

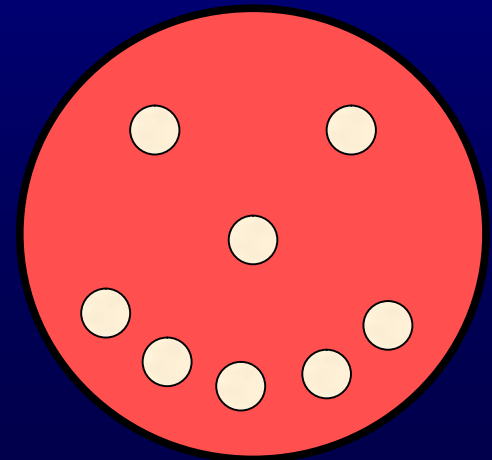
Antimicrobial Susceptibility Testing Update

or

Are breakpoints driving us to our breaking point*?

*Breaking point = a critical moment of
personal stress (Wikipedia)

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At the conclusion of this talk, you will be able to.....

- ◆ List some of the new recommendations for antimicrobial susceptibility testing and reporting as published in **CLSI M100-S20** and **CLSI M100-S20-U** (June 2010 Update).
- ◆ Discuss reporting results from testing **cephalosporins** and **carbapenems** against **Enterobacteriaceae**.
- ◆ Describe strategies for **implementation of revised breakpoints** into clinical laboratory testing protocols.

CLSI AST Standards August 2010

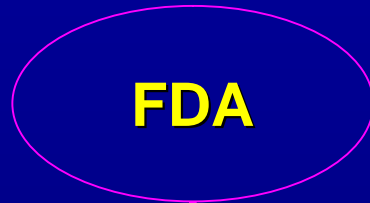
- ◆ **M100-S20 Tables (January 2010)***
 - Revised cephalosporin & aztreonam breakpoints (Enterobacteriaceae)
- ◆ **M100-S20-U (June 2010)**
 - Revised carbapenem breakpoints (Enterobacteriaceae)
- ◆ **M02-A10 Disk Diffusion Method (2009)****
- ◆ **M07-A8 MIC Method (2009)****



**Standards
Setting**

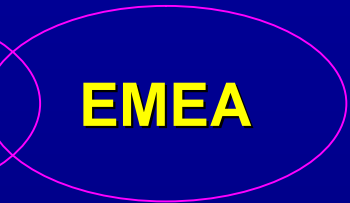


Regulatory



**Standards
Setting**

Regulatory



Sets breakpoints

Sets breakpoints

Sets breakpoints

**Reassesses
breakpoints**

**2010 - developing
mechanism to reassess
breakpoints**

**EMEA sets breakpoints
through EUCAST**

Manufacturers of AST systems must use FDA breakpoints

- **CLSI = Clinical and Laboratory Standards Institute (formerly NCCLS)**
- **EUCAST = European Committee on Antimicrobial Susceptibility Testing**
- **EMEA = European Medicines Agency**

Ceftriaxone Prescribing Information - FDA Breakpoints

http://media.pfizer.com/files/products/uspi_ceftriaxone.pdf

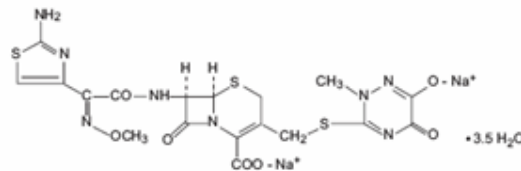
ceftriaxone for injection, USP Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftriaxone and other antibacterial drugs, ceftriaxone should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7²-(Z)-(D-methylxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is C₁₉H₁₈N₆Na₂O₇S₃•3.5H₂O. It has a calculated molecular weight of 661.60 and the following structural formula:



Ceftriaxone for injection is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriaxone for injection solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone for injection contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

CLINICAL PHARMACOLOGY

Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (IV) infusion of a 0.5, 1 or 2 g dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL or 350 mg/mL concentrations) or 1 g dose in healthy subjects are presented in Table 1.

Table 1 Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/Route	Average Plasma Concentrations (mcg/mL)									
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr	36 hr
0.5 g IV*	82	59	48	37	29	23	15	10	5	5
0.5 g IM										
250 mg/mL	22	33	38	35	30	26	16	ND	5	5
0.5 g IM										
350 mg/mL	20	32	38	34	31	24	16	ND	5	5
1 g IV*	151	111	88	67	53	43	28	18	9	9
1 g IM	40	68	76	68	56	44	29	ND	ND	ND
2 g IV*	257	192	154	117	89	74	46	31	15	15

Aerobic gram-negative microorganisms:

- Acinetobacter calcoaceticus*
- Enterobacter aerogenes*
- Enterobacter cloacae*
- Escherichia coli*
- Haemophilus influenzae* (including ampicillin-resistant and beta-lactamase producing strains)
- Haemophilus parainfluenzae*
- Klebsiella oxytoca*
- Klebsiella pneumoniae*
- Moraxella catarrhalis* (including beta-lactamase producing strains)
- Morganella morganii*
- Neisseria gonorrhoeae* (including penicillinase- and nonpenicillinase-producing strains)
- Neisseria meningitidis*
- Proteus mirabilis*
- Proteus vulgaris*
- Serratia marcescens*

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

NOTE: Many strains of the above organisms that are resistant to multiple antibiotics, e.g., penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.

Aerobic gram-positive microorganisms:

- Staphylococcus aureus* (including penicillinase-producing strains)
- Staphylococcus epidermidis*
- Streptococcus pneumoniae*
- Streptococcus pyogenes*
- Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., *Enterococcus (Streptococcus) faecalis*, are resistant.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.¹ Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftriaxone powder. The MIC values should be interpreted according to the following criteria² for aerobic organisms other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp., including *Streptococcus pneumoniae*:

MIC (mcg/mL)
<8
16-32
≥64

Interpretation
(S) Susceptible
(I) Intermediate
(R) Resistant

The following interpretive criteria² should be used for testing *Haemophilus* species using

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg ceftriaxone disc should provide the following zone diameters in these laboratory test quality control strains:³

Microorganism	ATCC [®] #	Zone Diameter Ranges (mm)
<i>Escherichia coli</i>	25922	29 - 35
<i>Staphylococcus aureus</i>	25923	22 - 28
<i>Pseudomonas aeruginosa</i>	27853	17 - 23
<i>Haemophilus influenzae</i>	49247	31 - 39
<i>Neisseria gonorrhoeae</i>	49226	39 - 51
<i>Streptococcus pneumoniae</i>	49619	30 - 35

Anaerobic Techniques: For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods.⁴ The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤16	(S) Susceptible
32	(I) Intermediate
≥64	(R) Resistant

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the following MIC values for the indicated standardized anaerobic dilution⁴ testing method:

Method	Microorganism	ATCC [®] #	MIC (mcg/mL)
Agar	<i>Bacteroides fragilis</i>	25285	32 - 128
	<i>Bacteroides thetaiotaomicron</i>	29741	64 - 256
Broth	<i>Bacteroides thetaiotaomicron</i>	29741	32 - 128

ATCC[®] is a registered trademark of the American Type Culture Collection.

INDICATIONS AND USAGE

Before instituting treatment with ceftriaxone, appropriate specimens should be obtained for determination of its susceptibility to the obtaining results of susceptibility testing.

ant bacteria and maintain the effectiveness of ceftriaxone should be used only to treat or strongly suspected to be caused by susceptible information are available, they should be bacterial therapy. In the absence of such data, patterns may contribute to the empiric selection

ne treatment of the following infections when

by *Streptococcus pneumoniae*, *Staphylococcus philus parainfluenzae*, *Klebsiella pneumoniae*, *Proteus mirabilis* or *Serratia marcescens*, *Streptococcus pneumoniae*, *Haemophilus* (ing strains) or *Moraxella catarrhalis* (including

rates were observed with a single dose of therapy. In a second study comparable cure ceftriaxone and the comparator. The potentially be balanced against the potential advantages (DIES).

ed by *Staphylococcus aureus*, *Staphylococcus*

CLSI and FDA and EUCAST breakpoints may differ because

- ◆ Different criteria used to set breakpoints
- ◆ Sometimes different dosing regimens; different clinical indications
- ◆ Some breakpoints set many years ago and not yet reassessed by respective agency

Examples (Enterobacteriaceae):

Agent	CLSI	FDA	EUCAST
Ceftriaxone	$\leq 1^*$	≤ 8	≤ 1
Gentamicin	≤ 4	≤ 4	≤ 2
Meropenem	$\leq 1^*$	≤ 4	≤ 2

*new 2010

Status of FDA Breakpoint Revisions

- ◆ **FDA Amendments Act (FDAAA) of 2007** contains 200 provisions re: drug marketing/labeling
 - requires FDA to update drug labels
- ◆ **FDA Guidance Documents (2009)**
 - Will consider breakpoints of national or international standards organizations
 - Describes approach for pharmaceutical companies to update breakpoints in prescribing information
- ◆ **CLSI leadership maintaining close watch**

Enterobacteriaceae - Cephalosporins

Revised... Breakpoints (MIC µg/ml)*

Agent	CLSI 2009 (Old)			CLSI 2010 (New)		
	Susc	Int	Res	Susc	Int	Res
Cefazolin	≤8	16	≥32	≤1	2	≥4
Cefotaxime	≤8	16-32	≥64	≤1	2	≥4
Ceftriaxone	≤8	16-32	≥64	≤1	2	≥4
Ceftazidime	≤8	16	≥32	≤4	8	≥16
Aztreonam	≤8	16	≥32	≤4	8	≥16
Cefepime**	≤8	16	≥32	<i>No change</i>		

* January 2010

** No change; also reevaluated and no change for cefuroxime, cefoxitin, cefotetan, cefmetazole

Corresponding disk diffusion breakpoints also revised

Enterobacteriaceae - Carbapenems

Revised... Breakpoints (MIC $\mu\text{g/ml}$)*

Agent	CLSI 2010 (Old)			CLSI June 2010 (New)		
	Susc	Int	Res	Susc	Int	Res
Doripenem	-	-	-	≤ 1	2	≥ 4
Ertapenem	≤ 2	4	≥ 8	≤ 0.25	0.5	≥ 1
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4

*June 2010

Corresponding disk diffusion breakpoints also revised

Table 2A Enterobacteriaceae

- ◆ Dosing information reflects FDA-approved standard adult dosing listed in Prescribing Information (Drug Label)
- ◆ When implementing revised breakpoints, laboratories MUST inform ID and Pharmacy that these were the dosing regimens on which the breakpoints were based
- ◆ NOT intended for labs to list this on patient report

Test/Report Group	Antimicrobial Agent	Disk Content	Zone Diameter Breakpoints, nearest whole mm			MIC Interpretive Standard (µg/mL)			Comments
			S	I	R	S	I	R	
CEPHEMS (PARENTERAL) (including cephalosporins I, II, III, and IV. Please refer to Glossary I.) (Continued)									
A	Cefazolin	30 µg	–	–	–	≤ 1	2	≥ 4	(9) Disk diffusion interpretive criteria for cefazolin when using the revised MIC interpretive criteria listed here have not yet been established. (10) MIC interpretive criteria are based on a dosage regimen of at least 1 g every 8 h. See comment (7).
U	Cephalothin	30 µg	≥ 18						(13) Interpretive criteria are based on a dosage regimen of 1 g every 24 h for ceftriaxone and 1 g every 8 h for cefotaxime.
B	Cefepime	30 µg	≥ 18	15–17	≤ 14	≤ 8	16	≥ 32	(12) Interpretive criteria are based on a dosage regimen of 1 g every 8 h or 2 g every 12 h. See comment (7).
B B	Cefotaxime or ceftriaxone	30 µg 30 µg	≥ 26 ≥ 23	23–25 20–22	≤ 22 ≤ 19	≤ 1 ≤ 1	2 2	≥ 4 ≥ 4	(13) Interpretive criteria are based on a dosage regimen of 1 g every 24 h for ceftriaxone and 1 g every 8 h for cefotaxime. See comment (7).
R	Cefotetan	30 µg	> 16	13–15	< 12	< 16	32	> 64	

Why did CLSI lower cephalosporin, aztreonam, and carbapenem breakpoints for Enterobacteriaceae? (1)

- ◆ **Most of these breakpoints** were established over 20 years ago (before ESBLs and when virtually all Enterobacteriaceae were “S” to carbapenems)
- ◆ **Newer tools / data** to establish breakpoints (e.g., PK/PD with Monte Carlo simulations)
- ◆ Lowering breakpoints would have minimal impact on % “S” for most 3rd generation cephalosporins, aztreonam, and carbapenems
- ◆ Increased knowledge of old and newer **β -lactam resistance mechanisms**

Why did CLSI lower cephalosporin, aztreonam, and carbapenem breakpoints for Enterobacteriaceae? (2)

- ◆ **Re: cephalosporin and aztreonam breakpoints**
 - **CLSI ESBL test** only standardized for *E. coli*, *Klebsiella spp.* and *Proteus mirabilis* (mid 1990s)
 - ESBLs occur in other species
 - ESBLs not always detected if multiple R mechanisms present
- ◆ **For ESBL positive isolates:**
 - **Low MICs** to selected cephalosporins associated with being poor substrates for specific ESBL
 - Animal studies indicated **% T > MIC** did not differ for ESBL positive vs. ESBL negative *Enterobacteriaceae*
 - Animal studies showed **no inoculum effect** w/ ESBL producers

Why did CLSI lower cephalosporin, aztreonam, and carbapenem breakpoints for Enterobacteriaceae? (3)

◆ Re: Carbapenem breakpoints

– Modified Hodge test

- Subjective interpretation**
- Does not detect all carbapenem “R” mechanisms**

Old Paradigm

Emergence of a new β -lactamase
(e.g., ESBL or carbapenemase)

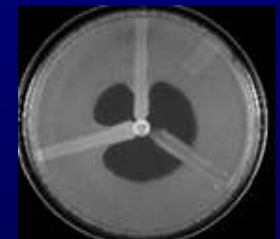


Perform screen test for resistance mechanism
(elevated MICs near “S” breakpoint are “suspicious”)



ESBL

Perform special confirmatory test
for resistance mechanism



MHT



Change the susceptibility report if resistance
mechanism is detected

New Paradigm

Isolation of Enterobacteriaceae



Perform tests for susceptibility and apply the new “lower” breakpoints



Report the susceptibility results for treatment purposes - no editing of “S” results



Perform special tests for resistance mechanisms only for infection control and epidemiological purposes

- Organization
- Clinical breakpoints
- Expert rules
- MIC distributions
- Zone diameter distributions
- EUCAST disk diffusion test
- Meetings
- EUCAST Presentations
- Documents
- Information for industry
- Links

The European Committee on Antimicrobial Susceptibility Testing – EUCAST

Expert rules

EUCAST expert rules are a tabulated collection of expert knowledge on intrinsic resistances, exceptional resistance phenotypes and interpretive rules that may be applied to antimicrobial susceptibility testing in order to reduce errors and make appropriate recommendations for reporting particular resistances.

Warning! On the 27th of April 2010 EUCAST published new breakpoints for 3rd and 4th gen cephalosporins and aztreonam (see breakpoint tables). A comment was added to breakpoints tables - *[Cephalosporin] breakpoints for Enterobacteriaceae will detect clinically important resistance mechanisms (including ESBL). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In*

www.eucast.org

Warning! On the 27th of April 2010 EUCAST published new breakpoints for 3rd and 4th gen cephalosporins and aztreonam (see breakpoint tables). A comment was added to breakpoints tables - *[Cephalosporin] breakpoints for Enterobacteriaceae will detect clinically important resistance mechanisms (including ESBL). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.*

Website changes

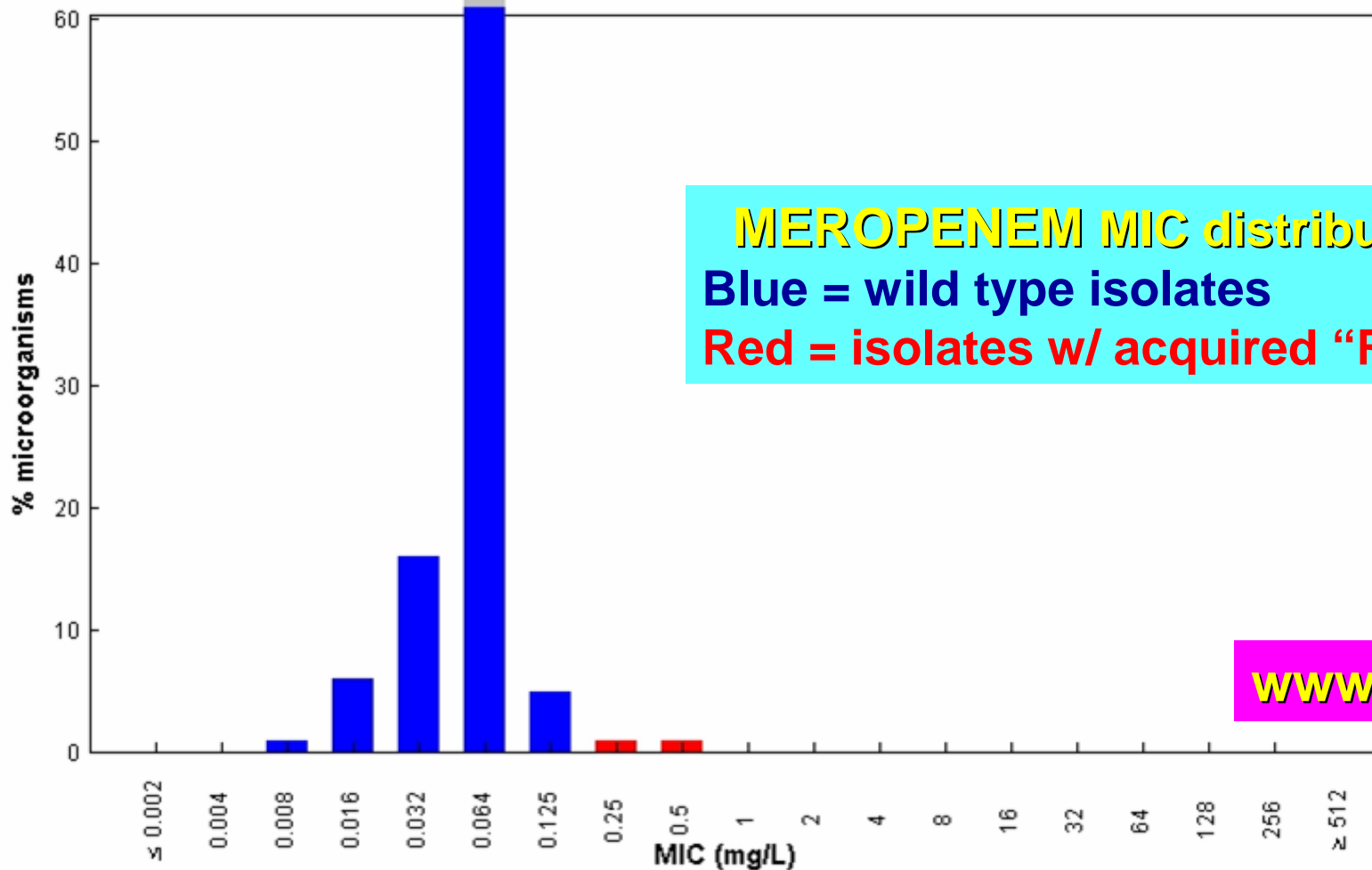
Setting / Revising Breakpoints

Data Used by CLSI

- ◆ MIC distributions of “wild type” or normal populations of bacteria
 - Wild type = no acquired “R” mechanisms
- ◆ MICs associated with clinical outcome
 - Very limited “new” data for older drugs
- ◆ Pharmacokinetic-pharmacodynamic (PK-PD) analysis

Meropenem / *Klebsiella pneumoniae*
EUCAST MIC Distribution - Reference Database 2010-08-25

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MEROPENEM MIC distribution example
Blue = wild type isolates
Red = isolates w/ acquired “R” mechanism

www.eucast.org

MIC
Epidemiological cut-off: WT ≤ 0.125 mg/L

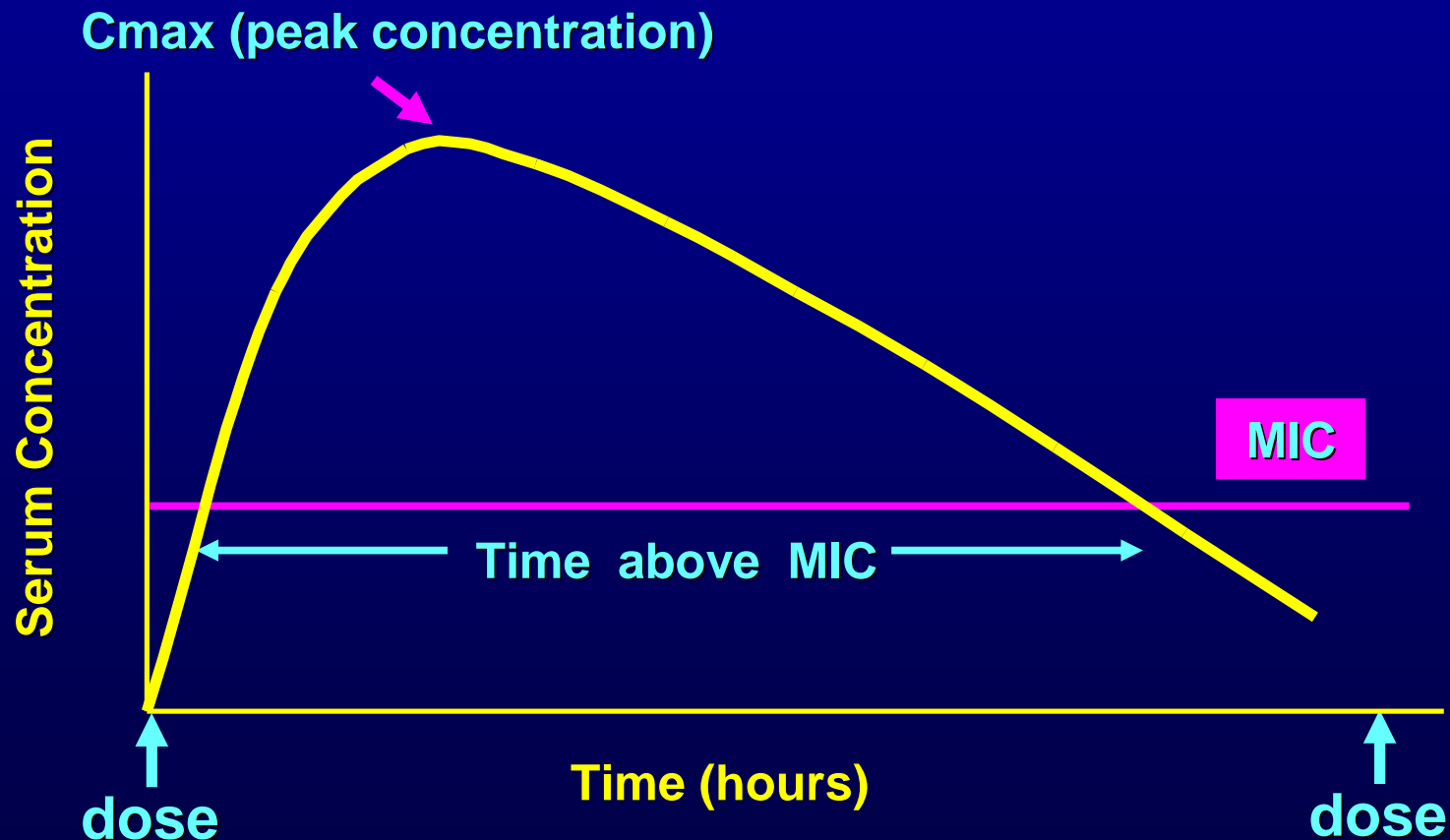
18171 observations (67 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

What is PK/PD?

- ◆ **PK: pharmacokinetics** - the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body
 - Relates to drug concentration over time
- ◆ **PD: pharmacodynamics** - the relationship between concentration of drug and its antimicrobial effects over time in vivo
- ◆ **PK/PD** can project potential efficacy of antimicrobial agents in vivo

Key reference = Craig WA. 1998. CID. 26:1-10.

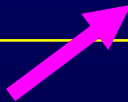
PK-PD Goal (“Target”) for β -lactams = % of time during dosing interval that drug level exceeds MIC ($\%T > \text{MIC}$)



PK-PD Target Attainment for β -lactams

- ◆ **Bacteriostatic and bactericidal activity of β -lactams depends on duration of time that free (unbound) drug levels exceed MIC (% T > MIC)**

Antimicrobials	Free Drug % Time > MIC	
	Bacteriostatic (%)	Bactericidal* (%)
Cephalosporins	35-40	60-70
Penicillins	30	50
Carbapenems	20-30	30-40



*3 log reduction in colony-forming units

Factors that Affect PK-PD Target Attainment

- ◆ Distribution of pathogen MICs
- ◆ Drug protein binding
- ◆ Drug dosing
- ◆ Drug administration (e.g. infusion times)
- ◆ Patient characteristics that affect drug distribution and clearance

Monte Carlo Simulation

- ◆ Examine PK-PD data by simulating dosing regimens and drug levels among a large sample of patients and various MICs for pathogens that would be treated with the drug
 - Plug in various dosages and drug levels that might be encountered in many different patients (e.g., 1000)
- ◆ Used to answer question...What percentage of patients are likely to attain the “target”?

For carbapenems = %T > MIC

- 40% = bactericidal activity

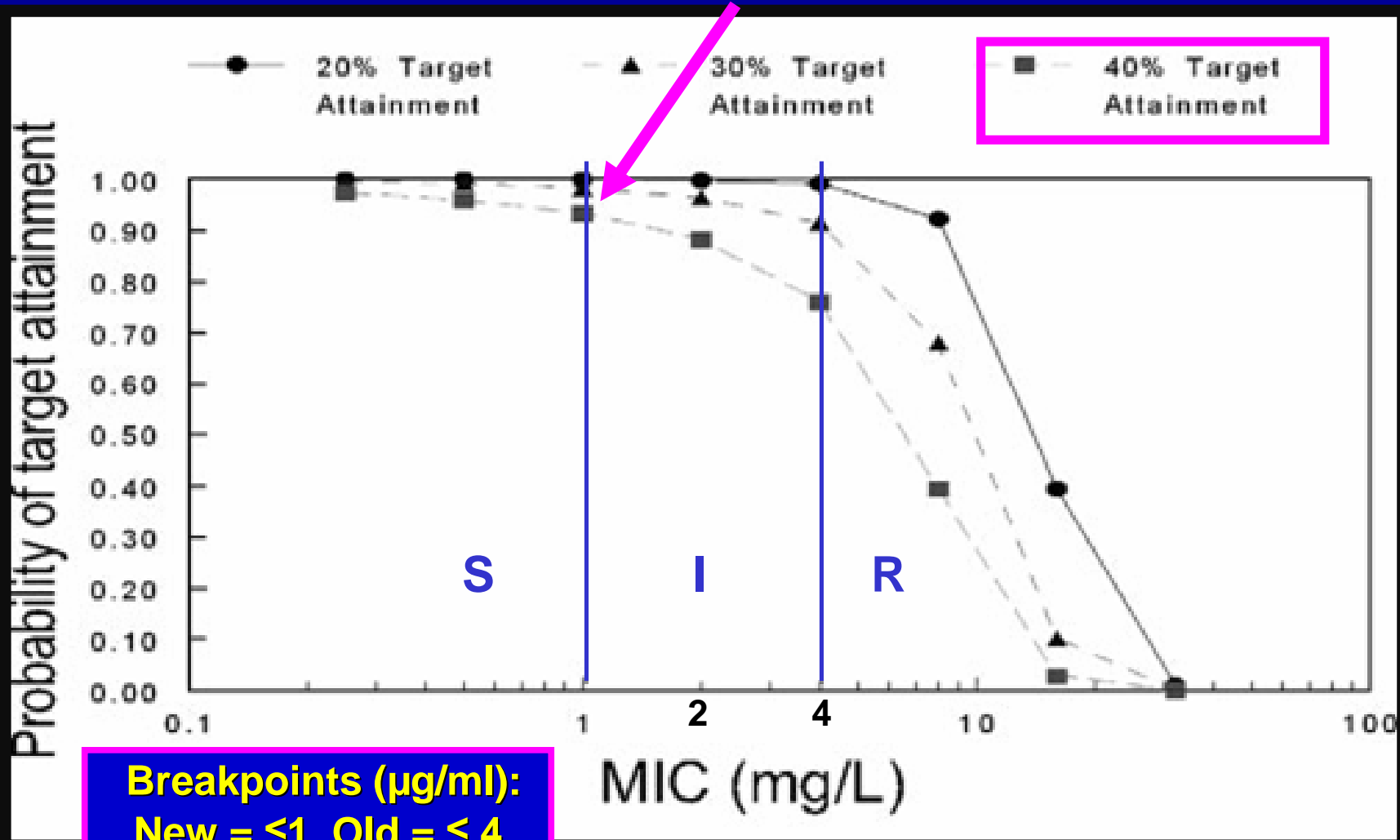
What PK-PD data were used to revise breakpoints?

- ◆ Monte Carlo simulations
- ◆ Studies in animal models and results extrapolated to humans
- ◆ Limited clinical data

Goal - determine PK-PD MIC breakpoint that could predict the likelihood that a specific drug dose would be effective against an organism with a specific MIC

Enterobacteriaceae
Carbapenem Breakpoint
Changes

Probability of Target Attainment Imipenem 1g every 8h



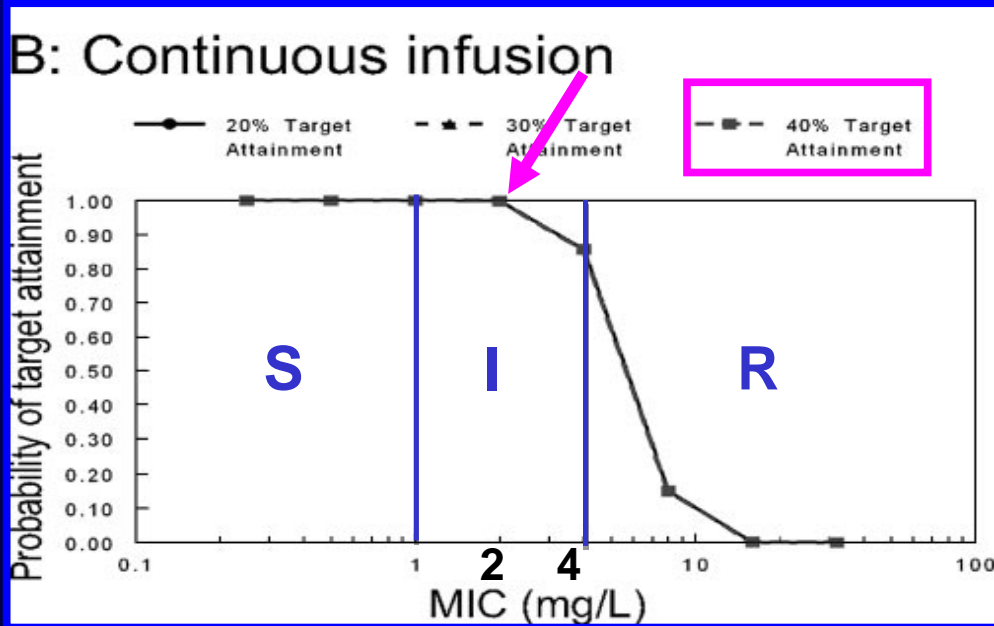
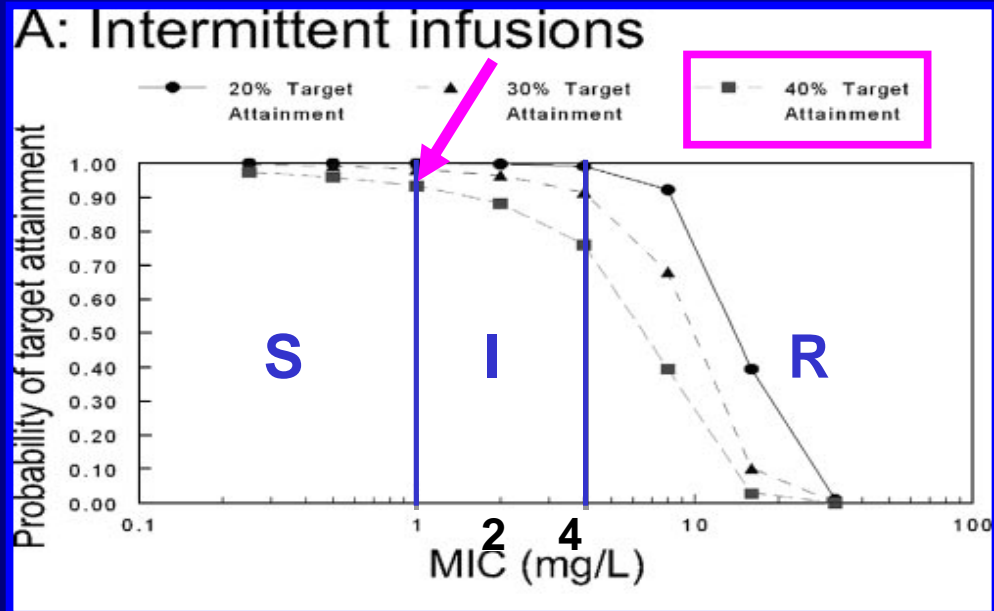
New CLSI Carbapenem Dosage Comment

“Because of limited treatment options for infections caused by organisms with carbapenem MICs or zone diameters in the intermediate range, clinicians may wish to design carbapenem dosage regimens that use maximum recommended doses and possibly prolonged intravenous infusion regimens as has been reported in the literature.”

CLSI M100-S20 (June 2010)

Imipenem Probability of Target Attainment

**New Breakpoints
($\mu\text{g/ml}$):
 ≤ 1 S 2 I ≥ 4 R**



Klebsiella pneumoniae

**Final Report Option
New Carbapenem
Breakpoints**

	<u>MIC ($\mu\text{g/ml}$)</u>
amikacin	>32 R
aztreonam	>32 R
cefepime	>32 R
ceftazidime	>32 R
ceftriaxone	>32 R
ciprofloxacin	>4 R
gentamicin	>8 R
meropenem	2 I
piper-tazobactam	>128 R
tobramycin	>8 R
trimeth-sulfa	>4/76 R

**“Unusual resistance;
Infectious Diseases consult
suggested”**

Enterobacteriaceae

% Capture of Carbapenemases at MIC ($\mu\text{g/ml}$)

Antimicrobial Agent	New CLSI Breakpoints			Old CLSI Breakpoints
	S	I	R	
Imipenem	≤ 1 0%*	2 14%	≥ 4 86%	$\leq 4 / 8 / \geq 16$
Meropenem	≤ 1 1.2%	2 15%	≥ 4 84%	$\leq 4 / 8 / \geq 16$
Ertapenem	≤ 0.25 0%	0.5 0.3%	≥ 1 99.7%	$\leq 2 / 4 / \geq 8$
Doripenem	≤ 1 0%	2 2.3%	≥ 4 97.7%	≤ 0.5 (FDA BP)

N = 474 Enterobacteriaceae; 328 KPC or MBL strains

*** % of carbapenemase producers that have imipenem MIC $\leq 1 \mu\text{g/ml}$**

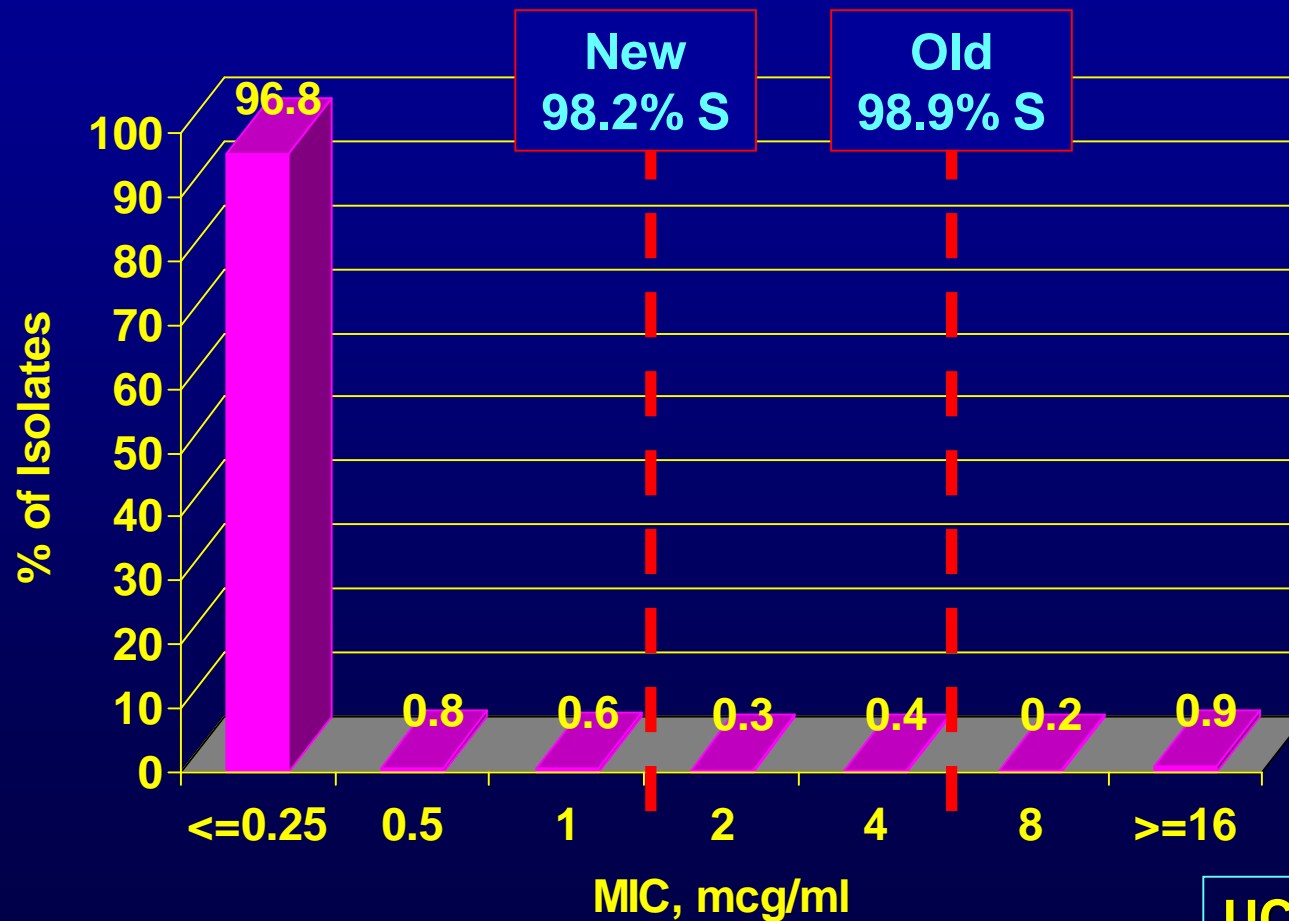
CLSI Agenda Book, January 2010.

What does all this mean for UCLA?

A retrospective look at UCLA Data

- ◆ **Limitations of available MIC data**
 - **Urine isolates** are tested on a panel that does not encompass low concentrations that capture all new lowered breakpoints
 - For **results edited to “R”** because of positive ESBL or carbapenemase test, original MIC is not retrievable

Meropenem MIC Distributions Enterobacteriaceae (non-urine) N=1355 New vs. Old BPs



Enterobacteriaceae (all sources) Meropenem MICs and Carbapenemase

Organism	# Patients w/ Meropenem MIC ($\mu\text{g/ml}$) @			
	≤ 1	2*	4*	≥ 8 & carbapenemase +ve
<i>C. freundii</i>	160	-	-	1
<i>E. aerogenes</i>	155	-	1	2
<i>E. cloacae</i>	349	1	2	1
<i>K. pneumoniae</i>	1137	-	2	9

* no carbapenemase detected

New meropenem breakpoints ($\mu\text{g/ml}$): <1 S, 2 I, ≥ 4 R

UCLA 7/1/09 – 6/30/10

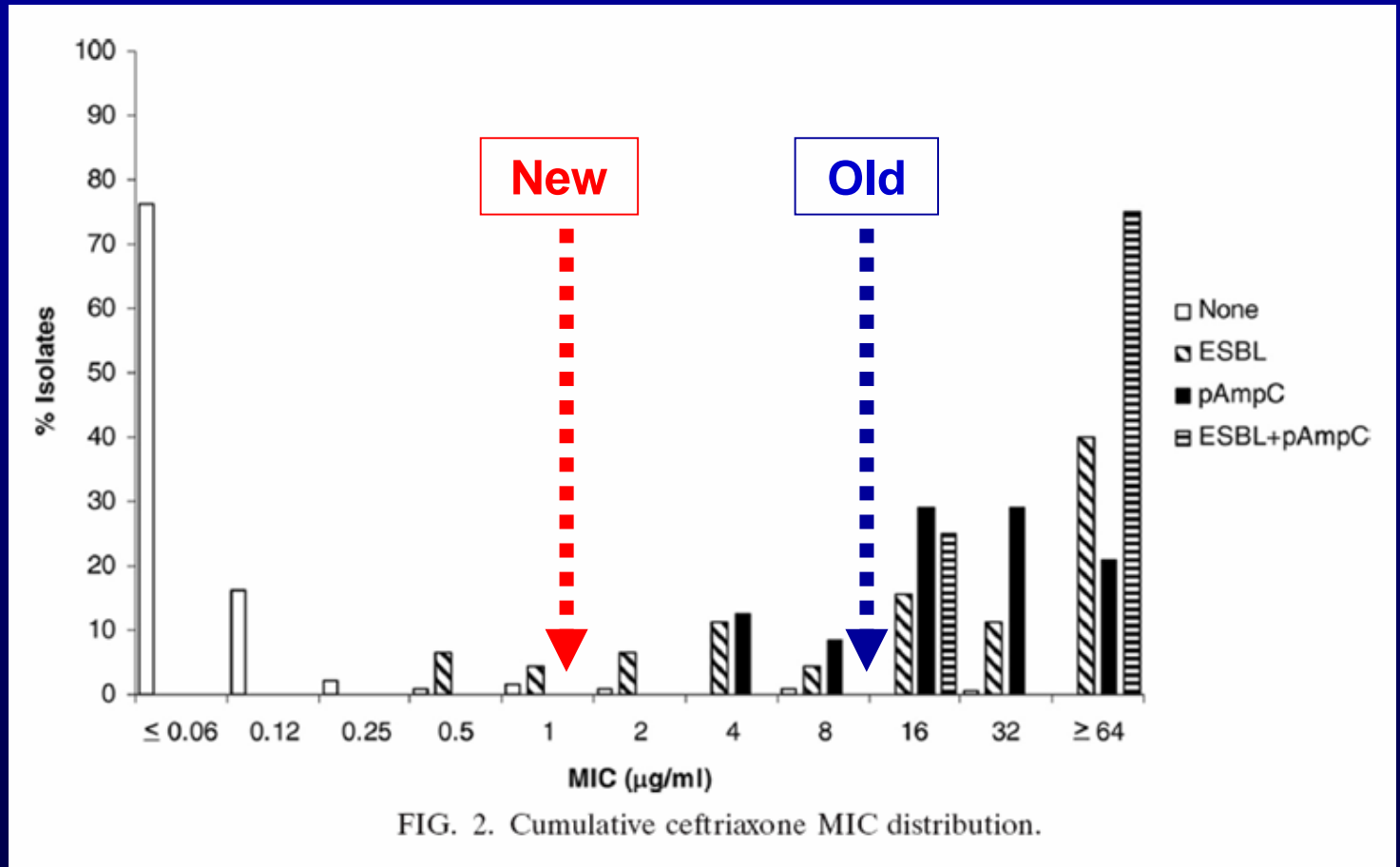
Expected Results for Carbapenemase-Producers

Carbapenem Breakpoints	
Old Breakpoints	New Breakpoints
Carbapenemase-producing isolates often tested “S” to one or more carbapenem: doripenem ertapenem imipenem meropenem	Carbapenemase-producing isolates will USUALLY test “I” or “R” to ALL carbapenems ALL carbapenemase-producing isolates will test “I” or “R” to ertapenem .

Enterobacteriaceae
Cephalosporin and Aztreonam
Breakpoint Changes

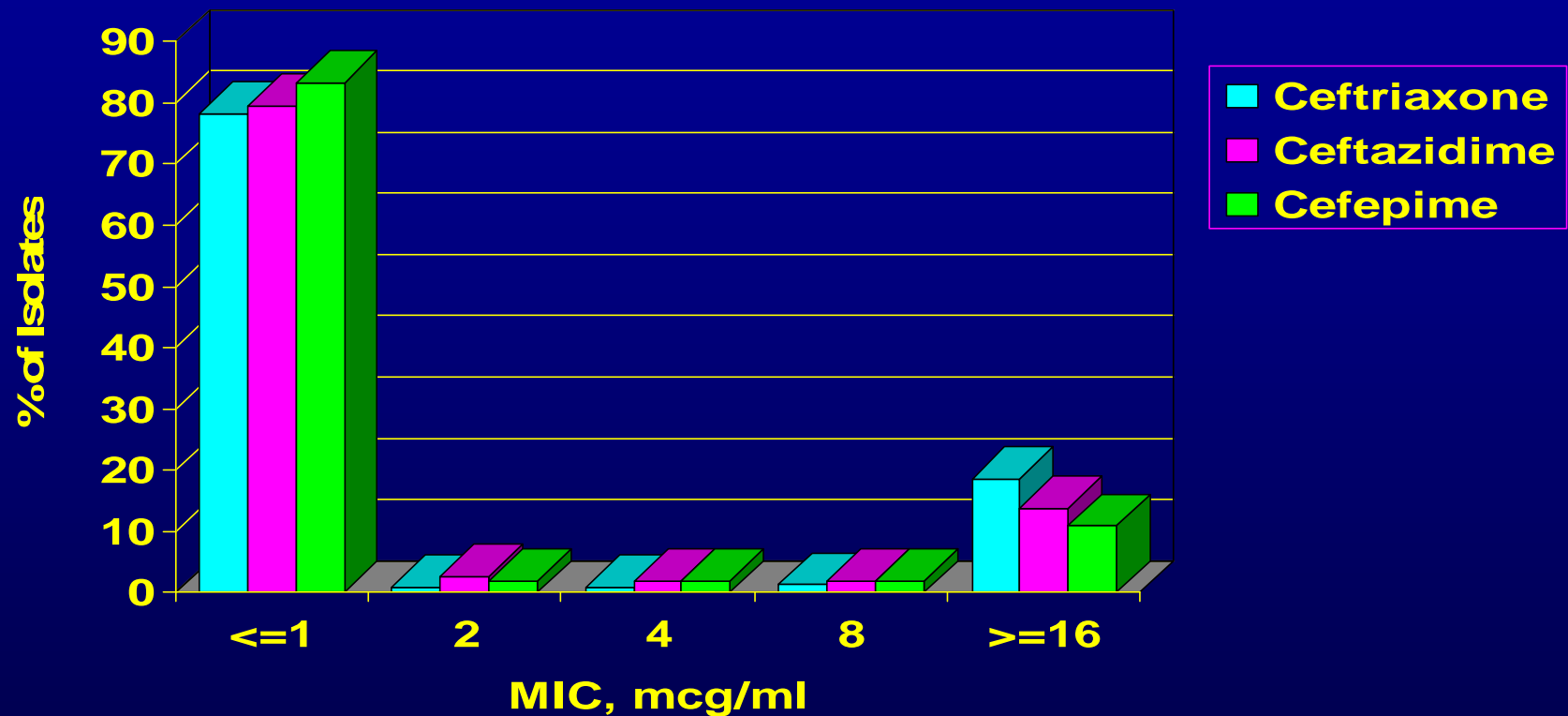
Cumulative Ceftriaxone MIC Distribution for Isolates w/ ESBL, Plasmid-mediated(p) AmpC, ESBL + pAmpC Impact of Revised (New) and Old Breakpoints

Klebsiella spp.
and *E. coli*
(n=264)



Kohner et al. 2009. J Clin Microbiol. 47:2419.

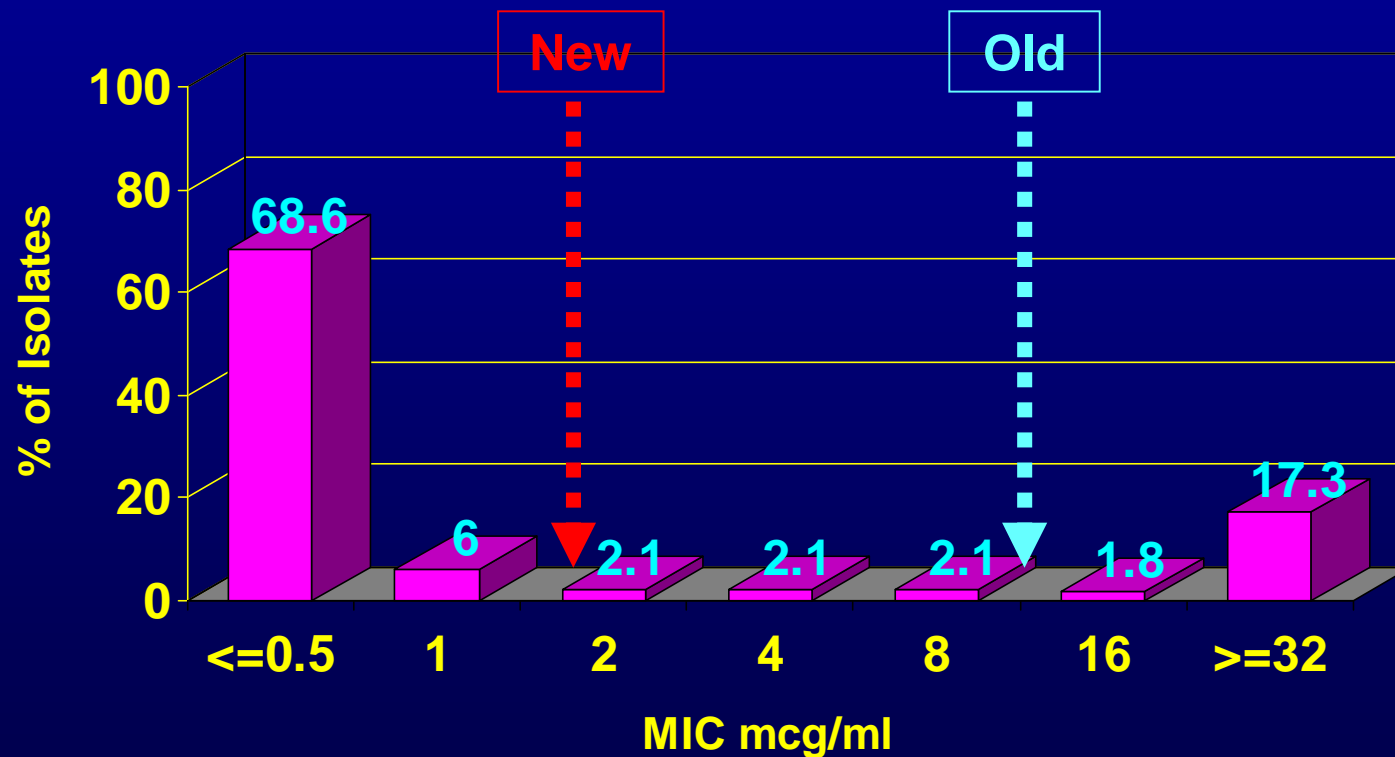
Ceftriaxone, Ceftazidime, Cefepime MIC Distribution *Enterobacteriaceae* (n=27,415)



Worldwide Sentry Program 2007-2009
Courtesy of Ronald Jones, MD

Ceftriaxone MIC Distribution

C. freundii, *E. aerogenes*, *E. cloacae*, *S. marcescens*
(non-urine) N=383



UCLA 2009

Enterobacteriaceae (non-urine) New vs. Old Cephalosporin BPs

Organism	N	%S @ MIC ($\mu\text{g/ml}$)	
		Ceftriaxone	
		New ≤ 1	Old ≤ 8
<i>C. freundii</i>	43	65	72
<i>E. aerogenes</i>	51	69	71
<i>E. cloacae</i>	182	70	77
<i>S. marcescens</i>	107	88	95

E. coli, Klebsiella spp., Proteus mirabilis **% ESBL positive**

Organism	N*	% ESBL positive
E. coli	4601	3.3
K. oxytoca	167	3.5
K. pneumoniae	939	4.1
P. mirabilis	474	0.4

***One isolate / patient**

E. coli, Klebsiella spp., Proteus mirabilis **ESBL positive**

Organism	N	# patients with ESBL positive isolates that tested S to:*		
		CTAX	CTAZ	CTAX & CTAZ
E. coli	108	1	13	3
K. oxytoca	3	-	-	1
K. pneumoniae	38	1	-	-
P. mirabilis	2	-	1	-

***based on disk diffusion testing**

- 20/151 = 13.2% ESBL positive isolates would test “S” to cefotaxime (CTAX) or ceftazidime (CTAZ) or both with new BPs**
 - 16/20 isolates were from urine**

UCLA 2/1/10 – 6/30/10

Expected Results for ESBL-Producers

Cephalosporin Breakpoints

Old Breakpoints	New Breakpoints
<p>Any ESBL-producing isolates that tested “S” to extended-spectrum cephalosporins were reported as “R” to:</p> <ul style="list-style-type: none">cefotaximeceftazidimeceftriaxonecefepime	<p>ESBL-producing isolates may not test “R” to ALL of the extended-spectrum cephalosporins</p> <p>ESBL-producing isolates will test “R” to AT LEAST ONE of the extended-spectrum cephalosporins</p>

Escherichia coli

	<u>MIC ($\mu\text{g/ml}$)</u>
amikacin	>32 R
ampicillin	>32 R
cefazolin	>32 R
cefepime	8 S
ceftazidime	1 S
ceftriaxone	>32 R
ciprofloxacin	≤ 0.25 S
gentamicin	≤ 0.5 S
piper-tazobactam	>128 R
tobramycin	1 S
trimeth-sulfa	>4/76 R

ESBL-producing *E. coli*

Possible AST results that might be obtained and reported using new breakpoints.

Why was cefepime breakpoint not lowered?

- ◆ Monte Carlo simulation showed **target attainment** to support susceptible breakpoint at $\leq 8 \mu\text{g/ml}$
 - 2 g every 12 h = 91%
 - 1 g every 8 h = 100%(goal of **50% T > MIC** attained for MIC = 8 $\mu\text{g/ml}$)
- ◆ 75% of US treatment courses are **3 to 4 g per day**
- ◆ Murine thigh model data supported breakpoints of $\leq 8, 16, \geq 32 \mu\text{g/ml}$ even with high inoculum
- ... **but “controversial”**
- ◆ Some use EUCAST breakpoints ($\mu\text{g/ml}$) (≤ 1 S, >4 R)
- ◆ Some edit “S” to “R” if ESBL positive

**CLSI M100-S19. 2009
Group A**

GROUP A PRIMARY TEST AND REPORT	<i>Enterobacteriaceae</i> ¹
	Ampicillin ²
	Cefazolin ² Cephalothin ^a
	Gentamicin Tobramycin

**Table 1
“Drugs to Test/Report”
Enterobacteriaceae**

Revised... location of cephalothin

Cephalothin

**CLSI M100-S20. 2010
Group U**

GROUP U SUPPLEMENTAL FOR URINE ONLY	Cephalothin ^a
	Lomefloxacin or ofloxacin
	Norfloxacin
	Nitrofurantoin
	Sulfisoxazole
	Trimethoprim

Why did cephalothin get moved?

- ◆ As related to Enterobacteriaceae, oral cephalosporins are used primarily for **uncomplicated UTIs**
- ◆ Results from testing cephalothin can be used to represent **other oral cephalosporins**
 - cefadroxil, cefpodoxime, cephalexin, loracarbef
- ◆ **Cephalothin for injection** no longer available in USA

Enterobacteriaceae

T/R	Agent	Disk diffusion (mm)			MIC (µg/ml)			Note
		Susc	Int	Res	Susc	Int	Res	
A	Cefazolin	-	-	-	≤1	2	≥4	a
U	Cephalothin	≥18	15-17	≤14	≤8	16	≥32	b

^a Disk diffusion interpretive criteria for cefazolin when using revised MIC breakpoints listed here have not yet been established. MIC breakpoints are based on a dosage regimen of at least 1 g every 8 h.

^b Cephalothin interpretive criteria should only be used to predict results of the oral agents, cefadroxil, cefpodoxime, cephalexin, and loracarbef. Older data which suggest that cephalothin results could predict susceptibility to some other cephalosporins may still be correct but there are no recent data to confirm this.

CLSI M100-S20. Table 2A.
T/R = test/report group

What narrow-spectrum cephalosporin do you report on urine isolates of Enterobacteriaceae?

Cefazolin Only*	Cephalothin only	Cefazolin + cephalothin	Other
49 (71%)	9 (13%)	6 (9%)	5 (7%)

***Cefazolin results likely used to predict activity of oral narrow-spectrum cephalosporins (e.g., cephalexin) that might be used for uncomplicated UTIs (uUTIs)**

**ASM DivC and Clinmicronet Listserve informal survey
69 responses (April 2010)**

% Susceptible Cefazolin UCLA 2009 (non-urine¹ and urine isolates²)

Organism	N	≤1 µg/ml (2010 BP)	≤2 µg/ml ³ (2011 BP)	≤8 µg/ml (Old BP)
<i>E. coli</i> (urine)	3425	NA	NA	89
<i>E. coli</i> (non-urine)	377	32	57	74
<i>K. pneumoniae</i> (urine)	591	NA	NA	93
<i>K. pneumoniae</i> (non-urine)	241	50	81	87
<i>P. mirabilis</i> (urine)	339	NA	NA	95
<i>P. mirabilis</i> (non-urine)	97	0	10	92

NA = not available

¹ Tested using CLSI reference broth microdilution method

² Outpatient specimens only; tested using Vitek

³ 2011 cefazolin “S” breakpoint will change to ≤2 µg/ml

CLSI Reference Methods vs Commercial Methods and CLSI vs FDA Breakpoints (interpretive criteria)

It is important for users of M02-A10, M07-A8, and the M100 Informational Supplement to recognize that the standard methods described in CLSI documents are reference methods. These methods may be used for routine antimicrobial susceptibility testing of clinical isolates, for evaluation of commercial devices that will be used in clinical laboratories, or by drug or device manufacturers for testing of new agents or systems. Results generated by reference methods, such as those contained in CLSI documents, may be used by regulatory authorities to evaluate the performance of commercial susceptibility testing devices as part of the approval process. Clearance by a regulatory authority indicates that the commercial susceptibility testing device provides susceptibility results that are substantially equivalent to results generated using reference methods for the organisms and antimicrobial agents described in the device manufacturer's approved package insert.

CLSI breakpoints may differ from those approved by various regulatory authorities for many reasons, including the following: different databases, differences in interpretation of data, differences in doses used in different parts of the world, and public health policies. Differences also exist because CLSI proactively evaluates the need for changing breakpoints. The reasons why breakpoints may change and the manner in which CLSI evaluates data and determines breakpoints are outlined in CLSI document M23—*Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters*.

Following a decision by CLSI to change an existing breakpoint, regulatory authorities may also review data in order to determine how changing breakpoints may affect the safety and effectiveness of the antimicrobial agent for the approved indications. If the regulatory authority changes breakpoints, commercial device manufacturers may have to conduct a clinical laboratory trial, submit the data to the regulatory authority, and await review and approval. For these reasons, a delay of more than the suggested CLSI "tentative" period of one year may be required if an interpretive breakpoint change is to be implemented by a device manufacturer. In the United States, laboratories that use Food and Drug Administration (FDA)-approved susceptibility testing devices are allowed to use existing FDA interpretive breakpoints. Either FDA or CLSI susceptibility interpretive breakpoints are acceptable to clinical laboratory accrediting bodies. Policies in other countries may vary.

Following discussions with appropriate stakeholders such as infectious disease practitioners and the pharmacy department, as well as the Pharmacy and Therapeutics and Infection Control committees of the medical staff, newly approved or revised breakpoints may be implemented by clinical laboratories. CLSI disk diffusion test breakpoints may be implemented as soon as they are published in M100. If a device includes antimicrobial test concentrations sufficient to allow interpretation of susceptibility and resistance to an agent using the CLSI breakpoints, a laboratory could, after appropriate validation, choose to interpret and report results using CLSI breakpoints.

Brief CLSI and FDA Breakpoint (BP) Story

- Might be delay in addition of new BPs to commercial system
- Use of CLSI or FDA BPs is acceptable to accrediting bodies; thus can use "Old" (same as FDA BPs) or "New" CLSI BPs
- Labs can validate (verify) new BPs on commercial system

CLSI M100-S20. pp. 18.

Steps to Implementing New CLSI Cephalosporin and/or Carbapenem Breakpoints (1)

1. Determine if **low concentrations** are available on panel
 - All drugs?
 - Some drugs?
 - Work around possible??
2. Discuss with **stakeholders** (lab director, infectious diseases, pharmacy, infection control, others)

Steps to Implementing New CLSI Cephalosporin and/or Carbapenem Breakpoints (2)

3. Perform “verification”

- Approx. 30 isolates / results for each drug
- Review “S, I, R” results w/ new breakpoints
- Note: no changes to your QC protocol needed

4. Make computer / protocol changes

Verify New Breakpoints

S, I, R

**Routine AST system
(new breakpoints)**

=

S, I, R

**Reference AST system
(new breakpoints)**

**Reference AST system = disk diffusion, reference
broth or agar dilution MIC, other MIC?**

Acceptable =

≥90% overall categoric agreement

No very major errors (false “S”)

≤7% combined major (false “R”) and minor errors (I/R or I/S)

Status of New Breakpoint Concentrations Available on Commercial AST Systems¹

Antimicrobial	MicroScan	Phoenix	Sensititre	Vitek2	Etest
Aztreonam	X	X	X	X	X
Cefazolin	-	-	X	-	X
Cefotaxime	X	-	X	X	X
Ceftriaxone	X	-	X	X	X
Ceftazidime	X	X	X	X	X
Doripenem	-	-	X	X	X
Ertapenem	X	-	X	-	X
Imipenem	X	X	X	X	X
Meropenem	X	X	X	X	X

¹For some, only available on specific panel types (e.g., ESBL)

Some concerns about the new breakpoints.....(1)

Cephalosporins and aztreonam breakpoints

- ◆ Eliminating ESBL confirmatory test will result in reporting some cephalosporins as “S” for some ESBL positive strains
- ◆ Clinical data limited for using cephalosporins to treat ESBL producers when MICs are low
- ◆ No change for cefepime quite controversial
- ◆ Cefazolin breakpoints not appropriate for oral cephalosporins for UTI

Some concerns about the new breakpoints.....(2)

Carbapenem breakpoints

- ◆ Some favor ≤ 2 $\mu\text{g/ml}$ (same as EUCAST breakpoint) as ≤ 1 $\mu\text{g/ml}$ may be too conservative and drive increased use of polymyxins for multidrug-R isolates

Other

- ◆ Labs using **commercial test systems** must use published FDA breakpoints
 - Approx. 70% of USA labs use commercial test
 - Labs can verify new CLSI breakpoints

UCLA Decisions re: Revised Enterobacteriaceae Breakpoints

- ◆ Adopt revised **carbapenem** breakpoints
 - Perform MHT on request
 - (note: meropenem concentrations on urine panels not low enough; will test isolates “R” to ceftriaxone and piperacillin-tazobactam by reference MIC method)
- ◆ Adopt revised **cephalosporin** breakpoints
 - Continue ESBL testing (*E. coli*, *Klebsiella*, *P. mirabilis*)
 - Edit “S” results to “R” for cephalosporins, penicillins, and aztreonam for ESBL producers
 - Inform Infectious Diseases of ESBL-producing isolates that have “S” MICs to one or more cephalosporins or aztreonam for follow up
 - **Cefazolin**
 - Use old breakpoints (S, MIC ≤ 8 $\mu\text{g/ml}$) for urine isolates (limitations understood by medical staff)
 - Use new 2011 breakpoints (S, MIC ≤ 2 $\mu\text{g/ml}$) for other isolates



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The Subcommittee on Antimicrobial Susceptibility Testing is composed of representatives from the professions, government, and industry, including microbiology laboratories, government agencies, healthcare providers and educators, and pharmaceutical and diagnostic microbiology industries. Using the CLSI voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting.

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CLSI Meeting Summaries

The ASM is a member of the Clinical Laboratory Standards Institute (CLSI). CLSI's mission is to develop best practices in clinical and laboratory testing and promote their use throughout the world, using a consensus-driven process that balances the viewpoints of industry, government, and the health care professions. The ASM has a delegate to the CLSI, responsible for attending Committee meetings and voting on new guidelines on behalf of ASM. Susan Sharp, Ph.D., is ASM's delegate and Stephen Cavalieri, Ph.D., is ASM's alternate delegate.

- June 2010 CLSI Meeting Summary
- January 2010 CLSI Meeting Summary
- June 2009 CLSI Meeting Summary
- January 2009 CLSI Meeting Summary

August 25, 2010 – Opinion Articles on CLSI Changes to Cephalosporin breakpoints with the *Enterobacteriaceae*

Opinion articles were written by two experts in clinical microbiology who are both very familiar with the CLSI and the process that led up to the 2010 change in the cephalosporin breakpoints with the *Enterobacteriaceae*. These articles represent the PRO and CON assessments of the CLSI changes and are referenced for your further investigation. These opinion articles were reviewed by the PSAB Committee on Laboratory Practices. The Committee on Laboratory Practices thanks the authors, Paul C. Schreckenberger, Ph.D., and Stephen G. Jenkins, Ph.D., for their contribution to the understanding of this issue.

- [CLSI Changes to Cephalosporin breakpoints with the *Enterobacteriaceae* - PRO](#)
- [CLSI Changes to Cephalosporin breakpoints with the *Enterobacteriaceae* - CON](#)

For more information:



More information on Breakpoints

<http://www.asm.org/index.php/policy/clsi-meeting-summaries.html?title=CLSI+Meeting+Summaries>

Thank you!

...and thank you to Jean Patel, Mary Jane Ferraro and CLSI for sharing some information for this presentation

