The Integral Role of PK-PD in Development & Maintenance of Interpretive Criteria

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On behalf of

Clinical and Laboratory Standards Institute (CLSI)

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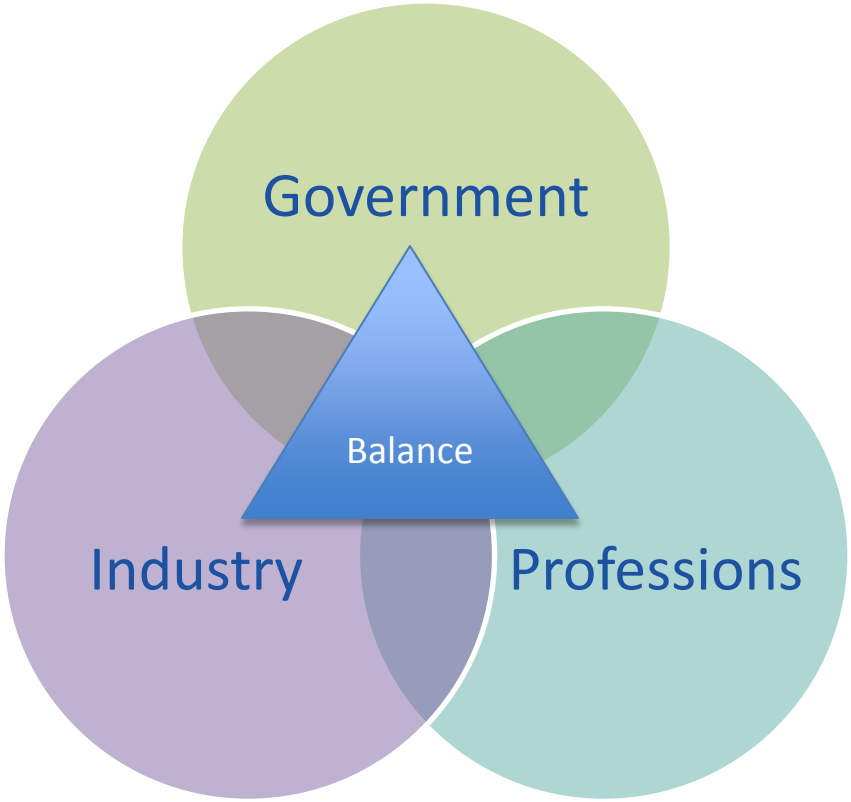

- Meetings are open to everyone.
- Meeting materials are publically available.
- Interests are balanced.
- Conflicts of interest are fully disclosed.

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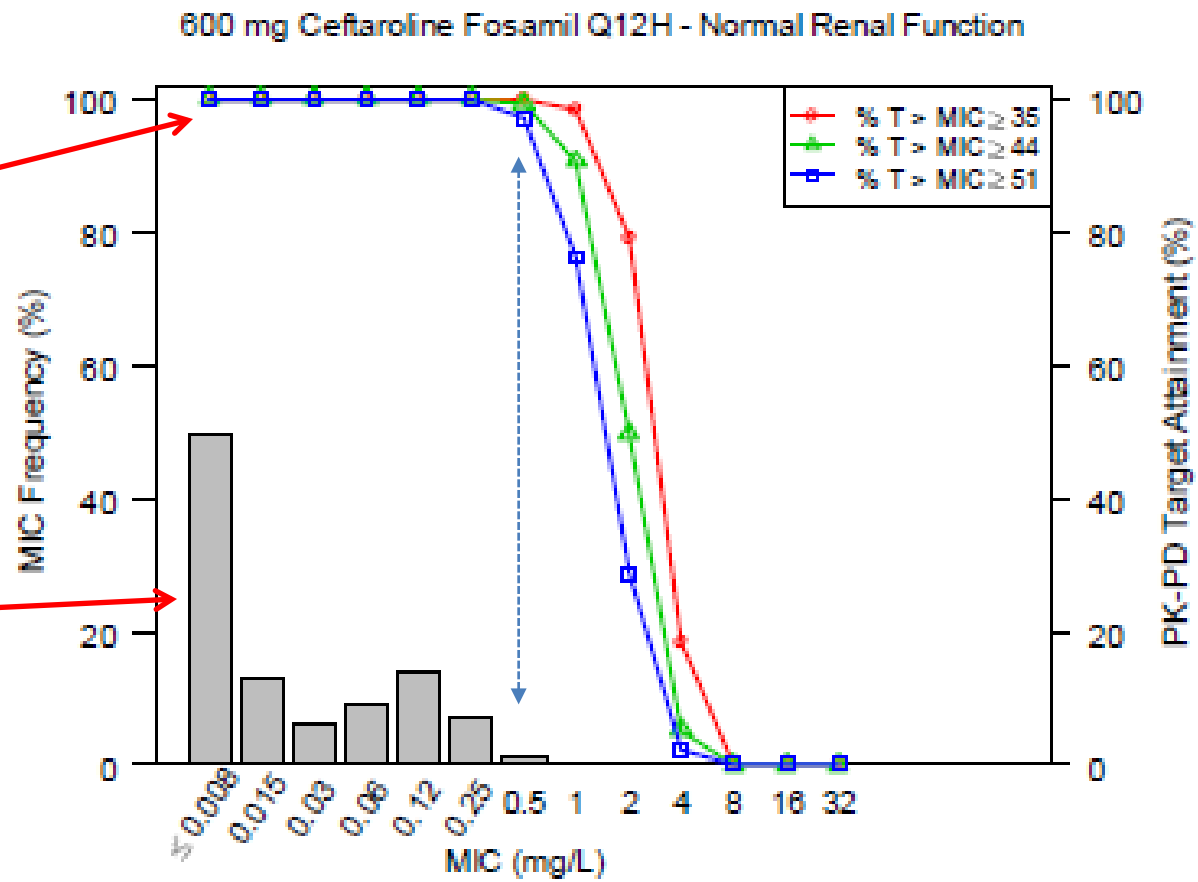
The integral role of PK-PD: 3 Themes

1. **Initial clinical trials usually are inadequate to give full insight into best breakpoints**
   - **Recent example: Ceftaroline**
2. Our empty pipeline: Good stewardship requires continued innovation in breakpoints
   - And this, in turn, is very dependent on PK-PD
   - Two stories: Cefepime & Penicillin G
3. Practical implications
   - The clinical laboratory is changing

Ceftaroline in CABP: *S. pneumoniae*

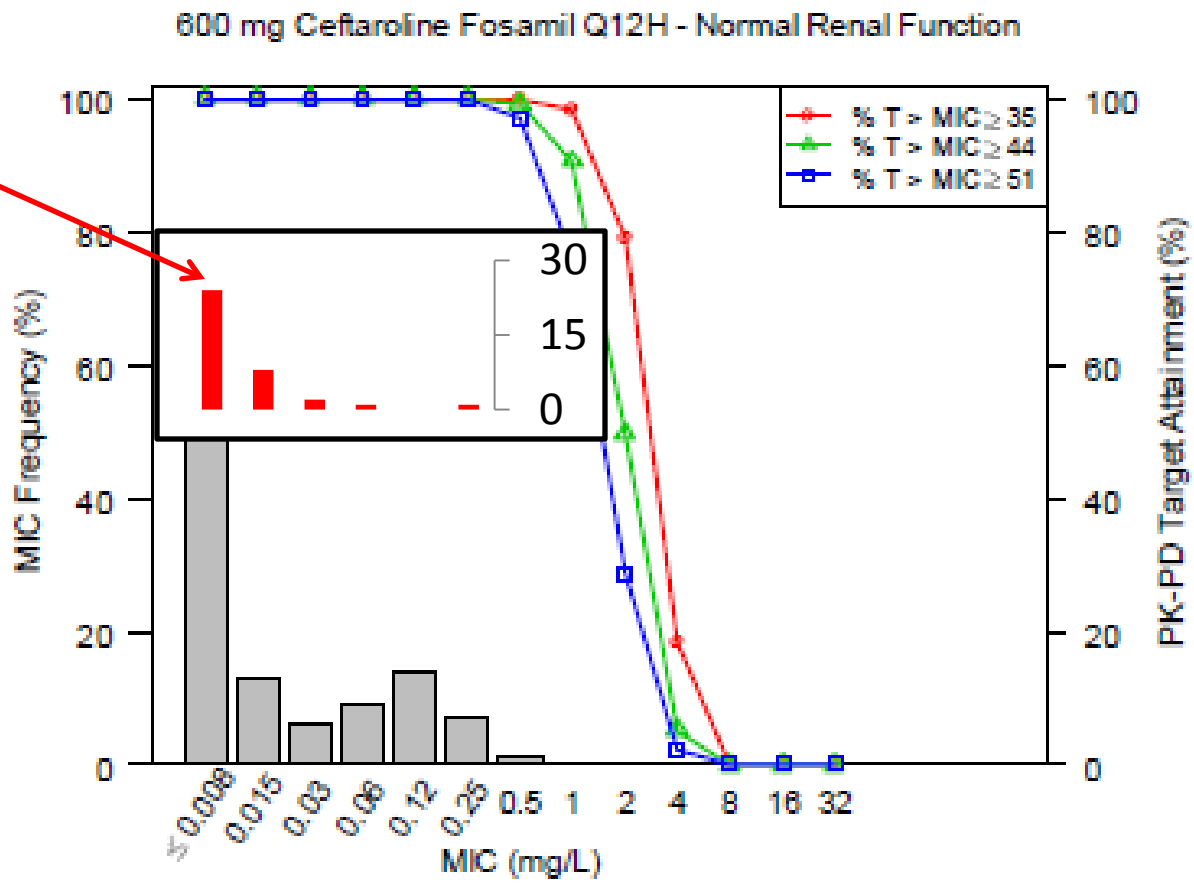
- PK-PD shows ≥ 97% target attainment up to an MIC = 0.5 mg/L
  - Lines: % target attainment for %T > MIC of 35, 44, and 51%
  - In grey: MIC population distribution for *S. pneumoniae*



Source: Section 9.2.3 and figure 9.2.3-1 from 4 May 2012 data package presented to CLSI on ceftaroline

Ceftaroline in CABP: *S. pneumoniae*

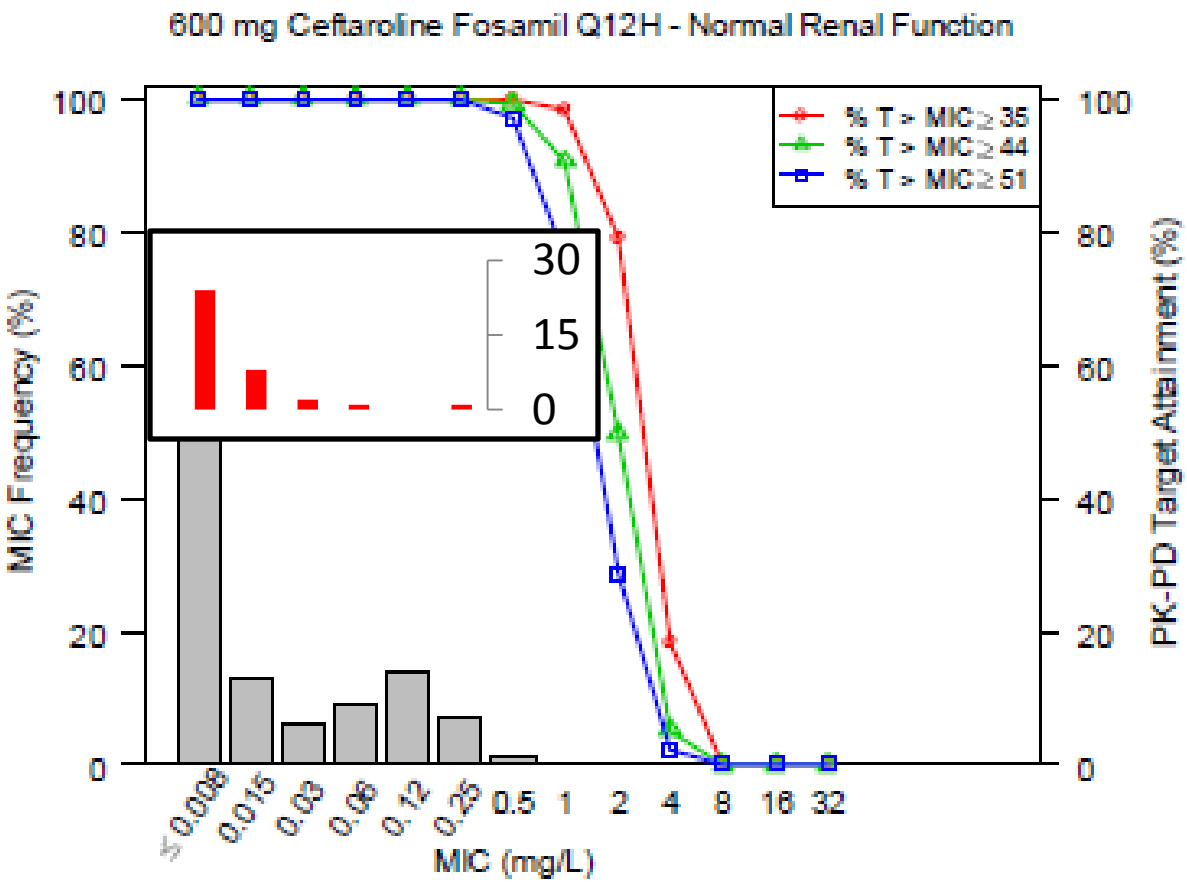
- Trial isolates mirrored wild-type MIC distribution
  - Inset graph: MICs of trial isolates
    - 24 @ ≤ 0.008
    - 8 @ 0.015
    - 2 @ 0.03
    - 1 @ 0.06 & 0.25
  - Clinical Failures
    - 4 @ 0.008
    - 2 @ 0.015
  - Others: Success



Source: Figure 9.2.3-1 and Table 9.2.2-1 from 4 May 2012 data package presented to CLSI on ceftaroline

Ceftaroline in CABP: *S. pneumoniae*

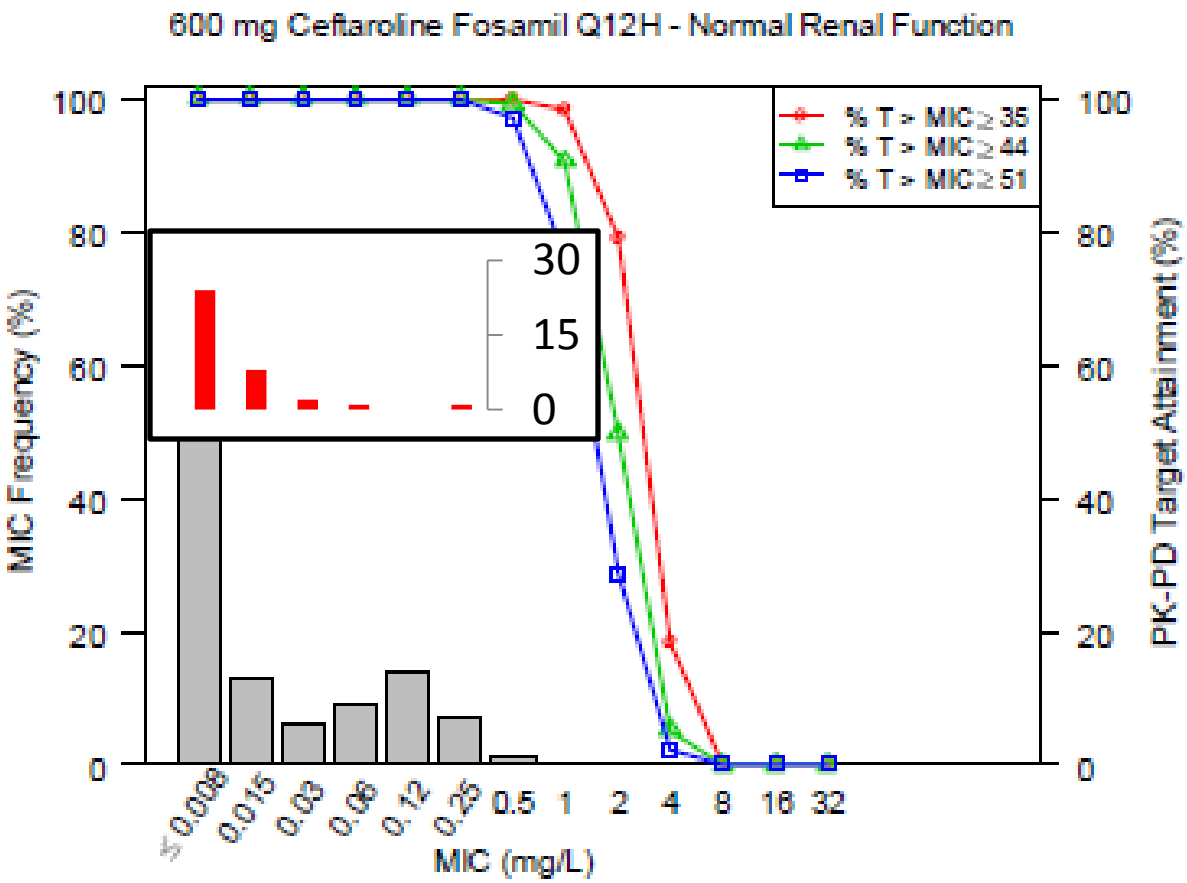
- What do you do?
  - Only 4 isolates at MIC ≥ 0.03 mg/L
  - Setting S cut-off at ≤ 0.015 mg/L would cause 34% of current isolates to be reported as non-susceptible



Source: Figure 9.2.3-1, Table 9.2.2-1, and Table 9.2.4-1 from 4 May 2012 data package presented to CLSI on ceftaroline

Ceftaroline in CABP: *S. pneumoniae*

- Resolution: Considering PK-PD, consistent clinical data, & wild-type distribution, (S)usceptible defined as
  - FDA: ≤ 0.5 mg/L
  - EMA: ≤ 0.25 mg/L
  - CLSI: ≤ 0.5 mg/L



Source: Figure 9.2.3-1 and Table 7.1.3.3.1-1 from 4 May 2012 data package presented to CLSI on ceftaroline. July 2013 US PI (Teflaro), ZINFORO EMEA SMPC (as accessed online 27 Sep 2013), and CLSI meeting minutes.

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Recent CLSI review of cefepime

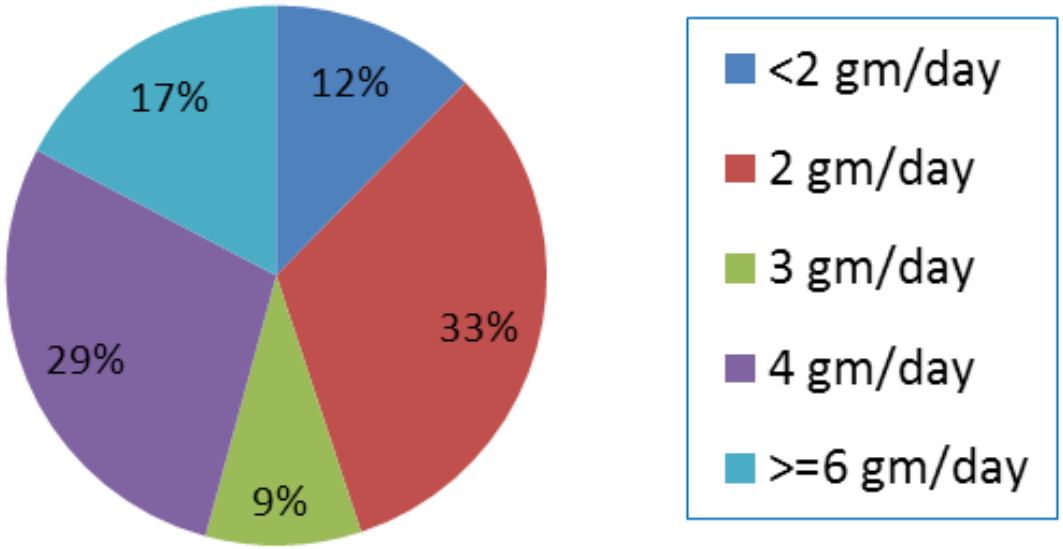
- Concern: Current breakpoints might be too high for Enterobacteriaceae
  - Current: S $\leq$ 8 mg/L, I = 16 mg/L, R $\geq$ 32 mg/L
  - Breakpoints were set based on the highest approved daily dosage of cefepime
  - Evidence of clinical failures for isolates with MICs of 4mg/L and 8mg/L, especially when low- to mid-range daily dosages were used

US label: Approved regimens

Site/Infection Type	Dose	Frequency	Total Daily Dose
Mild to Moderate UTI	0.5-1g	12h	1-2g
Severe UTI	2g	12h	4g
Mild to severe pneumonia	1-2g	12	2-4g
Moderate to severe SSTI	2g	12h	4g
Complicated IAI	2g	12h	4g
Neutropenic fever	2g	8h	6g

What dosages are most prescribed?

Cefepime Regimens at ~120 US Hospitals (27,694/6 months)



- **45% of usage: ≤ 2 g/d**
- CAVEAT: Not possible to adjust these data for rate of dose reductions due to impaired renal function

Subsequent review removing patients with renal impairment discharge codes yielded similar results: 49% given ≤ 2 g/d (personal communication, Sep 2013, Jean Patel, CDC)

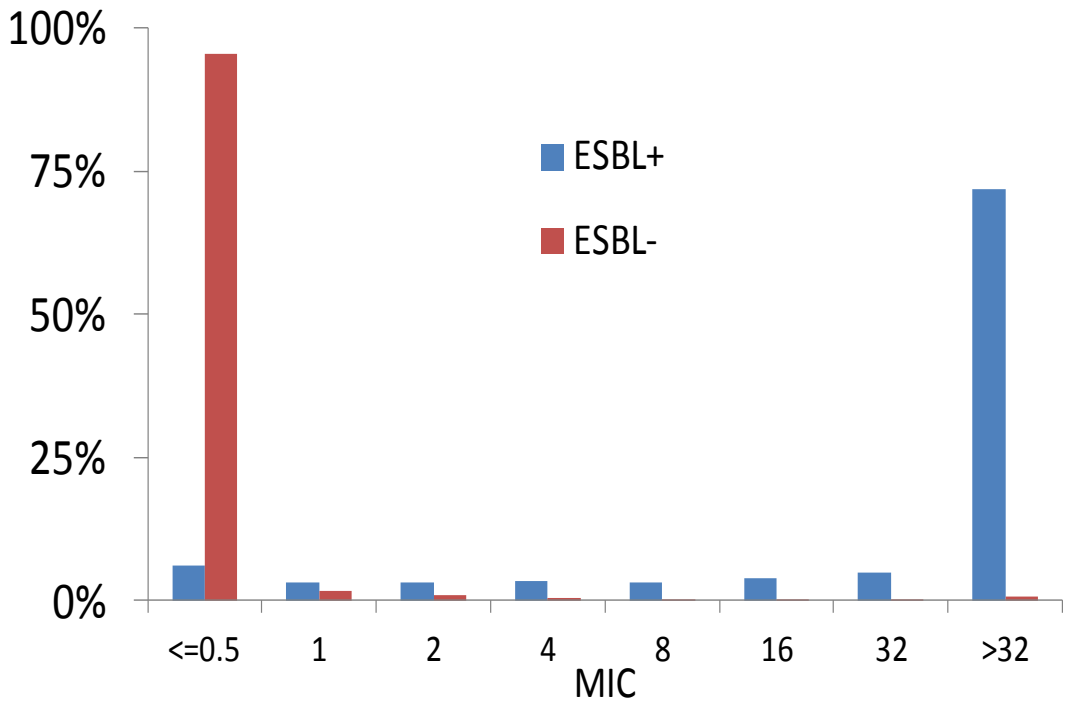
Data courtesy of Vikas Gupta, Pharm.D., BCPS, Director, CareFusion MedMined™ services

What breakpoints are suggested by the available data?

Data Source	Dose	Susceptible Breakpoint	Comment
Micro Data	N/A	1 mg/L	
Monte Carlo Simulation of PK-PD Data	1g 12h	2 mg/L	Based upon a target of 50% T > MIC for 90% of the population
	1g 8h	2-4 mg/L	
	2g 12h	4 mg/L	
	2g 8h	8 mg/L	
Clinical Outcome	1g 8h	2-4 mg/L	

The problem is with ESBL-producing strains

- Global data on Ent'bacteriaceae[1] MIC frequency from SMART[2] 2002-2012
- ESBL+ (14,263)
- ESBL- (55,274)



[1]Data as provided to June 2013 CLSI AST subcommittee on phenotypically characterized isolates of *E. coli, K. pneumoniae, K. oxytoca*, and *P. mirabilis*. [2]Study for Monitoring Antimicrobial Resistance Trends, Source: Robert Badal, IHMA

Recent clinical outcome data for ESBL-producing *Enterobacteriaceae*

MIC	3g/d	4g/day	6 g/day
0.5 mg/L	S S		
1 mg/L	S F		S
2 mg/L	S S	F F	
4 mg/L	S	F F	
8 mg/L	F F	S F F	

Best available recent outcome data

- 17 cases from Lee NY et al. CID 56:488-495, 2013 supplemented by unpublished data from the authors
- Outcomes: S = Clinical Success; S = Clinical Success + micro persistence
  F = Clinical Failure

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1 mg/L	S F		S
2 mg/L	S S	F F	No data!
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Best available recent outcome data

- 17 cases from Lee NY et al. CID 56:488-495, 2013 supplemented by unpublished data from the authors
- Outcomes: S = Clinical Success; S = Clinical Success + micro persistence
  F = Clinical Failure

- Conclusion: No data at highest dosage/MIC, many confounders, N very small → hard to make strong inferences from these clinical data

What to do?

- Cefepime is an important drug
  - When isolates are labeled I or R …
  - … use of a carbapenem often follows
- There are very few new Gram-negative drugs
  - We can’t afford to lose this one
- But, the pattern of low(er) dosage regimen usage suggests that current breakpoints are putting patients at risk

CLSI Conclusion

- New breakpoints
  - S ≤ 2 mg/L (zone diameter: ≥ 25 mm)
  - S-DD 4-8 mg/L (zone diameter: 19-24 mm)
  - R ≥16 mg/L (zone diameter: ≤ 18 mm)

- What is S-DD?
  - SDD = Susceptibility is Dosage-Dependent

About S-DD

- What's between S and R? The problem with I…
  - Does it mean Indeterminate? Intermediate? Inconclusive?
  - All are used variously with the result that I is often taken to effectively mean R … even if a higher dose would work
  - MS (moderately susceptible) and MR (moderately resistant) are also flawed: They don't tell you what to do
- S-DD: Susceptibility is dose (or dosage) dependent
  - Communicates what we know – a higher dose is indicated
  - Has been used for antifungal susceptibility testing for years
  - We think the user community can handle this and that use of S-DD allows us to get the maximum from cefepime

S-DD: The Definition

Current draft text for CLSI's M-100 summary document:

- The "susceptible-dose dependent" category (S-DD) implies that susceptibility is dependent on the drug dose that is used.
- In order to achieve levels that are likely to be clinically effective against isolates with MICs or disk zone diameters in this category, it is necessary to use a dose higher than the dose that was used to establish the susceptible category.

Another example: Penicillin and *Streptococcus pneumoniae*

Breakpoint	S	I	R
PRE-2008			
Penicillin	≤0.06	0.12 – 1.0	≥2

- Pre-2008, one set of breakpoints was used for both meningitis and nonmeningitis infections.
- These breakpoints overcalled resistance for pneumonia
- Comments that “intermediate” isolates causing pneumonia could be treated with high-dose penicillin were not widely understood
- Effect: We lost an effective treatment for this cause of pneumonia

Another example: Penicillin and *Streptococcus pneumoniae*

Breakpoint	S	I	R
PRE-2008			
Penicillin	≤0.06	0.12 – 1.0	≥2
POST-2008			
Penicillin (meningitis)	≤0.06		≥0.12
Penicillin (nonmeningitis)	≤2	4	≥8

- Review of the available information (observational clinical data + PK-PD) supported S ≤ 2 mg/L for non-meningeal infections
- Action: Breakpoints by isolate source were created
- This distinction is easily applied by the clinical laboratory
- Impact: Perceived "Resistance" was eliminated for non-meningeal isolates and a valued drug was restored

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Practical Issues

- Updates to interpretive criteria will continue
  - E.g., CLSI plans to consider S-DD for other drugs
- Laboratory information systems (LIS) can accommodate changes such as this
  - Most newer systems can display “S-DD” plus additional text as desired
  - Can use “D” for “S-DD” to maintain single letter text
- We are still learning: Simple categories best for now
  - By-site adjustments appear tricky as infection may spread from most obvious site OR primary site may be subtle→ err upwards; S-DD seems best suited to address MIC ranges
  - Doses change by age and organ function

Safety & Stewardship

- Safety
  - As long as higher doses have been studied for safety, it is rational to encourage their use for specific situations even if not specifically studied for that indication at that dosage
- Stewardship
  - Using a higher dose where required by new insight simply makes good sense – using suboptimal doses will drive resistance and clinical failure
  - We need to get the most we can from every drug

Conclusions

Our answers to the AC questions

- Within the limits of approved dosages & exposures, can you adjust recommended dosages for specific situations based on PK-PD considerations?
  - YES
- Can interpretive criteria be created and applied to address specific situations (isolate source, isolate genus or species, drug dose)?
  - YES

Summary

- By the very nature of MIC distributions, isolates with MICs at boundaries are less common
  - As a result, clinical data alone may not provide direct support for breakpoints suggested by PK-PD
- Good stewardship requires us to
  - Get the most out of every drug
  - Continue to adjust breakpoints and breakpoint definitions
  - All of which requires reliance on PK-PD
- Laboratory practice is evolving in support
  - Interpretive reports can give significant user guidance.
  - Care needed in building complex interpretive criteria, but by-category approaches have been successfully deployed

Thank you!