How changes in the regulatory landscape will impact future anti-infective therapy development

John H. Rex, Vice President
Head of Infection Global Medicines Development
AstraZeneca Pharmaceuticals
john.rex@astrazeneca.com

Slides happily shared – just drop me a note

Two themes

- New pathways for approval of antibacterials
  - PK-PD at the heart of it all
- Approaches to interpretive breakpoints
  - Again, PK-PD points the way

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A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

John H Rex, Barry I Eisenstein, Jeff Alder, Mark Goldberger, Robert Meyer, Aaron Dane, Ian Friedland, Charles Knirsch, Wendy R Sanhai, John Tomayko, Cindy Lancaster, Jennifer Jackson

The fundamental role of PK-PD in Tier B and Tier C development programs

The paradigm gap

- For registration, we traditionally expect
  - Two substantial trials per indication (e.g., two UTI trials)
  - Typical size & cost/trial: ~1,000 patients, ~$50-70m
- This presumes ready availability of substantial numbers of patients with the target disease
- But, what if the target disease includes requirement for a specific less common pathogen or type of resistance?
  - Less common pathogen: *Pseudomonas*
  - Emerging form of resistance: KPC or Metallo-ß-lactamase
- When only limited clinical data are possible, current paradigms give no easy way forward
  - Waiting for widespread resistance means we can't anticipate the epidemic

The antibiotic paradigm gap
Existing regulatory framework

Traditional Development:

Two well-controlled, adequately powered Phase III studies per body site to demonstrate safety and efficacy

Focused on body sites of infection

The "Animal Rule:"[1]

For cases when studies in humans are unethical; Approval based on human safety studies and preclinical (non-human) efficacy studies

Focused on infectious agent

[1]In the US, defined in 21 CFR 314·600–650. No specific equivalent exists in the EU regulatory framework, but the idea is discussed in Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2. London: European Medicines Agency, 2011.

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Pathogen-focused development as a middle path

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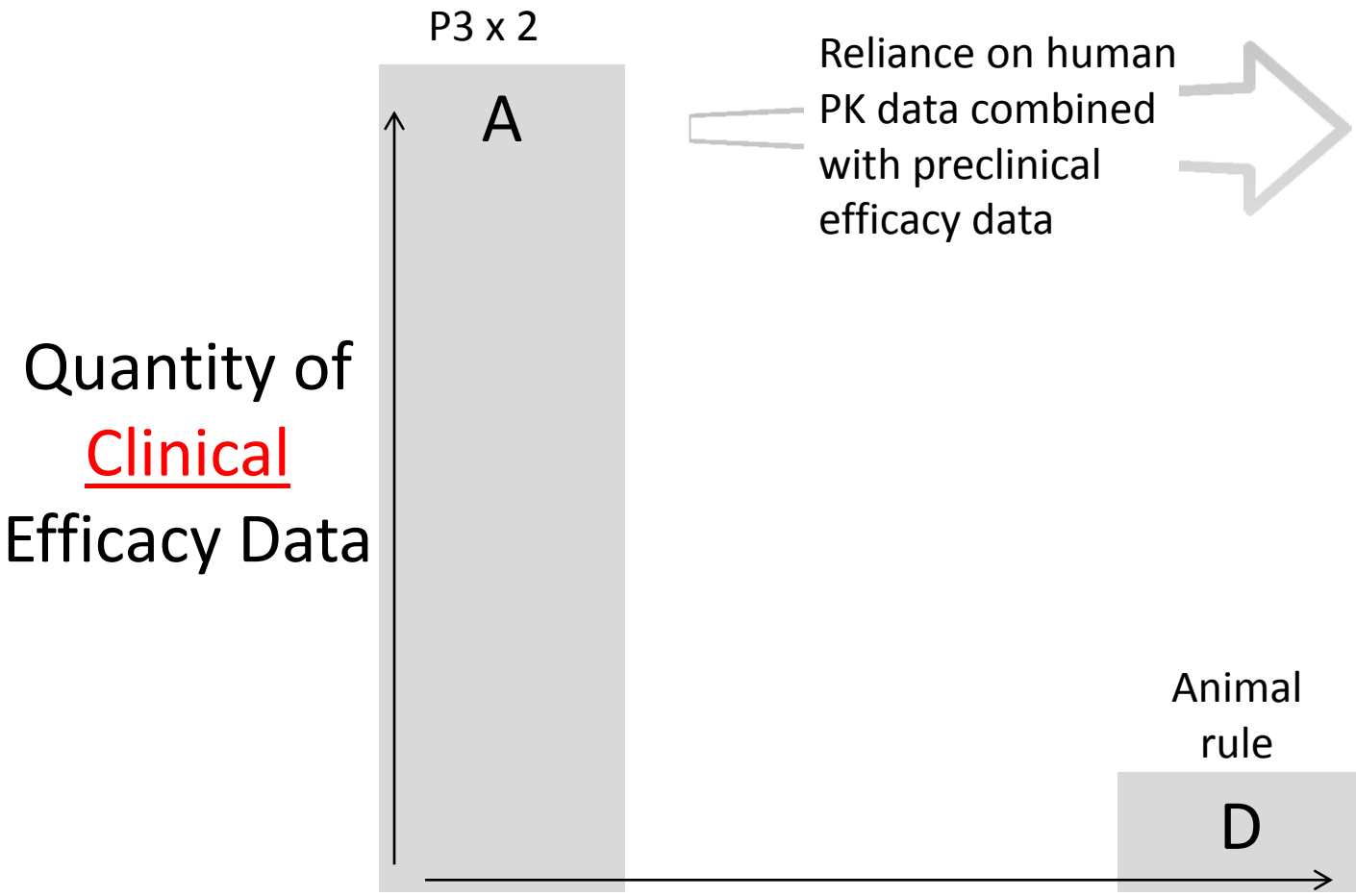
Addressing unmet need via Four Tiers

A & D are familiar…

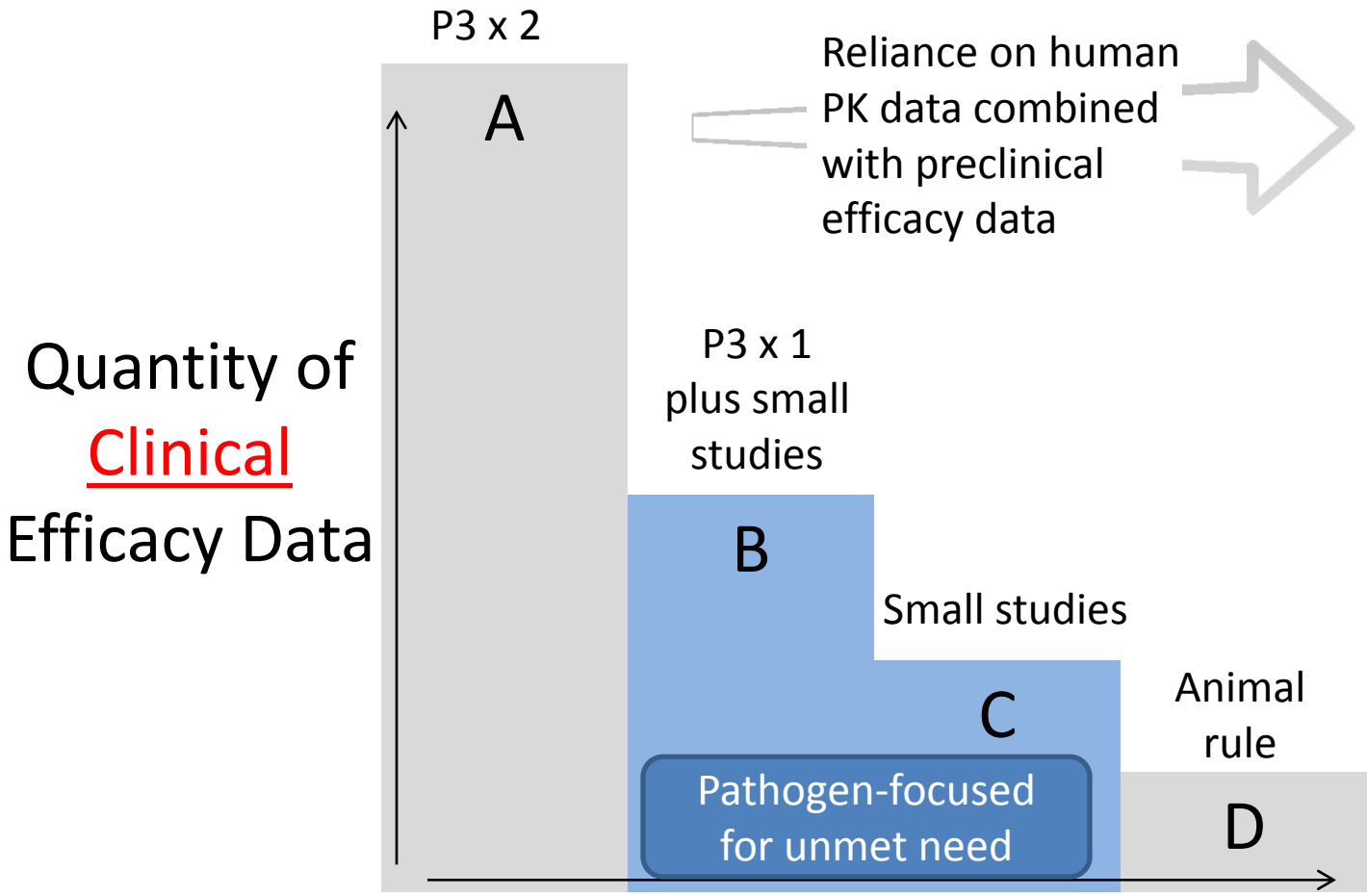


Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

Rex et al. Lancet Infect Dis 2013; 13: 269-75

Addressing unmet need via Four Tiers

A & D are familiar, B & C are new



Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

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Tier Overview: Preclinical

Attribute	Tier B	Tier C
Example spectrum	**Broad** with MDR pathogen coverage	**Narrow** MDR pathogen coverage
Example target pathogen	MDR Enterobacteriaceae (also covers non-MDR)	*Pseudomonas aeruginosa* **only**
Challenge in studying MDR pathogen in large numbers?	Yes	Yes
Detailed insight into:		
Microbiology including mechanism of action and resistance?	Yes	Yes
Animal models that mimic human disease?	Yes	Yes
Exposure-response in animals?	Yes	Yes

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Tier Overview: Clinical

Attribute	Tier B	Tier C
Detailed PK/PD justification of dose selection in humans[1]	Yes	Yes
Can do "standard" P3 study vs. *susceptible* organisms?	Yes[2]	No
Randomized comparative data generated?	Yes (single body site, vs. standard comparator)	Yes (multiple body sites, vs. BAT[3])
Able to do "usual strength" statistical inference testing?	Yes, but only in the standard P3 study	No
Pooling of data across infection sites proposed?	Yes	Yes
Reliance on a totality-of-evidence approach?[4]	High	Even higher

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin, PK known in healthy volunteers and relevant patient groups. [2]This provides relevant efficacy data if MDR pathogens have same susceptibility to new agent as do non-MDR pathogens. [3]BAT = Best Available Therapy, standardized insofar as possible. [4]All drug reviews consider the totality of evidence, but the reliance on such things as PK-PD predictions and pooled responses across sites will be very high here.

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Tier B/C Development Programs[1]

- **Tier B:** Two treatment studies (one large, one small)
  - Standard P3 study of Drug B vs. standard comparator at standard body site
    - No expectation of enrolling any resistant pathogens!
    - Provides general data on activity of Drug B
  - Open-label salvage study of Drug B for MDR pathogens
- **Tier C:** Two treatment studies + one observational study
  - Prospective, randomized, open-label study of Drug C vs. BAT[2] across multiple body sites. N ≅ a few 100
  - Open-label salvage study for MDR pathogens (no BAT exists)
  - Observational study of (inadvertent) ineffective therapy for the target pathogen (estimates placebo response)[3]

[1]Detailed examples are available. [2]BAT = Best Available Therapy, standardized insofar as possible. [3]There is no easy way to provide a good control group: Ineffective therapy does not mean no therapy and also might quickly be replaced with active therapy. One might also use modern data (pharmacometric estimates of placebo response rates: AAC 56:1466, 2012), pharmacometric analyses with the new drug, or historical estimates of true placebo response rates.

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What is the status of these ideas?

- EMA: Final addendum[1] released 24 Oct 2013
  - Clearly describes Tier B & C as acceptable pathways
  - A Tier C variant using external controls is also described
- FDA: Draft "Unmet Need" guidance[2] released July '13
  - It is less detailed than the EMA addendum, but signals significant flexibility and a desire for dialogue
  - Recent specific interactions have shown that Tier B- and Tier C-like programs can be acceptable
- In short, all conversations point to the same ideas
  - Careful PK-PD work can point to a dose
  - The registration program can take many forms

[1]EMA/CHMP/351889/2013; Committee for Human Medicinal Products (CHMP); Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. [2]DHHS/FDA/CDER: Guidance for Industry Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases

Two themes

- New pathways for approval of antibacterials
  - PK-PD at the heart of it all

- Approaches to interpretive breakpoints
  - Again, PK-PD points the way

Interpretive breakpoints

- Interpretive breakpoints[1] are the rules used to provide predictive categories of Susceptible, Intermediate, or Resistant (S, I, and R) that give health care providers a quick guide to possible antibiotic choices

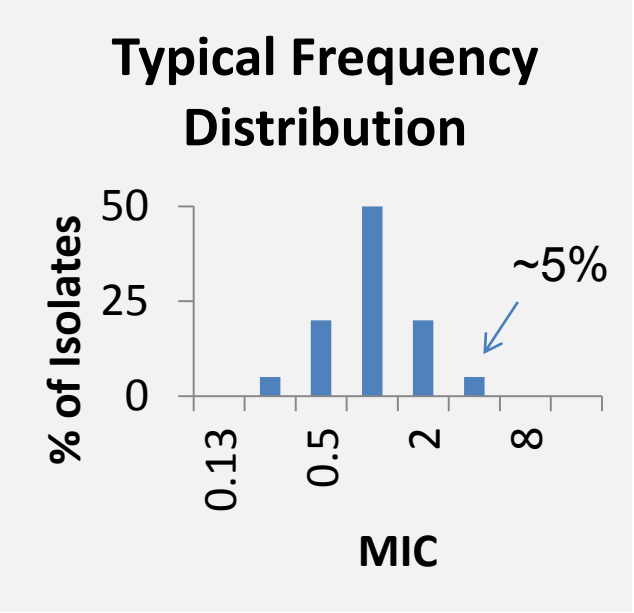
- This sounds simple – does the drug inhibit the bacteria or not? But, the problem becomes complex very quickly[1,2]
  - The idea of "the drug" has to be translated into "the concentration of the drug at the relevant body site when the patient is given a specific dosage regimen."
  - The drug's concentration in patients rises and falls with dosing whereas testing in the laboratory can only for practical purposes be done at fixed drug concentrations.
  - Experience has shown that infections differ in terms of the intensity of drug effect needed.
  - Not at all body sites are the same in terms of drug penetration!

- Despite this complexity it has been possible to develop breakpoints for most bug-drug combinations that offer a good aid to drug selection

[1]Ambrose PG et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It's not just for mice anymore. Clin Infect Dis 2007;44:79-86. [2]Ambrose PG et al. Frequentist and bayesian pharmacometric-based approaches to facilitate critically needed new antibiotic development: overcoming lies, damn lies, and statistics. Antimicrob Agents Chemother 2012;56:1466-70.

The Breakpoint Challenge

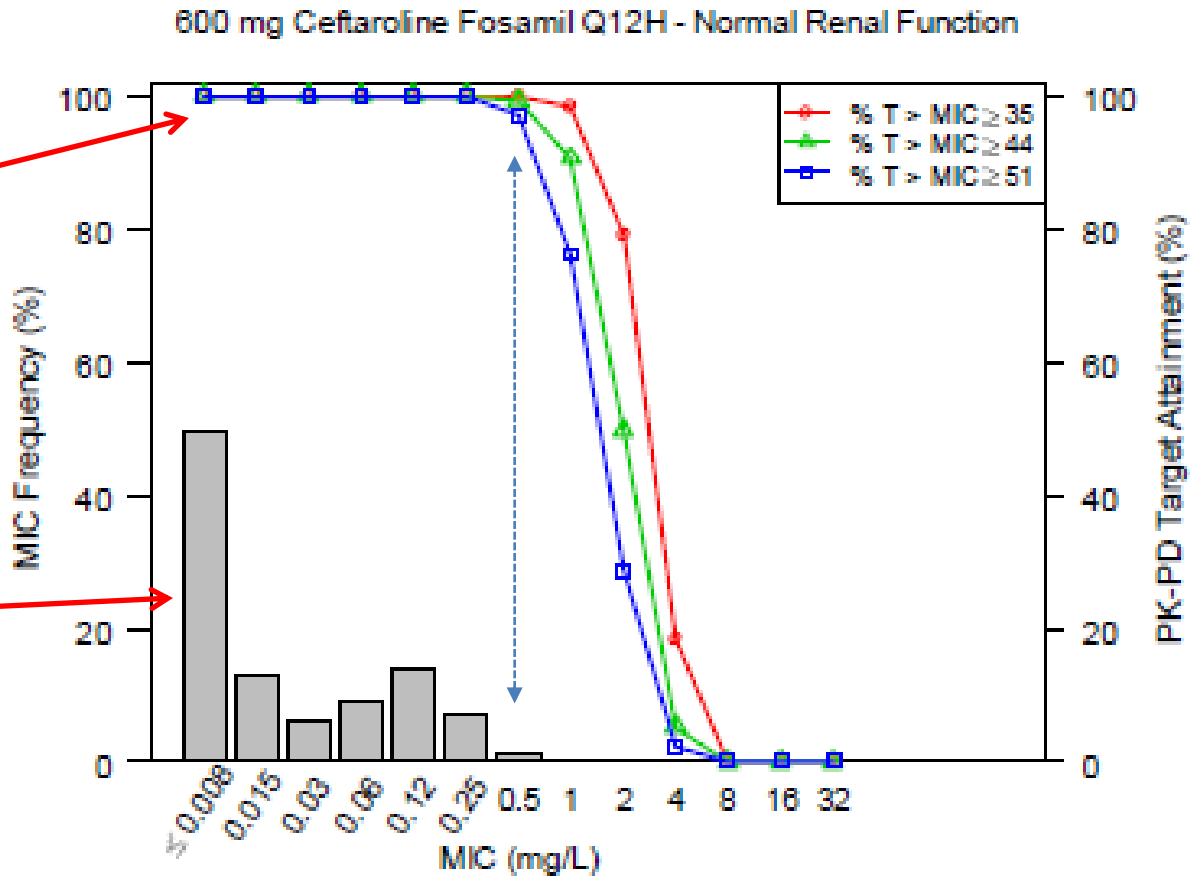
- Breakpoints can only rarely be set based on clinical data
  - MIC distributions usually span 4-5 dilutions
  - Relatively few patients are infected with isolates at the highest MIC



- This problem gets worse as trial programs get smaller
- Thus, breakpoints will be too low if we limit breakpoints to MICs for which we have clinical data
- Let's look at an example of this problem…

Ceftaroline in CABP: *S. pneumoniae*

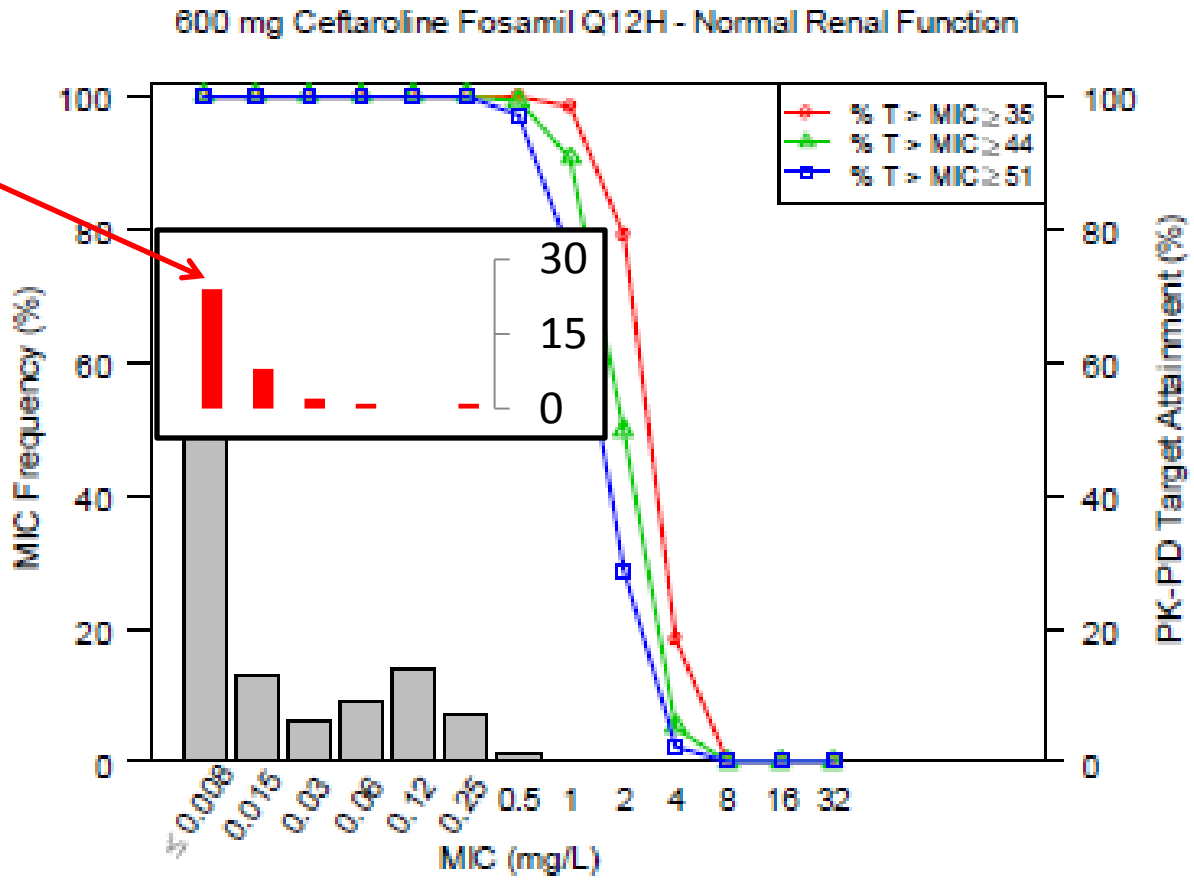
- PK-PD shows ≥ 97% target attainment up to an MIC = 0.5 mg/L
  - Lines: % target attainment for %T > MIC of 35, 44, and 51%
  - In grey: MIC population distribution for *S. pneumoniae*



Source: Section 9.2.3 and figure 9.2.3-1 from 4 May 2012 data package presented to CLSI on ceftaroline. Data available upon request.

Ceftaroline in CABP: *S. pneumoniae*

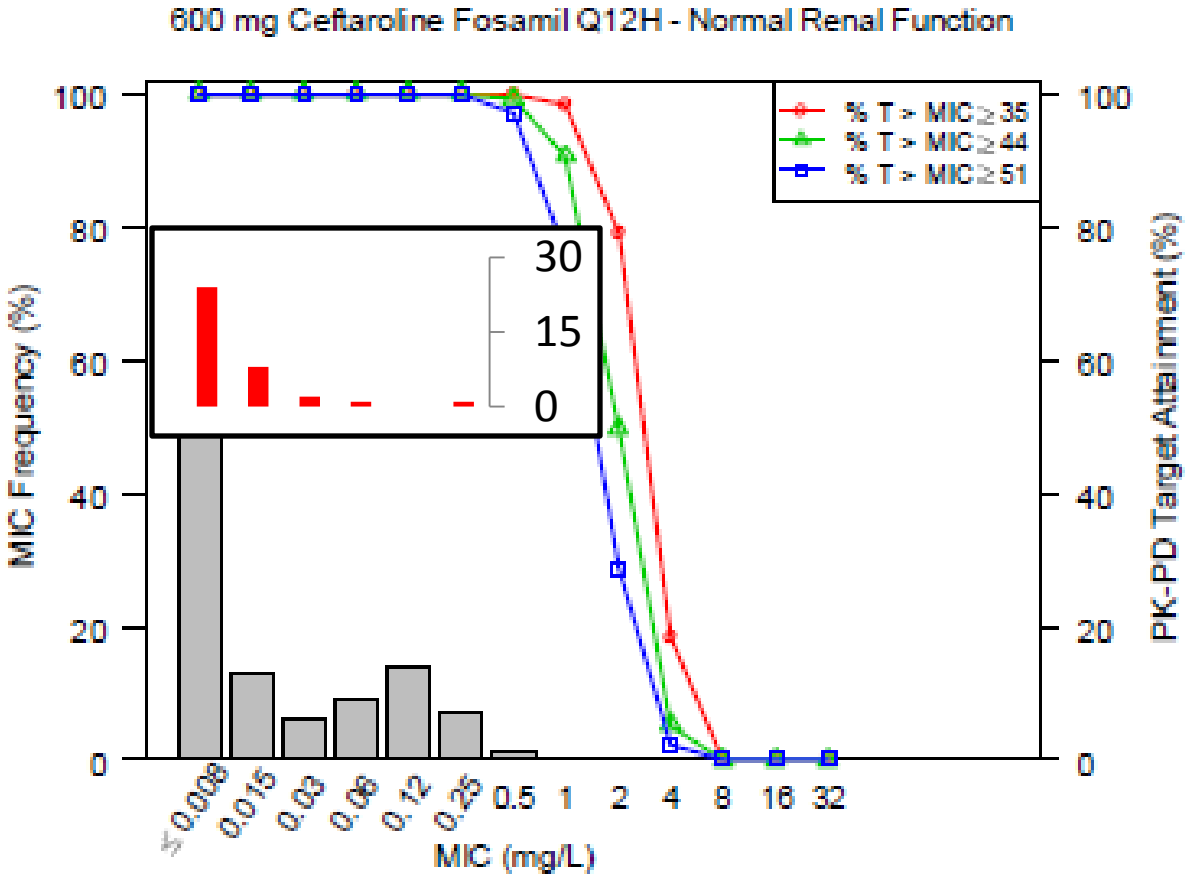
- Trial isolates mirrored wild-type MIC distribution
  - Inset graph: MICs of trial isolates
    - 24 @ ≤ 0.008
    - 8 @ 0.015
    - 2 @ 0.03
    - 1 @ 0.06 & 0.25
  - Clinical Failures
    - 4 @ 0.008
    - 2 @ 0.015
  - Others: Success



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

Ceftaroline in CABP: *S. pneumoniae*

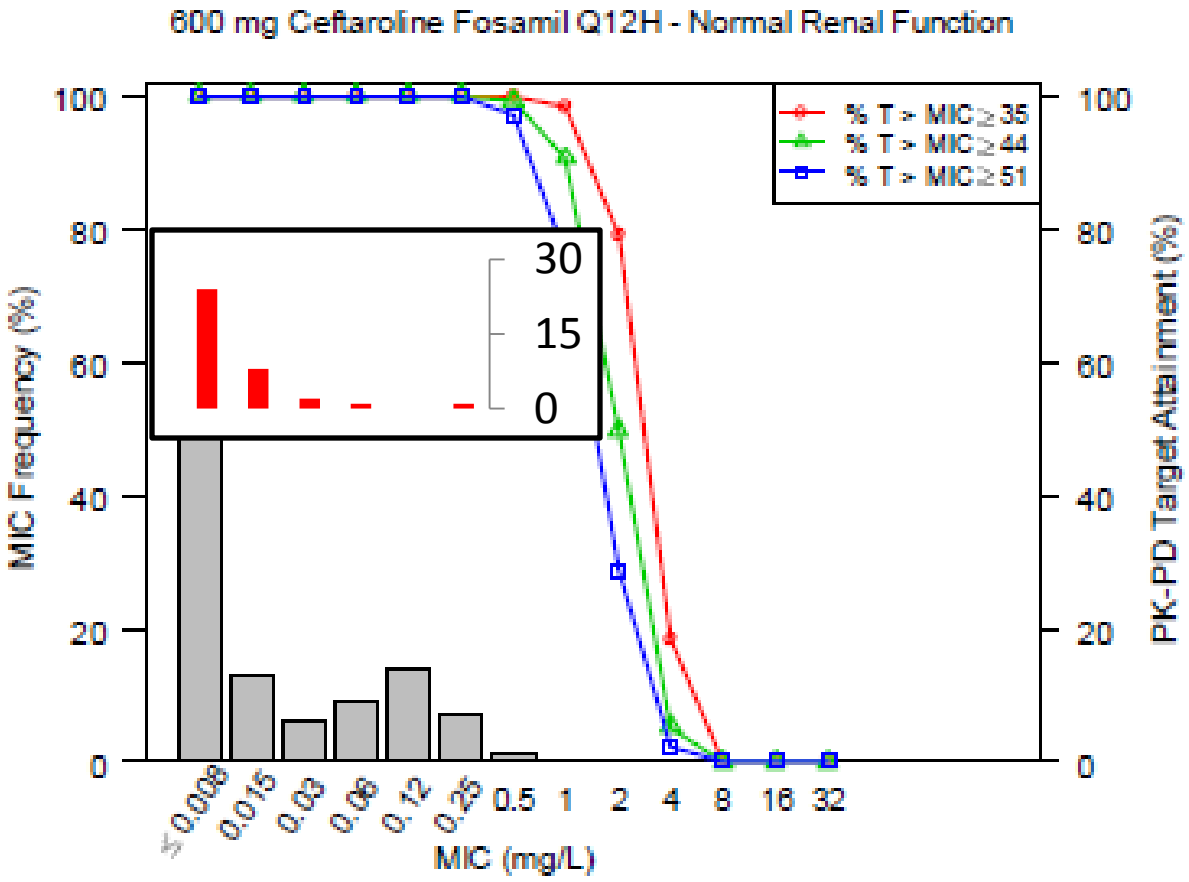
- What do you do?
  - Only 4 isolates at MIC ≥ 0.03 mg/L
  - Setting S cut-off at ≤ 0.015 mg/L would cause 34% of current isolates to be reported as non-susceptible



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. Data available upon request.

Ceftaroline in CABP: *S. pneumoniae*

- Resolution: By 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. CLSI materials available upon request.

Summary

Our head is round so that our thinking can change direction (Francis Picabia)

Summary: Mind the gap

- An approach to the paradigm gap is suggested
  - PK-PD is at the heart of it all
  - This science is really very compelling
- These new options are desperately needed[1,2,3]
  - By acting quickly to create approaches to describe and manage the uncertainty of small data packages,
  - We will provide patients with timely access to urgently needed, life-saving antibiotics and
  - We will avoid the paradoxical situation of being forced in the future to accept even greater degrees of therapeutic uncertainty as antimicrobial resistance progresses.

[1]Hersh et al., Clinical Infectious Diseases 54:1677, 2012. Among 562 respondents in a 2011 survey of the Emerging Infections Network (EIN), 64% reported using colistin during the previous year and 63% reported caring for a patient with an infection resistant to all available antibacterials. [2]Boucher HW et al. Clin Infect Dis 56:1685-94, 2013. [3]Rex et al. Lancet Infect Dis 2013; 13: 269-75.