Harmonization of antimicrobial susceptibility testing breakpoints in Europe: implications for reporting intermediate susceptibility

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Harmonization of antimicrobial susceptibility testing breakpoints across Europe has resulted in the reintro-
duction of the intermediate susceptibility categorization into the BSAC susceptibility testing method for a wide
range of antibiotic pathogen test pairs. The implications of this, for laboratories and prescribers, are discussed.

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Historically, there have been multiple guidelines for antimicrobial susceptibility testing in Europe, often with different MIC breakpoints dividing organisms into categories of susceptibility. Consequently, the same organism causing similar infections in different countries might be reported as susceptible or resistant, depending on the guidelines followed. In the absence of differences in dosing, it is illogical to report different susceptibilities in different countries, and the differences make comparisons for surveillance purposes very difficult. In 2002 there was agreement among the active European national susceptibility testing committees to participate in a project to harmonize antimicrobial breakpoints, including previously established breakpoints. The committees involved were the British Society for Antimicrobial Chemotherapy, UK (BSAC), the CA-Comité de l’Antibiogramme de la Société Française de Microbiologie, France (CA-CAFM), the Commissie Richtlijnen Gevoeligheidsbepalingen, the Netherlands (CRG), the Deutsches Institut für Normung, Germany (DIN), the Norwegian Working Group on Antibiotics, Norway (NWGA), and the Swedish Reference Group of Antibiotics, Sweden (SRGA). This work is being undertaken by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which was set up by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) with the support and collaboration of the national susceptibility testing committees, and has been funded by ESCMID and the national committees with grant support from the European Union and, currently, the European Centre for Disease Prevention and Control (ECDC).

The harmonization process¹ involves comprehensive review of breakpoints and includes application of more recent techniques, such as pharmacodynamic analysis, and current data, where available, on susceptibility distributions, resistance mechanisms and clinical outcome related to in vitro tests. There is also extensive discussion within EUCAST and the national committees, and proposals are subject to wide consultation with national representatives of almost all European countries and with the pharmaceutical and susceptibility testing device manufacturers. The harmonization process has now been completed for all commonly used agents.²

For new agents submitted for licensing by the European Medicines Agency (EMEA), the setting of harmonized breakpoints is part of the licensing procedure and is covered by an EMEA Standard Operating Procedure that governs the process of setting breakpoints for new agents by EUCAST.³ Breakpoints for tigecycline, daptomycin and doripenem have been set through this process, and others are in progress.

In the wider interests of international standardization of susceptibility testing, and the need to update older breakpoints in the light of current knowledge, these developments are welcomed by all the participating national breakpoint committees. It is also highly desirable that EUCAST breakpoints are harmonized with the US Clinical and Laboratory Standards Institute (CLSI) breakpoints.⁴ However, progress in this direction is at present unlikely due to differences in the organizational structures and funding of CLSI and EUCAST, and the different relationships to regulatory authorities—EMEA in Europe and the Food and Drug Administration (FDA) in the USA.

The European breakpoints are incorporated into national methods as they are agreed. The implication of the harmonization process is that over time some MIC breakpoints will change and these changes will be reflected, where necessary, in corresponding changes to zone diameter breakpoints in disc diffusion methods. The BSAC standardized disc susceptibility testing method was published in 2001.⁵ Since then, various changes to the recommendations, including revision of breakpoints by EUCAST, have been included in annual updates in this journal and posted on the BSAC website.⁶ It is appreciated that changes in the method require additional work for laboratories in changing templates and laboratory information systems, but
the benefits of international standardization are considerable, and the review of some older breakpoints is undoubtedly warranted. The process of harmonization of clinical breakpoints by EUCAST is now complete and the vast majority of changes will be incorporated into the BSAC disc diffusion method by 2010.

Almost all of the harmonized susceptible breakpoints agreed to date are the same or only one dilution different from existing BSAC breakpoints. There will be some effects on percentages of susceptible isolates but in general these are small. However, there are a few exceptions where the impact is greater. For example, with previous BSAC breakpoints for ertapenem ($S \leq 2 \text{ mg/L}$, $R > 2 \text{ mg/L}$), 96.7% of isolates of Enterobacter spp. in the 2005 BSAC resistance surveillance programme would be reported susceptible; but with current harmonized breakpoints ($S \leq 0.5 \text{ mg/L}$, $R > 1 \text{ mg/L}$) only 79.8% are susceptible, 9.9% intermediate and 10.3% resistant. Most isolates with ertapenem MICs $> 0.5 \text{ mg/L}$ are derepressed AmpC producers or extended-spectrum $\beta$-lactase (ESBL) producers, and the MICs are significantly higher than those for wild-type isolates (MIC $< 0.06 \text{ mg/L}$). In the absence of evidence that isolates with MICs $> 0.5 \text{ mg/L}$ respond to therapy, the intermediate-resistant designation is appropriate. Conversely, with previous BSAC breakpoints for gentamicin ($S \leq 1 \text{ mg/L}$, $R > 4 \text{ mg/L}$), 57.4% of isolates of Pseudomonas aeruginosa in the 2005 BSAC resistance surveillance programme would be reported susceptible, 35.6% intermediate and 7.0% resistant; however, with current harmonized breakpoints ($S \leq 4 \text{ mg/L}$, $R > 4 \text{ mg/L}$) there is no intermediate category and 93.0% are susceptible. A breakpoint of 4 mg/L avoids splitting the wild-type susceptible population, which was a problem with the previous BSAC breakpoints.

One potential area of confusion accentuated with the harmonized breakpoints relates to more extensive use of the intermediate category based on EUCAST clinical breakpoints. In practice, some national committees, particularly the BSAC, have regarded the intermediate category as of limited value because of the implicit uncertainty of clinical response. Consequently, most intermediate and resistant categories have been combined and reported as resistant since the early 1990s. Prior to this, when the modified Stokes method was widely used for disc susceptibility testing in the UK, the intermediate category was routinely reported by British laboratories. The European harmonization process is resulting in some intermediate categories being reintroduced and it is important that clinicians and microbiologists should understand the meaning of intermediate susceptibility reports. In line with the European consensus and the recently agreed International Organization for Standardization (ISO) reference method for determination of MICs by broth microdilution, the clinical categories of susceptibility defined by EUCAST MIC breakpoints are: susceptible, a level of antimicrobial susceptibility associated with a high likelihood of therapeutic success; intermediate, a level of antimi crobial susceptibility associated with uncertain therapeutic effect; and resistant, a level of antimicrobial susceptibility that results in a high likelihood of therapeutic failure.

Classification of a potential pathogen into the intermediate category may be viewed in a number of ways. Most of these have equal validity but, in general, the preclinical or clinical evidence that an intermediate category has value is limited. This is in contrast to the clear clinical predictive value of susceptible and resistant categorization.

Intermediate susceptibility can be considered to have several meanings. First, it implies that an infection due to an isolate classified as intermediate may be appropriately treated in body sites where the drug is concentrated. The most obvious situation where this applies is in the urinary tract. The BSAC previously recognized the need for higher breakpoints for uncomplicated urinary tract infections by providing specific higher breakpoints for use in such infections. With the current EUCAST breakpoints the intermediate category may be regarded as susceptible for uncomplicated urinary tract infections. Given the not inconsiderable technical and pharmacokinetic issues in assessing antibiotic penetration into most tissues it would be advisable not to take a similar approach with other tissues, e.g. antibiotics that are concentrated in lung extracellular lining fluid (ELF) or alveolar macrophages (AMs). In addition, although all susceptible breakpoints are set using serum-based pharmacokinetic and pharmacodynamic targets, they appear highly predictive for tissue-based infection in most circumstances.

The second use of the intermediate category is to warn prescribers that if they wish to use the drug in question then it will have to be given at a larger (at least double) dose if a standard dosing frequency is being used. Alternative approaches to therapy of infections caused by pathogens classified as intermediate to $\beta$-lactams (or agents where the relevant pharmacodynamic parameter is time over MIC) would be to give the same dose more frequently or give the same dose by prolonged or continuous infusion. However, even if these novel dosing strategies are adopted, the target pathogens are still likely to have borderline MIC values for the agent in question, so increasing the risk of selection of resistance. In addition, strains with borderline MICs due to efflux resistance mechanisms may respond differently to a dose increase compared with those with varied MICs related to target site modification or enzyme production.

A preferable approach may be to use an antibacterial agent for which the strain has a wild-type MIC well below the clinical breakpoint. This approach should certainly be employed with vancomycin-intermediate Staphylococcus aureus, where existing evidence would not support high-dose vancomycin as a suitable therapy for strains with MICs $\geq 2 \text{ mg/L}$. A more controversial approach would be to treat the infection by combining a drug classified as intermediate with a second agent. This approach is largely without evidence and cannot be recommended, as the clinical evidence for combination antibiotic therapy improving infection outcomes is poor and adverse event rates are increased.

The final, and for some perhaps the most compelling, justification for the intermediate category is that it provides a buffer zone that should prevent small uncontrolled but inevitable technical factors from causing major discrepancies in interpretation, i.e. ‘$S$ to $I$’ or ‘$R$ to $I$’ rather than ‘$S$ to $R$’ or ‘$R$ to $S$’.

Different emphasis is placed on the meaning of the intermediate category in different guidelines, but however the category is used it is important that clinicians understand what is meant by ‘intermediate’ in a laboratory report. Diagnostic laboratories wishing to retain simple susceptible or resistant reporting may consider combining susceptible and intermediate results for urinary tract isolates and reporting them as susceptible, and combining intermediate and resistant results for pathogens from other sites and reporting them as ‘non-susceptible’. However, the recent approaches to setting breakpoints used in...
the harmonization process give greater confidence in the breakpoints and in use of the intermediate category.

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References