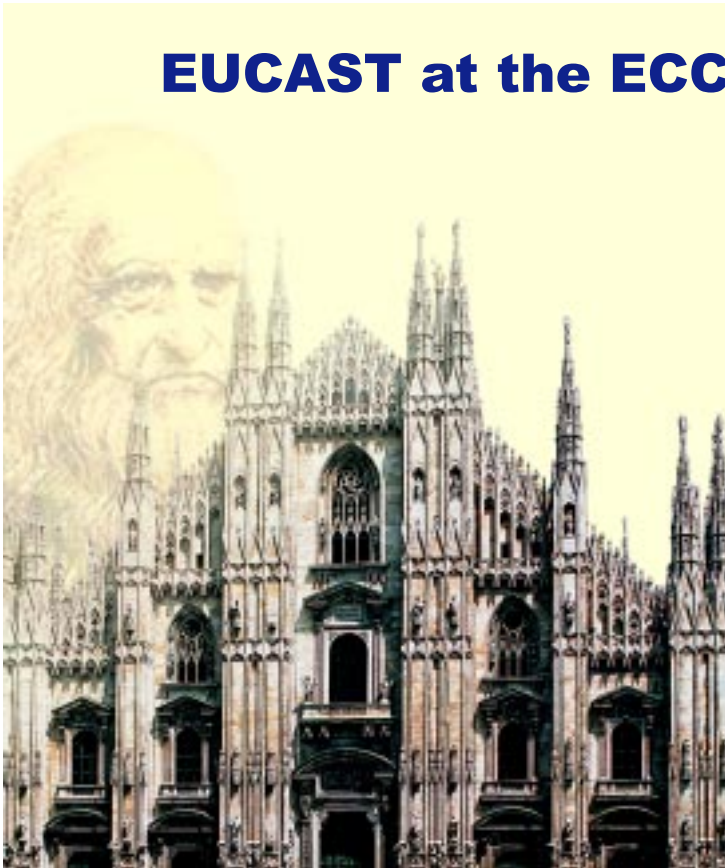




No. 4, February 2002

N **EUCAST** *Newsletter*

EUCAST at the ECCMID 2002 in Milan



Meeting of the Main Committee

The next meeting of the EUCAST Main Committee will be held at the 12th ECCMID in Milan on **Friday, April 26, from 11.00-13.00 in room A6 at the Fiera Milano**

This is immediately following the EUCAST workshop in the same room. The committee meeting is an open meeting; observers are welcome.

EUCAST Workshop

EUCAST has organised a workshop on breakpoints in susceptibility testing to be held on **Friday, April 26, from 10.00-11.00 in room A6 at the Fiera Milano**

Pharmacodynamic or epidemiological breakpoints for susceptibility testing?

Chairman: Dr. Johan Mouton, Nijmegen, The Netherlands

- ☛ **Pharmacodynamic breakpoints for susceptibility testing**
Dr. Alasdair MacGowan
Bristol, United Kingdom
- ☛ **Epidemiological breakpoints for susceptibility testing**
Dr. Gunnar Kahlmeter
Växjö, Sweden

New EUCAST Chairman



Gunnar Kahlmeter MD, PhD, took over the chair of EUCAST from Ian Phillips after the ECCMID in Istanbul last year.

A clinical microbiologist educated at the University of Lund, Sweden, and a lecturer of the medical faculties of Lund University and Uppsala University in Sweden, he is currently head of the Department of Clinical Microbiology at Central Hospital in Växjö, Sweden. He is an official advisor to the Swedish Institute for Infectious Disease Control and heads the Swedish external reference laboratory on susceptibility testing and resistance surveillance in Växjö.

Dr. Kahlmeter has been the chairman of the SRGA-M (Swedish Reference Group of Antibiotics Methodology subcommittee) since 1986. He has been the webmaster of the SRGA web-page (www.srga.org) since it was started in 1996 and has published in the fields of pharmacokinetics, antimicrobial susceptibility testing, antimicrobial resistance surveillance and quality assurance.

He is married and has three children aged 23, 21 and 17. Major interests outside MIC distributions and zone diameter histograms are music, sailing and skiing.

The Future of EUCAST

The future of EUCAST has not yet been decided. The board of ESCMID has asked us to use one year to try to find a way forward for EUCAST. We were asked to come up with a proposal for a future EUCAST in time for the ECCMID in Milan, April 2002. I am happy that Derek Brown has agreed to stay on as the EUCAST Scientific Secretary.

Our starting point was the recurring question: Why not give up EUCAST and subscribe to the NCCLS way of doing things? While links with the NCCLS are to be strongly encouraged and may eventually lead to a unified approach to susceptibility testing, there are the two major reasons for wanting a European breakpoint committee:

- ◆ Europe should not relinquish the academic process involved in setting breakpoints.
- ◆ Although many countries in Europe have neither experience in setting breakpoints nor national breakpoint committees, several countries do (including France, Germany, Norway, Spain, Sweden, Netherlands, and the UK). During the last 6 months I have visited almost all the national groups. It is clear that, unless Europe can form a common strategy for the future, based on the work and experience of the national committees, the national breakpoint committees will continue their work as before and we will be no closer to a common European strategy.

Another important question was, "Why do the existing breakpoint committees and/or reference groups on antibiotics (such as

BSAC in the UK, CRG in the Netherlands, DIN in Germany, MENSURA in Spain, NWGA in Norway, SFM in France, SRGA in Sweden) take little or no interest in what is going on in EUCAST?" There are several reasons:

- ◆ They feel little ownership;
- ◆ They already have a lot to do and their time and resources are limited;
- ◆ There is a lot of hard work and quite a few compromises to be made if we shall embark on creating a common "European system". That work must be done and those compromises made by the existing European national groups, which means that the responsibility for this and the power to do it must be given to the national groups.

Considering the importance of having the national breakpoint committees involved in the future of EUCAST, I have spent one day with each of the breakpoint committees of Europe. So far (February 2002), I have visited Sweden (that was handy), the Netherlands, France, the United Kingdom and Norway. I have had discussions with representatives of Germany and Austria. Each of the breakpoint committees have summarised their views in writing. Also, the views of the representatives of the European Antimicrobial Resistance Surveillance System (EARSS) have been sought, and the pharmaceutical industry and device manufacturers will be invited to give their opinions in time for the annual general meeting in Milan.

The Future of EUCAST continued

The ESCMID board was given a verbal report in December 2001 and will receive a full report at the end of February 2002. This report will contain a proposal that will be based on the discussions with the national groups and others.

It is hoped that we can find a way forward and that this proposal will contain European breakpoints, a European system for quality assurance in which all laboratories can be encouraged to take part, and a logical tie-up between breakpoints, quality assurance and surveillance of antimicrobial resistance in Europe.

Our next meeting will take place at the ECCMID in Milan at the end of April. By then, it is hoped that all national breakpoint committees and all national representatives and the representatives of pharmaceutical industry and device manufacturers on EUCAST will have an outline of a proposal for a future EUCAST.



Gunnar Kahlmeter, EUCAST Chairman

EUCAST Subcommittees

Most of the subcommittees were set up to produce documents covering specific areas of antimicrobial susceptibility testing. Several of the subcommittees have produced documents that have been or are soon to be published in CMI, so the work of these groups is close to completion. Membership of subcommittees includes those with specific expertise in the particular areas, and to some extent, broad representation of different national groups was encouraged. Further details of the subcommittees are available on the EUCAST section of the ESCMID website (www.escmid.org). Published documents are also available on the website in pdf format.

Subcommittees: Coordinators:

Terminology	Prof. Ian Phillips Calle Cabello 7 Malaga 29012 SPAIN E-mail: iphillips@attglobal.net	The latest version of the terminology document (Definitive Document E.Def 1.2) is published in CMI 2000;6:503-508. The purpose is to promote the uniform application of terminology to methods used for determination of susceptibility to antimicrobial agents.
Breakpoints	Prof. Ian Phillips (see above) Prof. John Degener University Hospital Department of Microbiology NL-9700 Groningen THE NETHERLANDS Phone: + 31-50-363 35 10 Fax: + 31-50-363 35 28 E-mail: j.e.degener@med.rug.nl	The document describing the process of setting breakpoints (Definitive Document E.Def 2.1) is published in CMI 200;6:570-572. This process was applied to breakpoints for linezolid (Definitive Document E.Def 4.1), published in CMI 2001; 7:1-3, and discussions are under way regarding breakpoints for three new agents.
Dilution Methods	Prof. Bernd Wiedemann Pharmazeutische Mikrobiologie der Universität Bonn Meckenheimer Allee 168 D-53115 Bonn GERMANY Phone: + 49-228-73 52 72 Fax: + 49-228-73 52 67 E-mail: b.wiedemann@uni-bonn.de	A document on determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution (Definitive Document E.Def 3.1) was published in CMI 2000;6:509-515. A discussion document on a broth microdilution method (E.Dis 5.1) has been prepared and will be published in the near future in the form of an insert in CMI.
Automated Methods	This subcommittee is no longer active	

EUCAST Subcommittees continued

Subcommittees: Coordinators:

<p>Quality Assurance</p>	<p>Dr. Derek Brown Clinical Microbiology and Public Health Laboratory Addenbrooke's Hospital Hills Road Cambridge CB2 2QW UNITED KINGDOM Phone: + 44-1223-25 70 20 Fax: + 44-1223-24 27 75 E-mail: dfjb2@cam.ac.uk</p>	<p>A discussion document on approaches to quality assurance of antimicrobial susceptibility tests (E.Dis 9.1) will be published in the near future as an insert in CMI.</p>
<p>Antifungal Susceptibility Testing</p>	<p>Dr. Juan-Luis Rodriguez-Tudela Mycology Reference Laboratory National Center for Microbiology Instituto de Salud Carlos III Ctra. Majadahonda-Pozuelo Km.2 E-28220 Majadahonda SPAIN Phone: + 34-91-509 79 66 Fax: +34-91-509 79 61 E-mail: juanl.Rodriguez-tudela@isciii.es</p>	<p>Three documents on susceptibility testing of fungi are being prepared, on fermentative yeasts, non-fermentative yeasts and filamentous fungi. The first of these, a discussion document (E.Dis 7.1) on determination of minimum inhibitory concentrations by broth microdilution of fermentative yeasts, has been prepared and will be published in the near future as an insert in CMI.</p>
<p>Mycobacterial Methods</p>	<p>Dr. Francis Drobniowski PHLS Mycobacterium Reference Unit Guy's, Kings and St. Thomas School of Medicine Bessemer Road London SE22 8QF UNITED KINGDOM Tel: + 44-208-693 1312 Fax: + 44-207-346 6477 E-mail: f.drobniowski@kcl.ac.uk</p>	<p>A discussion document (E.Dis 8.1) on antimicrobial susceptibility testing of <i>Mycobacterium tuberculosis</i> has been prepared and will be published in the near future as an insert in CMI.</p>
<p>Intracellular and Cell-Associated Pathogens</p>	<p>Dr. Geoff Ridgway Department of Clinical Microbiology The University College London Hospitals Grafton Way London WC1E 6DB UNITED KINGDOM Tel: +44-207-693 1312 Fax: +44-207-388 8514 E-mail: g.ridgway@uclh.org</p>	<p>A discussion document covering susceptibility testing of various intracellular and cell-associated pathogens (E.Dis 6.1) has recently been published in CMI 2001(12);7 insert;1-10.</p>
<p>Molecular Methods</p>	<p>Prof. Peter M. Hawkey Public Health Laboratory Birmingham Heartlands Hospital Bordesley Green East Birmingham B9 5SS UNITED KINGDOM Tel: + 44-121-424 1240 Fax: + 44-121-772 6229 E-mail: p.m.hawkey@bham.ac.uk hawkeyp@heartsol.wmids.nhs.uk</p>	<p>A discussion document on susceptibility testing by molecular methods is currently being prepared.</p>

EUCAST Publications

All EUCAST documents are published in *Clinical Microbiology and Infection*, the official publication of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Published documents are also available on the EUCAST section of the ESCMID website (www.escmid.org). The following have been published or are in the late stages of preparation.

All published documents are also available on the website
<http://www.escmid.org>
in pdf format

Definitive Document E.Def 1.2	<i>Clinical Microbiology and Infection</i> 2000;6:503-8 Terminology relating to methods for the determination of susceptibility of bacteria to antimicrobial agents.
Definitive Document E.Def 2.1	<i>Clinical Microbiology and Infection</i> 2000;6:570-2 Determination of antimicrobial susceptibility test breakpoints.
Definitive Document E.Def 3.1	<i>Clinical Microbiology and Infection</i> 2000;6:509-15 Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution.
Definitive Document E.Def 4.1	<i>Clinical Microbiology and Infection</i> 2001;7:1-3 Linezolid breakpoints.
Discussion Document E.Dis 5.1	In preparation Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth microdilution.
Discussion Document E.Dis 6.1	<i>Clinical Microbiology and Infection</i> 2001 (Insert in issue number 12);7:1-10 Antimicrobial susceptibility testing of intracellular and cell-associated pathogens.
Discussion Document E.Dis 7.1	In preparation Determination of minimum inhibitory concentrations by broth microdilution of fermentative yeasts.
Discussion Document E.Dis 8.1	In press Antimicrobial susceptibility testing of <i>Mycobacterium tuberculosis</i>.
Discussion Document E.Dis 9.1	In preparation Quality assurance of antimicrobial susceptibility tests.
Discussion Document E.Dis 10.1	In preparation Antimicrobial susceptibility testing by molecular methods.

NCCLS Subcommittee on Antimicrobial Susceptibility Testing



Boston, June 2001

Once again, the Subcommittee, with Dr. Mary Jane Ferraro in the chair, met in Boston at the Hyatt Harborside Hotel, from where we enjoyed a splendid view of the city skyline across the harbour – at least, when we were not catching the violent tail of a tropical storm.

On the day before the main meeting, I attended Dr. Karen Bush's working group on extended - (not expanded!) spectrum beta-lactamases (ESBL), which are causing increasing clinical problems and, as they diversify, proving increasingly difficult to detect. The lively discussion was continued in the main meeting on the following day.

In the preamble to the full meeting, we were told that there would in future be a \$250 attendance fee for individuals and representatives of professional societies who are not members of NCCLS. The usual announcements were made about the publication of documents, the most important for us being the latest editions of M2 and M7, which will go into a further cycle of revision from January 2002, M11 (anaerobes) and M39 P (addressed by our own ESGARS). Documents M24 (mycobacteria) and M32 (Mueller-Hinton broth) are expected soon, and a new project on mycoplasma AST has just started.

The first item on the main agenda was ESBLs. After a discussion on the definition of an ESBL, screening tests were considered at length, since it has become clear that the use of cefpodoxime 2mg/L produces very many false-positive results. It was agreed that a concentration of 8mg/L lost little in sensitivity, and yielded the same information as cefotaxime and ceftazidime together at the same concentration, for *E. coli* and klebsiella. Discussion on the blanket recommendation that all cephalosporins, penicillins and aztreonam should be reported as resistant if an ESBL is detected opened the "can of worms" of beta-lactam breakpoints, which were held by some members of the Subcommittee to be too high. I welcomed the decision to re-evaluate these breakpoints – one of the main areas of disagreement between many European systems and the NCCLS.

During discussions on a letter arising from the development of new interpretive guidelines for cefotaxime and ceftriaxone, to be published by NCCLS for the benefit of those who devise guidelines for the treatment of pneumococcal infection, I suggested that publication should be in European as well as US journals. In discussions on *Str. pneumoniae*, I drew attention to the confusing listing of penicillin and amoxycillin with widely differing breakpoints. It finally became clear that there is no parenteral preparation of amoxycillin available in the USA, and that penicillin breakpoints are appropriate for meningitis, while those for amoxycillin are for non-meningitis – but problems are not easily resolved without further work. Breakpoints of cefpirome for pneumococci, beta- and alpha-haemolytic streptococci were also discussed.

Decisions were made on a variety of more routine topics: quality control results for the desfluoroquinolone BMS 284756; the use of acetic acid as a solvent for macrolides (look out for the detail!); disc breakpoints for mecillinam and *E. coli*; and a variety of QC modifications. There was a progress report on susceptibility testing of *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. Further data were supplied on linezolid: it remains true that recognised resistance determinants in enterococci are detectable only in isolates for which MICs of linezolid are 8mg/L or more (supporting, I believe, EUCAST breakpoints!). Discussion of the use of penicillin or ampicillin AST results to predict those for imipenem or piperacillin-tazobactam for enterococci led to agreement that it was appropriate in the latter case, but that more information was needed for the former. There was also discussion on penicillin and oxacillin AST of coagulase-negative staphylococci, which will lead to revised recommendations. There was a seemingly interminable discussion related to textual modifications to NCCLS AST documents. A working party had laboured valiantly, but most of their suggestions were further modified – to what end must await publication. During breaks in this session I was able to report on the activities of EUCAST, leaving copies of our last newsletter and of our publications to date with the Subcommittee. Finally, Mr. Folkerts, the chairman of the Susceptibility Test Manufacturers Association (STMA), drew attention to the need to oppose the FDA proposal to withdraw AST in-vitro data from package inserts – and the Subcommittee appeared to concur. He also provided exhaustive lists of antibiotic abbreviations used by disc manufacturers – surely in need of rationalisation.



Tampa, January 2002

It will seem strange to some that, although I am no longer chairman of EUCAST, I continue to attend and report on the NCCLS AST biannual meetings. The explanation is that the appointment of Adviser to the AST is made by NCCLS and not by ESCMID. At the request of the president of ESCMID, I have not resigned the appointment in order to allow my successor time to acclimatize himself to EUCAST responsibilities, but intend to do so at the end of this year.

The meeting began as usual with a full day of Working Group meetings. I took part in those on quality control and text and table revisions. The afternoon was taken up by a discussion on antimicrobial susceptibility testing in relation to bioterrorism, and a new group hopes to produce guidance by the middle of the year on susceptibility testing methods for *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis* and perhaps *Burkholderia mallei* and *pseudomallei*.

The main meeting on the following day started with a review of the status of relevant NCCLS publications. The annually revised M100 – the tables of breakpoints on which so many rely – was newly available as M100-S11, supplementing M2 and M7, which will be available as the new editions M2-A8 and M7-A6 in January 2003. Much of the meeting was directly or indirectly related to proposals for change. Publications during 2001 have included M23-A2 (susceptibility testing criteria and quality control) and M11-A5 (anaerobes), while those planned for 2002 include M42-R (fish pathogens), M32-A (Mueller-Hinton broth), M24-A (mycobacteria), M39-A (recording and reporting data), M33-A (viruses), M38-A (filamentous fungi), M31-A2 (veterinary) and M27-A2 (yeasts). Many of these documents are the responsibility of other NCCLS groups, but all concern susceptibility testing.

Requests for the establishment of interpretive criteria for new agents always take a great deal of the Subcommittee's time, and ertapenem was no exception. A particular problem was the interpretation of tests on staphylococci. Although proposed criteria worked well for MSS, MRS were allocated to S, I and R, although the drug is not indicated for therapy of MRS infections regardless of the in-vitro results. Although some rather complex breakpoints were eventually agreed, in line with what the FDA had already decided, there was a decision to start a process for the review of

the evidence on the antistaphylococcal activity of carbapenems, cepheems and beta-lactamase inhibitor combinations. It will be important for EUCAST to have input in these discussions in the light of the generally lower breakpoints for these drugs in Europe, even among those who use NCCLS methodology.

Among the myriad of topics raised during the consideration of other items on the agenda, I noted the following that might interest EUCAST members: new QC ranges (for ticarcillin-clavulanate and *E.coli*, for cefepime and pneumococci, among others); detection of ESBLs; testing of *B. cepacia* and *Stenotrophomonas maltophilia*; the frequency of QC tests; the continuing rarity of fluoroquinolone-resistant *Haemophilus influenzae*, solvents for macrolides; the relevance of current fluoroquinolone breakpoints to *Salmonella typhi*; anomalies between breakpoints for similar antibacterials; and the loss of plasmids from QC organisms stored at –20 degrees. Attention was drawn to the potentially harmful effects on antibiotic development of a proposal from the FDA for the tightening of measures of statistical significance for assessments of new antimicrobials. This would lead to the need to recruit often impossibly large numbers of patients for some clinical situations. I must also mention an excellent review by Keith Klugman of the performance of penicillins in the therapy of infections caused by penicillin-resistant (ie MICs of 2-4mg/L) pneumococci. The variety of topics covered during these meetings is astounding!

Finally, we saw the text of a letter from NCCLS on new meningitis and non-meningitis breakpoints for pneumococci and cefotaxime and ceftriaxone. I asked that the letter be sent for publication in CMI as well as to American journals in view of its important implications for those involved in the therapy of serious pneumococcal infection. Those who wish to comment can do so via EUCAST or directly.

The next meeting of the AST Subcommittee – which I take to be the last that I shall attend – will be in Boston, in June 2002.

Ian Phillips

