CLSI Guidelines on Epidemiological Cutoff Values

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Breakpoints vs Epidemiological Cutoff Values (ECVs)
Breakpoints

Based upon a number of factors:

- MIC distributions (species specific)
  - Including both wild type and molecularly proven resistant isolates
- Pharmacokinetics/Pharmacodynamics
- Outcome data

Allow us to determine whether a given bug/drug combination is likely to work
Epidemiological Cutoff Values (ECVs)

- Based upon the MIC distribution alone
- Do not allow us to determine whether a given bug/drug combination is likely to work only whether a particular MIC value is “normal” (wild type) or “not normal” (non-wild type)
What is an ECV?

- CLSI working definition-
  - the minimal inhibitory concentration/minimal effective concentration value that separates fungal populations into those with and without acquired and/or mutational resistance based on their phenotypes (minimal inhibitory concentration)
Phenotype as a definition of wild type…

- We make an assumption of wild type based on MIC

- Wild type is determined based on the MIC value to the specific drug
  - A *Candida albicans* isolate with an FKS mutation and a micafungin MIC of 4 µg/ml would be non-wild type for micafungin
  - The same isolate, with a fluconazole MIC of 0.125 µg/ml would be considered wild type for fluconazole
How are ECVs determined?

- Visual method
- 95% rule
- Normalized resistance interpretation
- Multimodal analysis
- Iterative statistical method
How are ECVs determined?

- Visual method
  - View the distribution histogram
  - Look for the population at the lower end of the distribution
How are ECVs determined?

*Candida albicans* and fluconazole MIC distribution

5,265 isolates
How are ECVs determined?

- 95% rule
  - This is essentially an MIC$_{95}$
  - The ECV is the MIC the encompasses $\geq 95\%$ of the wild type population
How are ECVs determined?

*Candida albicans* and fluconazole MIC distribution

5,265 isolates
How are ECVs determined?

- Iterative statistical method
  - This method utilizes a program that models the log-transformed MICs at the lower end of the distribution and calculates the mean and standard deviation of the modeled distribution
  - The ECV is the MIC that captures ≥97.5% of the modeled distribution
  - Allows an ECV to be determined even with a population with many non-wild type isolates

How are ECVs determined?

*Candida albicans* and fluconazole MIC distribution

Encompasses ≥ 97.5% of wild type population

Rules for establishing an ECV

- Species identification must be molecular (for molds and yeasts) or MALDI-TOF (for yeasts)
- The data must be generated by a minimum of 3 different laboratories
  - There is a method for weighing the data if a preponderance comes from one laboratory
- More than 100 independent isolates must be tested
Do ECVs identify non-wild type isolates?

**C. glabrata** micafungin MIC distribution

- **Number of isolates**: 1,380
- **ECV**: Red arrow indicates a significant increase in the number of isolates at a specific MIC level.
Do ECVs identify non-wild type isolates?

C. glabrata micafungin MIC distribution

Number of isolates

MIC in µg/ml

0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8

Wild type
FKS mutations

ECV
Do ECVs identify non-wild type isolates?

**C. glabrata** micafungin MIC distribution

<table>
<thead>
<tr>
<th>MIC in µg/ml</th>
<th>Wild type</th>
<th>FKS mutations</th>
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</thead>
<tbody>
<tr>
<td>0.03</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
<td>12</td>
<td>2</td>
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<tr>
<td>0.12</td>
<td>10</td>
<td>4</td>
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<tr>
<td>0.25</td>
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<td>6</td>
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<tr>
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<tr>
<td>8</td>
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</tbody>
</table>
Do ECVs identify non-wild type isolates?

A. fumigatus itraconazole MIC distribution

Jacques Meis, personal communication
Do ECVs identify non-wild type isolates?

*A. fumigatus* voriconazole MIC distribution

- No mutation
- TR34/L98H

Jacques Meis, personal communication
# Published ECVs vs CLSI breakpoints

<table>
<thead>
<tr>
<th>Species</th>
<th>ECV µg/ml</th>
<th>Breakpoint (S) µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td><em>C. guilliermondii</em></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>0.06</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Some final thoughts…

- ECVs will only be established for species and antifungal combinations for which there is thought to be clinical efficacy
  - For example, no ECVs for *Cryptococcus* and echincandins

- ECVs can be established for any species as long as there are enough isolates too test
Some final thoughts…

- ECVs may promote more susceptibility testing because they will allow MIC values to be put into context
  - Right now, too many times we have to say “We can test that, but we won’t know what the numbers mean”
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