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, toxicity, 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.earrs.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 Antimicrobial 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 Commisie Richtlijnen Gevoeligheidsbepalingen, The Netherlands (3), DIN (Deutsches Institut fur 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 (EMEA). The FDA and EMEA 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. Several 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.org/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 consulta-
tion to the EUCAST General Committee, to affiliated groups, and to industry. The final
decision is taken by consensus in the steer-
ing committee, taking into account any
comments made during the consultation
process. In this way, the considerable ex-
pertise and traditions of the national
breakpoint committees are utilized, and
the national committees take responsi-
bility 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 Direc-
torate General for Health and Consumer
Affairs of the European Union. Industry
does not contribute financially, but indus-
try members are asked to supply the com-
mittee with the data needed for determin-
ing breakpoints for new and existing an-
timicrobials, to give opinions on interpret-
ing data, and to comment on proposed
breakpoints.

Following the restructuring in 2002,
EUCAST has achieved several goals. All na-
tional committees have agreed to express
breakpoints in a common format, as ≤S and
R>, which is also the format chosen by
EMEA. A series of documents on method-
ological aspects, terminology, the deter-
mination of MIC values in bacteria and fun-
gi, 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 pheno-
typic resistance development has been de-
scribed (17) and implemented for four
classes of drugs (aminoglycosides, fluoro-
quinoles, glycopeptides, and oxazolidi-
ones). 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 be-
low). The clinical breakpoints for aminoo-
glycosides, fluoroquinolones, glycopep-
tides, and linezolid have been re-evaluat-
ed, 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. To-
gether 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 in-
volved 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 pro-
cess for establishing antimicrobial break-
points is a compromise among clinical,
epidemiological, and methodological as-
pects. The perfect antimicrobial break-
point (i) has clinical value, i.e., there is a
relation between categorization as
“susceptible” and therapeutic success and
between “resistance” and clinical failure;
(ii) has epidemiological value, i.e., the
breakpoint will distinguish between mi-
croorganisms lacking acquired or muta-
tional mechanisms of resistance and mi-
croorganisms with resistance mechanisms;
and (iii) allows reproducible susceptibility
testing in the laboratory. Rarely is it possi-
ble to achieve these goals simultaneously
with only a single breakpoint. EUCAST has
recognized this and differentiates between
clinical breakpoints, which are aimed pri-
marily at predicting better versus worse
outcomes and epidemiological cut-off val-
es, which are aimed primarily at early de-
tection 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 mi-
croorganisms.

In recent years, the measurement of
resistance and resistance development has
increased in importance. Investigation and
description of the forces driving antimicro-
bial resistance development and interven-
tion 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 har-
monize clinical breakpoints for Europe but
also to develop a set of breakpoints for
epidemiological use (17). These epidemi-
ological breakpoints are referred to as epi-
demiological cutoff values so that they are
not confused with clinical breakpoints. The
effects of using the latter were recently in-
vestedigated by applying them to the EARS
database (18). The differences in resist-
ance rates as measured by the various clin-
ical 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 epidemiologi-
cal 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 resis-
tance rate of 24.1%. Both clinical break-
points and epidemiological cut-off values
are available on the EUCAST website.

The setting of breakpoints for clinical
categorization of microorganisms is large-
ly, but not exclusively, based on scientific
considerations. Factors with a sound scien-
tific basis are microbiology (drug activity
against target species, resistance mecha-
nisms and their effect on MIC values and
clinical outcome, and methodological
factors, such as inoculum density), phar-
macology and toxicology (and their con-
straints on dosing and the variation of
pharmacokinetic properties in the patient
population intended for treatment), and
pharmacokinetic-pharmacodynamic rela-
tionships. 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 pa-
tients, for society, in reimbursement
systems, and for manufacturers), whether
there are viable alternatives, and the “level
playing field,” i.e., the fairness of a break-
point decision in relation to other drugs in
the same class. Breakpoint committees
need to change their original decisions, re-
sulting 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 ther-
aputic indications and practices, new re-
sistance 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 anti-
microbial breakpoints to evolve. However, the evolution of breakpoints is painful because (i) a multitude of documents need to be amended, distributed, and imple-
mented by authorities, manufacturers, and laboratories; (ii) manufacturers of antimicro-
bial susceptibility testing devices need to make alterations to media, dilutions, algorithms, package inserts and manuals, and interpretive criteria in automated sys-
tems; (iii) laboratories across the world need to implement the new breakpoint in their antimicrobial susceptibility testing systems, sometimes having to wait for the manu-
facturer of an automated system to make the necessary (and sometimes expen-
sive) changes – laboratory manuals, SOPs, and computer systems also need to be up-
dated; (iv) the education of clinicians, medical students and laboratory personnel is affected; and (v) the rates of antimicro-
bial resistance in resistance surveillance programs are often affected, sometimes drasti-
cally, 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 un-
less 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 re-
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 exist-
ing antimicrobials. Before harmonizing breakpoints for existing drugs, it is impor-
tant to determine whether the breakpoint differences can be explained by differences in dosing, chemical formulations, clinical indications, or target organisms. There-
fore, 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 theoret-
ical 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 in-
stances, 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 break-
point committees is distributed according to the formal consultation process de-
scribed above. The final decision is taken by the EUCAST steering committee, and a table of breakpoints for the class of antimici-
robial 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 break-
points are posted. Implementation of the new breakpoints rests with the national break-
point 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 world-
wide. The proportion of organisms no longer belonging to the wild type (micro-
organisms with acquired or mutational resistance) varies considerably and is, for many organism-antimicrobial combina-
tions, increasing all over the world. The fact that the MIC distribution for a wild-
type microorganism is the same irrespec-
tive of where and where in the world the microorganisms were collected and irre-
respectively of whether the strains are of hu-
man 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 organ-
isms range from 0.016 to 0.064 μg/ml (Fig. 1); for ciprofloxacin and E. coli, from 0.04 to 0.032 μg/ml (Fig. 2); for van-
comycin and Staphylococcus aureus, from 0.5 to 2 μg/ml; and for fluconazole and Candida albicans, from 0.064 to 0.5 μg/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 in-
clude the following: (i) availability of de-
fined wild-type MIC distributions permits the setting of breakpoints that do not di-
vide the wild-type distributions, which would preclude reproducibility of suscepti-
bility testing; (ii) wild-type MIC distribu-
tions are used to define epidemiological cutoff values (microbiological break-
points) 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 distribu-
tions provide a public reference to the expected MIC value of a particular drug for a particular organism that has not devel-
oped resistance to the drug in question. EUCAST has undertaken the task of collect-
ion and public display on the Internet of aggregated species- and drug-specific MIC distribu-
tions. (For further description of the concept of MIC distributions of wild-
type bacteria, see www.eucast.org and refer-
ence 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 pro-
grams or be included in the software of automated susceptibility testing devices.
EUCAST and NCCLS
While there is no formal decision-making relationship between EUCAST and the NCCLS, the former and current chairman 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 Organization) 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.

References


ESCIMID School of Clinical Microbiology and Infectious Diseases

Szeged, Hungary, 25 June – 2 July 2005

A one-week course dedicated to postgraduate and continuous medical education. The programme covers most of the relevant topics in clinical microbiology and infectious diseases, thus being of particular interest to young MDs at the end of their specialty training as well as those wishing to broaden their professional knowledge. By providing short reviews and well-selected case studies, the ESCMID School helps the students to prepare for their examination.

For details and registration see the ESCMID homepage at www.escmid.org, ESCMID School.

Organised by the ESCMID Education Committee under the auspices of the University of Szeged