# Establishing MIC breakpoints and the interpretation of in vitro susceptibility tests

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The purpose of undertaking susceptibility testing, by whatever method, is to attempt to integrate the drug potency against a population of potential pathogens with the pharmacokinetics of the antimicrobial and, whenever possible, to review this relationship in the light of clinical experience following therapy in clinical trials. Breakpoints are discriminatory antimicrobial concentrations used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate or resistant. Clinical, pharmacological, microbiological and pharmacodynamic considerations are important in setting breakpoints. The ideal mix of these factors is under constant discussion. Different countries have different approaches to this problem but, by and large, their approaches have much in common which has allowed for the recent progress in setting European breakpoints through the European Committee on Antimicrobial Susceptibility Testing (EUCAST). This paper attempts to summarize the philosophy of the British Society for Antimicrobial Chemotherapy (BSAC) Working Party in conjunction with EUCAST in its approach to setting breakpoints and to update the activities of the Working Party since it initially published breakpoints. The formula outlined by the BSAC Working Party in 1991 has again been used to set the breakpoints presented here. However, in future, BSAC clinical breakpoints will reflect those set by EUCAST, and this year new breakpoints for fluoroquinolones, aminoglycosides, glycopeptides and linezolid are included. The Working Party accepts that in the light of new knowledge, there is a need to reassess how clinical breakpoints are defined, and this paper also summarizes the future activities of the Working Party with EUCAST/in this important area.

## Introduction

The need to know whether an organism is likely to respond to antimicrobial therapy is as old as chemotherapy itself, and the background has been covered in this Supplement by Wheat.[1] A number of mechanisms exist by which one may establish the breakpoint between a susceptible and resistant population of bacteria. In the USA, the Clinical Laboratory Standards Institute (CLSI), formerly NCCLS, publishes such guidance,[2] and has significant influence in many parts of the world. Other countries, however, have a different philosophy and different methodological details. Within Europe, there are six active national breakpoint committees, the Comite de l Antibiogramme de la Societe Francaise de Microbiologie (CA-SFM)[3], France; German Institute for Standardisation (DIN), Germany; the Norwegian Working Group on Antibiotics (NWGA), Norway; Swedish Reference Group for Antibiotics (SRGA)[4], Sweden; the Commissie Richtlijenen Gevoeligneids Depalingen (CRG), The Netherlands; and the BSAC Working Party on Susceptibility Testing, United Kingdom. The activities of these Committees is now co-ordinated through the European Committee on Antimicrobial Susceptibility Testing (EUCAST) which is a standing committee of the European Society for Clinical Microbiology and Infectious Diseases (ECCMID), and part funded by the European Union (EU).

All methods used attempt to integrate the pattern of in vitro potency and pharmacodynamics of an antibacterial against a population of bacteria with the pharmacokinetics of the antimicrobial and then, where possible, to review this relationship in the light of clinical experience. All have many problems in common. These include the following:
(i) The need for antimicrobial group testing; namely, can one agent be taken as representative of others? Commercially and scientifically this is a thorny problem.
(ii) How to take into account the changing dosing regimens (for example, penicillin and ampicillin dosing for pneumococci with intermediate susceptibility).
(iii) Infections at specific sites, including the urinary tract, and the possible need for site-specific breakpoints.
(iv) The role of the intermediate category between susceptible and resistant populations.
(v) How to deal with organism-antimicrobial combinations where a substantial proportion of the distribution of susceptibility straddles the pharmacodynamic breakpoint.
It has been said that it would be far simpler to choose one international method of susceptibility testing and breakpoint determination, and the method usually suggested is that of the CLSI. An increasing number of the scientific community believe that there should be a 'European' method. The different methods have both strengths and weaknesses. For example, the CLSI utilizes inocula and media with which the BSAC Working Party and other bodies have fundamental problems. Moreover, the CLSI breakpoints are, in this Working Party's view, not conservative enough, tending to be higher than those of the BSAC. In addition, it now seems clear that breakpoints can be considered in two ways. The first is a value which divides bacteria into those which are likely to respond to antimicrobial chemotherapy and those which do not. The second is a microbiological approach which seeks to identify strains which do not belong to the normal (antibiotic nieve) population.

We believe the primary function of *in vitro* antimicrobial susceptibility testing in clinical laboratories is to provide information to prescribers on the choice of appropriate chemotherapy, whether it be for therapy in specific patients, or to help in antimicrobial policy formulation. Here the use of clinical breakpoints is needed. Increasingly, routine susceptibility testing is also seen as having public health significance, in that the data generated can be used to track the occurrence and prevalence of antimicrobial resistance in the geographical area served by the laboratory. This needs to be supported by identification to a species level in many situations. Here the use of microbiological breakpoints may be best. While the clinician expects the laboratory to provide

information categorizing isolates as susceptible, intermediate or resistant, such categories are not optimal for epidemiology.

The definitions now proposed by EUCAST divide definitions into clinical breakpoints and wild type cut-offs.

(a) Clinically resistant
A micro-organism is defined as clinically resistant by a level of antimicrobial susceptibility which results in a higher than expected likelihood of therapeutic failure.
A micro-organism is categorised as clinically resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system.
This breakpoint may be altered with legitimate changes in some circumstances.

(b) Clinically susceptible
A micro-organism is defined as clinically susceptible by a level of antimicrobial susceptibility which results in an improved, or the desired, therapeutic outcome.
A micro-organism is categorised as clinically susceptible (s) by applying the appropriate breakpoint in a defined phenotypic test system.
This breakpoint may be altered with legitimate changes in some circumstances.

(c) Clinically intermediate
A micro-organism is defined as clinically intermediate by a level of antimicrobial susceptibility which results in an indeterminate therapeutic outcome.

(d) Wild types and microbiological resistance
Microbiological resistance is defined as a reduction in susceptibility from the wild type distribution of susceptibility for a species in a defined phenotypic test system.
A micro-organism is categorised as belonging to the wild type (WT) for a species by applying the appropriate wild type cut-off value in a defined phenotypic test system.
The cut-off value will not be altered by changing circumstances.
Microbiological resistance may or may not affect clinical response to antimicrobial therapy.

In order to categorize strains as susceptible, intermediate or resistant, breakpoint antibiotic concentrations are used. Here we review the current BSAC approach to setting a clinical breakpoint and discuss the alterations to the process that the Working Party are currently considering.

**Current procedures for establishing individual breakpoints.**
The majority of the published BSAC breakpoints were chosen 10 years ago, were not exhaustive, and related to the agents most commonly used at that time.[5] The impetus for the initial choice came from the members of the Working Party. A discussion paper was produced for the membership of the Society and some minor amendments were then made following representations from members. The BSAC Working Party, unlike theCLSI,[2] has never had significant input from industry. The breakpoint, once decided, was communicated to the relevant pharmaceutical company.

The definition of breakpoint that is used here is as follows: a breakpoint is a discriminating concentration used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate or resistant.

The setting of clinical breakpoints is a controversial subject and the focus of much debate among infection specialists, regulators and industry. In the past this process was seen as arbitrary and lacking in consistency. In the last decade, an increasing knowledge of pharmacodynamics has allowed
more rationality to be introduced into discussion about breakpoints.

At present we believe that pharmacodynamic principles should be used to set breakpoints for penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones. The situation with other agents is less clear. A discussion paper on pharmacodynamic guidelines to develop breakpoints for the above drug classes was consulted on in 2003. In addition, the BSAC is now involved with EUCAST in setting breakpoints. This year, final EUCAST breakpoints for aminoglycosides, fluoroquinolones, glycopeptides and linezolid have been agreed and these are now incorporated as separate tables. The breakpoints for other agents established using the principles set out in 1991 in 'A Guide to Sensitivity Testing', a report of the Working Party on Antibiotic Sensitivity Testing of the BSAC[5] are still in use.

The BSAC Working Party considers the four features of both antimicrobial and pathogen must be considered when deciding upon a breakpoint: (i) the distribution of susceptibilities: (ii) pharmacodynamics of the drug: (iii) pharmacological properties of the antimicrobial: and (iv) clinical outcome data. However, difficulties can arise in reconciling these three.

The BSAC Working Party agrees with EUCAST that the relevant factors in setting breakpoints for new antimicrobials are in Europe:-

- national similarities and differences regarding highest and lowest doses, available formulations, clinical indications and practices, and potential pathogens
- multiple MIC distribution of relevant species, collected in the EUCAST wild type distribution programme (www.eucast.org), are assessed and wild type cut-off values determined (WT $\leq$ Xmg/L)
- dose effect relationships obtained in in vitro studies, animal studies and humans (pK/pD data) is evaluated
- modelling processes such as Monte Carlo simulations may be used to assist the process of breakpoint setting
- clinical data relating to outcome of MIC values
- breakpoints suggested by the European national committees will be compared and discussed
- consensus breakpoints will be sought
- resulting breakpoints will be tested against each of the major potential pathogen MIC distributions to ensure that they do not divide the wild type populations. This would obviate a reproducible S, I & R categorisation in clinical laboratory testing. The ensuing breakpoints may differ between species
- the BSAC via EUCAST may refrain from setting breakpoints if the species considered is a poor target for the antimicrobial or there is insufficient evidence that the species is a good target for the agent

Similar factors will be considered when harmonising clinical MIC breakpoints for existing drugs.

**Microbiological considerations**
The use of purely clinical and/or pharmacodynamic or pharmacokinetic data may produce breakpoints that will result in laboratory results with poor reproducibility. The MIC is seen as the gold standard for assessing an antibiotic's potency, but is a crude measure with limitations.

However, all other susceptibility test methods should be validated against an MIC determined by a standard methodology. Breakpoints that fall in the troughs of bimodal or polymodal MIC distribution are most likely to yield a reproducible categorization of susceptible, intermediate or resistant, while those breakpoints that lie in the middle of a continuous distribution will result in poor reproducibility. It may, therefore, be necessary to shift breakpoints or to introduce two breakpoints to help diminish the impact of this problem. Different species differ in their MIC distributions, and therefore it may be necessary to choose breakpoints that relate to the more common and/or important organisms. Breakpoints chosen with deference to the majority of clinical isolates may result in a classification of 'susceptible' for organisms with specific resistance mechanisms that affect clinical outcomes. It may consequently be necessary to shift breakpoints to reduce this problem.

In most cases, the distribution of susceptibilities (MICs) for a bacterial population to an antimicrobial is either unimodal (the bacteria are innately susceptible or resistant) or bimodal (a susceptible population and a population possessing a mechanism or mechanisms of resistance, for example *Escherichia coli* with and without the TEM-1 enzyme). Setting breakpoints defined by such distributions should not cause problems. For example, Figure 1 shows innately susceptible or resistant populations as defined and, if supported by pharmacokinetic considerations, a breakpoint can be readily derived. Figure 2 shows an example of a bimodal distribution and if the pharmacokinetics suggest a breakpoint between the two populations, again there should be few problems. Difficulties do arise in the example shown in Figure 3, when the pharmacokinetics suggest a breakpoint around the apex of the normal distribution curve (an example being cefuroxime with Enterobacteriaceae) or when there is a substantial 'shoulder' of organisms, possessing a known mechanism of resistance, that overlaps with the normal or susceptible strains, as shown in Figure 4. However, it must be
understood that for certain drug-pathogen combinations that have susceptibility distributed over a wide range of MIC values it can be difficult, and sometimes almost impossible, to choose a meaningful breakpoint that will yield consistent results in an acceptably high proportion of tests.

The Working Party recognize that susceptibility patterns to certain agents may change with time and place. This may mean that clinical breakpoint recommendations should change to enable laboratories, for example, to recognize and report such changes in resistance. Vancomycin resistance in *Staphylococcus aureus* is a case in point, where changes may need to be made in the future.

**Pharmacological and pharmacokinetic features**

Implicit in choosing a breakpoint is the assumption that the concentration of an antimicrobial at the site of infection is one of the important features likely to determine the outcome of therapy. It is unusual to have a body of information available on the tissue levels achieved at numerous sites, and equally little is known of the effect that local or general disease can have upon such concentrations. For these reasons serum concentrations are used as surrogates for those in tissue.

The original BSAC formula is as follows:[5]

Breakpoint concentration = $\frac{C_{max}}{et}$ f X s,

where $C_{max}$ = maximum serum concentration following a stated dose at steady state, and usually at 1 h post-dose.

e = factor by which the $C_{max}$ should exceed the MIC. Normally a value of four is used, but this may be less for compounds that achieve high tissue concentrations in relation to their serum levels.

f = factor to allow for protein binding, which affects both an antimicrobial's *in vitro* activity in serum and, when high, the pharmacokinetics. For protein binding <70%, f = 1; for protein binding 70-90%, f = 0.5; and for protein binding >90%,f = 0.2.
t = factor (normally 1) to allow for the serum elimination half-life. For a serum elimination half-life of between 1 and 3 h, t = 1; if it is >3 h, t = 0.5; or if it is <1 h, t = 2.
s = shift (or reproducibility) factor mentioned above. Typically, s = 1 and should not normally be <0.5 or >2.

Since the formula was first proposed, considerably more is now understood about the pharmacodynamic properties of different classes of antimicrobials, the rate at which bacteria are killed and, increasingly, the effect on clinical cure. The formula has now been replaced by the EUCAST process for clinical breakpoint setting.

When breakpoints for particular sites, for example urine, are under consideration, data on the concentrations attained at that site and the presence of microbiologically active metabolites should also be addressed. Interactions between parent compounds and their metabolites, if relevant, should also be considered. A feature of certain antimicrobials, particularly some of the macrolide group, is their high tissue concentrations yet low serum levels. It is difficult to judge a meaningful breakpoint in these conditions. However, by utilizing a different value of e and correlating with clinical outcome data, a breakpoint can be established.

A feature not yet addressed is the impact that a particular choice of breakpoint might have upon the emergence of resistance amongst pathogens to a particular antimicrobial. There is increasing evidence that the use of an antimicrobial when MICs for infecting organisms are very close to the MIC breakpoint may be associated with the emergence of resistance.[6] It is possible that this should be factored into future breakpoint determinations.

**Clinical issues**
The whole of the rationale for determining a clinical breakpoint is predicated on the fact that an organism designated as 'susceptible' should respond to the usual dose of the agent. A 'resistant' organism should not respond and an 'intermediate' one may or may not respond to standard doses, yet would have an increased chance of responding to a greater dose if the infection is at a site where the antimicrobial is actively concentrated. It is of major concern that such information is often lacking. To confound the issue, all involved in the treatment of infections know of patients who respond satisfactorily to therapy when pathogens are 'resistant' and fail to respond to appropriate therapy for 'susceptible' pathogens. The Working Party is happy to receive information on clinical response rates for groups of pathogens treated in testing situations where knowledge of the MIC of the pathogen is known. If convincing evidence is presented that the chosen breakpoint should be altered, the Working Party will take such information into account in re-assessing a breakpoint. The CLSI, having close links with the drug licensing authority, the FDA,[2] has a greater ability to 'capture' such clinical information more readily than the BSAC does the UK. However, for new agents the BSAC now accesses such data through EUCAST which has a close relationship with European Regulators. (The European Agency for the Evaluation of Medicinal Products: EMEA).

**The process of 'setting' a breakpoint**
EUCAST Procedure for Setting Breakpoints (6a)
EUCAST has formalized the procedure for setting breakpoints for new and existing antimicrobials. Before harmonizing breakpoints for existing drugs, it is important to determine whether the

breakpoint differences can be explained by differences in dosing, chemical formulations, clinical indications, or target organisms. Therefore, information from each of the committees on how the drug is perceived and used nationally is collected at an initial stage. The target organisms are defined and agreed on. Wild type distributions of MIC values for target organisms are collected, and epidemiological cut-off values are determined. Resistance mechanisms and their effects on drug activity and clinical outcome are identified. Pharmacological, toxicological, and pharmacokinetic data are collected, and a set of pharmacokinetic variables (concentrations following standard dosages, protein binding, half-life, area under the curve, etc.) are defined and used to determine a theoretically correct breakpoint based on pharmacokinetic-pharmacodynamic relationships, including Monte Carlo simulations. The theoretical breakpoint is compared with existing breakpoints (if breakpoints already exist) set by the national committees, including the CLSI, and with the wild-type MIC distributions of target microorganisms to ensure that wild-type MIC distributions are not divided. In that case, the breakpoint for one or several species or groups of species may be shifted one dilution step up or down to prevent poor reproducibility in the laboratory. In these cases, explanatory comments are provided, and in some instances, notes are added regarding the dosing regimens. Finally, checks that the breakpoints are not in conflict with clinical outcome data are made. The tentative breakpoint decision made by the steering committee in concert with national breakpoint committees is distributed according to the formal consultation process described above. The final decision is taken by the EUCAST steering committee, and a table of breakpoints for the class of Antimicrobial is published on the EUCAST website and in *Clinical Microbiology and Infection*. A document describing the rationale for the decision is published on the EUCAST website when, or shortly after, the breakpoints are posted. Implementation of the new breakpoints rests with the national breakpoint committees, who subsequently need to change their national inhibition zone diameter breakpoints to reflect the EUCAST breakpoints.

BSAC National Breakpoints

The Working Party initially obtains information on the pharmacokinetics of an antimicrobial that is often of a preliminary and unconfirmed nature. The MICs for a range of relevant pathogens (at least 500 strains) are determined according to the Society's described method,[7] or equivalent and the distribution of MICs (as shown in Figures 1-4) is determined. From the pharmacokinetics and dynamics an initial breakpoint, with s = 1, can be determined. In the majority of cases only a minor adjustment of s is required to account for the distribution of MICs.

Setting zone size breakpoints for the BSAC standardized method

The zone sizes obtained from 6 mm discs loaded with different amounts of antibiotic are then obtained for the same isolates tested with the BSAC standardized disc diffusion method.[7] Scattergram analysis for these strain zone diameter and MIC data are then constructed as shown in Figure 5. The error-rate-bounded analysis of Metzler & DeHaan[8] is then applied. A false-resistant and false-susceptible rate can be calculated and the zone diameter breakpoint adjusted so that these rates are as low as possible. The Working Party usually considers acceptable limits to be <5% and <1%, respectively, believing that false-resistant reporting to be of lesser clinical consequence than false susceptible. In addition, it is believed that zone sizes of >36 mm are undesirable as they cause difficulty in reading the plates in a laboratory setting. Hence, if such large zones are found, a lower content disc may be more appropriate.

Occasionally it is found that certain groups of pathogens and antimicrobials (for example *Pseudomonas aeruginosa* and the fluoroquinolones) give consistently high rates of false reporting. In such instances a further organism-specific analysis can be undertaken, and different breakpoints and disc contents considered. Finally, as shown in the hypothetical example given in Figure 5, acceptable false reporting rates are obtained and hence, at a tentative breakpoint

concentration of 1 mg/L, a zone diameter of 20 mm is chosen to distinguish best between susceptible and resistant organisms.

**Group representative susceptibility testing**

Numbers of closely related antimicrobials are marketed, yet a laboratory can only test a selected few. The use of one agent to represent a family of closely related compounds is a contentious matter and it is best to test the antibiotic which will be used in clinical practice. However, if this is not possible, then use of group representatives is an alternative.[5] In short, the lesser of evils is to choose a representative that is the least active of the family of compounds. This may lead to increased 'false resistant' reporting to a more active member. This is of less clinical danger than predicting the susceptibility of a less active agent based upon information obtained by susceptibility testing of a more active compound. However, if a particular agent in a group is used locally, that agent should be tested.

**Future developments of the Working Party**

The Working Party hopes to endorse EUCAST clinical breakpoints for iv cephalosporins in 2005/06.

Finally, the Working Party believes that the subject of breakpoints is extremely fluid. New clinical information becomes available, new compounds come on to the market and automation plays an increasing role. All this requires the Working Party to have an open-minded approach and it welcomes input from all concerned.

**Proposed interpretative breakpoints for individual antimicrobial agents**

Previously, the proposed interpretative breakpoints for individual antimicrobial agents were defined in Tables 1.4.I 1.4.II and 1.4.III of the last Working Party Report.[5]
Table 1.4.III was subsequently updated and reprinted in 1996.[9] The same format is used in revised Table 1.4.I (now Table I), Table 1.4.11 (now Table II) and Table 1.4.III (now Table III), with the exception that antimicrobials are now classified according to the British National Formulary (BNF) chapter 5 subheadings.[10] In addition, the low breakpoint now defines the susceptible category, and the high breakpoint defines the resistant category. However, two broad groups of organisms are still recognized:
Group I: staphylococci, streptococci, *Moraxella catarrhalis* and *Haemophilus influenzae* (Table I).
Group II: Enterobacteriaceae and *Pseudomonas* spp. (Table II).

Table IV shows urinary breakpoints.

Where EUCAST breakpoints exist, the former BSAC breakpoints and supporting data have been removed from Tables I, II and III.

EUCAST/BSAC breakpoints for these agents are given on Table V, aminoglycosides; Table VI, glycopeptides; Table VII, oxazolidinones; and Table VII, fluoroquinolones.

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**Table I.** Breakpoint concentrations of antibiotics (mg/L) for staphylococci, streptococci, *M. catarrhalis* and *H. influenzae*

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| 5.1.1 Penicillins[a,b,c] | | | | | | | | | |
| 5.1.1.1. Benzyl penicillin & phenoxymethyl penicillin | | | | | | | | | |
| benzyl penicillin | 1.2 g iv | 50 | 55 | 1 | 0.8 | 2 | 0.03 | 0.12 | 0.25 |
| 5.1.1.2 Penicillinase-resistant penicillins | | | | | | | | | |
| flucloxacillin | 1 g iv | 25 | 95 | 0.2 | 1.1 | 1 | 4 | 4 | 8 |
| methicillin[d] | 1 g iv | 10 | 30 | 1 | 0.5 | 2 | 4 | 4 | 8 |
| oxacillin[d] | 1 g iv | 25 | 93 | 0.2 | <1 | 2 | 4 | 2 | 4 |
| 5.1.1.3 Broad-spectrum penicillins[a,b] | | | | | | | | | |
| amoxycillin | 0.5 g po | 10 | 20 | 1 | 1 | 1 | 0.5 | 1 | 2 |
| ampicillin | 0.5 g po | 5 | 20 | 1 | 1.5 | 1 | 0.5 | 1 | 2 |
| co-amoxiclav[e] | 0.5 g po | 10 | 20 | 1 | 1 | 1 | 0.5 | 1 | 2 |
| 5.1.1.4 Anti-pseudomonas penicillins | | | | | | | | | |
| piperacillin ± tazobactam | 4 g iv | 80 | 20 | 1 | 1 | 1 | 0.12 | 2 | 4 |
| ticarcillin ± clavulanate[e] | 3 g iv | 120 | 55 | 1 | 1.2 | 1 | 0.06 | 2 | 4 |
| 5.1.2 Cephalosporins, cephamycins & other ß-lactams[e] | | | | | | | | | |
| Cephalosporins and cephamycins | | | | | | | | | |
| cefaclor | 500 mg po | 15 | 25 | 1 | 0.8 | 2 | 0.5 | 1 | 2 |
| cefadroxil | 1000 mg po | 15 | 20 | 1 | 1.2 | 1 | 0.25 | 1 | 2 |
| cefepime | 2 g iv | 50 | 17 | 1 | 1.8 | 1 | 0.25 | 2 | 4 |
| cefixime | 400 mg po | 3.7 | 70 | 0.5 | 3.2 | 0.5 | 1 | 1 | 2 |
| cefodizime | 1 g iv | 75 | 81 | 0.5 | 3.3 | 0.5 | 0.12 | 2 | 4 |
| cefotaxime | 2 g iv | 30 | 40 | 1 | 1.1 | 1 | 0.12 | 1 | 2 |
| cefotetan | 2 g iv | 100 | 85 | 0.5 | 3.5 | 0.5 | 0.25 | 4 | 8 |
| cefoxitin | 2 g iv | 30 | 72 | 0.5 | 1 | 1 | 1 | 4 | 8 |
| cefoperazone | 2 g iv | 120 | 90 | 0.5 | 1.6 | 1 | 0.25 | 4 | 8 |
| cefpirome | 2 g iv | 60 | 9 | 1 | 1.8 | 1 | 0.12 | 1 | 2 |
| cefpodoxime | 200 mg po | 2.5 | 25 | 1 | 2.4 | 1 | 1 | 1 | 2 |
| cefprozil | 500 mg po | 9.3 | 40 | 1 | 1.2 | 1 | - | - | - |
| ceftazidime | 2 g iv | 70 | 10 | 1 | 2.0 | 1 | 0.25 | 2 | 4 |
| ceftibuten | 400 mg po | 20 | 63 | 1 | 2 | 1 | 0.25 | 1 | 2 |

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| ceftriaxone | 2 g iv | 180 | 95 | 0.2 | 7.5 | 0.5 | 0.06 | 1 | 2 |
| cefuroxime | 750 mg iv | 35 | 30 | 1 | 1.3 | 1 | 0.12 | 1 | 2 |
| cefuroxime | 250 mg po | 4.6 | 30 | 1 | 1.3 | 1 | 1 | 1 | 2 |
| cephalexin | 500 mg po | 17 | 10 | 1 | 1 | 1 | 0.5 | 2 | 4 |
| cefamandole | 1 g iv | 60 | 70 | 0.5 | 1 | 1 | 1 | 8 | 16 |
| cephazolin | 1 g iv | 70 | 80 | 0.5 | 1.8 | 1 | - | - | - |
| cephradine | 1 g iv | 30 | <10 | 1 | 1 | 1 | 0.25 | 2 | 4 |
| Other ß-lactams[e] | | | | | | | | | |
| aztreonam | 2 g iv | 100 | 56 | 1 | 1.7 | 1 | 0.25 | 8 | 16 |
| imipenem | 1 g iv | 60 | 25 | 1 | 1 | 1 | 0.25 | 4 | 8 |
| meropenem | 1 g iv | 55 | 7 | 1 | 1 | 1 | 0.25 | 4 | 8 |
| 5.1.3 Tetracyclines | | | | | | | | | |
| ertapenem | 1 g iv | 150 | 92 | 0.2 | 4 | 0.5 | 0.25 | 4 | 8 |
| demeclocycline | 300 mg | 2.0 | 54 | 1 | 13 | 0.5 | 1 | 1 | 2 |
| doxycycline | 200 mg | 3.3 | 8.8 | 0.5 | 20 | 0.5 | 1 | 1 | 2 |
| minocycline | 100 mg | 1.5 | 76 | 0.5 | 14 | 0.5 | 1 | 0.5 | 1 |
| oxytetracycline | 250 mg | 2 | 31 | 1 | 9.2 | 0.5 | 1 | 1 | 2 |
| tetracycline | 250 mg | 1.8 | 43 | 1 | 8.5 | 0.5 | 1 | 1 | 2 |
| 5.1.4 Aminoglycosides | | | | | | | | | |
| gentamicin | | | | | | | | | |
| amikacin | | | | | | | | | See |
| netilmicin | | | | | | | | | Table V |
| tobramycin | | | | | | | | | |
| 5.1.5 Macrolides | | | | | | | | | |
| erythromycin | 500 mg po | 2 | 18 | 1 | 1.2 | 1 | 1 | 0.5 | 1/16[h] |
| azithromycin | 500 mg po | 0.4 | 31 | 1 | 50 | 0.5 | 1 | 0.25[h]/1 | 8[h]/2 |
| clarithromycin | 500 mg po | 2.1 | 80 | 0.5 | 3.4 | 0.5 | 1 | 0.5 | 1/32[h] |
| 5.1.6 Clindamycin | | | | | | | | | |
| clindamycin | 300 mg po | 4 | 94 | 0.2 | 2.4 | 1 | 0.5 | 0.5 | 1 |
| 5.1.7 Some other antibiotics | | | | | | | | | |
| chloramphenicol | 1 g po | 12 | 53 | 1 | 5/1 | 0.5 | 0.25 | 2[i] | 4 |
| fusidic acid | 0.5 g po | 30 | 97 | 0.2 | 9.0 | 0.5 | 0.25 | 1 | 2 |

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| vancomycin | | | | | | | | | See Table VI |
| teicoplanin | 400 g iv | | | | | | | | See Table VI |
| quinupristin/dalfopristin | 7.5 mg/kg iv | 7 | <70 | 1 | 1.5 | 1 | 1 | 2 | 4 |
| linezolid | | | | | | | | | See Table VII |
| 5.1.8 Sulphonamides and trimethoprim | | | | | | | | | |
| trimethoprim | 200 mg po | 3 | 44 | 1 | 10 | 0.5 | 0.5 | 0.5 | 1 |
| 5.1.9 Antituberculous drugs | | | | | | | | | |
| rifampicin | 600 mg po | 85 | 70 | 1 | 3.4 | 0.5 | 0.25 | 1/0.06[j] | 2/0.12[j] |
| 5.1.12 Quinolones | | | | | | | | | |
| ciprofloxacin | | | | | | | | | See Table VIII |
| gatifloxacin | | | | | | | | | See Table VIII |
| gemifloxacin | | | | | | | | | See Table VIII |
| levofloxacin | | | | | | | | | See Table VIII |
| moxifloxacin | | | | | | | | | See Table VIII |
| ofloxacin | | | | | | | | | See Table VIII |

[a] For *H. influenzae* and *M. catarrhalis*, test for ß-lactamase, since MICs may be close to the breakpoint, which has been shifted down in relevant cases to allow for this as far as possible.
[b]For enterococci use the breakpoints in Table II.
[c]For *S. pneumoniae*; breakpoint of 0.06 mg/L for susceptible, 0.12-1 mg/L for intermediate, ≥2 mg/L for resistant. Organisms requiring an MIC ≤1 mg/L are considered susceptible to ß-lactam antibiotics, except in infections of the CNS.
[d]Methicillin or oxacillin results are used to predict flucloxacillin susceptibility
[e]Do not report for methicillin-resistant staphylococci
[f]For enterococci, breakpoints for high=level resistance are ≤512 mg/L for susceptible, ≥1024 mg/L for resistant apply for gentamicin.
[h]Breakpoints for *H. influenzae*; strains with MICs below the low breakpoint are susceptible; those with MICs above the high breakpoint are resistant, others are intermediate.

[I]Breakpoint of ≤8 mg/L for staphylococci and streptococci.
[J]Rifampicin breakpoint for staphylococci is lowered to allow identification of a population with MICs of c. 0.5 mg/L, the significance of which is uncertain.

**Table II.** Breakpoint concentrations of antibiotics (mg/L) for Enterobacteriaceae and *Pseudomonas* spp.

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| 5.1.1 Penicillins | | | | | | | | | |
| 5.1.1.3 Broad-spectrum penicillins[a] | | | | | | | | | |
| amoxycillin | 1 g | 30 | 20 | 1 | 1 | 1 | 2 | 8 | 16 |
| ampicillin | 1 g | 30 | 20 | 1 | 1.5 | 1 | 2 | 8 | 16 |
| co-amoxiclav | 1 g | 30 | 20 | 1 | 1 | 1 | 2 | 8 | 16 |
| 5.1.1.4 Anti-pseudomonal penicillins | | | | | | | | | |
| piperacillin ± tazobactam | 4 g iv | 80 | 20 | 1 | 1 | 1 | 1 | 16 | 32 |
| ticarcillin ± clavulanate | 3 g iv | 120 | 55 | 1 | 1.2 | 1 | 0.5 | 16 | 32[b]/128[c] |
| 5.1.2 Cephalosporins, cephamycins & other ß-lactams | | | | | | | | | |
| Cephalosporins and cephamycins | | | | | | | | | |
| cefaclor | 500 mg po | 15 | 25 | 1 | 0.8 | 2 | 0.5 | 1 | 2 |
| cefadroxil | 1000 mg po | 15 | 20 | 1 | 1.2 | 1 | - | - | - |
| cefepime | 2 g iv | 50 | 17 | 1 | 1.8 | 1 | 0.12 | 1 | 2 |
| cefixime | 400 mg po | 3.7 | 70 | 0.5 | 3.2 | 0.5 | 1 | 1 | 2 |
| cefodizime | 1 g iv | 75 | 81 | 0.5 | 3.3 | 0.5 | 0.12 | 2 | 4 |
| cefotaxime | 2 g iv | 30 | 40 | 1 | 1.1 | 1 | 0.12 | 1 | 2 |
| cefotetan | 2 g iv | 100 | 85 | 0.5 | 3.5 | 0.5 | 0.25 | 4 | 8 |
| cefoxitin | 2 g iv | 30 | 72 | 0.5 | 1 | 1 | 1 | 4 | 8 |
| cefoperazone | 2 g iv | 120 | 90 | 0.5 | 1.6 | 1 | 0.25 | 4 | 8 |
| cefpirome | 2 g iv | 60 | 9 | 1 | 1.8 | 1 | 0.12 | 1 | 2 |
| cefpodoxime | 200 mg po | 2.5 | 25 | 1 | 2.4 | 1 | 1 | 1 | 2 |
| cefprozil | 500 mg po | 9.3 | 40 | 1 | 1.2 | 1 | - | - | - |
| ceftazidime | 2 g iv | 70 | 10 | 1 | 2.0 | 1 | 0.25 | 2[b]/8[c] | 4[b]/16[c] |
| ceftibuten | 400 mg po | 20 | 63 | 1 | 2 | 1 | 0.25 | 1 | 2 |
| ceftriaxone | 2 g iv | 180 | 95 | 0.2 | 7.5 | 0.5 | 0.06 | 1 | 2 |
| cefuroxime | 750 mg po iv | 35 | 30 | 1 | 1.3 | 1 | 1 | 8 | 32 |
| cephalexin | 500 mg po | 17 | 10 | 1 | 1 | 1 | 0.5 | 2 | 4 |
| cefamandole | 1 g iv | 60 | 70 | 0.5 | 1 | 1 | 1 | 8 | 16 |
| cephazolin | 1 g iv | 70 | 80 | 0.5 | 1.8 | 1 | - | - | - |
| cephradine | 1 g iv | 30 | <10 | 1 | 1 | 1 | 0.25 | 2 | 4 |
| Other ß-lactams | | | | | | | | | |

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| aztreonam | 2 g iv | 100 | 56 | 1 | 17 | 1 | 0.25 | 8 | 16 |
| imipenem | 1 g iv | 60 | 25 | 1 | 1 | 1 | 0.25 | 4 | 8 |
| meropenem | 1 g iv | 55 | 7 | 1 | 1 | 1 | 0.25 | 4 | 8 |
| 5.1.3 Tetracyclines | | | | | | | | | |
| demeclocycline | 300 mg | 2.0 | 54 | 1 | 13 | 0.5 | 1 | 1 | 2 |
| doxycycline | 200 mg | 3.3 | 8.8 | 0.5 | 20 | 0.5 | 1 | 1 | 2 |
| minocycline | 100 mg | 1.5 | 76 | 0.5 | 14 | 0.5 | 1 | 0.5 | 1 |
| oxytetracycline | 250 mg | 2 | 31 | 1 | 9.2 | 0.5 | 1 | 1 | 2 |
| tetracycline | 250 mg | 1.8 | 43 | 1 | 8.5 | 0.5 | 1 | 1 | 2 |
| 5.1.4 Aminoglycosides | | | | | | | | | |
| gentamicin[f] | | | | | | | | | See Table V |
| amikacin[g] | | | | | | | | | See Table V |
| netilmicin | | | | | | | | | See Table V |
| tobramycin | | | | | | | | | See Table V |
| 5.1.7 Some other antibiotics | | | | | | | | | |
| chloramphenicol | 1 g po | 12 | 53 | 1 | 5.1 | 0.5 | 1 | 8 | 16 |
| colistin | 3 MU iv | 15 | <10 | | 2.1 | 1 | 1 | 4 | 8 |
| 5.1.8 Sulphonamides and trimethoprim | | | | | | | | | |
| trimethoprim | 200 mg po | 3 | 44 | 1 | 10 | 0.5 | 0.5 | 0.5 | 4 |
| 5.1.12 Quinolones | | | | | | | | | |
| ciprofloxacin | | | | | | | | | See Table VIII |
| gatifloxacin | | | | | | | | | See Table VIII |
| gemifloxacin | | | | | | | | | See Table VIII |
| levofloxacin | | | | | | | | | See Table VIII |
| moxifloxacin | | | | | | | | | See Table VIII |
| ofloxacin | | | | | | | | | See Table |

| | | | | | | | | Breakpoint concentration (mg/L) | |
|---|---|---|---|---|---|---|---|---|---|
| Agents | Dose | Cmax (mg/L) | % protein binding | f | T (h) | t | s | susceptible ≤ | resistant ≥ |
| | | | | | | | | | VIII |

[a]Refers to iv doses only
[b]Breakpoint for Enterobacteriaceae
[c]Breakpoint for *Pseudomonas* spp.

**Table III.** Summary of breakpoint recommendations (concentration in mg/L)

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Staphylococci, streptococci, *M. catarrhalis, H. influenzae* | | Enterobacteriaceae, *Pseudomonas* spp. | |
| | susceptible ≤ | resistant ≥ | susceptible ≤ | resistant ≥ |
| 5.1.1 Penicillins<br>5.1.1.1. benzyl penicillin[a] | 0.12 | 0.25 | - | - |
| 5.1.1.2 Penicillinase-resistant penicillins | | | | |
| flucloxacillin | 4 | 8 | - | - |
| methicillin | 4 | 8 | - | - |
| oxacillin | 2 | 4 | - | - |
| 5.1.1.3 Broad-spectrum penicillins | | | | |
| amoxycillin | 1 | 2 | 8 | 16 |
| ampicillin | 1 | 2 | 8 | 16 |
| co-amoxiclav | 1 | 2 | 8 | 16 |
| 5.1.1.4 Anti-pseudomonas penicillins | | | | |
| piperacillin ± tazobactam | 2 | 4 | 16 | 32 |
| ticarcillin ± clavulanate | 2 | 4 | 16 | 32[b]/128[c] |
| 5.1.2 Cephalosporins, cephamycins & other ß-lactams | | | | |
| cefaclor | 1 | 2 | 1 | 2 |
| cefadroxil | 1 | 2 | - | - |
| cefepime | 2 | 4 | 1 | 2 |
| cefixime | 1 | 2 | 1 | 2 |
| cefodizime | 2 | 4 | 2 | 4 |
| cefotaxime | 1 | 2 | 1 | 2 |
| cefotetan | 4 | 8 | 4 | 8 |
| cefoxitin | 4 | 8 | 4 | 8 |
| cefoperazone | 4 | 8 | 4 | 8 |
| cefpirome | 1 | 2 | 1 | 2 |
| cefpodoxime | 1 | 2 | 1 | 2 |
| cefprozil | - | - | - | - |
| ceftazidime | 2 | 4 | 2[b]/8[c] | 4[b]/16[c] |
| ceftibuten | 1 | 2 | 1 | 2 |
| ceftriaxone | 1 | 2 | 1 | 2 |
| cefuroxime iv | 1 | 2 | 8 | 32 |
| cefuroxime po | 1 | 2 | 1 | 2 |

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Staphylococci, streptococci, *M. catarrhalis, H. influenzae* | | Enterobacteriaceae, *Pseudomonas* spp. | |
| | susceptible ≤ | resistant ≥ | susceptible ≤ | resistant ≥ |
| cephalexin | 2 | 4 | 2 | 4 |
| cefamandole | 8 | 16 | 8 | 16 |
| cephazolin | - | - | - | - |
| cephradine | 2 | 4 | 2 | 4 |
| aztreonam | 8 | 16 | 8 | 16 |
| imipenem | 4 | 8 | 4 | 8 |
| meropenem | 4 | 8 | 4 | 8 |
| 5.1.3 Tetracyclines | | | | |
| demeclocycline | 1 | 2 | 1 | 2 |
| doxycycline | 1 | 2 | 1 | 2 |
| minocycline | 0.5 | 1 | 0.5 | 1 |
| oxytetracycline | 1 | 2 | 1 | 2 |
| tetracycline | 1 | 2 | 1 | 2 |
| 5.1.4 Aminoglycosides | | | | |
| gentamicin | | | | See Table V |
| amikacin[d] | | | | See Table V |
| netilmicin | | | | See Table V |
| tobramycin | | | | See Table V |
| 5.1.5 Macrolides | | | | |
| erythromycin | 0.5 | 1/16[e] | - | - |
| azithromycin | 0.25[e] | 8[e]/2 | - | - |
| clarithromycin | 0.5 | 1/32[e] | - | - |
| 5.1.6 Clindamycin | | | | |
| clindamycin | 0.5 | 1 | - | - |
| 5.1.7 Some other agents | | | | |
| chloramphenicol | 2 | 4 | 8 | 16 |
| fusidic acid | 1 | 2 | - | - |
| vancomycin | | | | See Table VI |
| teicoplanin | | | | See Table VI |
| colistin | 4 | 8 | 4 | 8 |
| quinupristin/dalfopristin | 2 | 4 | - | - |
| linezolid | | | | See Table VII |

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Staphylococci, streptococci, *M. catarrhalis, H. influenzae* | | Enterobacteriaceae, *Pseudomonas* spp. | |
| | susceptible ≤ | resistant ≥ | susceptible ≤ | resistant ≥ |
| 5.1.8 Sulphonamides and trimethoprim | | | | |
| trimethoprim | 0.5 | 1 | 0.5 | 4 |
| 5.1.9 Antituberculous drugs | | | | |
| rifampicin | 0.06 | 0.12 | - | - |
| 5.1.12 Quinolones | | | | |
| | | | | See Table VIII |
| | | | | See Table VIII |
| | | | | See Table VIII |
| levofloxacin | | | | See Table VIII |
| moxifloxacin | | | | See Table VIII |
| ofloxacin | | | | See Table VIII |

[a]For *S. pneumoniae*, a breakpoint of ≤0.06 mg/L implies susceptible, 0.12-1 mg/L intermediate and ≥2 mg/L resistant. Organisms with an MIC ≤1 mg/L are considered susceptible to ß-lactam antibiotics, except in infections of the CNS.
[b]Breakpoint for Enterobacteriaceae
[c]Breakpoint for *Pseudomonas* spp.
[e]Breakpoint for *H. influenzae*

**Table IV**. Breakpoint concentrations (mg/L) for isolates from uncomplicated urinary tract infections[a]

| | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Enterococci, staphylococci, streptococci | | E. coli, Proteus spp, coliforms, Pseudomonas spp. | |
| | Susecptible ≤ | Resistant ≥ | Susecptible ≤ | Resistant ≥ |
| Ampicillin | 32 | 64 | 32 | 64 |
| Co-amoxiclav | 32 | 64 | 32 | 64 |
| Cephalexin | 32 | 64 | 32 | 64 |
| Mecilinam | 64 | 128 | 1 | 16 |
| Fosfomycin | 128 | 256 | 128 | 256 |
| Nitrofuranitoin | 32 | 64 | 32 | 64 |
| Trimethoprim | 2 | 4 | 2 | 4 |
| Nalidixic acid | 16 | 32 | 16 | 32 |
| Norfloxacin | 4 | 8 | 4 | 8 |
| Ciprofloxacin | 4 | 8 | 4 | 8 |

[a]For agents not listed, criteria given for systemic isolates may be used.
[b]For S. saprophyticus

## Table V Aminoglycosides – EUCAST/BSAC clinical MIC breakpoints

| Aminoglycosides[1] | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[5] S≤/R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobac-teriaceae* | *Pseudo-monas*[2] | *Acineto-bacter*[2] | *Staphylo-coccus* | *Entero-coccus*[3] | *Strepto-coccus A,B,C,G* | *S.pneu-moniae* | *H.influenzae M.catarrhalis* | *N.gonorr-hoeae* | *N.mening-itidis* | *Gram-negative anaerobes* | |
| Amikacin | 8/16 | 8/16 | 8/16 | 8/16[4] | -- | -- | -- | IE | -- | -- | -- | 8/16 |
| Gentamicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Netilmicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Tobramycin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.

2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.

3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and betalactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC>128 mg/L.

4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.

5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with **--** or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

## Table VI Glycopeptides – EUCAST/BSAC clinical MIC breakpoints

| Glycopeptides | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[2] S≤/R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobac-teriaceae* | *Pseudo-monas* | *Acineto-bacter* | *Staphylo-coccus*[1] | *Entero-coccus* | *Strepto-coccus A,B,C,G* | *S.pneu-moniae* | *H.influenzae M.catarrhalis* | *N.gonorr-hoeae* | *N.mening-itidis* | *Gram-negative anaerobes* | |
| Vancomycin | -- | -- | -- | 4/8 | 4/8 | 4/4 | 4/4 | -- | -- | -- | -- | 4/8 |
| Teicoplanin | -- | -- | -- | 4/8 | 4/8 | 4/4 | 4/4 | -- | -- | -- | -- | 4/8 |

1. *Staphylococcus aureus* may be categorized as falsely susceptible to glycopeptides as glycopeptide MICs for strains with reduced susceptibility are dependant on the test conditions, in particular the medium used.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with **--** or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

## Table VII Oxazolidinones – EUCAST/BSAC clinical MIC breakpoints

| Oxazolidinone | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobac-teriaceae* | *Pseudo-monas* | *Acineto-bacter* | *Staphylo-coccus*[1] | *Entero-coccus*[1] | *Strepto-coccus A,B,C,G* | *S.pneu-moniae* | *H.influenzae M.catarrhalis* | *N.gonorr-hoeae* | *N.mening-itidis* | *Gram-negative anaerobes* | |
| Linezolid | -- | -- | -- | 4/4 | 4/4 | 2/4 | 2/4 | -- | -- | -- | -- | 2/4 |

1. The S/I-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with **--** or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

## Table VIII Fluoroquinolones – EUCAST/BSAC clinical MIC breakpoints

| Fluoroquinolone[1] | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[7] S≤/R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Entero-bacteriaceae*[2] | *Pseudo-monas/* | *Acineto-bacter* | *Staphylo-coccus* | *Entero-coccus* | *Strepto-coccus A,B,C,G* | *S.pneu-moniae*[4] | *H.influenzae M.catarrhalis*[5] | *N.gonorr-hoeae* | *N.menin-gitidis*[6] | *Gram-negative anaerobes* | |
| Ciprofloxacin | 0.5/1 | 0.5/1 | 1/1 | 1/1[3] | -- | -- | 0.125/2 | 0.5/0.5 | 0.03/0.06 | 0.03/0.06 | -- | 0.5/1 |
| Levofloxacin | 1/2 | 1/2 | 1/2 | 1/2 | -- | 1/2 | 2/2 | 1/1 | IE | IE | -- | 1/2 |
| Moxifloxacin | 0.5/1 | -- | -- | IE | -- | IE | 0.5/0.5 | 0.5/0.5 | IE | IE | IE | 0.5/1 |
| Norfloxacin | 0.5/1 | -- | -- | -- | -- | -- | -- | -- | IE | -- | -- | 0.5/1 |
| Ofloxacin | 0.5/1 | -- | -- | 1/1[3] | -- | -- | 0.125/4 | 0.5/0.5 | 0.12/0.25 | IE | -- | 0.5/1 |

1. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national breakpoint committees.

2. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports of poor response with other *Salmonella* species.

3. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.

4. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.

5. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae.* An Intermediate category was not defined since only few clinically resistant strains have been reported.

6. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

7. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with **--** or **IE** in the table).

**-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.**
**IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.**