Welcome

Open Virtual Meeting

8 February 2023
OUR VISION

Optimal Antibiotic Usage Worldwide
Our Mission

- We support this vision by helping establish *in vitro* susceptibility test interpretive criteria (STIC)

- Given that EUCAST is the fastest growing and a highly influential susceptibility breakpoint consensus body globally...

- USCAST was formed in 2013 to
  - Provide a US voice to the EUCAST process
  - Provide breakpoint decision support to the US FDA and other interested parties and promote harmonization
And our Special Advisor
Our membership (voting)

- John S. Bradley, M.D.
- Alex J. Lepak, M.D.
- Emil P. Lesho, D.O.
- Erin K. McCreary, Pharm.D.
- Michael A. Pfaller, M.D.
- Robert R. Rennie, Ph.D.
- Stefan Riedel, M.D.
- Keith A. Rodvold, Pharm.D.
- Michael J. Rybak, Pharm.D.
- Marc Scheetz, Pharm.D.
Advisors (non-voting)

- Olga Lomovskaya, PhD
- Ryan K. Shields, PharmD
- Judith N. Steenbergen, Ph.D.
Funding

- USCAST is a New York State charitable corporation
  - 501 (c) (3) status from the IRS

- USCAST is funded by philanthropy
  - No money from pharmaceutical or susceptibility test device companies

  - All donations are reported to the IRS annually

  - USCAST committee members are volunteers
USCAST EC prioritizes

Working Group formed

Draft proposal/presentation

Presented to EC

Presented to Full Membership

Review public feedback

Public Comment Period

Full Membership Vote

Final vote and breakpoints set

Presented to Full Membership

Final vote and breakpoints set
Communication

- We communicate through our website, USCAST.org
  - Draft report documents for public comment and consultation
  - Virtual meeting announcements and recordings
  - Revised and final documents
- It’s all provided free of charge!
# General Breakpoint Process

## Clinical Data

- Exposure linked MIC-defined-pathogen outcomes in humans

## Pharmacokinetics/Pharmacodynamics

- Pharmacodynamic models and site-specific considerations
- Monte Carlo Simulations

## MIC distributions

- Consideration given to “wild-type” or “ECOFF” distributions
- Splitting MIC distribution is acceptable
Clinical Data

- Human studies associating exposure to pathogen MIC relationships to outcomes are highest level of evidence considered

- However, these data come with a lot of caveats that warrant close consideration
  - Study Design (retrospective observational vs RCT)
    - Patient populations with higher MICs in observational data
  - Disease State studied (e.g., applying cUTI registry trial to breakpoints at other infection sites)
USCAST PK/PD approach

- Consideration is given to the site of infection when selecting appropriate PK/PD infection model
- Endpoint for PK/PD targets
- Population pharmacokinetics, contemporary *in vitro* surveillance data, and simulation for PK/PD target attainment analyses are performed
- Weighing clinical, PK/PD target attainment, and microbiology data
- Harmonization whenever possible
## USCAST Breakpoints: Example

### 2019 Aminoglycoside Breakpoints (update pending 2023):

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antimicrobial Drug</th>
<th>MIC breakpoints in μg/mL Susceptible/Resistant&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacterales</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>≤4 / ≥8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>≤2 / ≥4</td>
</tr>
<tr>
<td></td>
<td>Gentamicin - pneumonia</td>
<td>≤1 / ≥4</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>≤2 / ≥4</td>
</tr>
<tr>
<td></td>
<td>Tobramycin - pneumonia</td>
<td>≤1 / ≥4</td>
</tr>
<tr>
<td><strong>Pseudomonas spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>≤2 / ≥8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>-</td>
</tr>
<tr>
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<td>Tobramycin</td>
<td>≤1 / ≥2</td>
</tr>
</tbody>
</table>
Urinary Tract Infection Breakpoints

- Optimal PK/PD considerations for UTI are unclear
- Cystitis
  - Importance of urinary concentrations
    - But is it the only consideration of importance?
  - Bacteriostasis versus $1 \log_{10}$ kill
    - Systemic or urinary exposures?
    - Does selection impact recurrence?
- Complicated urinary tract infections
  - A wide range of infections included here that differ significantly in their risk for failure and recurrence
    - How does PK/PD target (and degree of kill) impact these?
  - Systemic exposures and urinary concentrations both relevant
- USCAST plans to further assess this moving forward
Let’s talk about ECOFFs

An epidemiological cutoff (ECOFF) or “wild-type” distribution is meant to differentiate isolates with or without acquired resistance.

- Ideally, susceptibility breakpoint will coincide with this value:
  - Reliability of the test
  - Test validation and FDA approval

- This is rarely an issue with newer drugs as they are dosed in development to cover “wild-type” isolates.
As resistance evolves, this can become an issue

- Becomes apparent when trying to modernize breakpoints of “older drugs”
- Safe doses and MIC distributions may no longer coincide
- Reconciliation options include
  - Setting the breakpoint at either end of the wild-type distribution
    - Call some isolates “susceptible” that truly are not
    - Removing a potentially effective antimicrobial as an option
  - “Splitting the distribution”
    - Impact the reliability of the test and ability get an AST device approved

### Enterobacterales MIC distribution

- **PK/PD supported breakpoint**
- **Percent of Isolates at MIC value**
- **Amikacin MIC (mg/L)**
  - 0.25
  - 0.5
  - 1
  - 2
  - 4
  - 8
  - ≥ 16
USCAST Position

- While the preference is to not, USCAST will split the “wild-type” distribution as necessary.

- USCAST believes splitting the distribution puts fewer patients at risk for inadequate therapy than does setting breakpoint at upper margin of the “wild-type” distribution.

- It would be reasonable to err on the other side (remove the drug as a therapeutic option), but USCAST membership does not find that optimal in age of multi-drug resistance.
We cannot ignore the implications of splitting the distribution

- Lobbying the FDA
  - Remove the need for categorical agreement to get a device/test validated
  - Rely on essential agreement only

- Educational needs!
  - Clinicians need to be aware that results are ± 1 double dilution – particularly when the “split” is big and that needs to inform clinical decision making
USCAST: Future Directions

- Will NOT have comprehensive bug/drug tables
  - Many props to CLSI, EUCAST for this

- Focus on high impact comprehensive reviews where the expertise of USCAST can be leveraged
  - You will get three examples of this today!
  - Results are available for any other organization (e.g., CLSI, EUCAST) to use as they see fit

- USCAST will continue to work towards standards development organization (SDO) status so the FDA can apply our breakpoint recommendations directly
USCAST next steps

- We will scan currently available susceptibility breakpoints to determine which ones most likely need reassessment
  - Work with USCAST members and the community (i.e., YOU) to determine which to prioritize

- In 2023 will form urinary breakpoints working group

- Remain open to sponsor requests for breakpoint recommendations
Thank You