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No conflicts of interest

# CLSI Cephalosporin Breakpoint Revisions for Enterobacteriaceae


1. Dudley et al Clin Infect Dis 2013;56:1301-9
2. Tamma PD, Powers JH. Clin Infect Dis 2013;57:624-5
3. Thomson KS. 10.1093/cid/cit569 Clin Infect Dis 2013
4. Andes D, Craig WA. Clin Microbiol Infect 2005;11 Suppl 6:10-7

# Andes and Craig Paper: Basis for Revised CLSI Cephalosporin Breakpoints

1. Three meeting abstracts – no data to review

2. No methods provided - no indication of appropriateness or quality of data

3. Impossible to assess accuracy of
   a. Data
   b. Interpretation of data
   c. Conclusions

# Problems with PK/PD

- Does not take into account that PK/PD is based on MICs which can vary:
  - Inherent error of test ($\geq$ 2-fold)
  - Different test methods
  - Inoculum in lab is artificially low
- Target attainment – misleading hypothetical concept

# Therapeutic Outcomes Variable: Labile Drug vs β-lactamase

| Site of Infection | Condition of Excess | Outcome |
|---|---|---|
| Few β-lactamase producers<br>High antibiotic level | Antibiotic | Infection cured |
| Many β-lactamase producers<br>Low antibiotic level | β-lactamase | Therapeutic failure |

# Cephalosporin MICs ESBL-positive *E. coli*

| | | Microdilution MIC (µg/ml) | |
|---|---|---|---|
| ESBL | Inoculum CFU/ml | Cefotaxime | Cefepime |
| SHV-3 | $5 \times 10^5$ | 8 | 2 |
| SHV-3 | $5 \times 10^7$ | 1024 | 1024 |

# Report Susceptibility as Interpreted

"It's the MIC, Stupid!"

(No need for ESBL or carbapenemase tests for therapy)

# Discordant MICs for KPC Producers

Microdilution
Agar dilution
Automated tests
Etest
(Disk tests also problematic)


References

- Bratu et al 2005
  - Antimicrob Agents Chemother 49:776-778
  - Antimicrob Agents Chemother 49:3018-3020
  - Arch Intern Med 165:1430-1435
- Samra et al. 2007 Int J Antimicrob Agents 30:525-529.
- Pournaras et al 2010 J Clin Microbiol 48:2601-2604.

# KPC-producing *K. pneumoniae*: Carbapenem MICs (µg/ml)

| Isolate | Method | Meropenem | Ertapenem |
|---|---|---|---|
| 12 | VITEK 2 | ≥16 | 4 |
| | BD Phoenix | ≤1 | >4 |
| | Agar Dilution | 16 | 16 |
| | | | |
| 48 | VITEK 2 | ≥16 | ≤0.5 |
| | BD Phoenix | ≤1 | ≤0.5 |
| | Agar Dilution | 8 | 16 |

Thomson et al J Clin Microbiol 2007;45:2380-4

# Conclusions

- Flawed PK/PD  model data unacceptable basis for therapy of infected patients

- Human data – although sometimes imperfect = best available indicator of efficacy