International harmonization of breakpoints – is it possible?

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EUCAST, CLSI

B-DEBATE, Barcelona, 2013
Antimicrobial susceptibility testing of bacteria and fungi

• To choose appropriate therapy and predict clinical outcome in individual patients (clinical breakpoints)

• To obtain a basis for empiric therapy (clinical breakpoints)

• To screen for organisms with exceptional resistance
  – such as MRSA, VRE, ESBL, KPC, NDM, MDRTB etc using ECOFFs
  – to prevent dissemination in health care and community

• To determine the rate of resistance development (ECOFF and clinical breakpoints)
  – To understand and predict resistance development and then to form strategies to counteract antimicrobial resistance development and measure success and failures of strategies
Methods for susceptibility testing

• **Phenotypic test methods**
  
  based on **antimicrobial activity (MIC)** and **breakpoints**
  
  – MIC, disk diffusion, automated systems like Phoenix, Vitek2, Microscan
  – Predict susceptibility and resistance
  – Quantifiable

• **Genotypic test methods**
  
  based on the detection of a **resistance gene** or its **product**
  
  – mecA, vanA, vanB, ....PBP2, ... betalactamase detection (enzyme detection, Maldi Tof)
  – Predict resistance, not sensitivity
  – Not quantifiable
  – Useful for epidemiological purposes

• **By deduction – “expert rules”**
  
  – If MRSA then report all betalactam antibiotics R – or soon not?
    If ESBL-positive, then report betalactam antibiotics R – but not any longer!
    If erythromycin-resistant, then report all macrolide antibiotics as R;
  – **Some rules predict susceptibility, others resistance.**
  – Unreliable!
  – Not quantifiable!
Why harmonized breakpoints?

Breakpoints define resistance. With common breakpoints we speak a common language.
Breakpoints are needed for phenotypic testing

• **Clinical breakpoints**
  – to guide therapy
  – change over time
  – require harmonisation of indications and dosages

• **ECOFF**
  – to distinguish between isolates without (wild type) and with (non-wild type) resistance mechanisms
  – do not change over time
  – require definition of method
Phenotypic susceptibility testing is based on...
**ECOFF**

**Organism with MIC above ECOFF:**
- erroneous identification
- erroneous MIC-value
- resistance mechanism

Benzylpenicillin / Streptococcus pyogenes
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.
Organism with MIC above ECOFF:
- erroneous identification
- erroneous MIC-value
- resistance mechanism

Clinical breakpoints for S and R

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L
Distribution of MICs
defined by agent, species and test system.
Freely available on the internet (www.eucaest.org)

Cefotaxime / Klebsiella pneumoniae
EUCAST MIC Distribution - Reference Database 2011-02-05

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

Clinical breakpoints for S and R
(EUCAST and CLSI)
Breakpoints are needed for phenotypic testing

Clinical breakpoints
- to guide therapy
- may change over time
- may render the wild type MIC distribution of a species Susceptible, Intermediate or Resistant
- harmonization requires harmonization of indications and dosages

ECOFFs
- to distinguish, in a phenotypic test system, between isolates without (wild type) and with (non-wild type) resistance mechanisms
- do not change over time
- independant of host species (man, birds, cattle etc) and can be used to compare resistance when clinical breakpoints differ (between countries, human vs. veterinarian vs. food safety etc)
Breakpoints are determined by:

Breakpoint committees (CLSI, EUCAST)
Medicines agencies (FDA, EMA, national)

Pharmaceutical companies
AST companies
Colleagues who know better
• **Mandate** from ECDC, EMA and ESCMID and national breakpoint committees in Europe (BSAC, CA-SFM, CRG, DIN, NWGA, SRGA)

  – To determine and review breakpoints for existing and new agents for bacteria and fungi
  – To develop and standardise AST in Europe (methods, QC, education)
  – To act as an umbrella organisation for national AST (NACs) and breakpoint committees
  – To support education and training as provided by ESCMID, WHO, ECDC, NACs etc.
• CLSI has no mandate to determine breakpoints and there is no MoU between CLSI and FDA.
• Industry support has dwindled.
• Sales of recommendations is made difficult by EUCAST “freely available” guidelines.

*Chairmen from industry and profession on rotation*
CLSI and EUCAST breakpoints are different

“Only 32.5% agreement”

<table>
<thead>
<tr>
<th>Organisms</th>
<th>No. assessed</th>
<th>Same breakpoints</th>
<th>Overall agreement (%)</th>
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<tbody>
<tr>
<td></td>
<td>Agents</td>
<td>Criteria</td>
<td>Susceptible</td>
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<tr>
<td>Enterobacteriaceae</td>
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<td>60</td>
<td>10</td>
</tr>
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<td><em>P. aeruginosa</em></td>
<td>17</td>
<td>34</td>
<td>9</td>
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<tr>
<td><em>Acinetobacter</em> spp.</td>
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<td>20</td>
<td>5</td>
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<tr>
<td>Staphylococci</td>
<td>25</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Enterococci</td>
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<td>10</td>
<td>2</td>
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<tr>
<td><em>S. pneumoniae</em></td>
<td>27</td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td>All results</td>
<td>-</td>
<td>234</td>
<td>48</td>
</tr>
</tbody>
</table>

Courtesy Ron Jones, USA
Breakpoint inside USA needs harmonisation
(Summary of agreement between CLSI and USA-FDA PI criteria for 2013)

Example: Fluoroquinolones (FQ)

- 82 breakpoints across 13 organism groups and six FQs
- Agreement
  - 33.3% (moxifloxacin) to 100.0% (NA) by drug
  - 54.3% for Gram-positive cocci
  - 61.7% for Gram-negative pathogens

  - Only 58.5% overall agreement between CLSI and FDA

a. Most commonly used agents (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin and nalidixic acid [NA]).

Courtesy Ron Jones, USA
Breakpoints need to be reviewed at regular intervals!

- Dosages change
- Administration modes change
- Indications for therapy change
- New resistance mechanisms
- Tools to assess breakpoints develop

All EUCAST breakpoints are younger than 10 years
Countries interested in joining EUCAST and adopt its procedures and breakpoints are encouraged to form a National AST Committee.

NAC

A document describing a prototype NAC is available on website.
NAC

- **Antimicrobial susceptibility testing**
  - Form a coherent strategy at national level
  - Help laboratories with the implementation of breakpoints and methods
  - Education (national workshops, websites)
  - Liaison and consultation with EUCAST – via the General Committee and open consultations
  - Liaison with other national groups involved in antimicrobial stewardship or surveillance of resistance.

- QA

- (Antimicrobial Policies)
- (Antimicrobial Resistance Surveillance)
- (Antimicrobial Consumption)
National AST Committees (NACs) 2013

- Yes
- In the process of forming a NAC
- No
- No information

Countries not on the map: Australia, Iceland, Israel, USA
NACs Outside Europe

• Australia
  – Formed in 2012; backed by the ASM.
  – National decision to go over to EUCAST breakpoints and methodology.
  – The NAC is very active during consultations and takes part in SC meetings.

• USA
  – Formed in 2013; backed by several societies including IDSA.
  – Is seeking an agreement with FDA.
NACs Outside Europe

• **South Africa**
  - Formed in 2013; backed by the FIDSSA
  - National decision

• Several countries/laboratories have adopted EUCAST without national decisions or without informing EUCAST or soliciting the support of EUCAST.
Uptake of EUCAST guidelines
Data from EARS-Net EQA 2009 - 2012

Year | %
--- | ---
2009 | 22
2010 | 29
2011 | 48
2012 | 61

CLSI | EUCAST

ECDC/EARS-Net and UKNEQAS (C. Walton)
International harmonization of breakpoints – is it possible?

• **ECOFF** – international harmonisation is almost achieved.

• Clinical breakpoints – international harmonisation can be achieved, either because
  – All countries decide to “go EUCAST”
  OR
  – There is an initiative to create an “International breakpoint committee” as an evolution of the EUCAST model. The time for this will be when CLSI decides to stop setting clinical breakpoints and FDA, EMA, CDC and ECDC decide to promote the formation of an international committee.
International MIC- and zone diameter distribution website

• To create an international steering committee.
• To appoint a curator (or several)
• The MIC and zone diameter database will be managed according to rules determined by the steering committee.
• Ownership of data lies with the individual contributor.
• Ownership of software and software management tools lies with ECDC and ESCMID.
• All data displayed will be labelled “International MIC- and Zone diameter Distributions”
• The responsibility for and website management of the MIC- and zone diameter database lies with the steering committee and the curator.
• Copyright issues will be clarified
Ampicillin / Escherichia coli
International wild type MIC Distribution – Reference Database 2013-11-05

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)

% microorganisms

0 10 20 30 40 50 60

M IC: Epidemiological cut-off: WT = 8 mg/L

39220 observations (48 data sources)
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Questions

• Can we do without breakpoints in 10 years?

• Do we need internationally agreed breakpoints?

• Which model is right – the CLSI- or the EUCAST-model?

• International breakpoint committee – hosting and financing?
Thank you

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Problems with AST

- Phenotypic tests are **slow** (6, 8, 16 or 24 h)
- Phenotypic methods are still **not fully standardized**.
- Phenotypic tests require **breakpoints** and there is a lack of agreement between the “players” (CLSI vs. EUCAST and CLSI vs. FDA).
- Clinical breakpoints are not suitable for measuring resistance development as a biological phenomenon BUT **ECOFFs** are.
- Molecular tests predict resistance **but not susceptibility** and cannot be reliably quantified.
- **Automatic AST machines are outdated**, without further development, stuck with 96 test wells and lack all flexibility.