBL screening and phenotypic confirmatory tests that would detect these enzymes in susceptible Escherichia coli and Klebsiella species (and later Proteus mirabilis). A key aspect in the use and reporting of the results from ESBL testing was the direction to clinical laboratories that a positive confirmatory ESBL test should result in the reporting of all cephalosporins and aztreonam as “resistant” regardless of the MIC values.

Although the ESBL test identified isolates of E. coli, Klebsiella species, and P. mirabilis that produced these enzymes, it created a considerable increase in workload for clinical microbiology laboratories. Moreover, the test did not consider other clinically important β-lactamases not inhibited by clavulanic acid (eg, ampC). Many clinical isolates possess mixtures of ESBLs plus ampC β-lactamases; these strains could have a negative ESBL test and MICs in the susceptible category, but in a range where clinical response appeared to be compromised with usual dosage regimens. The number of strains in this category was significant; data from the 2000–2003 Sentry program showed that among a sample of 11,913 isolates of Enterobacteriaceae, 931 had MICs of 4 μg/mL or 8 μg/mL to cefotaxime or ceftiraxone (susceptible, but satisfying CLSI criteria for performing the ESBL screening test). Of these 931 isolates, E. coli or Klebsiella species accounted for only approximately half (422 or 45% for cefotaxime, and 528 or 57% for ceftiraxone) of the Klebsiella species bacteremia, Andes and Craig evaluated different cephalosporins in the treatment of Enterobacteriaceae producing various β-lactamases. These studies clearly established that PK-PD relationships for efficacy of cephalosporins against ESBL- or non-ESBL-producing isolates in animal models were similar (Figure 1) [6]. Thus, drug response in vivo for various β-lactamases was predicted by the MIC and existing PK-PD metrics, negating the need for additional factors or different $fT > MIC$ targets for ESBL-and non-ESBL-producing Enterobacteriaceae.

Despite these experimental data, other researchers have held that ESBL-producing Enterobacteriaceae will fail treatment with cephalosporins and aztreonam, regardless of MIC value. Careful inspection of many reports of cephalosporin treatment “failure” of infections caused by ESBL-producing Enterobacteriaceae with low MICs involved inadequate dosage regimens that would provide suboptimal PK-PD exposures, and would be expected to fail on these criteria [1, 7, 8]. In a review of published clinical outcomes in patients with E. coli or Klebsiella species bacteremia, Andes and Craig compiled clinical response data based on β-lactamase production (including ESBLs) and cephalosporin MIC used in treatment [6]. Of 42 cases identified, reduced clinical response was associated with increasing MIC, with a considerable decrease in efficacy for cephalosporin MICs >2 mg/L (Table 1; [6]). These data

**What Is Important in Bacterial Killing and Efficacy—the MIC or the Type of β-Lactamase Produced?**

A key issue in evaluating susceptibility breakpoints with new resistance mechanisms is whether PK-PD relationships for fully susceptible, wild-type bacteria are altered by different resistance mechanisms. Specifically, would ESBL-producing Enterobacteriaceae appear to be more “resistant” in treatment settings, regardless of the MIC, and require higher/more frequent dosing? (That is, do ESBL-producing strains require a higher percentage of a dosage interval during which free-drug concentrations remain above the MIC [$fT > MIC$] to achieve acceptable levels of efficacy in vivo?) Using ESBL-producing isolates in mouse models of infection, Andes and Craig evaluated different cephalosporins in the treatment of Enterobacteriaceae producing various β-lactamases. These studies clearly established that PK-PD relationships for efficacy of cephalosporins against ESBL- or non-ESBL-producing isolates in animal models were similar (Figure 1) [6]. Thus, drug response in vivo for various β-lactamases was predicted by the MIC and existing PK-PD metrics, negating the need for additional factors or different $fT > MIC$ targets for ESBL-and non-ESBL-producing Enterobacteriaceae.
were concordant with the above-described results in experimental models of infection where comparable f T > MICs to those obtained in humans demonstrated that the MIC and PK data, not the β-lactamase resistance mechanism, was the best predictor of in vivo efficacy.

Reevaluating and Setting Breakpoints
The CLSI consensus process provides formal procedures for setting or revising susceptibility breakpoints [9]. CLSI’s “M23” document specifically outlines several reasons for the reassessment of susceptibility breakpoints that applied to the cephalosporins and aztreonam, including:

- New resistance mechanisms (eg, ESBLs);
- New PK-PD data, including better understanding of PK-PD data not previously available or recognized;
- Recognition that new breakpoints would simplify testing and eliminate need for additional tests to detect specific resistance mechanisms;
- Elimination of differences in breakpoints between CLSI and other organizations setting breakpoints (eg, European Committee on Antimicrobial Susceptibility Testing [EUCAST], FDA);
- Interpretive criteria established using organisms of several species.

Of note, considerable data on PK-PD in animals and humans had emerged in the 2 decades following the initial approval and marketing of these agents. When this knowledge was applied, analyses indicated that the existing breakpoints were inconsistent with the current approach that was being applied to newer antimicrobial agents.

SUMMARY OF DATA EXAMINED TO GENERATE NEW MIC INTERPRETIVE CRITERIA FOR CEPHALOSPORINS AND ENTEROBACTERIACEAE
Clinical, PK-PD, and MIC distribution data constituted the types of information that were considered in revising the breakpoints. While highly desirable, clinical data from controlled or even uncontrolled trials were few, largely due to lack of contemporary studies and lapse of patent and market exclusivity that resulted in lack of the industry sponsor interest. Some retrospective series describing clinical response with ESBL producing isolates were available [1, 2, 6–8], but critical information concerning MIC, concomitant drug treatment, site of infection, and cephalosporin dosage regimen was usually not available. Thus, information beyond that provided in the response to cephalosporins by MIC assessment conducted by Craig et al [6] was not available. This resulted in increased dependence of other data, particularly PK-PD analyses.

PK-PD Considerations
PK-PD analyses using available data were conducted to determine if usual FDA-approved cephalosporin and aztreonam dosage regimens could provide target levels of drug exposures associated with bacterial killing in vivo for organisms with MICs at and below the selected susceptibility breakpoint. The
Results of the Monte Carlo simulations for each drug and dosage regimen are shown in Figure 2. These analyses compared the expected duration that free-drug serum or plasma concentrations of an antimicrobial exceeded several MIC values. Information on human pharmacokinetics, MICs, and target $fT >$ MIC values for cephalosporins were compiled from the literature. Pharmacokinetic parameters used in simulation were drawn from studies in normal volunteers because reliable patient or population pharmacokinetic data were not available for a majority of older drugs (PK parameters for drugs are listed in Supplementary Table 1). Simulation approaches such as that implemented in Monte Carlo methods can be used to generate $fT >$ MIC values for a population of individuals to determine the proportion of simulated patients that would expected to achieve a target level of exposure (eg, $fT >$ MIC of $\geq 50\%$) [4, 10].

Because PK data from only noncompartmental pharmacokinetic analyses of the drugs were largely available, a simple pharmacokinetic model was chosen for generating $fT >$ MIC values:

$$\text{Hours above MIC} = \frac{\ln(Dose/Vd) - \ln\text{MIC}}{\lambda_z},$$

where $\lambda_z$ is the slope of the terminal slope of the serum concentration vs time curve, MIC is the value for possible breakpoint MICs, and Vd is the volume of distribution adjusted for unbound drug (generally, $V_{\text{area}}$ or $V\beta$ was used for simulations).

Data were compiled for $fT >$ MIC values of 40%–60% using several dosage regimens. Where possible, the lowest US FDA-approved dosage regimen covering indications other than urinary tract infections was considered in susceptibility breakpoint decisions; in some cases, the most frequently used dosage regimen or a dosage regimen that would avoid splitting MIC distributions (see below) was used. For purposes of consistency for comparisons among drugs, $fT >$ MIC of 50% was the nominal target selected for comparisons and susceptibility breakpoint selection. For cephalosporins, this value corresponds with approximately a 1 log decline in bacterial counts in the neutropenic mouse thigh infection model and other infection models. The susceptible PK-PD breakpoint value was selected to be the MIC value that attained a PK-PD target in 90% of simulated patients for each drug. In general, lower values for PK-PD target attainment were used in decisions on an “intermediate” category.

Results of the Monte Carlo simulations for each drug and dosage regimen are shown in Figure 2.

**MIC Distributions**

The distribution of MICs for a cephalosporin or aztreonam for *E. coli* and *Klebsiella pneumoniae* from the Sentry 2001–2003 surveillance database were examined where available. This analysis considered how new breakpoints might shift populations of organisms, and whether a “peak” in the MIC distribution might fall on a susceptible breakpoint; the latter is problematic given that inherent variability in the test could result in a changed category interpretation (eg, susceptible to intermediate).

Inspection of MIC distributions and PK-PD breakpoints showed that for most drugs, the change in susceptible breakpoint for each drug resulted in shifting most ESBL-producing isolates into the nonsusceptible category; this is not surprising as most of the PK-PD derived breakpoints also centered around the MICs used for the ESBL screening test. For key extended-spectrum cephalosporins (ie, ceftriaxone and ceftazidime) and aztreonam, peak of the MIC distribution remained below the new susceptible breakpoints identified by the PK-PD analysis (eg, MIC <2 or 4 mg/L).

The MIC distributions for *E. coli* and *K. pneumoniae* presented some issues for the PK-PD breakpoints identified for some agents. For cefuroxime, a lower susceptible breakpoint seemed to be indicated for the dosage regimen of 750 mg every 8 hours, but this would have bisected the major bacterial populations. Ultimately, interpretative criteria remained unchanged, but a higher dosage regimen that supported a susceptible breakpoint was selected (1.5 g every 6 hours). For cefazolin, lower breakpoints were provisionally selected that shifted the majority of isolates into the intermediate or resistant ranges; susceptibility breakpoints for cefazolin were subsequently revised upward in 2011 and a higher dosage regimen was used as support (ie, 2 g every 8 hours [11]).

**Revised MIC Interpretive Standards and Corresponding Zone Diameter Breakpoints**

Table 2 shows the previous and revised susceptible breakpoints, with corresponding PK-PD target attainment data. In most cases, the susceptible breakpoints were reduced 2- to 4-fold from pre-2010 values. Notably, changes in breakpoints were referenced to a dosage regimen for the drug used for treatment of infection. In contrast to previous susceptible breakpoints, approximately 90% of patients receiving the indicated dosage regimen would be expected to have $fT >$ MIC of at least 50% for the new susceptibility breakpoints.

Analysis of MIC and zone diameters for disk testing of a large collection of clinical isolates was performed and identified corresponding zone diameter cutoffs that met criteria for acceptance according the CLSI documents (Table 3) [9, 11, 12].

**SPECIAL ISSUES**

**Cefepime Susceptibility Breakpoints**

After review of clinical and PK-PD data and MIC distributions for cefepime, breakpoints were not changed; however,
Figure 2. Percentage probability of pharmacokinetic/pharmacodynamic target attainment for cephalosporins and aztreonam. Line plots show the percent of 10,000 simulated patients expected to attain $fT > MIC$ (percentage of a dosing interval in which free-drug concentrations exceed the minimum inhibitory concentration) targets of 40%, 50%, or 60% with indicated dosage regimen. Bars show minimum inhibitory concentration distributions for isolates of *Escherichia coli* and *Klebsiella pneumoniae* from Sentry Surveillance 2001–2003. Abbreviation: MIC, minimum inhibitory concentration.
higher, FDA-approved dosage regimens of at least 1 g every 8 hours or 2 g every 12 hours were referenced as support for the existing breakpoints. These dosage regimens provided comparable levels of PK-PD target attainment for an \( f T > MIC \) target of approximately 50% at the susceptible breakpoint of 8 mg/L. Review of reported clinical failures due to susceptible bacteria based on these breakpoints were likely associated with underdosing of cefepime (doses <3 g/day) [1, 7]. (Note: Although supported by the data available at the time of the reassessment, CLSI plans to reevaluate these breakpoints in light of recently published data on safety and efficacy [13] and differences between CLSI and EUCAST breakpoints.)

**Cephalothin Susceptibility Breakpoints**

PK-PD analyses revealed that the susceptible breakpoint for cephalothin needed to be substantially lower to be consistent

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### Table 2. Summary of Pharmacokinetic/Pharmacodynamic Target Attainment for Cephalosporins and Aztreonam for Previous and New Susceptibility Breakpoints for Enterobacteriaceae, Reviewed by the Clinical and Laboratory Standards Institute

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Regimen</th>
<th>Pre-2010 Susceptible Breakpoint</th>
<th>New Susceptible Breakpoint</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Value (mg/L)</td>
<td>% PK-PD Target Attainment</td>
<td>Value (mg/L)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.5 g IV q8h</td>
<td>8</td>
<td>94</td>
<td>8</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1 g IV q8h</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g IV q24h</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g IV q12h</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>1 g IV q8h</td>
<td>8</td>
<td>81</td>
<td>4</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1 g IV q8h</td>
<td>8</td>
<td>54</td>
<td>4</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 g IV q8h or 2 g IV q12h</td>
<td>8</td>
<td>91–95</td>
<td>8</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>1 g IV q8h</td>
<td>8</td>
<td>23</td>
<td>...</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>1 g IV q8h</td>
<td>16</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>1 g IV q8h</td>
<td>16</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>1 g IV 12h</td>
<td>16</td>
<td>8</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; IV, intravenous; PK-PD, pharmacokinetic/pharmacodynamic; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours.

\( a \) Percentage target attainment represents the percentage of patients from a Monte Carlo simulation that would have free-drug serum concentrations exceeding the susceptible breakpoint for at least 50% of the dosage interval.

\( b \) New breakpoints could not be established for this agent based on limited data. This agent has limited availability in many countries. If considering using this agent for *Escherichia coli*, *Klebsiella* species, or *Proteus* species, extended-spectrum \( \beta \)-lactamase (ESBL) testing should be performed. If isolates test ESBL positive, the isolate should be considered resistant to this agent.

### Table 3. Revised and Pre-2010 Clinical and Laboratory Standards Institute Breakpoints for Cephalosporins and Aztreonam for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Drug (Dosage)</th>
<th>MIC (μg/mL)</th>
<th>Disk (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Revised</td>
<td>Pre-2010</td>
</tr>
<tr>
<td>Aztreonam (1 g q8h)</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Cefotaxime (1 g q8h)</td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td>Ceftriaxone (1 g q8h)</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Ceftriaxone (1 g q12h)</td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td>Ceftriaxone (1 g q24h)</td>
<td>≤1</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; R, resistant; S, susceptible.

\( a \) Minimum dosage linked to breakpoints.
with the other cephalosporins used against Enterobacteriaceae. Because cephalothin is no longer marketed in the United States and many other countries, the subcommittee originally planned to remove the existing breakpoints. However, the subcommittee further considered previous recommendations and practice by clinical laboratories of applying cephalothin interpretative criteria to predict the activity of certain oral cephalosporins for urinary tract isolates of Enterobacteriaceae. Although these correlations were established more than a decade ago, the existing cephalothin breakpoints were retained for use only to predict results for oral cephalosporins with FDA-approved indications for treatment of urinary tract infections (cefadroxil, cefpodoxime, cephalexin, and loracarbef).

ESBL Screening Test
When using the revised breakpoints, routine testing for ESBLs (screen plus phenotypic confirmation test) is no longer required. Although ESBL testing no longer has utility in treatment decisions when the new breakpoints are employed, the subcommittee recognized that the test may have utility in some settings for purposes of epidemiologic investigations and infection control practice. In addition, it may be necessary for some institutions to continue temporarily using the ESBL test (and CLSI’s pre-2010 recommendations for interpretative criteria) until their laboratories are able to validate and implement the revised MIC or disk breakpoints.

Pseudomonas aeruginosa
Following revision of Enterobacteriaceae breakpoints, a similar assessment was made by the subcommittee for P. aeruginosa. Similar to the Enterobacteriaceae, there were no clinical data to assist in identifying susceptibility breakpoints for cephalosporins and aztreonam, and thus PK-PD data and MIC distributions comprised the primary data to support decisions concerning revised breakpoints. The subcommittee recognized that only a few cephalosporins and aztreonam had clinical utility for P. aeruginosa infections. Thus, susceptibility breakpoints for only ceftazidime, cefepime, and aztreonam were reconsidered.

Studies in animal models of P. aeruginosa infection show that similar PK-PD metrics are associated with efficacy in vivo and in vitro models of infection, similar to that determined for Enterobacteriaceae [3]. Thus, susceptibility breakpoints similar to those determined for Enterobacteriaceae were considered; however, in contrast to Enterobacteriaceae, the distribution of MICs for P. aeruginosa isolates for aztreonam, cefepime, and ceftazidime were significantly higher, with mode values falling between 2 and 4 mg/L (Table 4). Thus, the doses and susceptibility breakpoints used for Enterobacteriaceae were likely unsuitable for use with P. aeruginosa.

PK-PD target attainment of higher dose regimens still within existing FDA-approved ranges was examined to determine if the existing susceptibility breakpoints would provide suitable PK-PD target attainment in simulated patients while not bisecting the MIC distribution of P. aeruginosa. Thus, the existing susceptibility breakpoints for cefepime, ceftazidime, and aztreonam were retained, but dosage regimens supporting these breakpoints were added. Given the poorer potency and lack of clinical usefulness of other cephalosporins for P. aeruginosa infections, the previously published susceptibility breakpoints of these agents against this organism were removed from CLSI tables. Approved susceptibility breakpoints and supportive dosage information are provided in Table 5.

IMPLEMENTATION OF NEW BREAKPOINTS
There are no regulatory barriers that prevent clinical laboratories from using revised susceptibility breakpoints for patient care. Although the susceptibility breakpoints were published in CLSI documents in provisional form in 2010 and final form in 2011, barriers to implementation remain, particularly in laboratories using commercial FDA-approved automated susceptibility testing systems. However, laboratories can implement these susceptibility breakpoints immediately through use

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>≤0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>&gt;128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>0.4</td>
<td>0.9</td>
<td>1.0</td>
<td>1.4</td>
<td>5.5</td>
<td>38.6</td>
<td>17.2</td>
<td>14.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>20.4</td>
</tr>
<tr>
<td>Cefepime</td>
<td>0.1</td>
<td>0.4</td>
<td>1.1</td>
<td>14.2</td>
<td>29.5</td>
<td>17.6</td>
<td>14.3</td>
<td>11.8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>11.1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>11.2</td>
<td>39.0</td>
<td>16.8</td>
<td>7.5</td>
<td>5.8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>19.7</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>...</td>
<td>0.1</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>1.4</td>
<td>4.3</td>
<td>7.2</td>
<td>14.0</td>
<td>...</td>
<td>...</td>
<td>21.7</td>
</tr>
</tbody>
</table>

Underlined values indicate mode value.
Abbreviation: MIC, minimum inhibitory concentration.
Table 5. Revised Minimum Inhibitory Concentration Breakpoints, Dosage Regimens, and Pharmacodynamic-Pharmacokinetic Target Attainment for Ceftazidime, Cefepime, and Aztreonam Against Pseudomonas aeruginosa

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>MIC Breakpoints</th>
<th>% PK-PD Target Attainment at Susceptible Breakpoint*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>1 g q6h or 2 g IV q8h</td>
<td>≤8</td>
<td>100</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1 g q6h or 2 g IV q8h</td>
<td>≤8</td>
<td>94</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 g IV q8h or 2 g IV q12h</td>
<td>≤8</td>
<td>91–95</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration; PK-PD, pharmacokinetic/pharmacodynamic; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours.

* Percentage PK-PD target attainment represents the percent of simulated patients with f T > MIC (percentage of a dosing interval in which free-drug concentrations exceed the MIC) of at least 50%.

of the disk test, or by conducting an appropriate in-house validation study. The Infectious Diseases Society of America has posted on its website guidance for such validation protocols (http://www.idsociety.org/Antimicrobial_Susceptibility_Testing/) [14].

SUMMARY

Increasing resistance of Enterobacteriaceae and Pseudomonas species to β-lactam antimicrobial agents necessitated reconsideration of susceptibility breakpoints for these agents. Because data from controlled clinical trials pre- or postregistration were not available, PK-PD principles from clinical and non-clinical data were applied for usual FDA-approved dosage regimens of these agents. This enabled these “older agents” to be brought to the level of standards and “best practice” of PK-PD currently applied for newer drugs.

Publication of revised CLSI interpretive standards for cephalosporins and aztreonam for Enterobacteriaceae and P. aeruginosa was accomplished after several years of careful analysis of clinical, microbiological, and clinical data using the consensus process. Although some regulatory issue remain to be solved (eg, FDA approval of breakpoint changes in automated susceptibility testing devices), clinical laboratories can implement the revised susceptibility breakpoints using the correlate zone diameter cutoffs, Etest methods, or by following procedures for validating broth dilution MIC methods from an automated susceptibility testing device in their own laboratories. Infectious disease clinicians, antimicrobial stewardship programs, and clinical microbiology laboratories are encouraged to implement the revised interpretive criteria to optimize antimicrobial therapy of infections due to Enterobacteriaceae and P. aeruginosa with these agents.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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