Anti-Infective Advisory Committee Meeting on Susceptibility Test Interpretive Criteria

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Background

- Susceptibility test interpretive criteria are set to
  - facilitate the selection of an antibacterial drug that would provide a high likelihood of the drug's antibacterial effect and increase the likelihood of a positive clinical outcome
  - reduce the likelihood that ineffective antibacterial therapies will be administered

Background

- Susceptibility test interpretive criteria are set at the time of approval of a new drug application. Data generally used to set these criteria include:
  - in vitro microbiology data for distributions of MICs or zone diameters for the drug against recent clinical isolates of the target pathogens
  - data from animal models of infection including PK/PD information
  - correlation of the MIC or zone diameter with clinical and microbiological outcome from clinical trials

Background

- More recently, the Agency has been updating susceptibility test interpretive criteria in antibacterial drug labeling
- During this process, some issues that merit further discussion have arisen
  - types of data that can be used to support the revisions
  - limitations of such data both from a quantitative and qualitative standpoint

Background and Rationale for Revised Clinical and Laboratory Standards Institute Interpretive Criteria (Breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and Aztreonam

Michael N. Dudley,[1] Paul G. Ambrose,[2] Sujata M. Bhavnani,[2] William A. Craig,[3] Mary Jane Ferraro,[4] and Ronald N. Jones;[5] for the Antimicrobial Susceptibility Testing Subcommittee of the Clinical and Laboratory Standards Institute

Clinical Infectious Diseases 2013;56(9):1301–9

	MIC (µg/mL)					
	Revised			Pre-2010		
Drug (Dosage)[a]	S	I	R	S	I	R
Aztreonam (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Cefotaxime (1 g q8h)	≤1	2	≥4	≤8	16–32	≥64
Ceftazidime (1 g q8h)	≤4	8	≥16	≤8	16	≥32
Ceftizoxime (1 g q12h)	≤1	2	≥4	≤8	16–32	≥64
Ceftriaxone (1 g q24h)	≤1	2	≥4	≤8	16–32	≥64

Clinical Infectious Diseases 2013;56(9):1301–9

Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase–Producing *Enterobacteriaceae*: MIC Matters

Nan-Yao Lee,[1,2] Ching-Chi Lee,[1,2] Wei-Han Huang,[4] Ko-Chung Tsui,[5,8] Po-Ren Hsueh,[6,7,a] and Wen-Chien Ko[1,2,3,a]

Conclusions. Based on the current Clinical and Laboratory Standards Institute susceptible breakpoint of cefepime (minimum inhibitory concentration ≤8 μg/mL), cefepime definitive therapy is inferior to carbapenem therapy in treating patients with so-called cefepime-susceptible ESBL-producer bacteremia.

Clinical Infectious Diseases 2013;56(4):488–95

Outcomes of Children With Enterobacteriaceae Bacteremia With Reduced Susceptibility to Ceftriaxone: Do the Revised Breakpoints Translate to Improved Patient Outcomes?

Pranita D. Tamma, MD, MHS, Harold Wu, BA,* Jeffrey S. Gerber, MD, PhD,† Alice J. Hsu, PharmD, BCPS, AQ-ID,‡ Tsigereda Tekle, MT, ASCP,§ Karen C. Carroll, MD,§ and Sara E. Cosgrove, MD, MS¶*

Conclusions: Our findings do not support the proposed clinical benefit of more conservative CLSI breakpoints. The revised breakpoints promote increased broad-spectrum β-lactam use. The need for lowered ceftriaxone breakpoints against Enterobacteriaceae in children needs to be reevaluated in larger prospective studies.

Pediatr Infect Dis 2013 Sep;32(9):965-969.

Issue at hand

- Microbiology
  - Increasing resistance; shifts in distribution of MICs
- Clinical
  - Some reports of clinical failures at higher MICs (at or below the susceptible breakpoint)
- Pharmacokinetics/Pharmacodynamics
  - Probability of target attainment analysis suggest that current susceptibility test interpretive criteria may need to be revised
- Limited treatment options available for the treatment of certain pathogens, need to maximize use of available therapies

Limitations of the Available Data

- Clinical
  - Little or no efficacy data from randomized clinical trials (RCTs)
  - Limited data regarding clinical outcomes at higher MICs
- Microbiology
  - New resistance mechanisms
- Pharmacokinetics/Pharmacodynamics
  - Targets generally based on animal models; consideration should be given as to when a static versus cidal target is optimal
  - While the probability of target attainment for a given PK/PD target provides a likelihood of clinical success, it is not a guarantee
  - The results are only as good as the component pieces: well-defined targets from animal models, population pharmacokinetic models, and probability of target attainment simulations

Examples

- Two hypothetical scenarios that highlight some of the issues. The hypothetical scenarios are based on issues we have seen; data are however masked/modified to de-identify the drugs
- Using these examples, we have tried to highlight some key concepts on which we seek the committee's advice
- Despite our best attempts, creating perfect hypothetical scenarios is extremely challenging

Key concepts in both examples

- Specific organism is included in product labeling for different indications
- Dosing regimens vary across different indications
- Efficacy data from RCTs only available for a specific indication at the dosing regimen included in product labeling
- Safety data from RCTs available at higher doses from other indications
- No major safety concerns with higher doses

Options

- Have one set of susceptibility test interpretive criteria based on the higher approved dosing regimen
  - Higher dose likely to be as effective as the lower dose
  - Safety at the higher dose known
- Set the susceptibility test interpretive criteria based on the lowest approved dosing regimen
- Have different susceptibility test interpretive criteria, one for each of the approved dosing regimens/indications

Scenario 1: Drug A

- A beta-lactam antibacterial drug approved for
  - Acute Bacterial Skin and Skin Structure Infections (ABSSSI) at a dosing regimen of 1 g IV q8h
  - Hospital Acquired Bacterial Pneumonia (HABP) at a dosing regimen of 2 g IV q8h
  - Osteomyelitis at a dose of 4 g IV q8h
- *Pseudomonas aeruginosa* is listed as a pathogen in ABSSSI and HABP indications and not in the osteomyelitis indication

Scenario 1: Drug A

- Currently, the susceptible breakpoint for *P. aeruginosa* is 8 mcg/ml
- Need to revise breakpoints as clinical failures reported at higher MICs (susceptible range), PK/PD data and surveillance data
- Clinical Data:
  - Safety data from randomized clinical trials in HABP at the 2 g IV q 8h dosing regimen and at 4 g IV q 8h in osteomyelitis
  - However, no safety or efficacy data are available for Drug A at the 2 g IV q 8h dosing regimen in patients with ABSSSI due to *P. aeruginosa*

Scenario 1: Drug A

- Three options are:
  - Change the susceptible breakpoint to 4 mcg/mL and increase the dose in the ABSSSI indication to match the dose in the HABP indication
  - Change the susceptible breakpoint to 2 mcg/mL for both ABSSSI and HABP based on the lowest exposure achieved with the 1 g IV q 8h dosing regimen
  - Change the susceptible breakpoint to 2 mcg/mL for ABSSSI and to 4 mcg/ml for HABP

Scenario 2: Drug B

- Drug B is a beta-lactam antibacterial drug approved for:
  - ABSSSI at a dosing regimen of 0.5 g IV q 12h
  - complicated Intra-Abdominal Infections (cIAI) at a dosing regimen of 1 gram IV q 8h
  - HABP at a dosing regimen of 2 g IV q 8h
- *Escherichia coli* is listed as a pathogen in all three indications

Scenario 2: Drug B

- Clinical Data
  - Safety data are available at 2 g IV q 8h dosing regimen for the HABP indication and at the 1 g IV q8h dosing regimen for cIAI
  - No efficacy or safety data from randomized clinical trials are available for Drug B at the 2 g IV q8h dosing regimen in patients with ABSSSI or cIAI

Scenario 2: Drug B

- Currently, the susceptible breakpoint for *E.coli* for Drug B is 8 mcg/ml.
- Limited clinical data from observational studies, surveillance data, emergence of resistance and probability of target attainment analysis suggest that the current susceptibility test interpretive criteria may need to be modified.

Scenario 2: Drug B

- Options:
  - Revise the susceptible breakpoints for *E. coli* to 0.5 mcg/ml, based on the lowest dosing regimen approved for ABSSSI.
  - Revise the susceptible breakpoints for *E. coli* to 4 mcg/ml and change the dosing regimens for ABSSSI and cIAI to 2 g IV q 8 h.
  - Have separate susceptible breakpoints for *E. coli*, for each of the approved indications and dosing regimens.

Outline for the day

- Presentations by representatives of professional organizations:
  - Infectious Diseases Society of America (IDSA): Dr. George Drusano MD
  - Pharmaceutical Research Manufacturers Association (PhRMA): Dr. John Mohr Pharm.D.
  - Clinical Laboratory Standards Institute (CLSI): Dr. John Rex MD
  - National Antimicrobial Susceptibility Testing Committee for the US (USCAST): Dr. Paul Ambrose Pharm.D.
  - Susceptibility Test Manufacturers Association (STMA): Bill Brasso

Outline for the day

- FDA Presentations
  - Ryan Owen Ph.D.: Discuss Scenario 1: Drug A
  - Peter Kim MD MS: Discuss Scenario 2: Drug B
- Review Teams
  - Drug A: Peter Coderre Ph.D. MBA; Benjamin Lorenz MD; Ryan Owen Ph.D.
  - Drug B: Avery Goodwin Ph.D.; Dakshina Chilukuri Ph.D.; Peter Kim MD MS

Question 1: Drug A

- Would it be acceptable to recommend the 2 g IV q 8h dosing regimen for both ABSSSI and HABP?

Please vote Yes/No.

  - If yes, please discuss your rationale
  - If no, please discuss alternate proposals

Question 2: Drug B

- Would it be acceptable to have different susceptibility test interpretive criteria for *E. coli* for each of the indications?
  - ABSSSI (500 mg q 12 h): 0.5 mcg/mL
  - cIAI (1 g q 8 h): 2 mcg/ml
  - HABP (2 g q 8h): 4 mcg/ml

Please vote Yes/No.

Question 2: Drug B

- If yes, please discuss
  - The practical implications of having different susceptibility test interpretive criteria for an organism for each of the different indications
  - The practical issues regarding conveying this information to a clinician
- If no, please discuss your rationale and alternate proposals

Thanks to the Team

- Kimberly Bergman
- Dakshina Chilukuri
- Peter Coderre
- Edward Cox
- J. Christopher Davi
- Maureen Dillon-Parker
- Avery Goodwin
- John Farley
- Katherine Laessig
- Benjamin Lorenz
- Peter Kim
- Eileen Navarro-Almario
- Ryan Owen
- David Roeder
- Susmita Samanta
- Thomas Smith
- Kerry Snow

Scenario #1
Drug A

Ryan P. Owen, Ph.D.
Office of Translational Sciences/ Office of Clinical Pharmacology

October 17, 2013

Anti-Infectives Advisory Committee

Outline

- Overview of susceptibility test interpretive criteria
- General Background
- Clinical
- Microbiology
- Clinical Pharmacology
- Summary
- Options

Factors Involved in Setting Breakpoints

- Multicomponent approach
  - Clinical
  - Microbiology
  - Clinical Pharmacology
- Moving Targets
  - Evolution and increased prevalence of new resistance mechanisms and changing susceptibility patterns
- Dose Dependence
  - Multiple dosing regimens
  - Selection of breakpoint is dose dependent

Pitfalls of Setting Susceptible Breakpoints

- Susceptible breakpoint is too high
  - May lead to treatment failures
- Susceptible breakpoint is too low
  - Could cause a viable therapeutic option to not be used
- Susceptible breakpoint is set based on a different dose than is being used clinically
  - Dosing regimen used clinically may differ from regimen used to set the breakpoint; this could lead to differences in patient outcome

An Ideal World

- Clinical: The safety and efficacy for a known drug at a given dosing regimen used in the treatment of an indication due to pathogen is well understood.
- Microbiology: Microbiological surveillance data are available, and the prevalence and impact of resistance mechanisms are known.
- Clinical Pharmacology: Robust population PK models are available, the PK/PD relationships are well characterized, and quality PTA simulations are available.

The Real World

- Clinical
  - Efficacy and safety data on the full range of dosing regimens may not be available from randomized controlled trials (RCTs)
  - Reliance on observational studies for safety and efficacy information
- Microbiology
  - Multiple resistance mechanisms
  - Limited surveillance data available
- Clinical Pharmacology
  - Available patient PK may be limited
  - Population PK models of variable quality

Scenario 1

Drug A

General Background for Drug A

- Drug A is β-lactam antibacterial drug widely used for the treatment of serious Gram-negative infections
- Originally approved in 1998
- The following indications and dosing regimens are approved
  - 1 g q8h for the treatment of ABSSSI
  - 2 g q8h for the treatment of HABP
  - 4 g q8h for osteomyelitis

General Background for Drug A

- Each indication is supported by randomized clinical trials (RCTs) at the specified dosing regimens
- *P. aeruginosa* is listed as a pathogen for both ABSSSI and HABP

General Background for Drug A

- The susceptibility test interpretive criteria for *P. aeruginosa* as originally established in the USPI are included in the table below:

	S (mcg/mL)	I (mcg/mL)	R (mcg/mL)
P. aeruginosa	≤ 8	16	≥ 32

- The original *P. aeruginosa* susceptible breakpoint is based on the 2 g q8h dosing regimen

Issue

- A change in Drug A's susceptible breakpoint for *P. aeruginosa* is being considered based on the following:
  - Shift in MIC distribution
  - Increase in proportion of isolates expressing resistance mechanisms at MICs ≤ 8 mcg/mL
  - Supportive PK/PD information

Background - Clinical

- No clinical efficacy or safety data exists for the treatment of ABSSSI due to *P. aeruginosa* infection with the 2 g q8h dosing regimen.
- Efficacy and safety data for ABSSSI due to *P. aeruginosa* at the 1 g q8h dosing regimen are available.
- Safety data are available from the 4 g q8h dosing regimen for osteomyelitis and the 2 g q8h dosing regimen for HABP.

Clinical Safety

- Most common serious adverse events (AE) associated with the use of Drug A (all dosing regimens):
  - Hypersensitivity reactions
  - Seizures (higher in patients with renal impairment)
  - *Clostridium difficile*-associated diarrhea (CDAD)

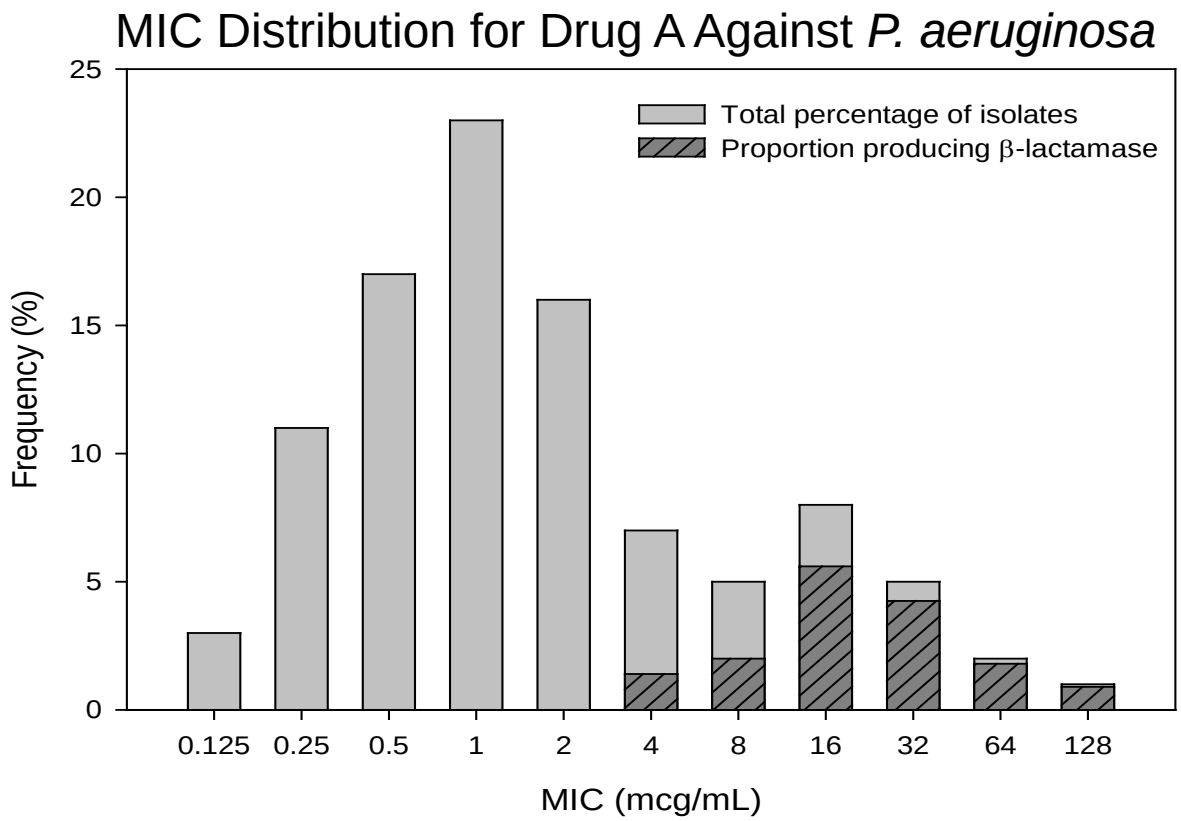
Clinical Safety

- Most common AEs for the 1 g q8h dosing regimen
  - Nausea
  - Headache
  - Constipation
  - Diarrhea
  - Anemia

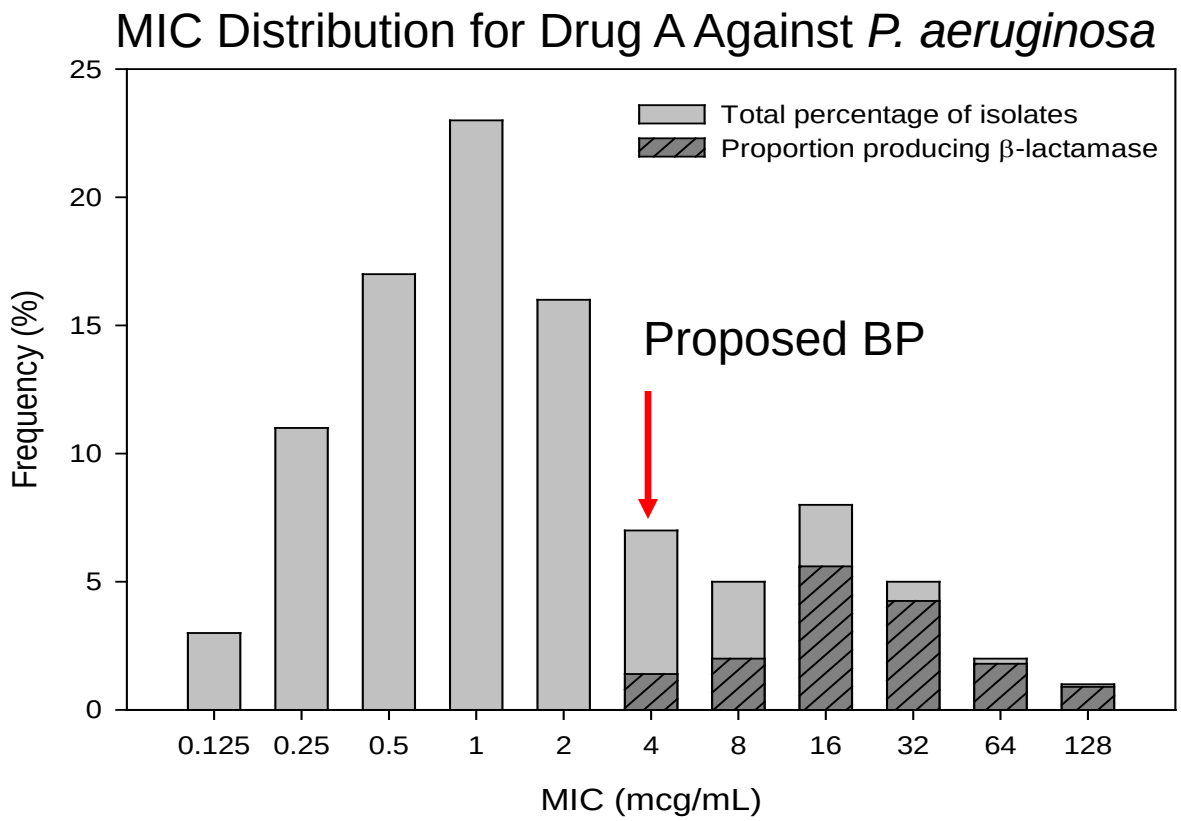
Clinical Safety

- Most common AEs for 2 g q8h and 4 g q8h dosing regimens
  - Diarrhea
  - Nausea/Vomiting
  - Headache
  - Rash
  - Pruritus
- Seizures were reported more commonly with 4 g q8h dosing regimen

Microbiology – MIC Distribution



Microbiology – MIC Distribution



Changes in β-lactamase-Producing Isolates Over Time

MIC	1998		2013	
	% Total Isolates	% of isolates at MIC value producing β-lactamase	% Total Isolates	% of isolates at MIC value producing β-lactamase
2	21	0	16	0
4	10	0	8	10
8	5	0	6	33
16	2	25	9	78

Table 1. MIC Susceptibilities for *Pseudomonas aeruginosa* isolates from Lower Respiratory Tract

		MIC (mcg/ml)					
Surveillance Study (year)	**N**	**MIC range**	**Mode**	**MIC90**	**nS (%)**	**nI (%)**	**nR (%)**
2011	900	≤0.03->64	0.50	16	762 (84.7)	63 (7.0)	75 (8.3)
2012	1293	≤0.03->64	0.50	16	1068 (82.6)	102 (7.9)	123 (9.5)
2013	1008	≤0.03->64	0.50	32	831 (82.4)	75 (7.5)	102 (10.1)

Background – Clinical Pharmacology

- A population PK model was developed using data from about 100 patients treated with Drug A.
- The PK model simulated a larger population of 8,000 subjects to determine target attainment.
- The PK-PD measure associated with the efficacy of Drug A is the percentage of time during the dosing interval that free-drug concentrations are above the MIC (free-drug %T>MIC).
- Animal models indicate that maximum bactericidal activity was associated with 50% *f*T > MIC.
- Probability of target attainment (PTA) for dosing regimens 1 g q8h and 2 g q8h by MIC was conducted.

Probability of Target Attainment

MIC (mcg/mL)	Dose: 1 g q8h	Dose: 2 g q8h
	50% *f*T>MIC	50% *f*T>MIC
1	0.95	0.96
2	0.87	0.95
4	0.70	0.88
8	0.41	0.72

Probability of Target Attainment

MIC (mcg/mL)	Dose: 1 g q8h	Dose: 2 g q8h
	50% *f*T>MIC	50% *f*T>MIC
1	0.95	0.96
2	0.87	0.95
4	0.70	0.88
8	0.41	0.72

Breakpoint at Initial Approval

- Clinical
  - Initial susceptible breakpoint defined from RCTs at the proposed dosing regimens
- Microbiology
  - MIC90: 8 mcg/mL
  - β-lactamase producing isolates: 1-2%
- Clinical Pharmacology
  - Not a driver of initial breakpoint
  - General knowledge of Drug A PK

Breakpoint Revisited – What Evidence has Accumulated

- Building on the 1998 evidence
- Clinical
  - Unknown whether increased MICs have led to increase in treatment failures for Drug A
  - Relationship between high baseline MIC and poor clinical outcome has been characterized for other drugs
- Microbiology
  - MIC90 of 32 mcg/mL
  - β-lactamase producing isolates: 20%
- Clinical Pharmacology
  - Enhanced tools (Refined Pop PK models, PTA, defined PK/PD relationships)

Breakpoint Revisited – What is Known

- The dosing regimens of 1 g q8h (for ABSSSI) and 2 g q8h (for HABP) are supported by RCT data from the initial clinical trials
- *P. aeruginosa* is a listed pathogen in both indications
- Safety data are available for doses as high as 4 g q8h
- Initial *P. aeruginosa* susceptible breakpoint was based on 2 g q8h dosing regimen
- Microbiology and Clinical Pharmacology information suggest that a change in the *P. aeruginosa* susceptible breakpoint may be necessary

Breakpoint Revisited – Not Known

- Safety and efficacy data for ABSSSI treated with 2 g q8h dosing regimen
- Definitive knowledge of an increase in treatment failures for Drug A at MIC values that are currently considered susceptible

Option A

- Set the *P. aeruginosa* susceptible breakpoint for Drug A at 4 mcg/mL based on a 2 g q8h dosing regimen and supportive microbiological and PK/PD evidence
- Pros
  - Simplifies the susceptible breakpoint to one option for *P. aeruginosa* infections across indications
  - Efficacy at 2 g q8h for ABSSSI should be equivalent or improved over 1 g q8h
- Cons
  - Safety needs to be supported by data from 2 g q8h HABP RCTs

Option B

- Institute separate *P. aeruginosa* breakpoints based on the respective approved dosing regimens. Likely a 2 mcg/mL breakpoint for *P. aeruginosa* ABSSSI treated with 1 g q8h and a 4 mcg/mL breakpoint for *P. aeruginosa* HABP treated with 2 g q8h.
- Pros
  - Data based on currently approved dosing regimens in product labeling
- Cons
  - May complicate laboratory susceptibility reporting
  - May lead to clinician confusion related to use of the appropriate breakpoint/dosing regimen combination for a particular infection

Option C

- Set the *P. aeruginosa* breakpoint for Drug A based on the lowest approved dosing regimen (1 g q8h). This would likely result in a susceptibility breakpoint of 2 mcg/mL across indications.
- Pros
  - Eliminates concern of clinical failure due to β-lactamase producing *P. aeruginosa*
  - Simplifies the susceptible breakpoint to one option for *P. aeruginosa* across indications
- Cons
  - Earlier loss of Drug A as a therapeutic option
  - Increased use of alternative antibacterial drugs

Scenario #2
Drug B

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FDA

October 17, 2013

Outline for Scenario #2

- General Background
- Clinical
- Microbiology
- Clinical Pharmacology
- Summary
- Options

Background

- Drug B is an intravenously administered β-lactam antibacterial drug
- Originally approved in the U.S. in the 1990's for the treatment of the following infections

Approved Dosing Regimens for Drug B

- Acute Bacterial Skin and Skin Structure Infections (ABSSSI):
  - 0.5 gram IV q 12 h
- Complicated Intra-Abdominal Infections (cIAI):
  - 1 gram IV q 8 h
- Hospital Acquired Bacterial Pneumonia (HABP):
  - 2 grams IV q 8 h

Clinical

- For each indication, safety and efficacy data derived from two adequate and well-controlled noninferiority trials
- *E. coli* listed as a pathogen for all three approved indications

Susceptibility Test Interpretive Criteria for Drug B

	Susceptible	**Intermediate**	**Resistant**
MIC (mcg/mL)	≤ 8	16	≥ 32

Clinical

- Recent case series in literature note clinical and microbiologic failures with Drug B in infections due to *E. coli* with minimum inhibitory concentrations (MICs) at higher end of susceptible range
- Prevalence of these high MIC *E. coli* has increased over the past several years since approval of Drug B

Clinical

- No new clinical trials conducted since the original registrational trials
- No clinical efficacy or safety data available from randomized controlled trials (RCTs) for treatment of ABSSSI or cIAI using high-dose HABP regimen (2 g IV q 8 h)

Clinical

- Treatment of ABSSSI and cIAI caused by high MIC *E. coli* using the high-dose HABP regimen (2 g IV q 8 h) limited to case reports in the literature
- Safety data for high-dose regimen (2 g IV q 8 h) available from RCTs in HABP

Clinical

- Safety profile of Drug B similar to that of other β-lactam antibacterial drugs
- Common serious adverse reactions with Drug B include hypersensitivity reactions, seizures, and *Clostridium difficile*-associated diarrhea

Clinical

- Seizures reported with higher frequency in patients with renal impairment
- In RCTs, frequency and severity of certain adverse reactions increased as the daily dose increased
  - For example: rash, diarrhea
- Overall, the AE profile was similar across all studied doses

Microbiology

- Drug B's Mechanism of Action
  - Bactericidal activity against both Gram-positive and Gram-negative bacteria
  - Inhibits cell wall biosynthesis through covalent binding to penicillin-binding proteins (PBPs), impeding the final transpeptidation step of peptidoglycan synthesis

Microbiology

- Mechanisms of Resistance
  - Enterobacteriaceae
    - production of β-lactamases that hydrolyze the drug
    - Class A ESBLs and, less often, Class A and B carbapenemases
  - *Pseudomonas aeruginosa*
    - chromosomal Class C β-lactamases or upregulation of efflux pumps
  - Gram-positive bacteria
    - typically mediated by alterations in PBPs

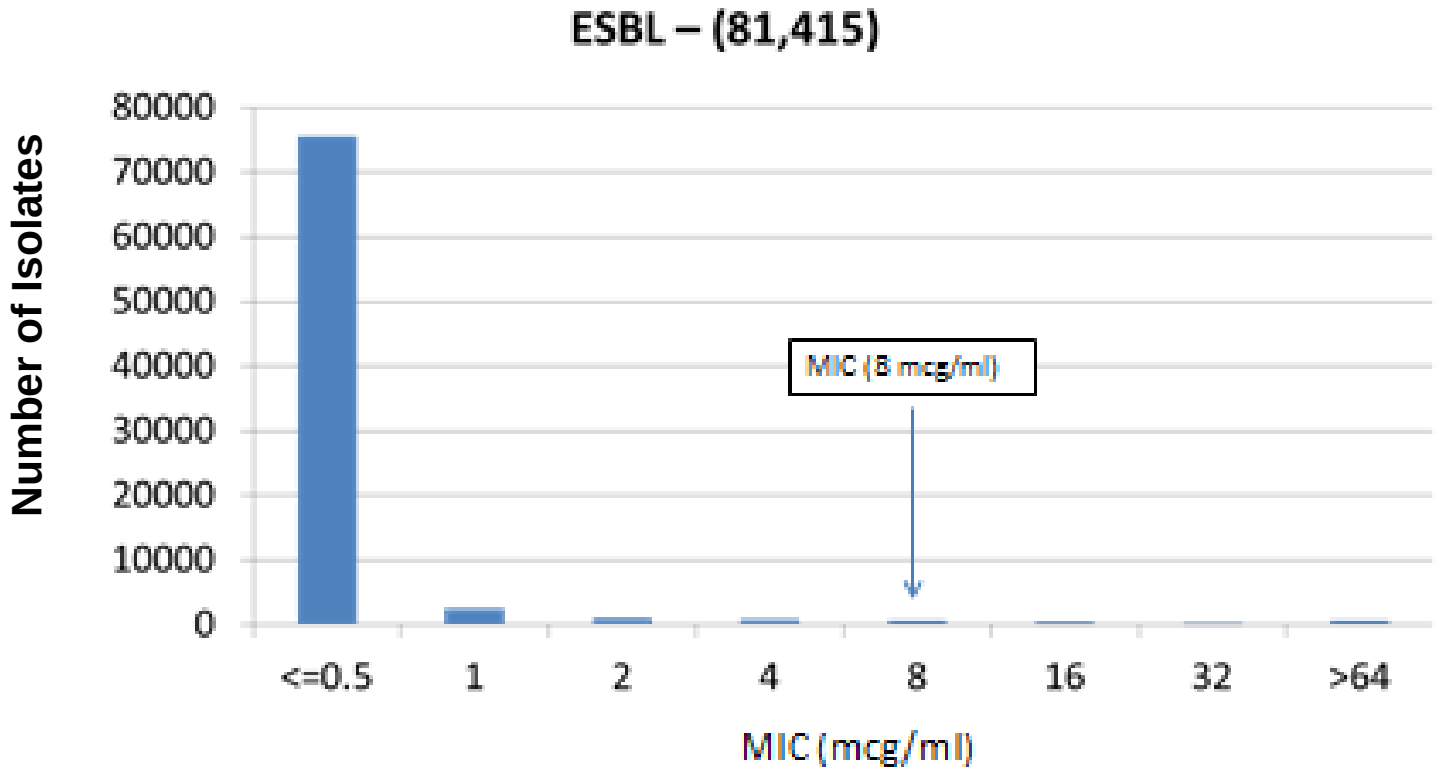
Microbiology

- Surveillance Studies
  - Surveillance study evaluated in vitro activity of Drug B against a large collection of clinical isolates in North America from 1998-2003
  - 98% of *E. coli* isolates susceptible to Drug B
  - 94% of *E. coli* producing Extended Spectrum β-lactamases (ESBLs) also susceptible to Drug B

Microbiology

- Surveillance Studies (continued)
  - Recent data indicate that Drug B continues to demonstrate efficacy against non-ESBL producing *E. coli,* as presented in the following figure.

Drug B MIC Distribution of ESBL Negative *E. coli*



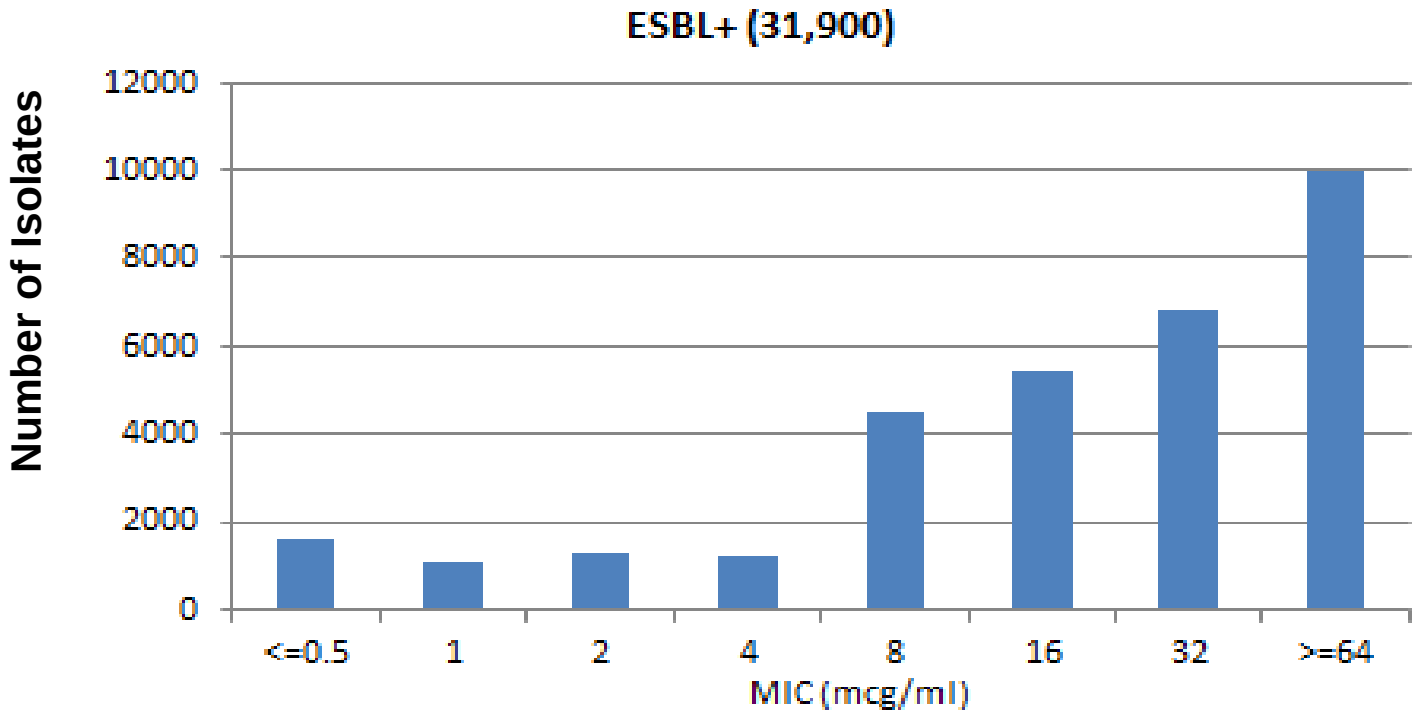
Microbiology

- However, recent surveillance has also identified *E. coli* producing novel ESBLs not detected at the time of original approval of Drug B
- Though these ESBL-positive isolates cluster at higher MICs (8 to ≥64 mcg/mL), a number of ESBL-positive isolates exist at lower MICs (down to ≤0.5 mcg/mL)

Microbiology

- Therefore, a specific MIC will not effectively exclude all ESBL-positive isolates
- However, depending on where the MIC is set, we may be able to exclude a greater number of ESBL-positive isolates (see the following figure)

Drug B MIC Distribution of ESBL Positive *E. coli*



Clinical Pharmacology

- A population PK model was developed using healthy adult data from six Phase I studies
- PK model simulated a larger population of 6000 subjects to determine target attainment
- PK-PD measure associated with efficacy of Drug B
  - percentage of time during the dosing interval that free-drug concentrations are above the MIC
    - free-drug %T>MIC

Clinical Pharmacology

- Percentage of simulated subjects achieving free-drug %T>MIC targets of 50% were determined as shown in the following table

Probability of Target Attainment

Regimen	MIC (mcg/mL)	fT>MIC ≥ 50%
ABSSSI 0.5 g IV q 12 h	0.125	1.00
	0.25	1.00
	0.5	.99
	1	.48
cIAI 1 g IV q 8 h	1	1.00
	2	.99
	4	.65
	8	.10
HABP 2 g IV q 8 h	2	1.00
	4	.99
	8	.65
	16	.10

Summary

- Drug B is approved for the treatment of:
  - ABSSSI at 0.5 gram IV q 12 h
  - cIAI at 1 gram IV q 8 h
  - HABP at 2 grams IV q 8 h

Summary (continued)

- *E. coli* listed as a pathogen in all three treatment indications (ABSSSI, cIAI, HABP)
- Current susceptibility test interpretive criteria may need to be modified based on:
  - limited clinical data with failures at higher end of susceptible range
  - recent microbiologic surveillance data showing higher percentage of *E. coli* with novel ESBLs testing out at lower MICs, but still exhibiting resistance
  - probability of target attainment analysis

Summary (continued)

- Reasonable to assume that there will be no loss of efficacy using high-dose HABP regimen (2 g IV q 8 h) for ABSSSI and cIAI
- Overall safety profile of Drug B consistent across the various indications and dosing regimens
- Given available safety data for high-dose HABP regimen, the benefit/risk assessment is favorable for using 2 g IV q 8 h for ABSSSI and cIAI

Three possible options moving forward…

Option 1:

- Set the susceptible breakpoint for *E. coli* at 0.5 mcg/mL, based on the lowest dosing regimen as approved for ABSSSI

Option 1: Pros and Cons

- Pros:
  - Eliminates current concern of clinical failure related to use of Drug B for high MIC *E. coli* infections
  - Simplifies the susceptible breakpoint to one option for *E. coli* across indications
- Cons:
  - Earlier loss of Drug B as a therapeutic option
  - Increased use of alternative antibacterial drugs

Option 2:

- Set the susceptible breakpoint for *E. coli* at 4 mcg/mL and change the dosing regimens for ABSSSI and cIAI to 2 g IV q 8 h

Option 2: Pros and Cons

- Pros:
  - Simplifies the susceptible breakpoint to one option for *E. coli* infections across indications
  - Increases Drug B exposure for high MIC *E. coli* infections
- Cons:
  - Safety needs to be supported by data from high-dose HABP RCTs

Option 3:

- Have separate susceptible breakpoints for *E. coli*, for each of the approved indications and dosing regimens as shown

Indication	Regimen	Potential Breakpoint (mcg/mL)
ABSSSI	0.5 gram IV q 12 hours	0.5
cIAI	1 gram IV q 8 hours	2
HABP	2 grams IV q 8 hours	4

Option 3: Pros and Cons

- Pros:
  - Safety & efficacy data based on currently approved dosing regimens in product labeling
- Cons:
  - May complicate laboratory susceptibility reporting
  - May lead to clinician confusion related to use of the appropriate breakpoint/dosing regimen combination for a particular infection

Thanks to the Team

- Kimberly Bergman
- Dakshina Chilukuri
- Peter Coderre
- Edward Cox
- J. Christopher Davi
- Maureen Dillon-Parker
- Avery Goodwin
- John Farley
- Katherine Laessig
- John Lazor
- Benjamin Lorenz
- Sumathi Nambiar
- Eileen Navarro-Almario
- Ryan Owen
- David Roeder
- Susmita Samanta
- Thomas Smith
- Kerry Snow