REVIEW

# Breakpoints for extended-spectrum β-lactamase-producing Enterobacteriacae: pharmacokinetic/pharmacodynamic considerations

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## ABSTRACT

An understanding of antibacterial pharmacokinetics and pharmacodynamics is central to setting clinical breakpoints. It is important to understand any impact that a resistance mechanism may have on these basic drug properties. With extended-spectrum β-lactamase (ESBL)-producing strains of Enterobacteriacae, it is known that MIC, and hence *T*>MIC, for β-lactams predicts outcome. Therefore, pharmacodynamic modelling can be used to set breakpoints for ESBL-producing bacteria with β-lactams.

**Keywords** *Escherichia coli*, extended-spectrum β-lactamase, Monte–Carlo simulation, pharmacodynamics, pharmacokinetics, review

*Clin Microbiol Infect* 2008; **14** (Suppl. 1): 166–168

## INTRODUCTION

The determination of clinical breakpoints for extended-spectrum β-lactamase (ESBL)-producing strains of Enterobacteriacae is an essential element of the laboratory support of antimicrobial therapy [1]. In addition, appropriate categorisation of strains as susceptible, intermediate or resistant to certain agents—especially β-lactams—ensures that appropriate infection control measures can be taken. A clinical breakpoint needs to have predictive value in terms of microbiological and/or clinical outcomes. Susceptibility has been defined by EUCAST as 'a level of antimicrobial activity associated with a high likelihood of therapeutic success' (http://www.EUCAST.org). In contrast, resistance is defined as 'a level of antimicrobial activity associated with a high likelihood of therapeutic failure'. If the breakpoint provides these relationships, then infection control and therapeutic decisions based on laboratory testing are likely to prevent adverse patient outcome and improve patient safety, and probably will be cost-effective.

In this article, the development of clinical breakpoints for β-lactam antibiotics against ESBL-producing *Escherichia coli*, *Klebsiella* spp. and some other Enterobacteriaceae is discussed. It is well-known that ESBL producers are often also resistant to a wide range of other antimicrobials, e.g., fluoroquinolones, aminoglycosides and dihydrofolate reductase inhibitors [2], and these are not discussed further.

Modern clinical breakpoints depend on three key areas of information, namely, pharmacodynamics, MIC values and distributions, and clinical trial data. In order to set a breakpoint related to a specific resistance mechanism, several factors are required:

1. The basic pharmacokinetic (PK)/pharmacodynamic (PD) properties of the drug class against which the resistance mechanism operates need to be known.
2. The impact of the resistance mechanism on the PK/PD relationships of drug concentration and outcome needs to be established—usually using in-vitro or in-vivo PD models.
3. It must be determined whether the existing tools used to decide breakpoints (i.e., models) are valid for the resistance mechanism.

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4. It must be determined whether the PK/PD prediction based on in-vitro, in-vivo and in-silico models can be validated in clinical trials.
5. It must be determined whether the proposed PK/PD breakpoints predict microbiological/clinical outcomes in humans.

The PD properties of β-lactams are well-described. β-Lactams show time-(non-concentration)-dependent killing within the therapeutic range, with moderate persistent effects against Gram-positive bacteria and minimal effects against Gram-negatives. The goal of dosing is to maximise the duration of pathogen exposure to the drug (i.e., to increase the time for which the drug remains over a threshold value); hence, *T*>MIC is regarded as the dominant PK/PD index [3].

The *T*>MIC, either *in vitro* or *in vivo* (neutropenic murine thigh models) for a static to one log pathogen kill at 24 h is taken to be most predictive of outcome in humans. For cephalosporins against Gram-negatives, this value is *c.* 25-40%, while for Gram-positives it is 20-30%. Carbapenems have a lower *T*>MIC value for a given effect than do cephalosporins, and if the requirement is to kill more than one log bacteria, then a higher *T*>MIC is needed (Table 1).

Data from the neutropenic murine thigh infection models obtained using a range of cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefepime) to treat bacteria with a range of ESBLs (TEM-3, TEM-7, TEM-10, TEM-12, TEM-26, SHV-2, SHV-4, SHV-5, SHV-7, CTX-M) has indicated that the *T*>MIC for static or bactericidal effects is the same, whether or not the strain carries an ESBL [4]. There are similar data for ertapenem (Table 2) [5]. In conclusion, these data indicate that the β-lactam MIC of an ESBL-producing strain can be used to predict likely human outcomes from PK/PD models; that is, as long as a certain *T*>MIC value is achieved, the microbiological outcome can be predicted. The data in Table 3 illustrate the effect of MIC on the antibacterial effect of ceftriaxone, piperacillin–tazobactam and ertapenem, at standard simulated human doses, on ESBL producers.

The use of Monte-Carlo simulations is central to clinical breakpoint determination. Monte-Carlo analysis is a mathematical tool that allows for random number generation within a defined distribution of values. It is used in setting breakpoints, as it allows the possible range of PK values to be modelled and combined. It also allows a range of MIC values to be modelled. Clearly, Monte-Carlo analysis is critically dependent on the quality of the data used to define the modelled distributions [6]. If these do not accurately represent the clinical situation of interest, then the model will not be predictive. Examples of Monte-Carlo simulations are shown in Tables 4 and 5 for ceftriaxone and piperacillin–tazobactam [7]. The analysis indicates that if the *T*>MIC target for ceftriaxone is *c.* 30%, as indicated by animal models, then this value will be achieved in

**Table 1.** The *T*>MIC antibacterial effect relationship for *Escherichia coli* in an in-vitro dilutional model simulating free drug concentration in humans

| Antibacterial effect at 24 h (log CFU/mL) | % *T*>MIC dosing for effect with | |
|---|---|---|
| | Ceftriaxone | Ertapenem |
| Static | 25 | 20 |
| −1 log drop | 40 | 25 |
| −2 log drop | 55 | 35 |
| −3 log drop | 70 | 50 |
| −4 log drop | 95 | 70 |
| $r^2$ | 0.98 | 0.98 |

**Table 2.** The antibacterial effect relationship of ertapenem against Enterobacteriaceae containing TEM or SHV β-lactamases in a neutropenic thigh infection model

| | *T*>MIC% | |
|---|---|---|
| | Static effect at 24 h | $ED_5$ at 24 h |
| Extended-spectrum β-lactamase (ESBL)+ | 17 ± 17 | 37 ± 17 |
| ESBL− | 21 ± 12 | 30 ± 23 |

**Table 3.** Activity of ceftriaxone (CEF), piperacillin–tazobactam (P-T) and ertapenem (ERTA) at simulated standard doses against extended-spectrum β-lactamase producers, studied in an in-vitro pharmacokinetic model

| | MIC (mg/L) | | | Kill at 24 h (log CFU/mL) | | |
|---|---|---|---|---|---|---|
| | CEF | P-T | ERTA | CEF | P-T | ERTA |
| *Escherichia coli* | 1.5 | 6 | 0.02 | 0 | −4.2 | −4.1 |
| | 4.0 | 8 | 0.06 | −2.7 | −2.8 | −4.1 |
| | 14.0 | 20 | 0.09 | +2.1 | −0.5 | −4.0 |
| *Klebsiella pneumoniae* | 40.0 | 28 | 0.12 | +1.8 | −1.7 | −4.0 |

**Table 4.** Monte-Carlo simulations and target attainment rates (TAR) for intravenous ceftriaxone 2 g every 24 h

| | TAR at *T*>MIC rates of | | | | |
|---|---|---|---|---|---|
| **MIC (mg/L)** | **20%** | **30%** | **40%** | **50%** | **60%** |
| 0.25 | 100 | 100 | 97 | 55 | 6 |
| 0.5 | 100 | 100 | 72 | 9 | 0 |
| 1.0 | 100 | 90 | 16 | 0 | 0 |
| 2.0 | 99 | 29 | 1.0 | 0 | 0 |
| 4.0 | 54 | 0 | 0 | 0 | 0 |

**Table 5.** Monte-Carlo simulations and target attainment rates (TAR) for intravenous piperacillin–tazobactam 4 g every 6 h

| | TAR at *T*>MIC rates of | | | | |
|---|---|---|---|---|---|
| **MIC (mg/L)** | **20%** | **30%** | **40%** | **50%** | **60%** |
| 4 | 100 | 100 | 100 | 100 | 99 |
| 8 | 100 | 100 | 100 | 99 | 83 |
| 16 | 100 | 100 | 97 | 57 | 9 |
| 32 | 100 | 83 | 13 | 1 | 0 |
| 64 | 24 | 2 | 0 | 0 | 0 |

>90% of patients, provided that the ceftriaxone MIC for the pathogen is ≤1 mg/L. An equivalent value for piperacillin–tazobactam is ≤16 mg/L. Work by Moczypamba *et al*. [8] has indicated that, with a *T*>MIC target of 20-30%, this value will be achieved in >99% of patients with standard doses of imipenem or meropenem against ESBL-producing strains. The equivalent value for ertapenem was ≥83% of patients.

In conclusion, the use of PK/PD models, human PKs and Monte-Carlo simulations allow rational clinical breakpoints to be proposed for ESBL-producing bacteria. Such proposals form the basis for discussion, which can be modified in the light of MIC distribution and clinical data. PK/PD modelling indicates that carbapenems (ertapenem, imipenem and meropenem) are likely to represent best therapy as a drug class for all ESBL producers. Other β-lactams are likely to present adequate therapy, provided that the strain MICs fall below the PK/PD breakpoint (Table 6).

How such proposed PK/PD breakpoints are incorporated into routine clinical microbiology testing and reporting systems after modification in the light of MIC and clinical data is a subject for further discussion.

**Table 6.** Pharmacokinetic/pharmacodynamic (PK/PD) systemic breakpoints for representative cephalosporins and penicillin against extended-spectrum β-lactamase-producing bacteria

| **Agent** | **PK/PD breakpoint for effective therapy MIC (mg/L)** |
|---|---|
| Cefotaxime | ≤1 |
| Ceftriaxone | ≤1 |
| Cefepime | ≤4–8 |
| Piperacillin–tazobactam | ≤16 |
| Temocillin | ≤4–8 |

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