

Harmonization of Antimicrobial Breakpoints in Europe – Can It Be Achieved?

Abstract

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is convened by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and supported by representatives of almost all European countries. It is financed by ESCMID, the European Union, and the national breakpoint committees of France, Germany, Norway, Sweden, the Netherlands, and the United Kingdom. The Committee has recently published harmonized European breakpoints for aminoglycosides, fluoroquinolones, glycopeptides, and linezolid and is currently addressing aztreonam, carbapenems and cephalosporins. EUCAST has recognized the inconsistencies between clinical breakpoints primarily aimed at predicting better (susceptible) versus worse (resistant) outcome and epidemiological cutoff values for early detection of antimicrobial resistance development. EUCAST clinical breakpoints are based primarily on pharmacokinetic-pharmacodynamic relationships but do take into account other factors, such as differences in dosing regimens, toxicology, resistance mechanisms, clinical outcome data, and wild-type MIC distributions. EUCAST has devised a system for collecting MIC distributions of wild-type bacteria and for setting epidemiological cutoff values. The output of EUCAST is freely available via the EUCAST website (www.euCAST.org).

Several different guidelines for antimicrobial susceptibility testing are used in European countries. This was highlighted some years ago with the introduction of the European Antimicrobial Resistance Surveillance System (EARSS), which organizes surveillance of resistance in bacteria causing invasive infections in 28 countries (www.earss.rivm.nl). To the best of our knowledge, there are seven internationally recognized committees defining antimicrobial minimum inhibitory concentration (MIC) breakpoints used in European countries for categorizing bacteria and fungi into susceptible (S), intermediate (I), and resistant (R). In alphabetical order, these are the BSAC (British Society for Antimicro-

bial Chemotherapy Working Party on Antimicrobial Susceptibility Testing, United Kingdom) (1), CA-SFM (Comité de l'Antibiogramme de la Société Française de Microbiologie, France) (2), the Commissie Richtlijnen Gevoeligheidsbepalingen, The Netherlands (3), DIN (Deutsches Institut für Normung, Germany) (4), NCCLS (National Committee for Clinical Laboratory Standards, United States) (5), Norwegian Working Group on Antimicrobials, Norway (6), and the SRGA (Swedish Reference Group of Antibiotics, Sweden) (7). The origins of these groups go back to the 1960s and 1970s. Their output is provided as professional recommendations, but occasionally, national agencies and/or programs (accreditation, quality assessment) may convert some aspects into "rules and regulations." The formal authority generally rests with national health authorities and/or drug evaluation agencies, such as the Food and Drug Administration (FDA) in the U.S., national agencies in Europe, and more recently, the European Medicines Evaluation Agency (EMA). The FDA and EMA are required to determine breakpoints as part of the process for registering new drugs, so official breakpoints are determined early in the life of a drug. The professional breakpoint committees usually address the breakpoints for a new drug at a later stage, often several months later, and consequently, breakpoints may be different from those set by the national agencies. The European national committees are appointed by national medical societies and are bodies of specialists, most often in clinical microbiology and infectious diseases but also in other specialties. A few committees also have representatives from industry. Each of the committees consists of 10 to 15 members. Apart from determining antimicrobial breakpoints, all are involved in educational aspects of antimicrobial use and susceptibility testing. Some of them (BSAC, DIN, CA-SFM, and SRGA) support complete "systems" of antimicrobial susceptibility testing, publishing not only MIC breakpoints, but also zone diameter breakpoints for diffusion methods, together with detailed recommendations on methodology and quality assurance. Sever-

al committees are involved in national surveillance of antimicrobial resistance and in external quality assurance programs. The Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have formed a joint committee addressing antifungal chemotherapy, the Nordic Reference group on Methods in Medical Mycology (www.srga.or/svamp/index.html). The different national committees have certainly influenced one another, but until recently, there has been no formal attempt to harmonize their output. Thus, Europe has at least seven different sets of antimicrobial breakpoints and a wealth of methods and abundant versions thereof. The introduction of automated systems has had little if any harmonizing effect, as the manufacturers feel obliged to comply with customer demands regarding national breakpoints.

ESCMID and EUCAST

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) (www.escmid.org) set up the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 1997. The committee was formed with a representative from each European country and six representatives from industry but with no formal relationship to the national breakpoint committees. Since the national breakpoint committees were not involved in EUCAST, they independently continued to do what they had always done. Europe then had the EUCAST guidelines in addition to the six active national committee recommendations and in some countries a substantial following for NCCLS. In the spring of 2002, EUCAST was restructured, and the major responsibility for the professional output of EUCAST was given to the active national breakpoint committees in Europe. A steering committee, consisting of representatives from each of the national breakpoint committees, two representatives of the EUCAST General Committee (which has a representative from each European country), a scientific secretary, and a chairperson, was formed. A new decision-making process was agreed on whereby tentative decisions made by the steering

committee and the national breakpoint committees are distributed for consultation to the EUCAST General Committee, to affiliated groups, and to industry. The final decision is taken by consensus in the steering committee, taking into account any comments made during the consultation process. In this way, the considerable expertise and traditions of the national breakpoint committees are utilized, and the national committees take responsibility for implementation of the decisions made by EUCAST.

EUCAST is funded by ESCMID, the national breakpoint committees, and, for the next 3 years, by a grant from the Directorate General for Health and Consumer Affairs of the European Union. Industry does not contribute financially, but industry members are asked to supply the committee with the data needed for determining breakpoints for new and existing antimicrobials, to give opinions on interpreting data, and to comment on proposed breakpoints.

Following the restructuring in 2002, EUCAST has achieved several goals. All national committees have agreed to express breakpoints in a common format, as $S \leq$ and $R >$, which is also the format chosen by EMEA. A series of documents on methodological aspects, terminology, the determination of MIC values in bacteria and fungi, breakpoints, etc., have been published in *Clinical Microbiology and Infection* and are now available on the EUCAST website (www.euCAST.org) (8–15). The website was created for the publication of EUCAST breakpoint tables, recommendations, news, and all other aspects of EUCAST activity. The concept of “epidemiological cutoff values,” sometimes called “species-specific microbiological breakpoints” (16), for the sensitive and early detection of phenotypic resistance development has been described (17) and implemented for four classes of drugs (aminoglycosides, fluoroquinolones, glycopeptides, and oxazolidinones). A website for the collection of large quantities of species-specific MIC distributions has been constructed, and software to collect and present these on the internet has been developed (see below). The clinical breakpoints for aminoglycosides, fluoroquinolones, glycopeptides, and linezolid have been re-evaluated, and the harmonized breakpoints have been published after a new procedure for harmonizing breakpoints for existing drugs was followed. Furthermore, a procedure for determining breakpoints for new drugs has

been developed and is currently available for comment on the EUCAST website. Together with EMEA and industry, a standard operating procedure (SOP) for this is being developed. The SOP will describe the formal role of EUCAST in determining breakpoints for new drugs and will allow it to be involved at an early stage in the registration process for new drugs.

EUCAST rationale for determining antimicrobial breakpoints for new and existing drugs

It must be recognized that the process for establishing antimicrobial breakpoints is a compromise among clinical, epidemiological, and methodological aspects. The perfect antimicrobial breakpoint (i) has clinical value, i.e., there is a correlation between categorization as “susceptible” and therapeutic success and between “resistance” and clinical failure; (ii) has epidemiological value, i.e., the breakpoint will distinguish between microorganisms lacking acquired or mutational mechanisms of resistance and microorganisms with resistance mechanisms; and (iii) allows reproducible susceptibility testing in the laboratory. Rarely is it possible to achieve these goals simultaneously with only a single breakpoint. EUCAST has recognized this and differentiates between clinical breakpoints, which are aimed primarily at predicting better versus worse outcomes and epidemiological cut-off values, which are aimed primarily at early detection of resistance. EUCAST has placed considerable emphasis on ensuring that the clinical breakpoint allows reproducible susceptibility testing of important target microorganisms, and in order to achieve this, the breakpoint must not divide wild-type MIC distributions of major target microorganisms.

In recent years, the measurement of resistance and resistance development has increased in importance. Investigation and description of the forces driving antimicrobial resistance development and intervention programs designed to influence the rates of resistance require breakpoints that correctly separate microorganisms with and without resistance mechanisms. For this reason, EUCAST aims not only to harmonize clinical breakpoints for Europe but also to develop a set of breakpoints for epidemiological use (17). These epidemiological breakpoints are referred to as epidemiological cutoff values so that they are

not confused with clinical breakpoints. The effects of using the latter were recently investigated by applying them to the EARSS database (18). The differences in resistance rates as measured by the various clinical breakpoints were at times pronounced. The single epidemiological breakpoints were not contentious and clearly indicated strains with resistance mechanisms. With *Escherichia coli* and ciprofloxacin, various clinical breakpoints gave resistance rates of 3.9 to 8.3%, whereas the epidemiological cut-off value gave a microbiological resistance rate of 12%; with *Streptococcus pneumoniae* and erythromycin, various clinical breakpoints gave resistance rates of 16.0 to 24.1%, and the epidemiological cut-off value gave a microbiological resistance rate of 24.1%. Both clinical breakpoints and epidemiological cut-off values are available on the EUCAST website.

The setting of breakpoints for clinical categorization of microorganisms is largely, but not exclusively, based on scientific considerations. Factors with a sound scientific basis are microbiology (drug activity against target species, resistance mechanisms and their effect on MIC values and clinical outcome, and methodological factors, such as inoculum density), pharmacology and toxicology (and their constraints on dosing and the variation of pharmacokinetic properties in the patient population intended for treatment), and pharmacokinetic-pharmacodynamic relationships. Other factors are less scientific and include the effect a decision may have on antibiotic policies and clinicians' choice of drugs, on economy (for individual patients, for society, in reimbursement systems, and for manufacturers), whether there are viable alternatives, and the “level playing field,” i.e., the fairness of a breakpoint decision in relation to other drugs in the same class. Breakpoint committees need to change their original decisions, resulting in an evolution of antimicrobial breakpoints.

Antimicrobial breakpoints need to evolve

A formal process is lacking by which the breakpoints for a drug or a class of drugs are re-evaluated either at intervals or when a new class member is presented for registration. Factors such as evolving therapeutic indications and practices, new resistance mechanisms, changing dosages, new pharmacokinetic knowledge, and the need to evaluate older compounds within a

class of antimicrobials as new compounds are introduced emphasize the need for antimicrobial breakpoints to evolve. However, the evolution of breakpoints is painful because (i) a multitude of documents need to be amended, distributed, and implemented by authorities, manufacturers, and laboratories; (ii) manufacturers of antimicrobial susceptibility testing devices need to make alterations to media, dilutions, algorithms, package inserts and manuals, and interpretive criteria in automated systems; (iii) laboratories across the world need to implement the new breakpoint in their antimicrobial susceptibility testing systems, sometimes having to wait for the manufacturer of an automated system to make the necessary (and sometimes expensive) changes – laboratory manuals, SOPs, and computer systems also need to be updated; (iv) the education of clinicians, medical students and laboratory personnel is affected; and (v) the rates of antimicrobial resistance in resistance surveillance programs are often affected, sometimes drastically, by a change in a breakpoint. This was recently demonstrated when a single change in the NCCLS cefotaxime breakpoint for *S. pneumoniae* brought the overall cefotaxime resistance rates in 2001 down from 24.9% to 16.0% for a large set of data (19).

The FDA, EMEA, and national medicine evaluation agencies are required to define breakpoints as part of the registration process for a new drug. However, they are not required to re-evaluate breakpoints unless formally requested to do so, and in practice, that is likely to happen only when there is a request for a higher breakpoint than that originally set by the agency. When breakpoint committees, lacking the legal constraint of the “agencies,” decide to re-evaluate breakpoints, it usually results in a lowering, not raising, of the breakpoints. In doing so, the committees are aware that the amount of work involved is quite daunting.

EUCAST procedure for setting breakpoints

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 commit-

tees 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 (20). The theoretical breakpoint is compared with existing breakpoints (if breakpoints already exist) set by the national committees, including the NCCLS, 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.

Wild-type distributions and epidemiological cut-off values

When comparable methodologies are used, the MIC distribution for any given drug for the wild-type population of any given microbial species is the same worldwide. The proportion of organisms no

longer belonging to the wild type (microorganisms with acquired or mutational resistance) varies considerably and is, for many organism-antimicrobial combinations, increasing all over the world. The fact that the MIC distribution for a wild-type microorganism is the same irrespective of when and where in the world the microorganisms were collected and irrespective of whether the strains are of human or veterinary origin is fundamental for setting epidemiological cut-off values. The typical MIC distribution for wild-type organisms covers three to four twofold dilution steps, e.g., for penicillin and *S. pneumoniae*, MICs of wild-type organisms range from 0.016 to 0.064 $\mu\text{g/ml}$ (Fig. 1); for ciprofloxacin and *E. coli*, from 0.04 to 0.032 $\mu\text{g/ml}$ (Fig. 2); for vancomycin and *Staphylococcus aureus*, from 0.5 to 2 $\mu\text{g/ml}$; and for fluconazole and *Candida albicans*, from 0.064 to 0.5 $\mu\text{g/ml}$. Definition of the MIC distributions for wild-type microorganisms by collecting large volumes of MIC data from all over the world has several benefits and is one of the tasks EUCAST has prioritized, the benefits include the following: (i) availability of defined wild-type MIC distributions permits the setting of breakpoints that do not divide the wild-type distributions, which would preclude reproducibility of susceptibility testing; (ii) wild-type MIC distributions are used to define epidemiological cutoff values (microbiological breakpoints) that separate the wild-type from the non-wild-type microorganisms; (iii) the aggregated wild-type MIC distributions provide a downloadable reference for the individual investigator, laboratory, manufacturer of susceptibility testing devices, pharmaceutical company, etc., who need to calibrate a susceptibility testing system or product; and (iv) wild-type MIC distributions provide a public reference to the expected MIC value of a particular drug for a particular organism that has not developed resistance to the drug in question. EUCAST has undertaken the task of collection and public display on the Internet of aggregated species- and drug-specific MIC distributions. (For further description of the concept of MIC distributions of wild-type bacteria, see www.eucast.org and reference 17). The epidemiological cut-off values can be applied to species-specific MICs (18) or inhibition zone diameter distributions (21) of strains collected in antimicrobial resistance surveillance programs or be included in the software of automated susceptibility testing devices.

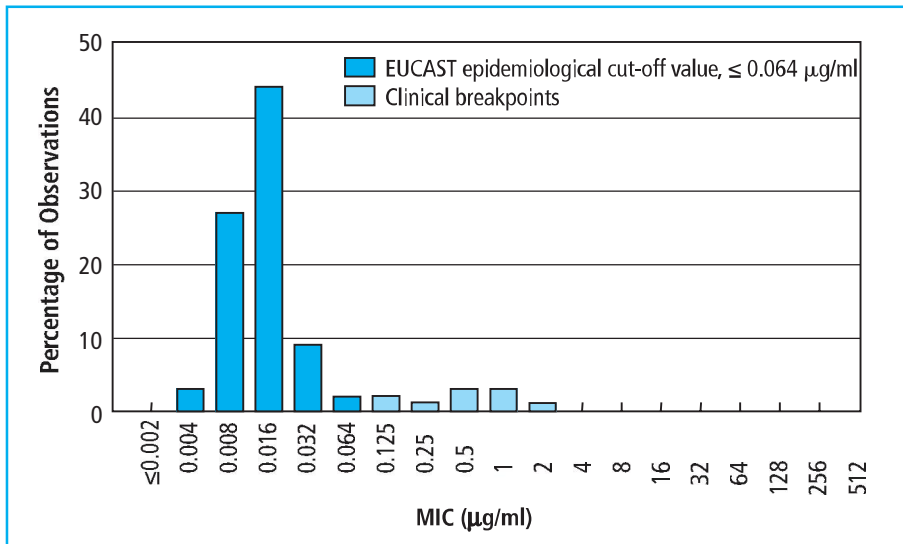


Figure 1. Benzylpenicillin-*Streptococcus pneumoniae* antimicrobial wild-type distributions of microorganisms – reference database EUCAST^a ^a 6,142 observations (13 data sources)

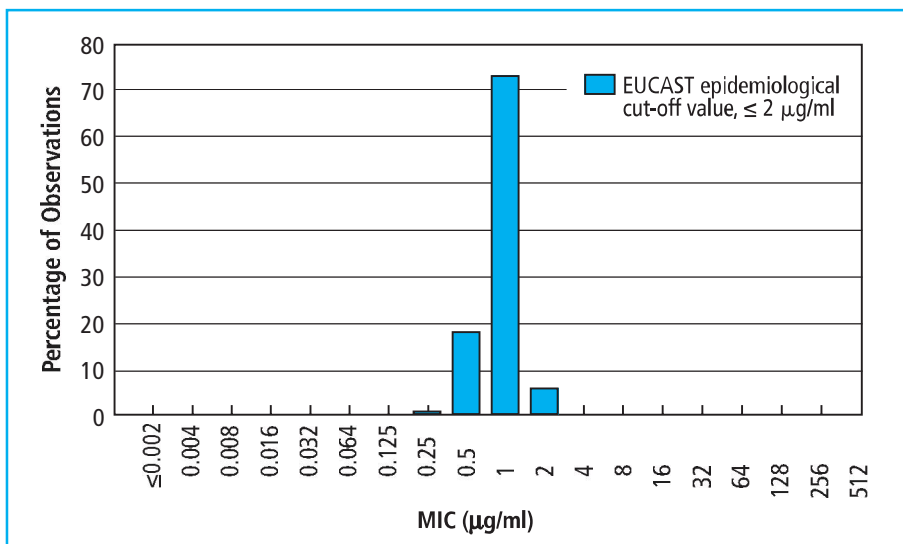


Figure 2. Vancomycin-*Staphylococcus aureus* antimicrobial wild-type distributions of microorganisms – reference database, EUCAST^b ^b 48,036 observations (17 data sources)

EUCAST and NCCLS

While there is no formal decision-making relationship between EUCAST and the NCCLS, the former and current chairmen of EUCAST have served since 1999 as formal Advisors to the NCCLS Subcommittee on Antimicrobial Susceptibility Testing. Also, there is an increasing tendency to share data and views on breakpoint setting. EUCAST, while harmonizing European breakpoints for existing drugs, tries to avoid making decisions that will generate new minor differences between the breakpoints of the two committees. Through initiatives in CEN (the European Standards

Organisation) and ISO (International Standards Organisation), the two groups are jointly involved in describing an international reference method for determining MIC values for non-fastidious microorganisms.

Achievement of harmonization of antimicrobial breakpoints in Europe

The European harmonization process now seems well on its way. Strategically important steps concerning the relationship between EUCAST on one hand and the

European Union, EMEA, and European programs for antimicrobial resistance surveillance on the other have been taken. However, for the process to be successful, antimicrobial MIC breakpoints need to be implemented. Implementation of the EUCAST breakpoints currently rests with the national breakpoint committees and with manufacturers of those commercially available systems that could implement EUCAST breakpoints in their interpretative software. Ultimately, the success of the European process will be in the hands of European microbiologists, but microbiologists in other countries should also be familiar with the process involved.

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