

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 susceptibility of 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 and microbiological considerations are important in setting breakpoints, and the ideal mix of these factors is unknown. Different countries have different approaches to this problem but, by and large, these approaches have much in common. This paper attempts to summarize the philosophy of the British Society for Antimicrobial Chemotherapy (BSAC) Working Party in its approach to setting breakpoints and to update the activities of the Working Party since it initially published breakpoints, approximately 10 years ago. The formula outlined by the BSAC Working Party in 1991 has been used to set the breakpoints presented here. The Working Party accepts that in the light of new knowledge, there is a need to reassess how breakpoints are defined, and this paper also summarizes the future activities of the Working Party.

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 National Committee for Clinical Laboratory Standards (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. The Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM)³ and the Swedish Reference Group for Antibiotics (SRGA)⁴ have attitudes (and hence methods) not dissimilar to those of the BSAC, although the agar media used may differ. The European Society for Clinical Microbiology and Infectious Diseases is currently considering its approach to this subject.

All methods used attempt to integrate the pattern of sus-

ceptibility of a population of bacteria with the pharmacokinetics of the antimicrobial and then, possibly, 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 integrate the newly emerging knowledge on pharmacodynamics with breakpoint determination.
- (vi) How to deal with organism–antimicrobial combinations where a substantial proportion of the distribution of susceptibility straddles the pharmacological breakpoint.

It has been said that it would be far simpler to choose one

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international method of susceptibility testing and breakpoint determination, and the method usually suggested is that of the NCCLS. 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 NCCLS utilizes inocula and media with which the BSAC Working Party and other bodies have fundamental problems. Moreover, the NCCLS breakpoints are, in this Working Party's view, not conservative enough, tending to be higher than those of the BSAC. This does not mean that there cannot be an internationally recognized standard method, but rather that different countries should produce guidance on methodology and breakpoints that reflect clinical and laboratory practice in that country. Breakpoint determination, being a process that must be continuously reviewed, is part of the BSAC standard method.

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 or prophylaxis in specific patients, or to help in antimicrobial policy formulation. 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. 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 of these categories are as follows.

Susceptible: susceptible implies that infection due to the bacteria tested will probably respond to that antibiotic.

Intermediate: intermediate implies an indeterminate or uncertain response is likely given standard dosing. In some circumstances increased doses would be effective.

Resistant: resistant implies that infection due to bacteria tested will probably not respond to that antibiotic.

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 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 the NCCLS,² has never had signifi-

cant input from industry, but, as discussed below, this may well change in the future. 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 breakpoints is a controversial subject and the focus of much debate among microbiologists, 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 could 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 is currently being prepared. In the meantime, we have continued to use 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

Three features of both antimicrobial and pathogen must be considered when deciding upon a breakpoint: (i) the distribution of susceptibilities; (ii) pharmacological properties of the antimicrobial; and (iii) clinical outcome data. However, difficulties can arise in reconciling these three.

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.

Establishing MIC breakpoints

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. The use of the somewhat maligned, or more accurately, misunderstood ‘s’ or shift factor originally described by the Working Party will assist in altering the breakpoint such that consistent results should be obtained. This is discussed in detail below. 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.

Owing to the need to avoid breakpoints that are species specific and hence more cumbersome to use in a laboratory setting, judgements will have to be made that may increase false reporting for some pathogens. For example, *Klebsiella* and *Serratia* spp. are less susceptible than other *Enterobacteriaceae* to some fluoroquinolones, but may

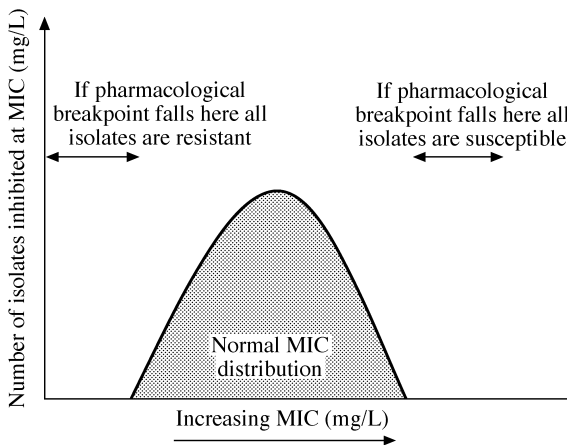


Figure 1. Identifying breakpoints: normal MIC distribution.

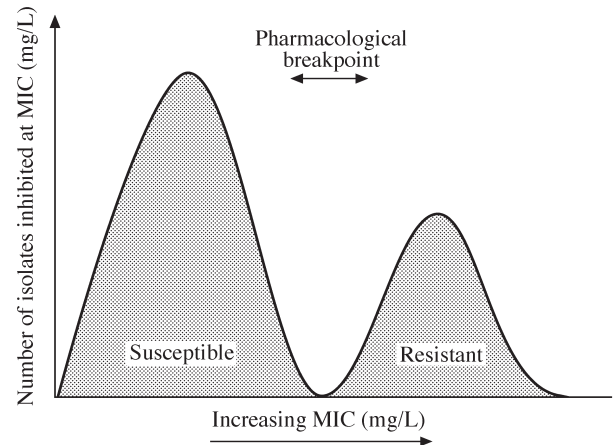


Figure 2. Impact of breakpoint on interpretation with bimodal MIC distribution.

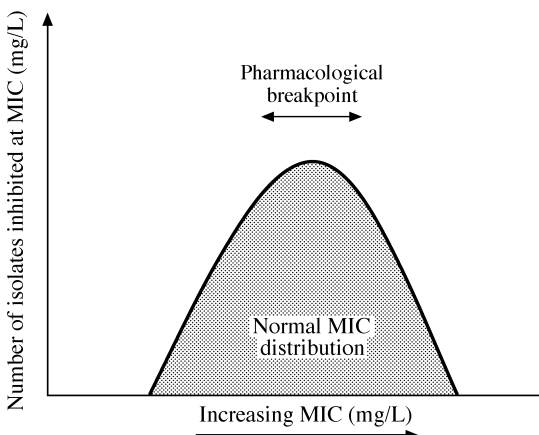


Figure 3. Impact of breakpoint on interpretation when the breakpoint falls in the middle of the MIC distribution.

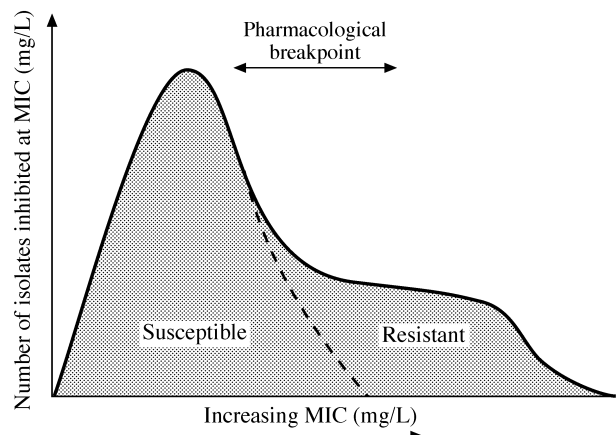


Figure 4. Impact of breakpoint on interpretation with overlapping MIC distribution.

well respond to therapy, while ‘wrongly’ being reported as resistant relative to breakpoints that have been optimized for other Enterobacteriaceae.

The Working Party recognize that susceptibility patterns to certain agents may change with time and place. This may mean that 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

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

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 BSAC formula, which by necessity is somewhat ‘rough and ready’, does encapsulate the various pharmacodynamic parameters. The area under the curve, essentially being an integration of serum concentration and time, is reflected by C_{\max} and t , and the ratio of peak concentration to MIC is also captured.

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 breakpoint is predicated on the fact that an organism designated as ‘susceptible’ should respond to the standard 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 NCCLS, having close links with the drug licensing authority, the FDA,² has a greater ability to ‘capture’ such clinical information more readily than does the UK (or any European) system.

The process of ‘setting’ a breakpoint

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 and the distribution of MICs (as shown in Figures 1–4) is determined. From the pharmacokinetics an initial breakpoint, with $s = 1$, can be determined. In the majority of cases only

Establishing MIC breakpoints

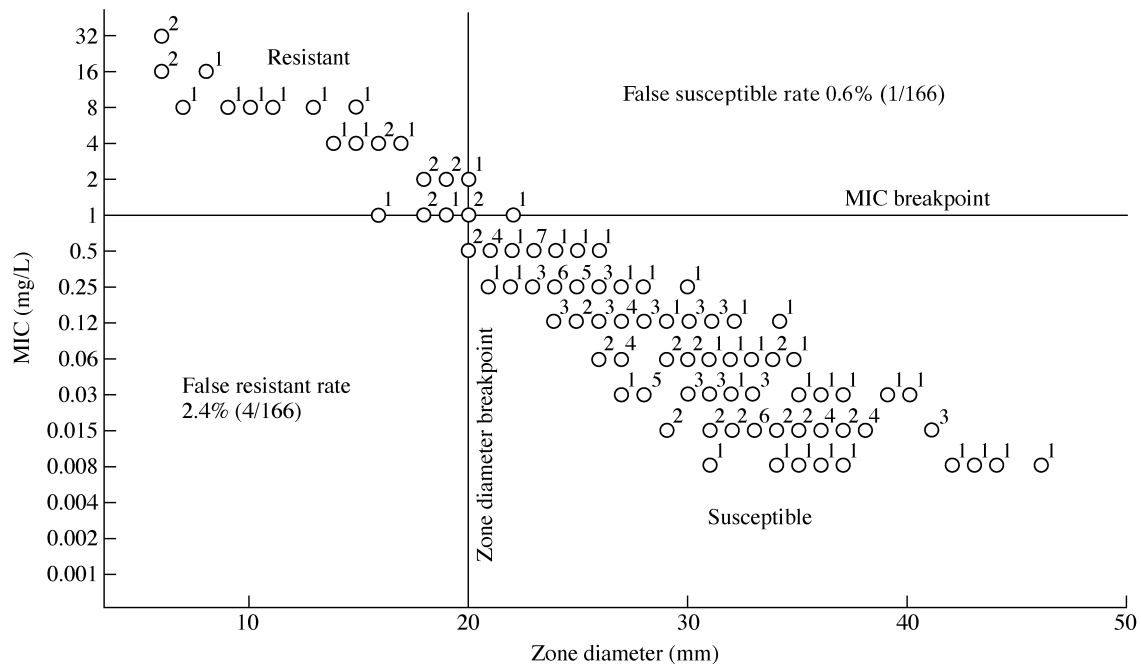


Figure 5. Standardized method of disc testing: scattergram of MICs against zone diameters.

a minor adjustment of s is required to account for the distribution of MICs.

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 & DeHaan⁸ 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

Increasing 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. The Working Party has not altered its original view and realizes that this may cause problems.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. The Working Party agrees that these arguments may not be sustainable in the case of many of the 'third-generation cephalosporins', where the least active compound may not be the best indicator of class resistance.

Future developments of the Working Party

It is interesting to compare the membership of the NCCLS and that of the BSAC Working Party. The former has considerable representation from both the FDA and the pharmaceutical and medical device industry. The BSAC has no formal input from the pharmaceutical industry, although the current membership does include such a member and two members from the medical device industry.

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

Agents	Dose	C _{max} (mg/L)	% protein binding	f	T (h)	t	s	Breakpoint concentration (mg/L)	
								susceptible ≤	resistant ≥
5.1.1 Penicillins ^{a,b,c}									
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}									
amoxicillin	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-pseudomonal penicillins									
piperacillin ± tazobactam ^e	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 and other β-lactams ^e									
Cephalosporins and cephamycins									
cefactor	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
cefpirrome	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

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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 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 β -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									
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	1.5 mg/kg	5	<10%	1	2	1	1	1	2
amikacin ^g	1.5 mg/kg	5	<10%	1	2.3	1	1	4	8
netilmicin	1.5 mg/kg	5	<10%	1	2.2	1	1	1	2
tobramycin	1.5 mg/kg	20	<10%	1	2.3	1	1	1	2
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
vancomycin	1 g iv	25	50	1	8	0.5	0.25	4	8
teicoplanin	400 g iv	60	90	0.5	90	0.5	0.25	4	8
quinupristin/dalfopristin	7.5 mg/kg iv	7	<70	1	1.5	1	1	2	4
linezolid	625 mg po	12	31	1	5	0.5	0.5	4	8
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	500 mg	2.5	40	1	4	0.5	1	1/2 ^k	2/4 ^k
gatifloxacin	400 mg	3.5	50	1	7.2	0.5	0.5	1	2

Table I. (Continued)

Agents	Dose	C _{max} (mg/L)	% protein binding	f	T (h)	t	s	Breakpoint concentration (mg/L)	
								susceptible \leq	resistant \geq
gemifloxacin	320 mg	1.1	60	1	7	0.5	0.25	0.25	0.5
levofloxacin	500 mg	5.5	30	1	7.4	0.5	0.75	2	4
moxifloxacin	400 mg	3.1	50	1	12	0.5	0.75	1	2
ofloxacin	400 mg	4.8	40	1	6	0.5	1	2	4

^aFor *H. influenzae* and *M. catarrhalis*, test for β -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.

^bFor enterococci use the breakpoints in Table II.

^cFor *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 β -lactam antibiotics, except in infections of the CNS.

^dMethicillin or oxacillin results are used to predict flucloroxacin susceptibility.

^eDo not report for methicillin-resistant staphylococci.

^fFor enterococci, breakpoints for high-level resistance are ≤ 512 mg/L for susceptible, ≥ 1024 mg/L for resistant.

^gFor staphylococci, a breakpoint of 4 mg/L implies susceptible, 8–16 mg/L intermediate and ≥ 32 mg/L resistant.

^hBreakpoints for *H. influenzae*; strains with MICs below the low breakpoint are susceptible; those with MICs above the high breakpoint are resistant, others are intermediate.

ⁱBreakpoint of ≤ 8 mg/L for staphylococci and streptococci.

^jRifampicin 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.

^kBreakpoints for *S. pneumoniae*.

In this respect, the BSAC is similar to other European groups. There are both benefits and drawbacks to this. Consensus can be achieved rapidly and free from commercial considerations. Conversely, lack of input from both regulatory and commercial realities may be to the detriment of the process. However, it is interesting to note that most European breakpoints tend to be more 'conservative' than those of the NCCLS.

The Working Party is currently considering the following.

- Increased input from industry
- A set protocol for the determination of tentative breakpoint MICs and zone diameters including:
 - (i) fixed costs for the Working Party to determine the values;
 - (ii) the ability to accept input from other parties.
- Regular re-evaluation of breakpoints in the light of increasing knowledge from pharmacodynamic studies.

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.II (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 The use of high and low breakpoints has been reduced and where possible, one value is now employed. 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.

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

Agents	Dose	C _{max} (mg/L)	% protein binding	f	T (h)	t	s	Breakpoint concentration (mg/L)	
								susceptible ≤	resistant ≥
5.1.1 Penicillins									
5.1.1.3 Broad-spectrum penicillins^a									
amoxicillin	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 and other β-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
cefprozime	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 β-lactams									
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	1.5 mg/kg	5	<10	1	2	1	1	1	2 ^b /8 ^c
amikacin	1.5 mg/kg	5	<10	1	2.3	1	1	4	8 ^b /32 ^c
netilmicin	1.5 mg/kg	5	<10	1	2.2	1	1	1	2 ^b /8 ^c
tobramycin	1.5 mg/kg	20	<10	1	2.3	1	1	1	2 ^b /8 ^c
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	1	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

Table II. (Continued)

Agents	Dose	C _{max} (mg/L)	% protein binding	f	T (h)	t	s	Breakpoint concentration (mg/L)	
								susceptible ≤	resistant ≥
5.1.12 Quinolones									
ciprofloxacin	500 mg	2.5	40	1	4	0.5	1	1	2 ^b /8 ^c
gatifloxacin	400 mg	3.5	50	1	7.2	0.5	0.5	1	2
gemifloxacin	320 mg	1.1	60	1	7	0.5	0.25	0.25	0.5
levofloxacin	500 mg	5.5	30	1	7.4	0.5	0.75	2	4
moxifloxacin	400 mg	3.1	50	1	12	0.5	0.75	1	2 ^b /8 ^c
ofloxacin	400 mg	4.8	40	1	6	0.5	1	2	4 ^b /16 ^c

^aRefers to iv doses only.^bBreakpoint for Enterobacteriaceae.^cBreakpoint for *Pseudomonas* spp.

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

	Group 1 Staphylococci, streptococci, <i>M. catarrhalis</i> , <i>H. influenzae</i>		Group 2 Enterobacteriaceae, <i>Pseudomonas</i> spp.	
	susceptible ≤	resistant ≥	susceptible ≤	resistant ≥
5.1.1 Penicillins				
benzylpenicillin ^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				
amoxicillin	1	2	8	16
ampicillin	1	2	8	16
co-amoxiclav	1	2	8	16
5.1.1.4 Anti-pseudomonal penicillins				
piperacillin ± tazobactam	2	4	16	32
ticarcillin ± clavulanate	2	4	16	32 ^b /128 ^c
5.1.2 Cephalosporins, cephamycins and other β-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
cefprome	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

Establishing MIC breakpoints

Table III. (Continued)

	Group 1		Group 2	
	Staphylococci, streptococci, <i>M. catarrhalis</i> , <i>H. influenzae</i>		Enterobacteriaceae, <i>Pseudomonas</i> 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	1	2	1 ^a	2 ^{b/8^c}
amikacin ^d	4	8	4	8 ^{b/32^c}
netilmicin	1	2	1	2 ^{b/8^c}
tobramycin	1	2	1	2 ^{b/8^c}
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	4	8	–	–
teicoplanin	4	8	–	–
colistin	4	8	4	8
quinupristin/dalfopristin	2	4	–	–
linezolid	4	8	–	–
5.1.8 Sulphonamides and trimethoprim				
trimethoprim	0.5	1	0.5	4
5.1.9 Anti-tuberculosis				
rifampicin	0.06	0.12	–	–
5.1.12 Quinolones				
ciprofloxacin	1/2 ^f	2/4 ^f	1	2
gatifloxacin	1	2	1	2
gemifloxacin	0.25	0.5	0.25	0.5
levofloxacin	2	4	2	4
moxifloxacin	1	2	1	2
ofloxacin	2	4	2	4 ^{b/16^c}

^aFor *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 β-lactam antibiotics, except in infections of the CNS.

^bBreakpoint for Enterobacteriaceae.

^cBreakpoint for *Pseudomonas* spp.

^dFor staphylococci, a breakpoint of ≤4 mg/L implies susceptible, 8–16 mg/L intermediate and ≥32 mg/L resistant.

^eBreakpoint for *H. influenzae*.

^fBreakpoint for *S. pneumoniae*.

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

	Group 1 Enterococci, staphylococci, streptococci		Group 2 <i>E. coli</i> , <i>Proteus</i> spp., coliforms, <i>Pseudomonas</i> spp.	
	susceptible ≤	resistant ≥	susceptible ≤	resistant ≥
Ampicillin	32	64	32	64
Co-amoxiclav	32	64	32	64
Cephalexin	32	64	32	64
Mecillinam	64 ^b	128 ^b	1	16
Fosfomycin	128	256	128	256
Nitrofurantoin	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

^aFor agents not listed, criteria given for systemic isolates may be used.

^bFor *S. saprophyticus*.

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