How Are CLSI Breakpoints Set?

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What We’ll Cover

• CLSI microbiology structure & process
• The information that is used
• The consensus process vs other options
• New drugs and new breakpoints
• Reevaluation of established breakpoints
Audience Response Question
The Structure of CLSI –
The Part That’s Important to Us

Micro Consensus Committee

Antimicrobial Susceptibility Testing (AST) Subcommittee

Working Groups of the AST Subcommittee
Strengths of the Process

• Consensus process
• Input from multiple parties/groups
• Large number of people involved
• Open and transparent
• Anyone can come forward with issues
Weaknesses of the Process

• Consensus process
• Input from multiple parties/groups
• Large number of people involved
• Open and transparent
• Anyone can come forward with issues
Alternatives to the Consensus Process

• Unnamed organization – maybe in Europe
• Small group of people (think 10ish)
• Groups invited to present data
• Decisions made behind closed doors
• No representatives of other interested groups
When Breakpoints Change – What is an “M23 Condition”?

• “Reassessment of interpretive criteria may become necessary as new information becomes available.”

• Emergence of new resistance (think KPCs)

• New PK/PD data

• Different dosing regimens emerge

• Data show BPs are not optimal for common uses of antimicrobials (i.e. PCN and *S. pneumo*)
What Information Does the CLSI Look At?

- Number of Isolates
- MIC (mcg/mL)

- 0.06: 300
- 0.12: 200
- 0.25: 150
- 0.5: 100
- 1: 4
- 2: 8
- 4: 16
- 8: 1
- 16: 0
Pharmacokinetics/Pharmacodynamics (PK/PD)

• In-vitro exposure/response data
• Human pharmacokinetics
• Animal models of infection
  – Neutropenic mouse thigh model
  – Other models
• Monte Carlo simulations based on 2 and 3
  – Only as good as the data you put in!
• Phase II and Phase III exposure/response data
Clinical Data

• Phase II and III registrations studies
• But what if its an old drug?
• MIC vs outcome data? The holy grail, but...
Problems with Changing Existing Breakpoints

• Where does the data come from?
• Limitations of the data – case series, etc.
• CLSI and FDA – the state of the relationship
• FDA and package inserts
  – Drugs
  – Devices
• New breakpoints, generics, and the FDA
New Drugs – The Ceftaroline Story

- A concerted effort to speed things up
- The rapporteur
- Ad-hoc working groups & teleconferences
- Meeting more than twice a year
- ???s and issues addressed before the meeting
- A success for the new process
- However don’t get too excited...
Lessons From the Ceftaroline Breakpoints

• The rapporteur system worked well
• The ad-hoc working group worked well
  – Stay small
  – Stay agile
• Having a sponsor to work with... IS HUGE!!
• Circulate materials prior to the full meeting
• Questions addressed prior to the full mtg
The GREAT News...
Do these numbers look similar?

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Reason to Celebrate?

• Not so fast...

• Sponsor to work with = money and data
  – New registration quality studies and data
  – Recent microbiology
  – Excellent PK/PD data

• For older drugs who does this?
Reevaluation of Existing Breakpoints - The Cefepime Wars

• Evaluated 3 times in the past decade

• In-vitro data didn’t change – note distributions

• PK/PD changed a little (not a precision weapon)

• But the clinical data...

• What dose should be used to set breakpoint?
Old and New Cefepime BPs - *Enterobacteriaceae*

<table>
<thead>
<tr>
<th></th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>Dose Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current BPs</td>
<td>≤8</td>
<td>16</td>
<td>≥32</td>
<td>1gm Q8h or 2gm Q12h</td>
</tr>
<tr>
<td>2014 BPs</td>
<td>≤2</td>
<td>4-8*</td>
<td>≥16</td>
<td>1gm Q12h**</td>
</tr>
</tbody>
</table>

But wait... There’s more!!!

* “I” is now “S-DD”

** S-DD requires:

- 1gm Q8h or 2gm Q12h for 4
- 2gm Q8h for 8
Lessons From Cefepime

• A strength and a weakness of the CLSI process
• If you don’t at first succeed...
• People on a mission
• However... you spend a bunch of time repeating work
• Did we get it correct this time?
Modified Hodge Test – What did I ever do to you?
# KPCs - Imipenem MICs by Inoculum

<table>
<thead>
<tr>
<th>Enterobacter spp. isolate</th>
<th>$10^4$ CFU/mL</th>
<th>$10^5$ CFU/mL</th>
<th>$10^6$ CFU/mL</th>
<th>$10^7$ CFU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>16</td>
<td>&gt;32</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>2</td>
<td>4</td>
<td>&gt;32</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>2</td>
<td>8</td>
<td>&gt;32</td>
</tr>
</tbody>
</table>

**Conclusions** - “The interpretation of the susceptibility of these strains differed considerably depending on the method and inoculum used.”

Reevaluation of Existing Breakpoints 2 - Carbapenems & *Enterobacteriaceae*

- Emergence of KPCs – KILL THE HODGE!!!
- The arrival of doripenem
- Older drugs – no PK/PD and very low MICs
- Better understanding of the PK/PD
- It’s a carbapenemase so it must be RESISTANT – right?
### KPCs – Déjà vu All Over Again?

<table>
<thead>
<tr>
<th></th>
<th># of Strains</th>
<th>MICs</th>
<th>% Time &gt; MIC for Stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae – KPC(-)</td>
<td>9</td>
<td>0.016-0.5</td>
<td>20-39%</td>
</tr>
<tr>
<td>KPC+ (mostly Klebsiella)</td>
<td>6</td>
<td>1-16</td>
<td>18-36%</td>
</tr>
</tbody>
</table>

**Conclusions** – The presence of KPCs had no major impact upon the % time > MIC necessary for in-vivo efficacy with dori, mero, and imi.
Carbapenemases Managed with Carbapenems – Clinical Data

• Case reports and retrospective data
• High mortality rates
• MICs and dosing often not reported
• Resistance, increasing age, comorbidities
• Better responses with lower MICs

Daikos GL & Markogiannakis A. Clin Microbiol Infect 2011;1135-41
Missing Data – The Carbapenem Story

• MIC distributions - ✓
• Monte Carlo simulations - ✓
• Detection of KPCs - ✓
• Unclear clinical data – is it all about the MIC?
• Breakpoints changed
## Carbapenem Breakpoints

<table>
<thead>
<tr>
<th></th>
<th>$S_{pre2010}/S_{current}$</th>
<th>$I_{pre2010}/I_{current}$</th>
<th>$R_{pre2010}/R_{current}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imipenem</strong></td>
<td>$\leq 4/\leq 1$</td>
<td>$8/2$</td>
<td>$\geq 16/\geq 4$</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>$\leq 4/\leq 1$</td>
<td>$8/2$</td>
<td>$\geq 16/\geq 4$</td>
</tr>
<tr>
<td><strong>Ertapenem</strong></td>
<td>$\leq 2/\leq 0.5$</td>
<td>$4/1$</td>
<td>$\geq 8/\geq 2$</td>
</tr>
<tr>
<td><strong>Doripenem</strong></td>
<td>NA/$\leq 1$</td>
<td>NA/2</td>
<td>NA/$\geq 4$</td>
</tr>
</tbody>
</table>
Conclusions

• The CLSI uses a consensus process
• It can be a little unwieldy sometimes but...
• Microbiologic, PK/PD, and clinical data are the cornerstones of BP setting
• New data can = the need for new BPs
• Often we don’t have all the data we would like