What Is This Breakpoint Really Telling Me? Interpreting Oral Cephalosporin Susceptibility in Clinical Practice

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August 29, 2026

Disclosures

- Prior part-time employment (11/2024 – 8/2025) with Fingerpaint Marketing, Inc. as Senior Director of Scientific Strategy for Abbvie, Inc. anti-infective portfolio
- Current CLSI Volunteer Work:
  - Member: Cefepime-Zidebactam Breakpoints Ad Hoc Working Group
  - Member: M100 Text and Tables Working Group
  - Advisor: CLSI AST Subcommittee
  - **Co-Chair: CLSI Oral Cephalosporins Breakpoints Ad Hoc Working Group**
    - This talk does not represent official CLSI position – opinions are my own

Objectives

1. Review the principles and process of establishing and periodically re-evaluating susceptibility testing interpretive criteria.

2. Describe the basis for and limitations of existing CLSI Enterobacterales oral cephalosporin and cefazolin surrogate breakpoints.

3. Recognize scenarios in which application of the CLSI Enterobacterales cefazolin surrogate breakpoint is not intended/endorsed.

Why do breakpoints vary?

- European Union Committee on Antimicrobial Susceptibility Testing (AST)
  - United States Committee on AST

- US Food and Drug Administration
  Center for Drug Evaluation and Research (CDER)

- Clinical and Laboratory Standards Institute
  AST Subcommittee

J Clin Microbiol. 2020;58(3):e01864-19

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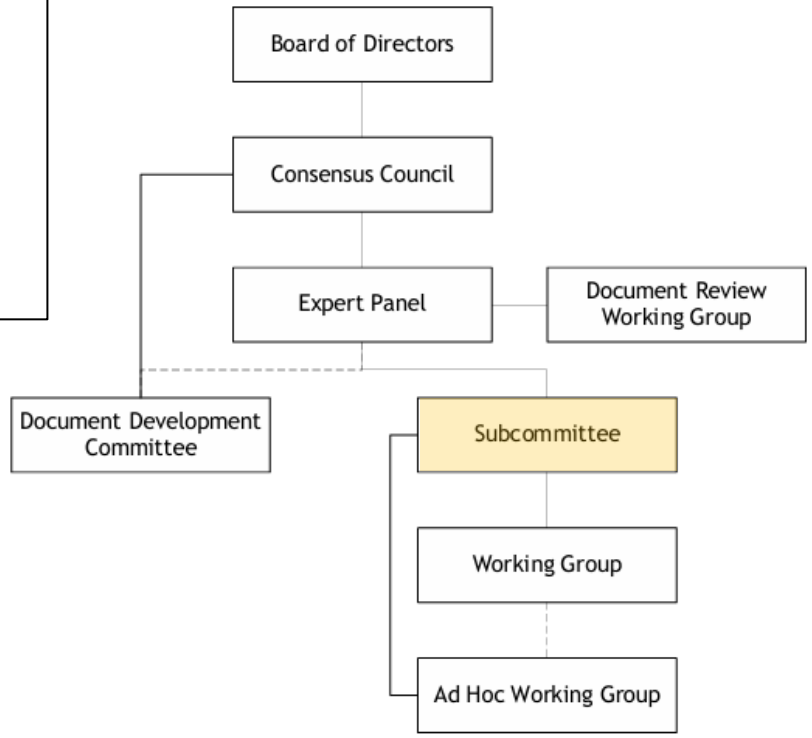
COMMENTARY

The Clinical and Laboratory Standards Institute Subcommittee on Antimicrobial Susceptibility Testing: Background, Organization, Functions, and Processes

Melvin P. Weinstein,[a] James S. Lewis II[b]



"Where there is scientific uncertainty, there is debate. In the case of breakpoint setting, scientific and technical debate is not a sign of ignorance or inconsistency. It is a necessary process…"

CLSI. Standards Development Policies and Processes. S-001, v10.0; 2026

J Clin Microbiol. 2020;58(3):e01864-19

Open Forum Infectious Diseases

MAJOR ARTICLE

Old In Vitro Antimicrobial Breakpoints Are Misleading Stewardship Efforts, Delaying Adoption of Innovative Therapies, and Harming Patients

Paul G. Ambrose,[1] Sujata M. Bhavnani,[1] David R. Andes,[2,3] John S. Bradley,[4,5] Robert K. Flamm,[6] Jason M. Pogue,[7] and Ronald N. Jones[6]; for the US Antimicrobial Susceptibility Testing (USCAST) Committee

How Big of a Problem Is Misleading Breakpoints?

In our view, a systematic evaluation of all commonly utilized older antimicrobial agents is urgently needed. Moreover, priority should be given to those intravenous agents utilized in the care of seriously ill patients. To date, USCAST has systematically examined 2 such antibiotic classes [1, 2] and recommended corrections to essentially all STIC for those classes. Preliminary evaluations of other classes, such as intravenous tetracycline, β-lactam, and others, indicate that many STIC corrections may be warranted.

Open Forum Infect Dis. 2020;7(7):ofaa084

Breakpoint setting is an iterative process

Chapter 4: Procedures for Establishing Breakpoints . .

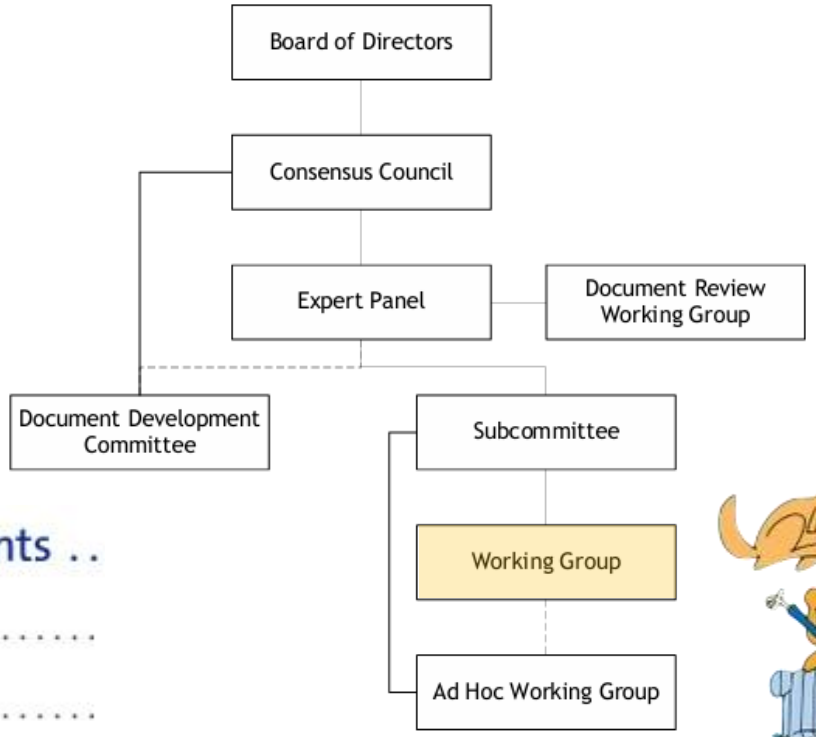
4.1 New Breakpoints . . . . . .

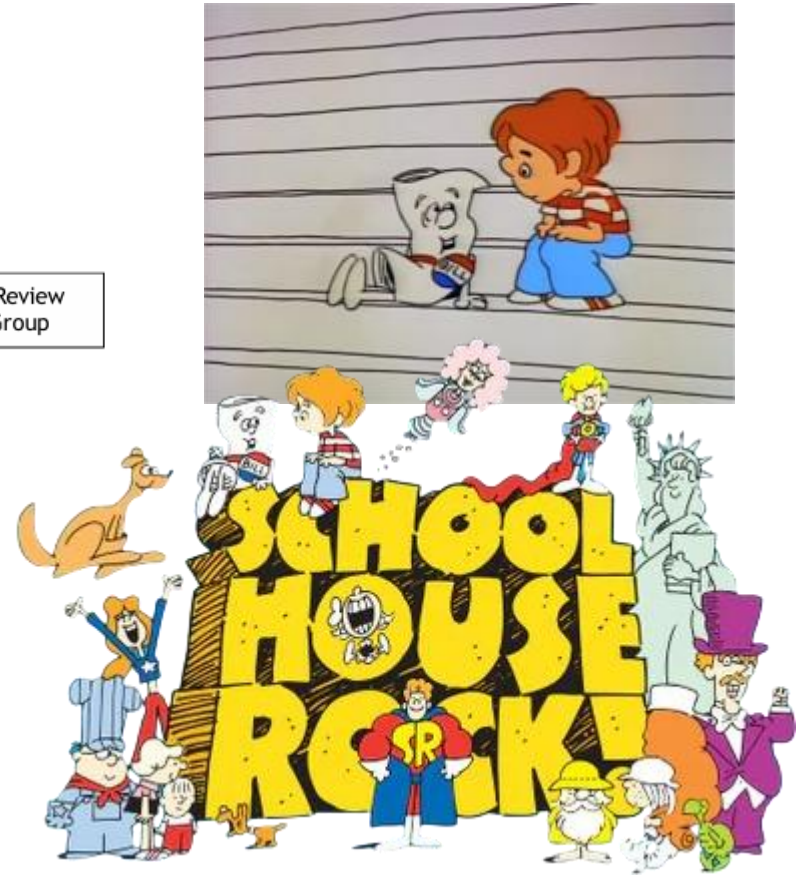
4.2 Breakpoint Revisions. . . . . .

4.3 Investigational Breakpoints. . . . . .

4.4 Periodic Bacterial Breakpoint Review. . . . . .

4.5 Rationale Documents . . . . . .



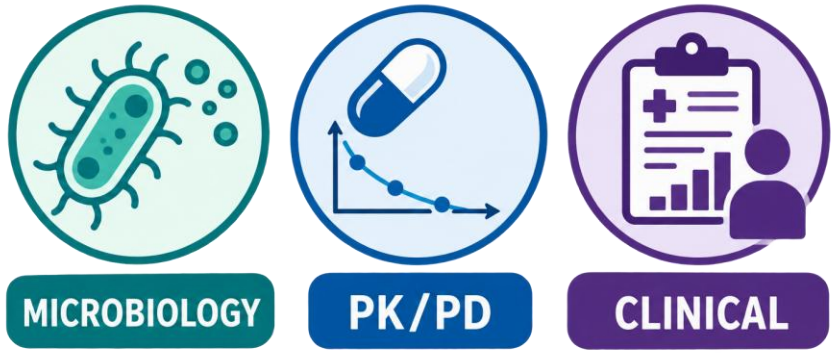


CLSI. Standards Development Policies and Processes. S-001, v10.0; 2026

J Clin Microbiol. 2020;58(3):e01864-19

By American Broadcasting Company - A screen shot from "I'm Just a Bill"., Fair use, https://en.wikipedia.org/w/index.php?curid=62824163

Data Sources



Chapter 5: Minimal Inhibitory Concentration Breakpoints. . . . . .

5.1 Epidemiological Cutoff Values . . . . . .

5.2 Nonclinical Pharmacokinetic/Pharmacodynamic Cutoff . . . . . .

5.3 Clinical Exposure–Response Cutoff . . . . . .

5.4 Clinical Cutoff . . . . . .

5.5 Consideration of the Cutoffs to Determine Breakpoints. . . . . .

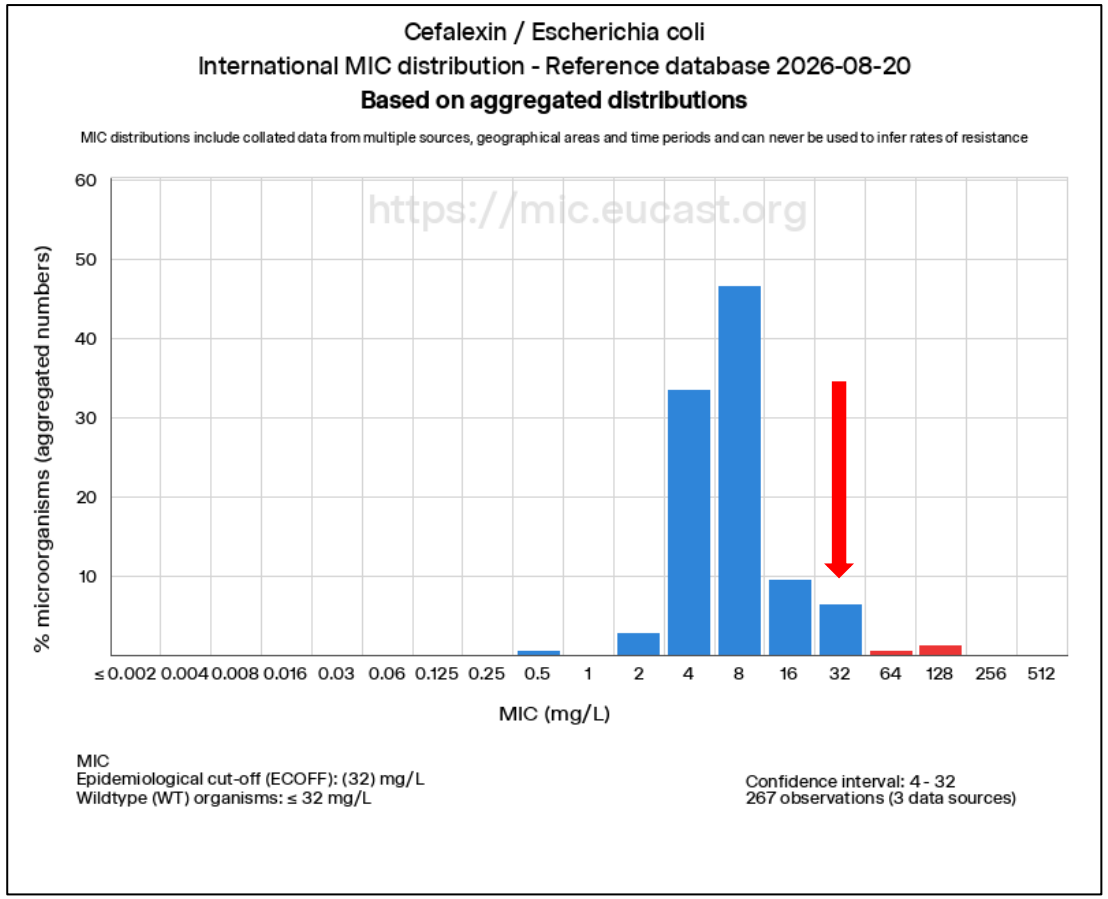
CLSI M23, 6th ed. (2023)

MIC Distributions & Epidemiological Cutoff Values (ECV)

ECV meant to distinguish wild-type (WT) from non-wild-type

ECV alone does NOT distinguish treatable from non-treatable

For breakpoint determination, indicates LOWEST possible MIC value



CLSI M23, 6th ed. (2023)

EUCAST. https://www.eucast.org/mic_and_zone_distributions_and_ecoffs

PK/PD Cutoff

For breakpoint determination, indicates HIGHEST possible MIC value

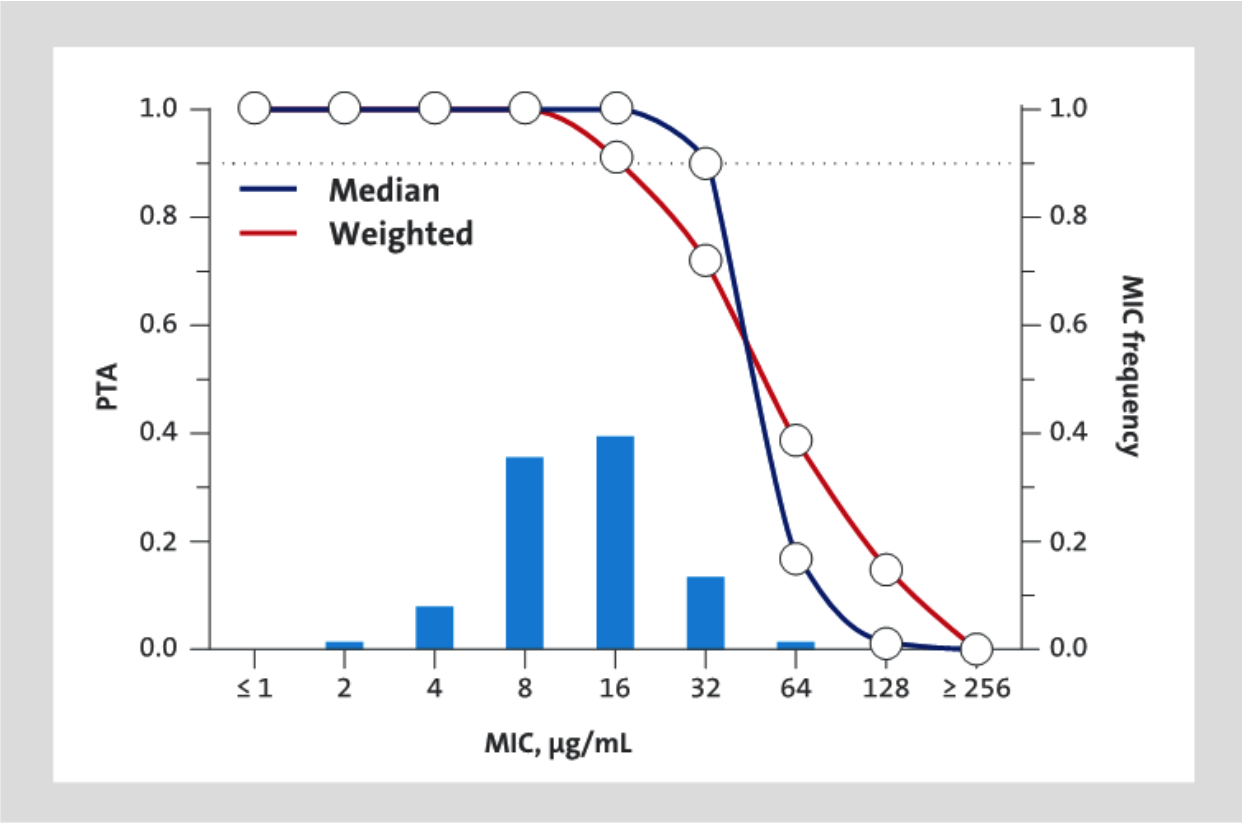
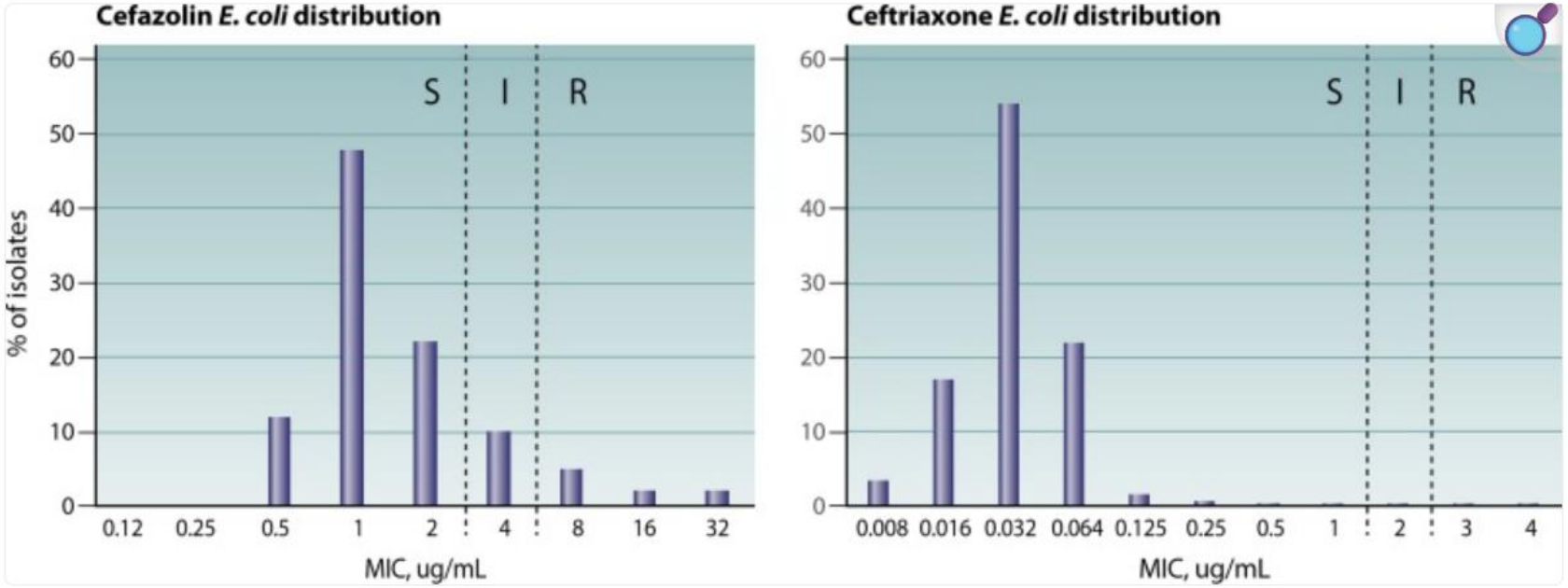


Figure 2. Schematic to Determine Nonclinical PK/PD Cutoff

Abbreviations: PAE, postantibiotic effect; PDI, pharmacokinetic/pharmacodynamic index; PK/PD, pharmacokinetic/pharmacodynamic; PTA, probability of target attainment.

CLSI M23, 6th ed. (2023)

Why avoid setting a breakpoint below the ECV?



Agreement or Error Category	Acceptance Criteria[1]
Category Agreement (CA)	≥90% CA
Essential Agreement (EA)	≥90% EA
Minor Error (mE)	≤10% mE
Major Error (ME)	<3% ME
Very Major Error (VME)	<3% VME[2]

Breakpoint set below ECV → Unable to reliably distinguish between interpretive categories → Unacceptable error rates → AST device unable to gain FDA clearance

Adapted from slide by Navaneeth Narayanan

J Clin Microbiol. 2018;56(4):e01934-17

Clinical Cutoff

IN VITRO ACTIVITY OF CEFPODOXIME AGAINST CLINICAL TRIAL ISOLATES OF CLAIMED PATHOGENS

Organism	Minimum Inhibitory Concentration (µg/ml)		
	N	50%	90%
E. coli	480	0.50	1
K. pneumoniae	63	0.25	0.50
P. mirabilis	63	0.06	0.25

WEIGHTED AVERAGE MIC DATA FOR CLINICAL ISOLATES FROM U.S. AND NON-U.S. LITERATURE

Organism (No. Studies)	Minimum Inhibitory Concentration (µg/ml)		
	Total N	50%	90%
E. coli (54)	4119	0.38	1.1
K. pneumoniae (36)	1871	0.14	3.3
P. mirabilis (41)	1732	0.08	1.0

Pathogen Eradication by MIC

Urinary Tract — *Escherichia coli*

MIC (mcg/mL)	Eradicated/Total	% Eradicated
128	1/1	100
8	1/1	100
2	5/5	100
1	13/14	93
.5	64/84	76
.25	58/73	79
.125	7/8	88
Totals	149/186	80

CLSI M23, 6th ed. (2023)

NCCLS AST Subcommittee Agenda Book. June 1992. pp 351-413

Practical considerations

- Disk diffusion testing and MIC/zone diameter correlation
- M100 Table 1 placement (guidance for cascade testing and reporting)
- Dosage (+/- infusion time) on which S or SDD breakpoint is based
- **Site of action/infection considerations (urine vs systemic breakpoints)**
- **Historical precedent for currently established breakpoints**
- Harmonization with FDA and EUCAST, if possible

CLSI Breakpoints are determined by the ***totality of data***, not a single data source

Adapted from slide by Navaneeth Narayanan

CLSI M23, 6th ed. (2023)

Question 1

Which of the following sources of data are considered when establishing and periodically re-evaluating susceptibility testing interpretive criteria (i.e., “breakpoints”)

A. Microbiological (e.g., MIC distributions, ECVs)
B. PK/PD (e.g., probability of target attainment analyses)
C. Clinical (outcomes stratified by MIC)
D. All of the above

Question 2

Which of the following best describes the evidence underpinning the existing CLSI Enterobacterales oral cephalosporin breakpoints?

A. Robust PK/PD data (e.g., drug specific systemic and urinary probability of target attainment analyses)
B. Robust clinical data (e.g., prospective, randomized controlled trials evaluating individual oral cephalosporins with outcomes stratified by MIC)
C. Contemporary microbiological data (e.g., modern, species-specific wild-type MIC distributions and ECVs)
D. None of the above

CLSI M100-ED36:2026 Table 2A Enterobacterales excerpt

CEPHEMS (ORAL)										
Cefazolin (U)[a] (surrogate test for oral cephalosporins and uncomplicated UTIs)	30 µg	≥ 15	–	–	≤ 14	≤ 16	–	–	≥ 32	**(22)** Breakpoints are for cefazolin when used as a surrogate test to predict results for the oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef when used for therapy of uncomplicated UTIs due to *E. coli, K. pneumoniae*, and *P. mirabilis*. Cefazolin tested as a surrogate may overcall resistance to cefdinir, cefpodoxime, and cefuroxime. If cefazolin tests resistant, test these drugs individually if needed for therapy.
Cefuroxime (oral)	30 µg	≥ 23	–	15-22^	≤ 14	≤ 4	–	8-16^	≥ 32	
Lo							–			sk een
Ce							–			
Ce							–			
Ce							–			
Ce							–			
Ce							–			disk een
Ce							–			
Ceftibuten (U, Inv.)[a]	30 µg	≥ 21	–	18-20^	≤ 17	≤ 8	–	16^	≥ 32	

Are these breakpoints intended for systemic infection or uncomplicated UTI?

Drug (Approval Year)	FDA indications for Enterobacterales	CLSI MIC BP	FDA STIC	Cefazolin Surrogate
Cephalexin (1971)	Bone infections: *P. mirabilis* Genitourinary tract infections, including acute prostatitis: *E. coli, P. mirabilis, K. pneumoniae* 250 mg q6h – 500 mg q12h x 7 – 14 d; max 4 g daily	None	None (2004 label references "class" cephalothin MIC ≤8/16/≥32)	✓
Cefaclor (1979)	UTI, including pyelonephritis: *E. coli, P. mirabilis, Klebsiella spp.* 250 mg q8h, duration unspecified	≤8/16^/≥32	None / CLSI BP not recognized (2004 label ≤8/16/≥32)	✓
Cefadroxil (1980)	UTI: *E. coli, P. mirabilis, Klebsiella spp.* 1 g daily or q12h; max 2 g daily	None	None (2002 label references "class" cephalothin MIC ≤8/16/≥32)	---
Cefuroxime (1987)	uUTI: *E. coli, K. pneumoniae* 250 mg q12h for 7-10 d	≤4/8–16^/≥32	≤4/8–16^/≥32 (2002 label)	✓
Cefixime (1989)	uUTI: *E. coli, P. mirabilis* 400 mg daily, duration unspecified	≤1/2^/≥4	≤1/2^/≥4 (2003 label)	---
Cefprozil (1991)	None	≤8/16^/≥32	None / CLSI BP not recognized (2004 label ≤8/16/≥32)	✓
Loracarbef (1991)	uUTI and uncomplicated pyelonephritis: *E. coli* 200 mg daily – 400 mg q12h x 7 – 14 d?	≤8/16^/≥32	None / CLSI BP not recognized (label unavailable)	✓
Cefpodoxime (1992)	uUTI: *E. coli, K. pneumoniae, P. mirabilis* 100 mg q12h x 7 d	≤2/4^/≥8	≤2/4^/≥8 (2004 label)	✓
Cefdinir (1997)	None	≤1/2^/≥4	None / CLSI BP not recognized (1999 label ≤1/2^/≥4)	✓

Cephalothin susceptibility testing as class representative for oral cephalosporins: is it time to move on?

Hien M. Nguyen [a,*], Christopher J. Graber [b]

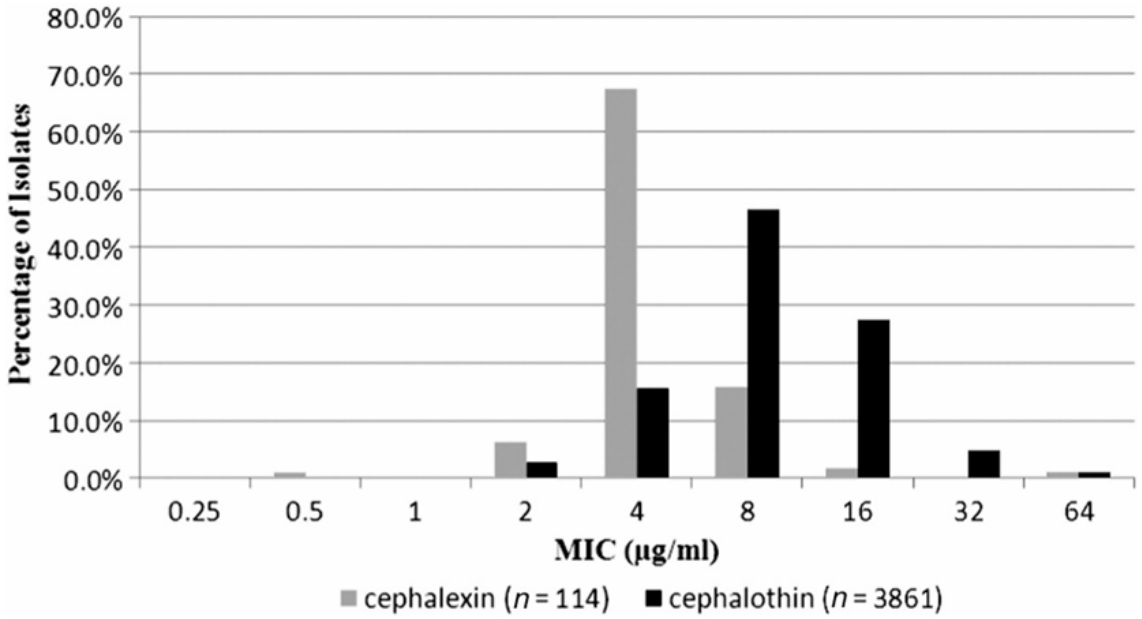


Fig. 1. MIC distributions of cephalothin and cephalexin against wild-type *E. coli* (EUCAST 2010–2013). Available at: http://www.eucast.org/mic_distributions/.

Cefazolin as a class representative for oral cephalosporins and uncomplicated urinary tract infections caused by indicated Enterobacteriaceae

The current M100-S23 document (CLSI, 2013) states that the predictability of cephalothin as a class marker was based on older data dating from the first M100 supplement in 1981, and the limitations of these data were emphasized by Nguyen and Graber (2013). Our *ad hoc* group examined more recent data gathered in 2009 for the ability of either cephalothin or cefazolin to predict susceptibility of a range of oral cephalosporins applied for uUTIs. Susceptibility testing was performed on a variety of enteric gram-negative bacilli at IHMA laboratory, a resistance surveillance monitoring laboratory. The isolates for this study were submitted from US laboratories from any body site and consisted of the following: 45% *Escherichia coli* (40% with β-lactamases), 30% *Klebsiella pneumoniae*, 15% *Proteus mirabilis* (10% with β-lactamases), and 10% other enteric bacilli (50% of which were resistant subgroups). Susceptibility testing was performed by the CLSI reference broth microdilution method (CLSI M07-A9, CLSI, 2012a). We confirmed that cephalothin does not accurately predict several oral cephalosporins including cephalexin and cefadroxil, both of which were listed as predicted by cephalothin in M100-S23 (CLSI,

Diagn Microbiol Infect Dis. 2013;76(4):483-5
Diagn Microbiol Infect Dis. 2013;77(4):381-2

Rationale for FDA's Position on the Use of Cefazolin Breakpoints as a Surrogate for Determining Breakpoints for Oral Cephalosporins for the Treatment of Uncomplicated Urinary Tract Infections

No clinical studies were provided that evaluated the efficacy of cefazolin or oral cephalosporins in the treatment of uUTI based on the proposed urine-specific breakpoint for *Enterobacterales*. The submitted materials included studies reviewing the microbiologic and clinical outcomes of uUTI when treated with oral cephalosporins without specifying the distribution of MICs of the urinary pathogens nor the association of MICs with the microbiological or clinical outcomes. No decision support logic was provided using urinary drug exposure-antibacterial response relationships nor probability of target attainment analyses in patients with uUTI.

FDA has determined that there are insufficient data at this time to support the proposed cefazolin susceptible MIC breakpoint of ≤16 mg/L as a surrogate for determining breakpoints for oral cephalosporins for the treatment of uUTIs due to *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. Therefore, no changes are recommended on the FDA STIC website.

FDA. *Rationale for FDA's Position on Cefazolin as an Oral Cephalosporin Surrogate.* 2022.

Cefazolin Breakpoints for Enterobacterales (Uncomplicated Urinary Tract Infections)

Table 1
Cefazolin versus cephalexin MICs cross-susceptibility table demonstrating 97.1% susceptible agreement (165/170 comparisons) at a breakpoint of ≤16 µg/mL (box).

Cefazolin MIC (µg/ml) \ Cephalexin MIC (µg/ml)	≤0.12	0.25	0.5	1	2	4	8	16	>16
>16							1	2	36
16							6	2	4
8						1	4	5	
4							16	27	1
2						1	73	9	
1						6	11		
0.5									
0.25									
≤0.12									

The circle represents the percentage of isolates (2.9%; 5 results) that cefazolin would indicate susceptible when cephalexin MICs were >16 µg/mL.

Figure 1. Cross-Susceptibility and Cross-Resistance of MICs for Cefazolin vs Oral Cephalosporins (Data were generated by Ronald Jones, MD, for the Ad Hoc Oral Cephalosporin Working Group of the CLSI Subcommittee on Antimicrobial Susceptibility Testing, on a defined collection of 186 isolates of Enterobacterales: 93 *E. coli* (40% with acquired β-lactamases), 62 *K. pneumoniae*, 31 *P. mirabilis* (10% with acquired β-lactamases). Cephalexin graph reprinted from *Diagnostic Microbiology and Infectious Disease*, Vol 77, Number 4, AN Schuetz, WB Brasso, JL Crandon, DJ Hardy, SG Jenkins, RN Jones, CC Knapp, LB Reller, Cefazolin as a class representative for oral cephalosporins and uncomplicated urinary tract infections caused by indicated *Enterobacteriaceae* [letter to the editor], pages 381-382, ©2013, with permission from Elsevier.[10] Breakpoints used in the cephalexin graph are from EUCAST [eucast.org/clinical_breakpoints/].)

Key Point:

The **cefazolin surrogate breakpoint** indicates >95% categorical agreement **based on an MIC ≤16 mcg/mL for BOTH agents**.

It is not based on a cefazolin MIC ≤16 mcg/mL compared to the "S" breakpoint in Table 2A for each oral cephalosporin (e.g., cefpodoxime MIC ≤2 mcg/mL)

Diagn Microbiol Infect Dis. 2013;77(4):381-2
CLSI. Rationale document MR08. 2020.

EUCAST Breakpoints

Cephalosporins[1]	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Cefaclor (uncomplicated UTI only)	IE	IE	
Cefadroxil (uncomplicated UTI only)	16	16	
Cefalexin (uncomplicated UTI only)	16	16	
Cefazolin (infections originating from the urinary tract), *E. coli* and *Klebsiella* spp. (except *K. aerogenes*)	0.001[2]	4[2]	
Cefixime (uncomplicated UTI only)	1	1	
Cefpodoxime (uncomplicated UTI only)	1	1	
Ceftibuten (infections originating from the urinary tract)	1	1	
Cefuroxime oral (uncomplicated UTI only), *E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp. and *P. mirabilis*	8	8	

Cephalosporins	Uncomplicated UTI
Cefadroxil	0.5-1 g x 2 oral
Cefalexin	0.25-1 g x 2-3 oral
Cefixime	0.2-0.4 g x 2 oral
Cefpodoxime	0.1-0.2 g x 2 oral
Ceftibuten	
Cefuroxime oral	0.25 g x 2 oral

EUCAST. *Clinical Breakpoint Tables*, v16.1. 2026.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Why do EUCAST have no systemic breakpoints for *Enterobacterales* with oral cephalosporins?

Version 2

There have been multiple questions from clinicians, particularly those working in orthopaedics, who have "successfully" used oral cephalosporins for prophylaxis and to treat *Enterobacterales* infections for many years". They ask what has changed and why these agents are now considered inappropriate.

In EUCAST rationale documents it is stated that *Enterobacterales* are inappropriate targets in sites other than uncomplicated urinary tract infection, but there is no further explanation. EUCAST discussions were originally considers oral cephalosporins inappropriate for treatment of infections in other sites than the urinary tract infection for several reasons:

1. Comparison of free drug pharmacokinetics with MICs alone indicates that inadequate exposures are achieved for most agents or are borderline at best (see table).
2. The relevant pharmacodynamic relationship indicative of activity of cephalosporins is *f*T>MIC and the target %*f*T>MIC is 40-50%. Approximate calculations based on common dosages indicate that activity is inadequate for all agents (see table). It should be emphasized that the figures in the table are based on pharmacokinetic parameter values for the mean of the population. Monte Carlo simulations would show that the %*f*T>MIC values are even less than those in the table for half the population treated.
3. Evidence of successful clinical use is anecdotal and may be unrelated to specific *Enterobacterales* isolates, which are rare in orthopaedic infection and often in mixtures of organisms both from bone and other sites.
4. Oral cephalosporins have mostly been used as "follow-up" therapy after successful parenteral treatment in hospital.

EUCAST. *Oral Cephalosporins and Enterobacterales Breakpoints.* July 14, 2020.

USCAST Breakpoints

Enterobacterales				
	Susceptible	**Intermediate**	**Resistant**	**Doses and relevant notes**
Cephalexin	No breakpoint recommended			*The available evidence does not support the use of either cephalexin or oral cefuroxime for any systemic infection due to Enterobacterales.*
Cefuroxime (oral)	No breakpoint recommended			
Cefpodoxime	≤ 1		≥ 2	*These STIC are based on high-dose cefpodoxime (400 mg q12h) and a net bacterial stasis endpoint. Therefore, they should only be applied to non-severe, uncomplicated infections.*

Note: no cefazolin breakpoints for Enterobacterales

USCAST – Breakpoints – Accessed 8.12.26

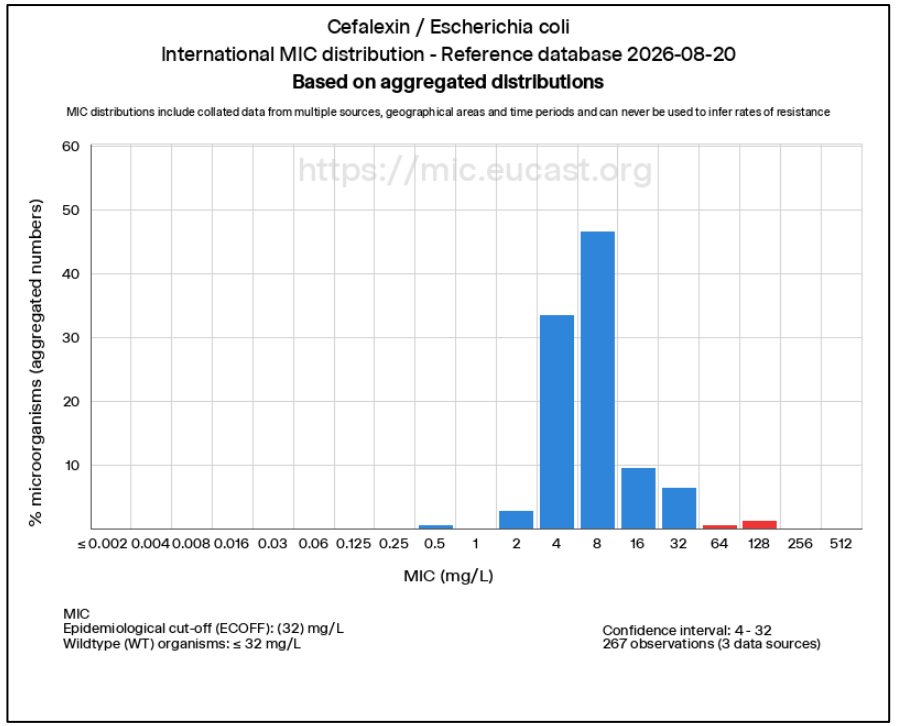
Where do we go from here?

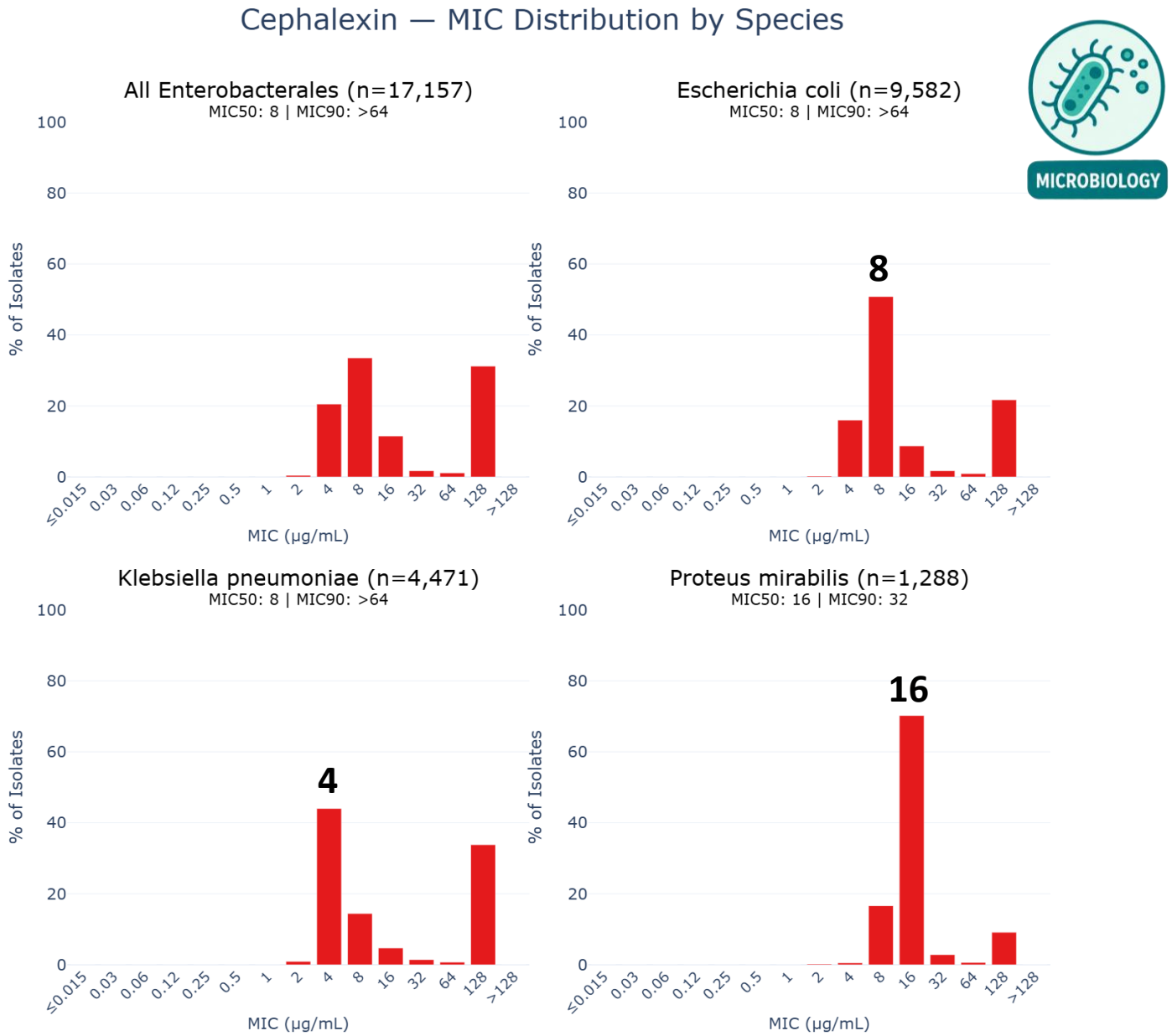
CLSI Oral Cephalosporins AHWG formed June 2025

So far: have reviewed data for cephalexin and cefpodoxime.

Cephalexin MIC Distributions/ ECV

Eucast ECV (ECOFF): 32 mcg/mL
USCAST ECV (ECOFF): 16 mcg/mL





EUCAST. https://www.eucast.org/mic_and_zone_distributions_and_ecoffs

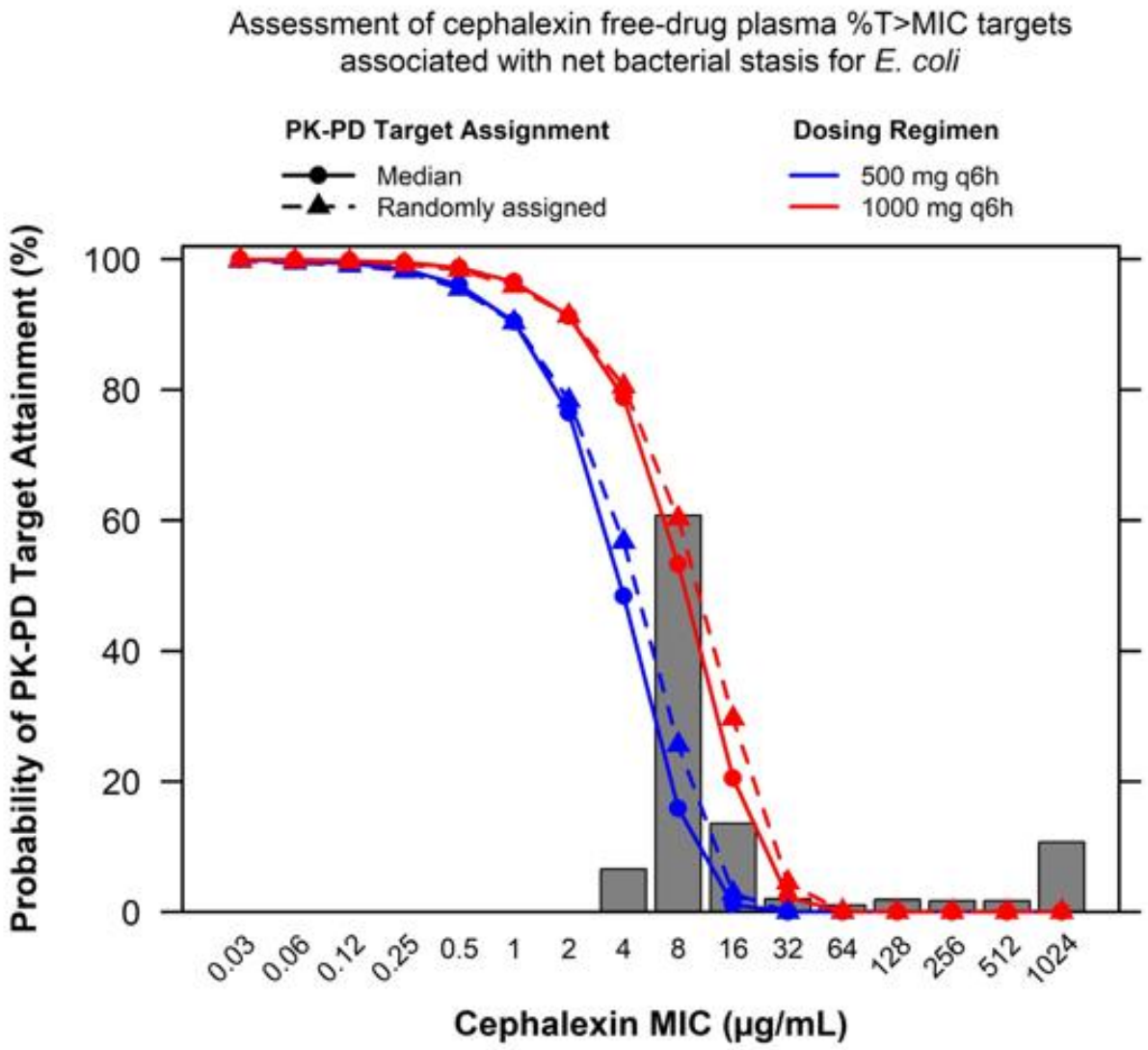
Oral Cephalosporin STIC Against S. aureus and E. coli. USCAST Virtual Public Meeting; 2024.

CLSI. *AST Subcommittee Meeting Agenda Summary Minutes.* June 2026.

USCAST: Probability of Target Attainment for *E. coli* in plasma

Target: ~60% *f*T>MIC (stasis)

MIC distribution of *E. coli* isolates (n=1,170) collected in USA in 2018 or 2021 provided by JMI



Oral Cephalosporin STIC Against S. aureus and E. coli. USCAST Virtual Public Meeting; 2024.

A pharmacokinetic-pharmacodynamic assessment of oral antibiotics for pyelonephritis

PD Target: 40% *f*T>MIC
(Craig, et al. DMID 1995)

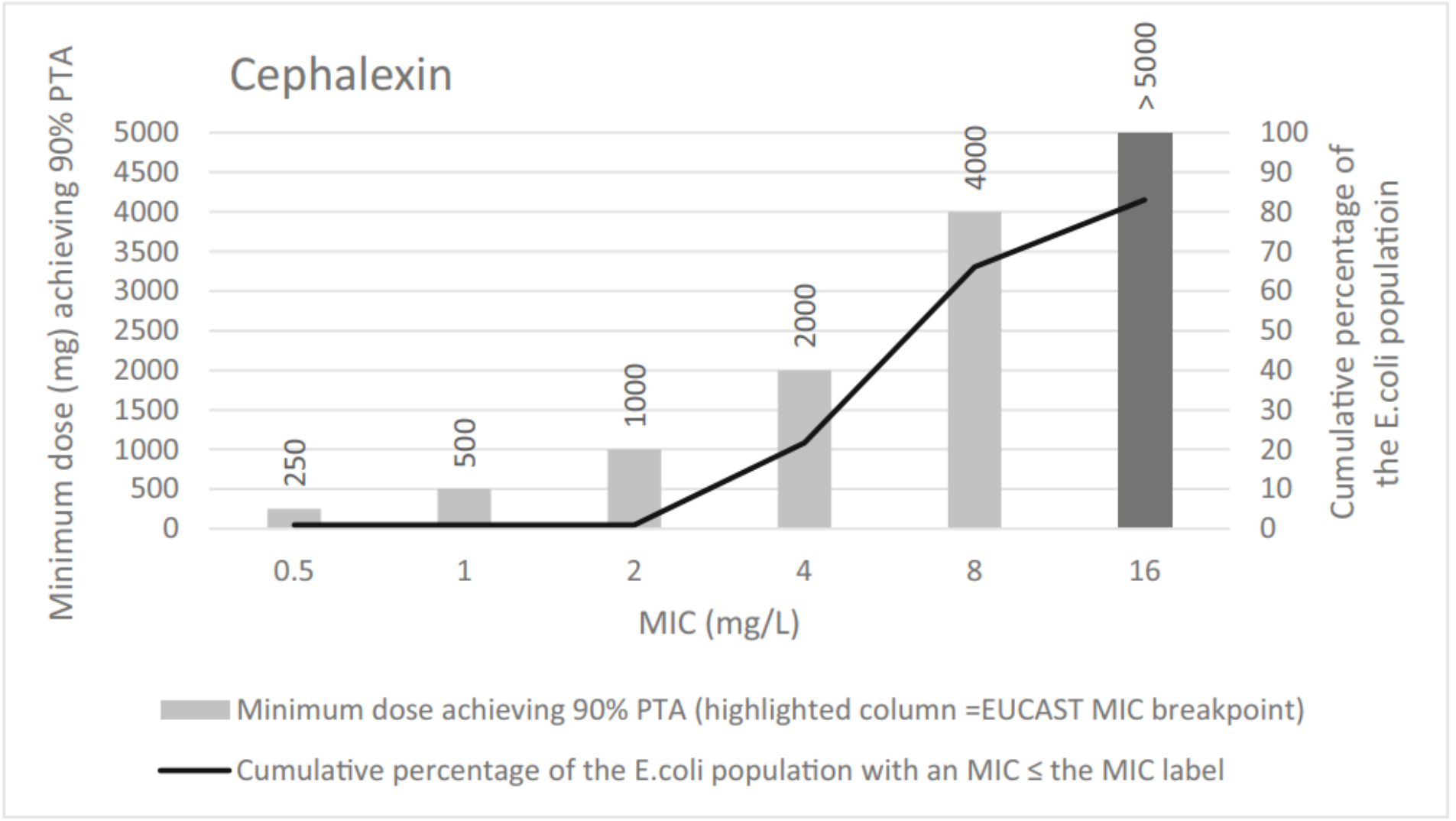
Table 5 Lowest dose of antibiotic achieving 90% CFR for specific populations of the Leeds *E. coli* bacteraemia isolates

	CFR for the population of MIC values							
	≤ MIC_{50}		≤ MIC_{90}		Whole population		≤ EUCAST susceptible [3]	
Antibiotics, frequency	Dose (mg)	CFR	Dose (mg)	CFR	Dose (mg)	CFR	Dose (mg)	CFR
Amoxicillin, every 8 h	> 10,000	.	> 10,000	.	> 10,000	.	2500	0.90
Amoxicillin-clavulanic acid, every 8 h	2100	0.91	8000	0.90	> 10,000	.	2100	0.91
Cephalexin, every 6 h	3500	0.91	4000	0.9	> 10,000	.	4000	0.9
Ciprofloxacin, every 12 h	50	0.98	700	0.9	> 10,000	.	200	0.96
Fosfomycin, every 24 h	1500	0.96	2000	0.91	3500	0.91	3000	0.9

The data presented are the lowest doses simulated for which the CFR was 0.9 or higher to the nearest 100 mg (or 50 mg if less than 100 mg). Simulations were stopped if doses exceeded 10 g without reaching a CFR 0.9

For *E. coli* isolates with MICs ≤16 mcg/mL (EUCAST breakpoint), **4,000 mg every 6 hours** required to achieve CFR >0.9.

Cattrall et al. *Eur J Clin Microbiol Infect Dis* 2019; 38: 2311–2321



PK/PD

PD Target: 40% *f*T>MIC
(Craig, et al. DMID 1995)

Cephalexin 1500 mg every 8 hours achieved a PTA of 0.85 for *E. coli* isolates with MICs of ≤4 mg/L.

Cattrall et al. *Eur J Clin Microbiol Infect Dis* 2019; 38: 2311–2321

Probability of target attainment of oral antimicrobials for *Escherichia coli* and *Klebsiella pneumoniae* based on Monte Carlo simulations

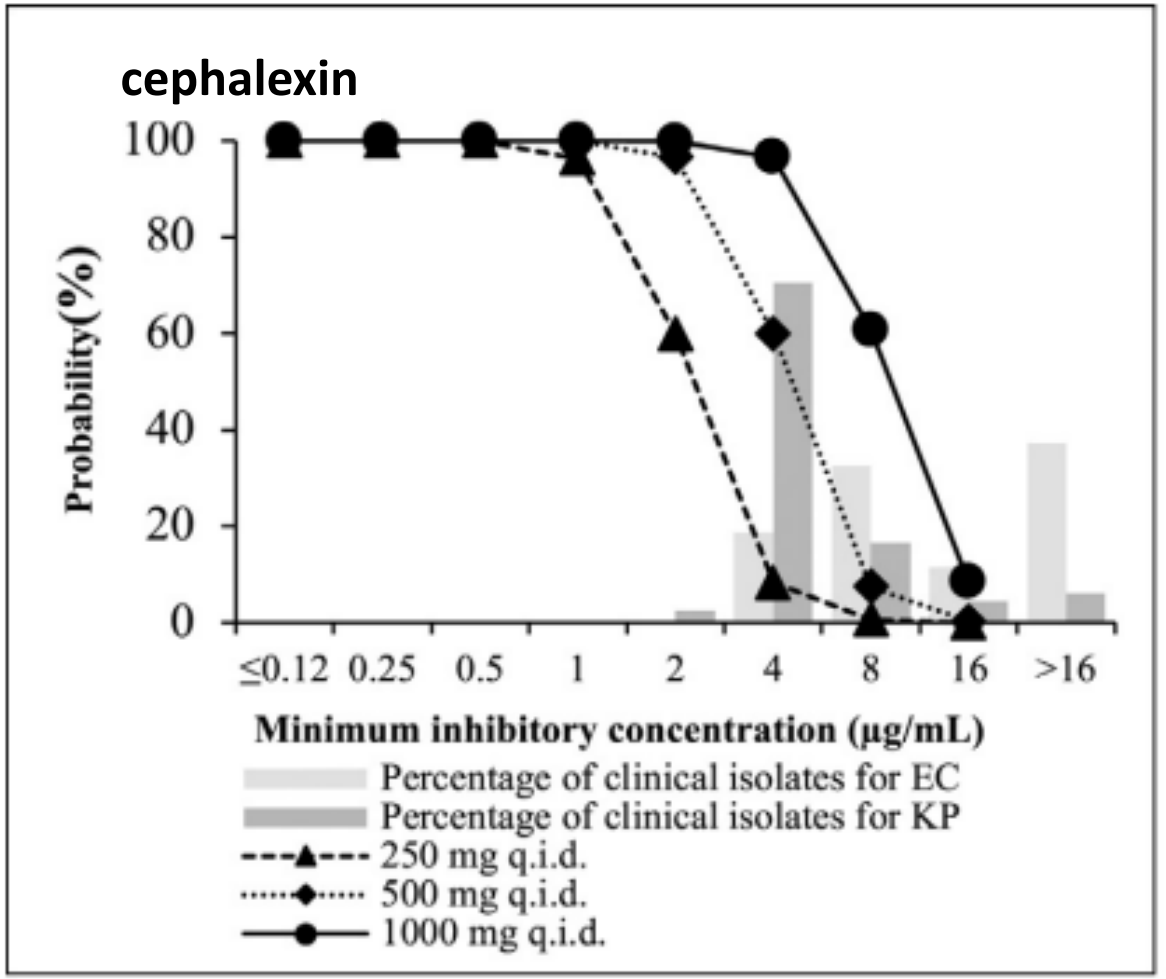
Tomoyuki Yamada[a,b,*], Kenta Minami[b,c], Kazutaka Oda[d], Kaoru Suzuki[a], Masami Nishihara[a], Kazuhisa Uchiyama[a], Akira Ukimura[b]

[a] Department of Pharmacy, Osaka Medical and Pharmaceutical University Hospital, Osaka, Japan

PK/PD

PTA >90% achievable with cephalexin MICs ≤**4 mg/mL**

PD Target: 40% *f*T>MIC
(Craig, et al. DMID 1995)



Yamada et al. *Diagn Microbiol Infect Dis* 2022; 103: 115662

Oral β-Lactams for Complicated Urinary Tract Infections: A Systematic Review and Point-Counterpoint Comparison With Trimethoprim/Sulfamethoxazole and Fluoroquinolones

Ashlan J. Kunz Coyne[1] | Jeannette Bouchard[2] | Spencer H. Durham[3] | Amy Y. Kang[4] | Kinsey M. Johannemann[5] | W. Justin Moore[6] | Kevin Nguyen[7] | James Sanders[8] | Colter Sheveland[9] | Grant Stimes[10] | Trang Trinh[11] | Elizabeth W. Covington[3] | on behalf of the ACCP Infectious Disease Practice and Research Network (PRN) Research Committee

Since cUTI could represent diverse clinical severities, studies were stratified by infection type evaluated. Comparative agents were stratified across systemic infection categories: pyelonephritis, bacteremia secondary to a 100% urinary source (i.e., study population included bacteremic UTI exclusively), and bacteremia secondary to a predominantly urinary source (i.e., study populations in which at least 50% of cases were bacteremic UTI). In contrast, uUTI was defined as an infection limited to the bladder in non-pregnant, immunocompetent adults with no structural or functional urinary tract abnormalities, typically presenting as acute cystitis.

Clinical studies categorized by:

- UTI (cystitis)
- Pyelonephritis without bacteremia
- Bacteremia from urinary source

Pharmacotherapy. 2026;46(3):e70118

Cephalexin Clinical Data

Infection Type	Study / Design	Groups	AST	IV lead-in	Total Duration
UTI	**Rath 2025** Retrospective Cohort Adults, ED d/c 70% uUTI; 30% cUTI *E. coli, K. pneumo, P. mirabilis*	**n=107 cephalexin 500 mg BID** **n=107 cephalexin 500 mg QID**	cefazolin surrogate "**per CLSI**": MIC ≤16 uUTI **MIC ≤2 cUTI**	x1 dose ~50% each group	Median 7 d
		No difference in clinical failure: overall 18.7% BID vs 15% QID (p=0.465); uUTI 8.1 vs 15%; cUTI 27.3 vs 30.3%			
Pyelo w/o BSI	**Angel 1990** Prospective RCT Pregnant adults, hospitalized *E. Coli, K. pneumo, P. mirabilis, E. cloacae*	**n=45 cephalexin** **1g load, then 500 mg q6h** n=45 IV cephalothin	cephalothin surrogate *E. coli* & *K. pneumo* 100% "S"	**None**	**14 d**
		No difference in clinical success: 91.4% PO vs 92.9% IV (p=NS)			
	Vogler 2018 Retrospective Cohort Adult females, ED d/c *E. coli, K. pneumo, P. mirabilis*	n=55 cephs (**n=40 cephalexin; 500 mg TID 50%**) n=43 FQ/TMP-SMX (**30% underdosed**)	"same generation surrogate" Resistance: 6% cephalexin, **3% cipro, 23% TMP-SMX**	78% oral cephs **53% FQ/TMP-SMX**	Median 10 d
		Clinical failure: cephs 0% vs FQ/TMP-SMX 23% (p<0.001)*			

Cephalexin Clinical Data

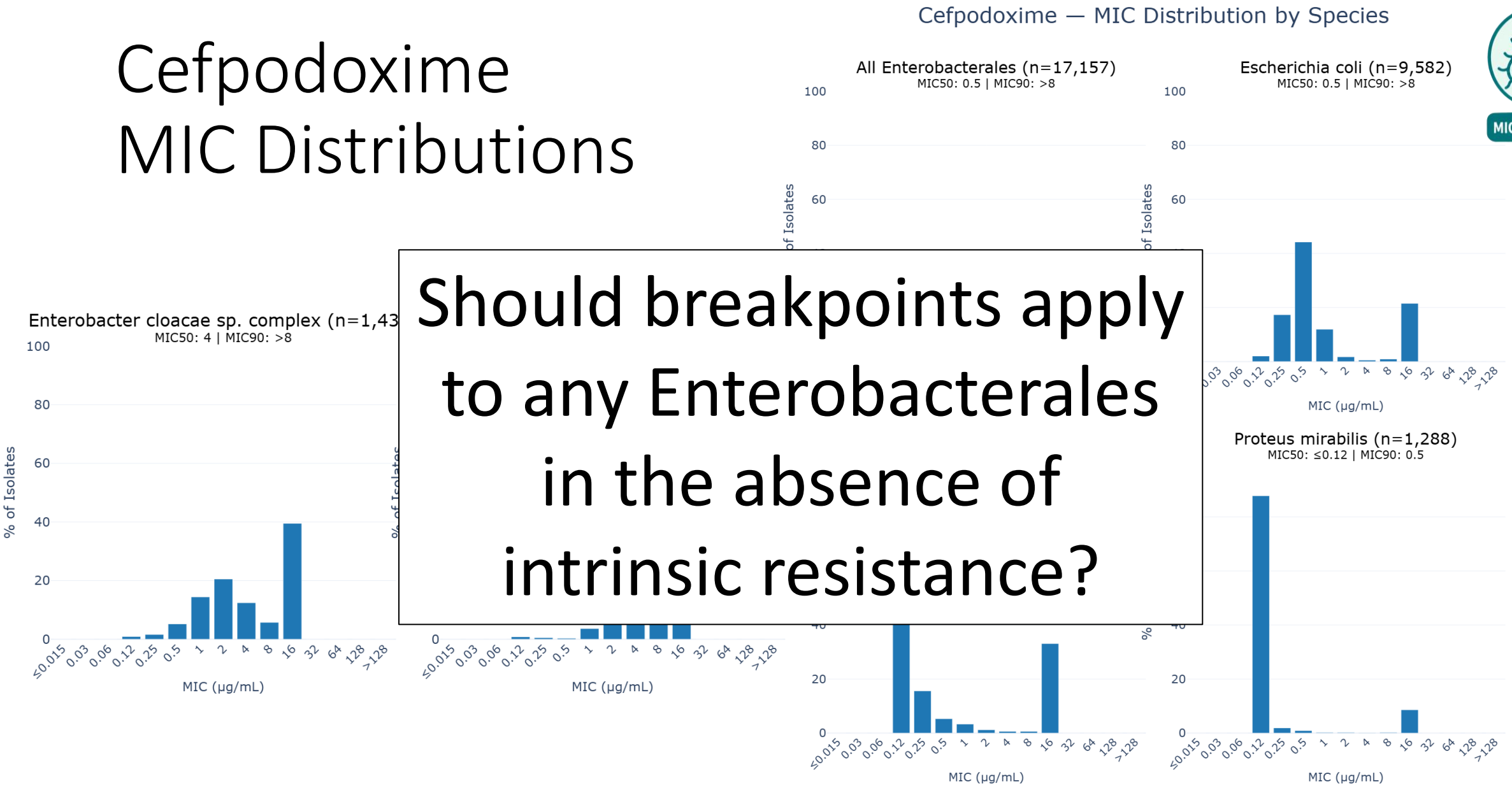
CLINICAL

Infection Type	Study / Design	Groups	AST	IV lead-in	Total Duration
BSI 2/2 UTI (≥50%)	**Mponponsuo 2023** Multicenter, Retrospective Cohort 50% UTI source Hospitalized, older adults (mean age 80 years) *E. Coli* (75%) ESBL, AmpC excluded	n=1,006 β-lactam (**n=300 cephalexin 500 mg – 1 g q6h**) n=1,006 FQ/TMP-SMX	Not specified	Yes, duration not specified	Mean 12 d
		Composite of 90-d all-cause mortality, recurrent BSI, and readmission favors FQ/TMP-SMX: 17% FQ/TMP-SMX vs 21.5% β-lactam aOR 0.74 (95% CI, 0.6-0.92) • **Driven by recurrent BSI**			
	Geyer 2023 Multicenter, Retrospective Cohort Adults *E. Coli* (77%)	n=75 High-dose β-lactam (**n=67 cephalexin 1 g TID**) n=119 FQ/TMP-SMX	cefazolin surrogate (MIC BP not specified)	Median 4 d	Median 11 d
		No difference in composite of 30-d recurrent BSI or mortality: 1.3% β-lactam vs 1.7% FQ/TMP-SMX, OR 1.27 (95% CI 0.11-14.2)			
	Alzaidi 2023 Multicenter, Retrospective Cohort Adults, 80% hospitalized *E. coli, Klebsiella spp.*	n=301 β-lactams **(n=128 cephalexin 500 mg – 1 g q12-6h)** n=165 High bioavailability β-lactams (HBBL) w/ cefazolin MIC ≤2 n=248 FQ	cefazolin surrogate (**MIC ≤2**)	Median 3 d	Median 11 d
		Recurrence-free days (through day 60) FQ vs HBBL w/ cefazolin MIC ≤2: aOR 1.93 (0.81, 4.55) p=0.135 Recurrence-free days (through day 60) FQ vs HBBL w/ ≤7d IV (n=238): aOR 2.23 (1.03,4.83) p=0.809			

Cephalexin Systemic Summary:

- Based on ECV: Can’t go lower than 16-32 mcg/mL
- Based on PK/PD Cutoff: Can’t go higher than 4 mcg/mL, and this is still <90% PTA and net bacterial stasis endpoint with HIGH dose
- Based on Clinical Cutoff: unknown, no data with cephalexin MICs

Cefpodoxime MIC Distributions



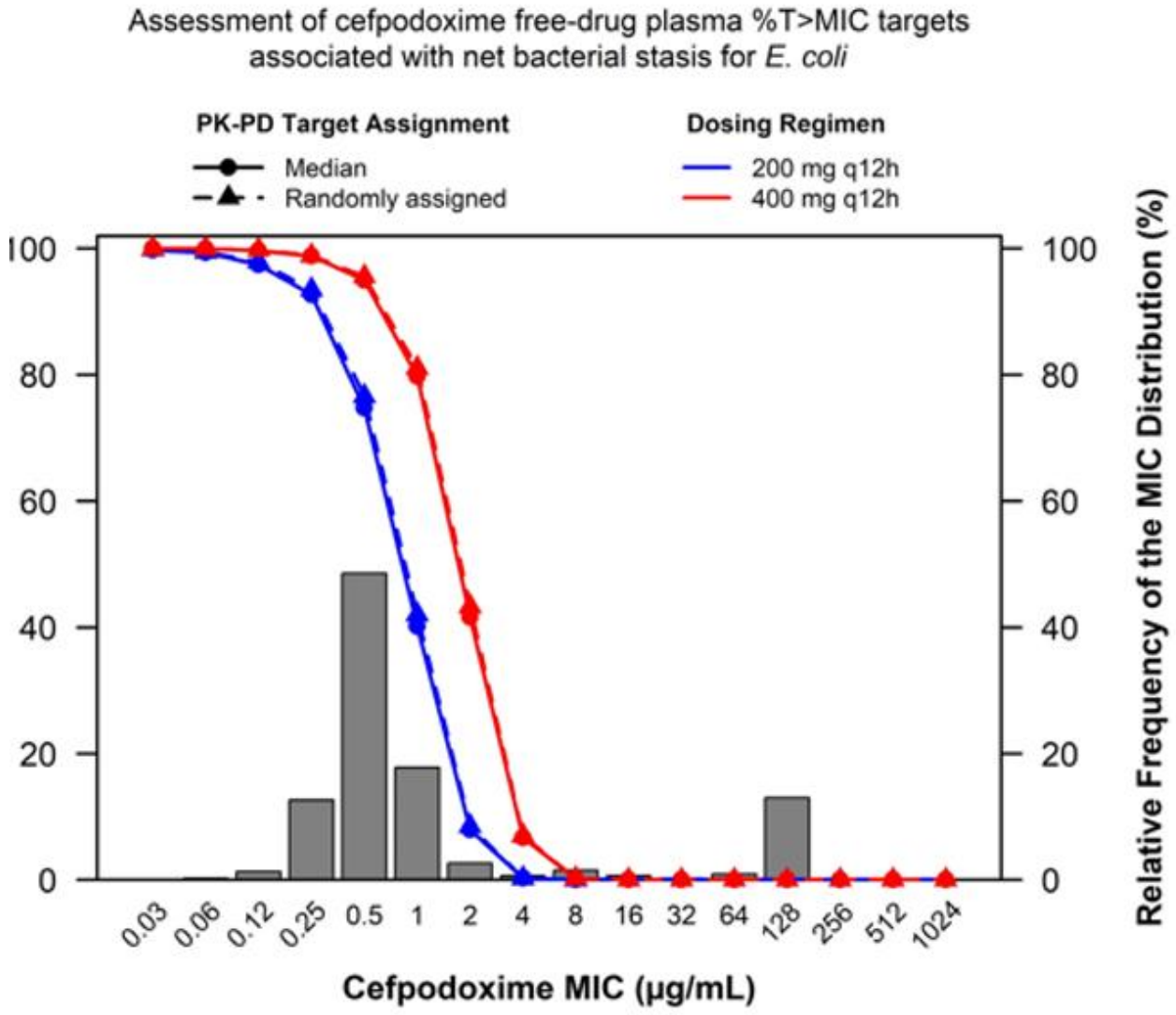
Should breakpoints apply to any Enterobacterales in the absence of intrinsic resistance?

CLSI. *AST Subcommittee Meeting Agenda Summary Minutes.* June 2026.

USCAST: Probability of Target Attainment for *E. coli* in plasma

Target: ~50% *f*T>MIC (stasis)

MIC Distribution of *E. coli* isolates (n=1,171) collected in USA in 2018 or 2021 provided by JMI



Oral Cephalosporin STIC Against S. aureus and E. coli. USCAST Virtual Public Meeting; 2024.

Cefpodoxime Registrational Trial Outcomes by MIC!

(for uncomplicated UTI)

IN VITRO ACTIVITY OF CEFPODOXIME AGAINST CLINICAL TRIAL ISOLATES OF CLAIMED PATHOGENS

Organism	Minimum Inhibitory Concentration (µg/ml)		
	N	50%	90%
E. coli	480	0.50	1
K. pneumoniae	63	0.25	0.50
P. mirabilis	63	0.06	0.25

WEIGHTED AVERAGE MIC DATA FOR CLINICAL ISOLATES FROM U.S. AND NON-U.S. LITERATURE

Organism (No. Studies)	Minimum Inhibitory Concentration (µg/ml)		
	Total N	50%	90%
E. coli (54)	4119	0.38	1.1
K. pneumoniae (36)	1871	0.14	3.3
P. mirabilis (41)	1732	0.08	1.0

Pathogen Eradication by MIC

Urinary Tract — *Escherichia coli*

MIC (mcg/mL)	Eradicated/Total	% Eradicated
128	1/1	100
8	1/1	100
2	5/5	100
1	13/14	93
.5	64/84	76
.25	58/73	79
.125	7/8	88
Totals	149/186	80

CLSI M23, 6th ed. (2023)

NCCLS AST Subcommittee Agenda Book. June 1992. pp 351-413

Cefpodoxime Postmarketing Clinical Data

CLINICAL

Infection Type	Study / Design	Groups	AST	IV lead-in	Total Duration
Uncomplicated UTI	**Hooten 2012** Prospective RCT Adult females outpatient *E. Coli* (75%)	n=**150 cefpodoxime 100 mg BID** n=150 ciprofloxacin 250 mg BID	cefpodoxime DD	No	3 d
		Clinical cure at 30 d favors ciprofloxacin: 82% cefpodoxime vs 93% ciprofloxacin (p=0.004) • History of UTI higher in cefpodoxime arm • Higher rate of vaginal *E. coli* colonization post-treatment with cefpodoxime • 81% (n=13/16) of cefpodoxime clinical failure *E. coli* isolates remained susceptible upon recurrence			
	Kavatha 2023 Prospective RCT Adult female outpatient *E. Coli* (72%)	n=**81 cefpodoxime 100 mg BID** n=82 TMP-SMX 1 DS PO BID	cefpodoxime DD	No	3 d
		No difference in clinical cure: 87% cefpodoxime vs 86% TMP-SMX No difference in bacterial eradication: 85% cefpodoxime vs 64% TMP-SMX			

No difference in bacteriological cure vs β-lactam comparators x7d (~80%) in registrational trials of cefpodoxime (also dosed as 100 mg BID)

Cefpodoxime Postmarketing Clinical Data

CLINICAL

Infection Type	Study / Design	Groups	AST	IV lead-in	Total Duration
Pyelo w/o BSI	**Fosse 2022** Retrospective Cohort Adults (91% female) ED d/c and outpatients *E. Coli* (31%), *Klebsiella spp.*	n=268 cephs **(n=190 cefpodoxime 100-200 mg BID)** n=211 FQ/TMP-SMX	Not specified	x1 dose 59% cephs 39% FQ/TMP-SMX	Median 10 d cephs 7 d FQ/TMP-SMX
		No difference in UTI recurrence at 30 d: 16% cephs vs 17% FQ/TMP-SMX (p=0.85)			
	Koehl 2025 Retrospective Cohort Adults (85% female) ED d/c *E. Coli* (40%)	n=647 cephs (**n=50 cefpodoxime)** n=204 FQ/TMP-SMX	cefazolin surrogate MIC ≤16	x1 dose 60% cephs 47% FQ/TMP-SMX	Median 11 d cephs 8 d FQ/TMP-SMX
		No difference in treatment failure at 14 d: 17% cephs vs 22.5% FQ/TMP-SMX			
	Lin 2022 Retrospective Cohort Adults (85% female) ED d/c *E. Coli* (~90%)	n=229 cephs **(n=64 cefpodoxime 100 – 400 mg BID)** n=109 FQ	cefazolin surrogate “per CLSI”	≤2 doses 92% cephs 78% FQ	Median 11 d cephs; 9 d FQ
		No difference in treatment failure (change in abx or return to ED) at 30 d: 15.3% cephs vs 17.4% FQ **Treatment failure higher for cefpodoxime (23.4%) and cephalexin (22.4%) vs cefuroxime (7.8%)**			

Difficult to attribute lack of difference in primary outcome to cefpodoxime as proportion of cephalosporin group was highly variable (7% – 70%), as was dosing (100 – 400 mg BID)

Cefpodoxime Postmarketing Clinical Data

Infection Type	Study / Design	Groups	AST	IV lead-in	Total Duration
BSI 2/2 UTI (≥50%)	**Sutton 2020** Multicenter, Retrospective Cohort Hospitalized Adults *E. Coli* (72%), *Klebsiella spp.*, *P. mirabilis*	n=955 β-lactam (**n=243 cefpodoxime 200 – 400 mg BID**) n=3,134 FQ/TMP-SMX	Not specified/ Heterogeneous	**Median 5 d cephs** 4 d FQ	**Median 14 d**
		No difference in composite of 30-d all-cause mortality or recurrent BSI: 4.4% β-lactam vs 3% FQ/TMP-SMX aRD 0.99% (95% CI, -0.42% - 2.4%)			
	Bjork 2023 Retrospective Cohort Adults *E. Coli* (65%)	n=65 cephs (**n=46 cefpodoxime 200 mg BID 70%**) n=65 FQ	Cefpodoxime DD	**Median 5 d cephs** 4 d FQ	**Median 14 d**
		No difference in treatment failure (90-day recurrent BSI or all-cause mortality): 15% cephs vs 12% FQ (p=0.61)			

Difficult to attribute lack of difference in primary outcome to cefpodoxime as proportion of cephalosporin group was highly variable (25% – 70%) and duration of IV therapy was prolonged (median 5 days)

Cefpodoxime Systemic Summary:

- Based on ECV: ? Probably no lower than 2 mcg/mL
- Based on PK/PD Cutoff: Probably no higher than 1 mcg/mL, <90% PTA net bacterial stasis endpoint with HIGH dose
- Based on Clinical Cutoff: unknown, only studies with cefpodoxime MICs are registrational trials for uUTI and no isolates at or above 2 mcg/mL with failures

In summary, SO FAR identified:

- Breakpoints that bisect modern WT MIC distributions
- Most breakpoints originally set by evaluating “cross-susceptibility” within cephalosporin class, especially earlier approvals

- Very limited PTA data
  - Available data published after existing breakpoints established
  - Largely unsupportive
  - Almost exclusively *E. coli*

- No substantial clinical data available for oral cephalosporins and Enterobacterales systemic infections of urinary origin.
- No robust data for clinical response by MIC for most agents, and none outside of uncomplicated UTI

Back to Question 2

Which of the following best describes the evidence underpinning the existing CLSI Enterobacterales oral cephalosporin breakpoints?

A. Robust PK/PD data (e.g., drug specific systemic and urinary probability of target attainment analyses)
B. Robust clinical data (e.g., prospective, randomized controlled trials evaluating individual oral cephalosporins with outcomes stratified by MIC)
C. Contemporary microbiological data (e.g., modern, species-specific wild-type MIC distributions and ECVs)
D. None of the above

Next steps:

- Will continue to review individual agents based on priority/relevance to current practice
  - (e.g., cefuroxime > cefixime > cefdinir > cefprozil > cefaclor)
- Consider urinary breakpoints?
  - Which drugs?
  - Generation of urinary PK/PD cutoff data has limitations
  - Likely different breakpoints than currently displayed in M100
  - Implications for cefazolin uUTI surrogate <=16 mcg/mL?
- Unanswered questions:
  - Should PK/PD targets differ for UTI and step-down therapy?
  - How do breakpoints apply to step-down therapy?

Patient Case

A patient has been receiving ceftriaxone for 2 days for *Escherichia coli* bacteremia of presumed urinary origin. Blood culture susceptibility results are now available with the following:

Case 1: Urine and blood cultures: *Escherichia coli*

Antimicrobial	MIC (mcg/mL)	Interpretive Category
Ampicillin	32	R
Ampicillin/sulbactam	8	S
Amoxicillin/clavulanate	8	S
Cefazolin (*complicated UTI or systemic infection)*	2	S
Cefazolin *(uncomplicated UTI)*	2	S
Ceftriaxone	1	S
Ciprofloxacin	2	R
Nitrofurantoin (*urine only*)	≤32	S
Piperacillin-tazobactam	≤8/4	S
Trimethoprim-sulfamethoxazole	4/76	R

Open Forum Infect Dis. 2025;12(9):ofaf435

Question 3

True or False: Based on current CLSI guidance, this result (blood and urine cultures: *E. coli*, cefazolin MIC ≤2 µg/mL) supports transitioning to cephalexin 1 g q6h to complete therapy.

A. True
B. False

Oral β-Lactams for Complicated Urinary Tract Infections: A Systematic Review and Point-Counterpoint Comparison With Trimethoprim/Sulfamethoxazole and Fluoroquinolones

Ashlan J. Kunz Coyne[1] | Jeannette Bouchard[2] | Spencer H. Durham[3] | Amy Y. Kang[4] | Kinsey M. Johannemann[5] | W. Justin Moore[6] | Kevin Nguyen[7] | James Sanders[8] | Colter Sheveland[9] | Grant Stimes[10] | Trang Trinh[11] | Elizabeth W. Covington[3] | on behalf of the ACCP Infectious Disease Practice and Research Network (PRN) Research Committee

[19] (see Table 2). Cephalexin was the most commonly prescribed cephalosporin, at a dose of 1000 mg every 6 h, consistent with consensus guidance, which supports use for *Enterobacterales* with MICs up to 2 mg/L. Another study found that high-dose

4.2.1 | Inability to Directly Test Oral β-Lactam Susceptibility and Reliance on Imperfect Surrogates

Cefazolin is currently established by the Clinical Laboratory Standards Institute (CLSI) as a surrogate antibiotic to infer susceptibility of seven oral cephalosporins for uUTI caused by *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* among urinary isolates exhibiting an MIC of ≤16 mcg/mL or MIC of ≤2 mcg/mL for non-urinary, systemic sources (Table 6) [43]. This practice

Multiple publications and institutional guidelines reference a CLSI cefazolin surrogate for systemic infections w/ MIC ≤2 mcg/mL…

Pharmacotherapy. 2026;46(3):e70118

Table 1. CLSI Cefazolin Breakpoints

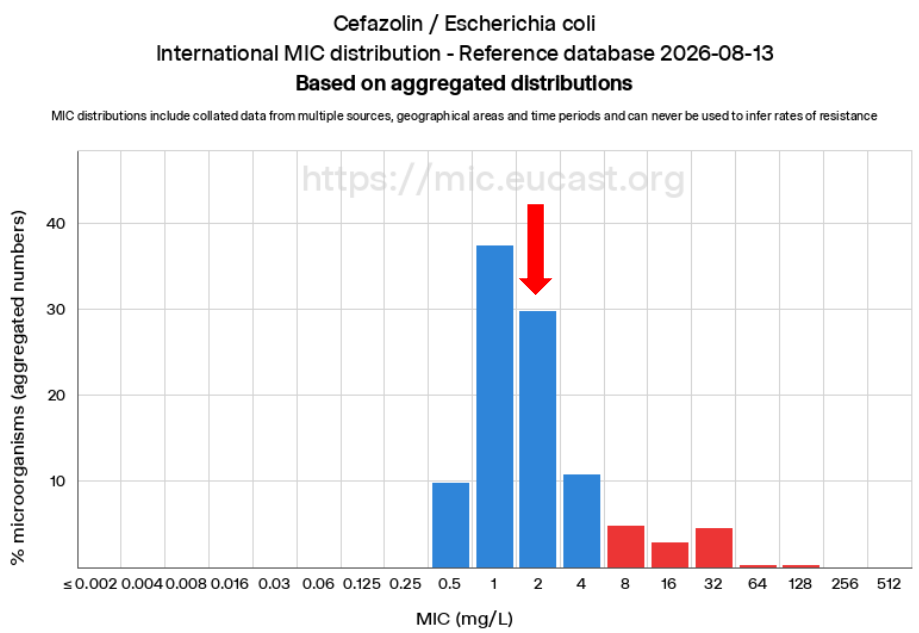
Reason for Testing	Breakpoints (µg/ml)			Dose
	Susc	Int	Res	
Predict cefazolin use for systemic infections	≤2	4	≥8	
Predict cefazolin use for uUTI	≤16	–	≥32	2 g every 8 h (IM or IV)
Surrogate for oral cephalosporins to use for uUTI	≤16	–	≥32	1 g every 12 h (IM or IV)

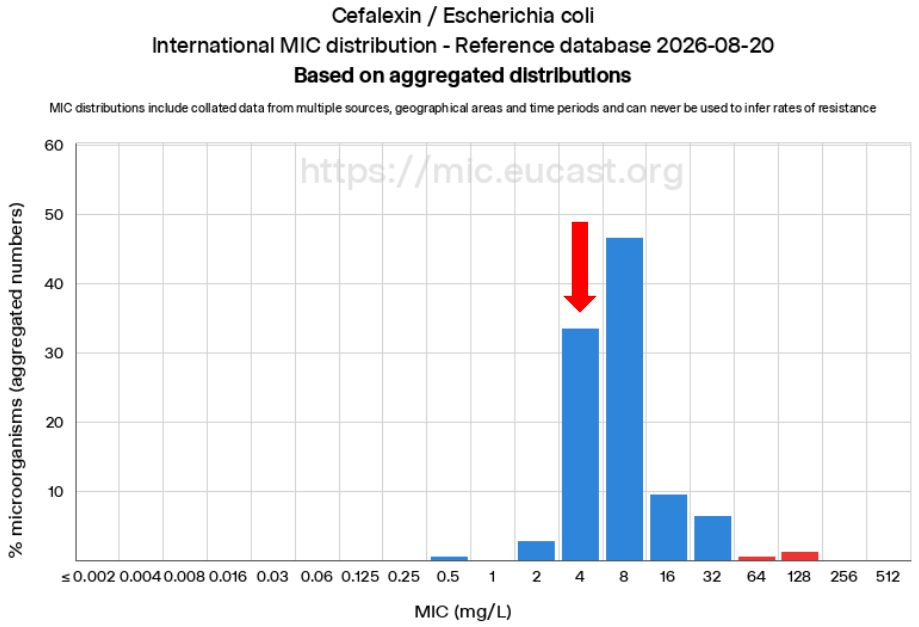
Abbreviations: IM = intramuscular; Int = intermediate; IV = intravenous; Res = resistant; Susc = susceptible; uUTI = uncomplicated UTI.

… but that does not exist!

https://clsi.org/about/press-releases/ast-news-update-2019-case-study/ - Accessed 8.12.26

Would a systemic cefazolin surrogate work?





Cefazolin MIC, µg/mL	≤ 0.12	0.25	0.5	1	2	4	8	16	> 16
> 16							1	2	36
16							6	2	4
8						1	4	5	
4							16	27	1
2						1	73	9	
1						6	11		
0.5									
0.25									
≤ 0.12									

Cephalexin MIC, µg/mL

Probably not for cephalexin if PK/PD targets underpinning systemic PK/PD cutoffs are correct

CLSI. Rationale document MR08. 2020. EUCAST. https://www.eucast.org/mic_and_zone_distributions_and_ecoffs

Question 3

True or False: Based on current CLSI guidance, this result (blood and urine cultures: *E. coli*, cefazolin MIC ≤2 µg/mL) supports transitioning to cephalexin 1 g q6h to complete therapy.

A. True
B. False

Does this mean we should avoid using high-dose cephalexin for PO step-down therapy in *E. coli* bacteremic UTI?

Not necessarily!

Lots of anecdotal success with this strategy following effective IV therapy. Can't ignore clinical data, even if insufficient for determination of a formal breakpoint.

Breakpoints vs. Step-Down Therapy

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PHARMACOLOGY

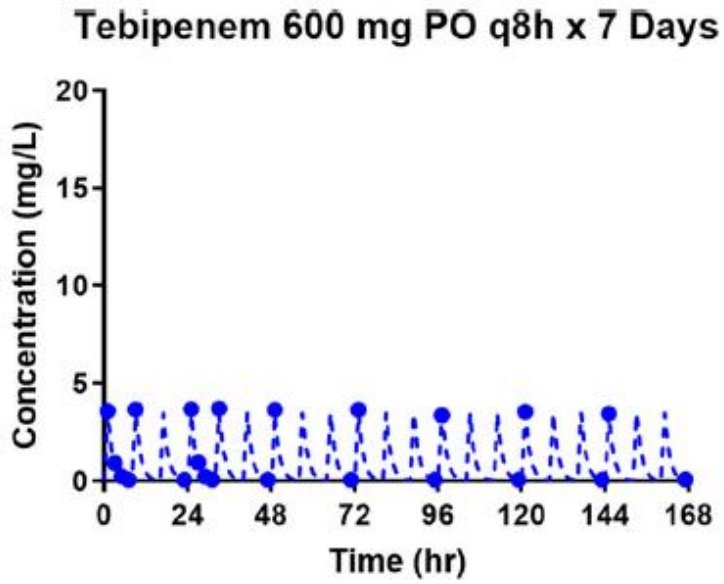
Evaluation of Oral Tebipenem as a Step-Down Therapy following Intravenous Ertapenem against Extended-Spectrum β-Lactamase-Producing *Escherichia coli* in a Hollow-Fiber *In Vitro* Infection Model

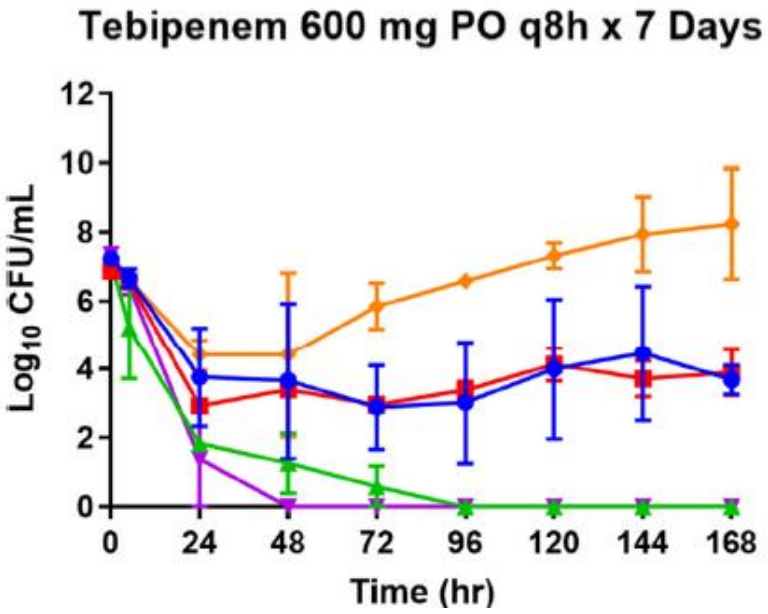
B. D. VanScoy,[a] S. Jones,[a] H. Conde,[a] L. V. Friedrich,[b*] N. Cotroneo,[b] S. M. Bhavnani,[a] P. G. Ambrose[a]

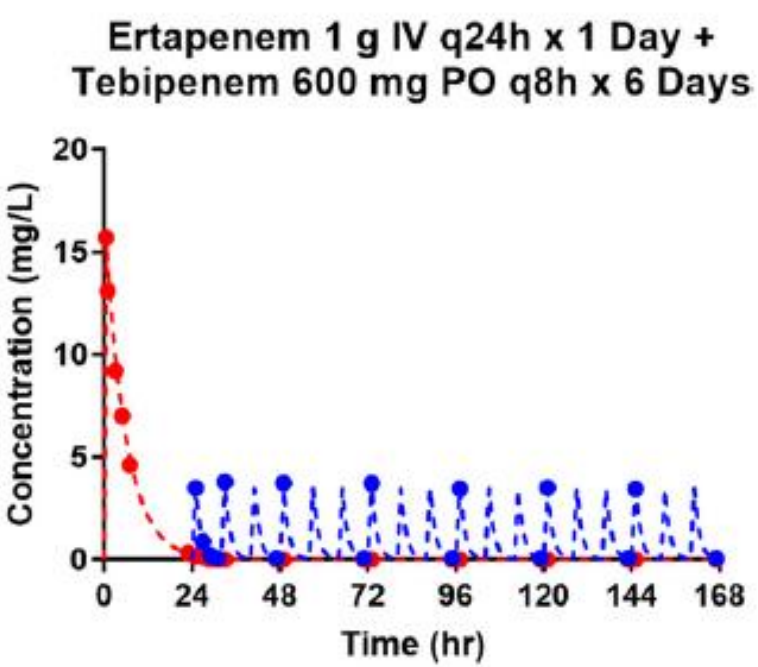
[a]Institute for Clinical Pharmacodynamics, Inc., Schenectady, New York, USA
[b]Spero Therapeutics, Inc., Cambridge, Massachusetts, USA

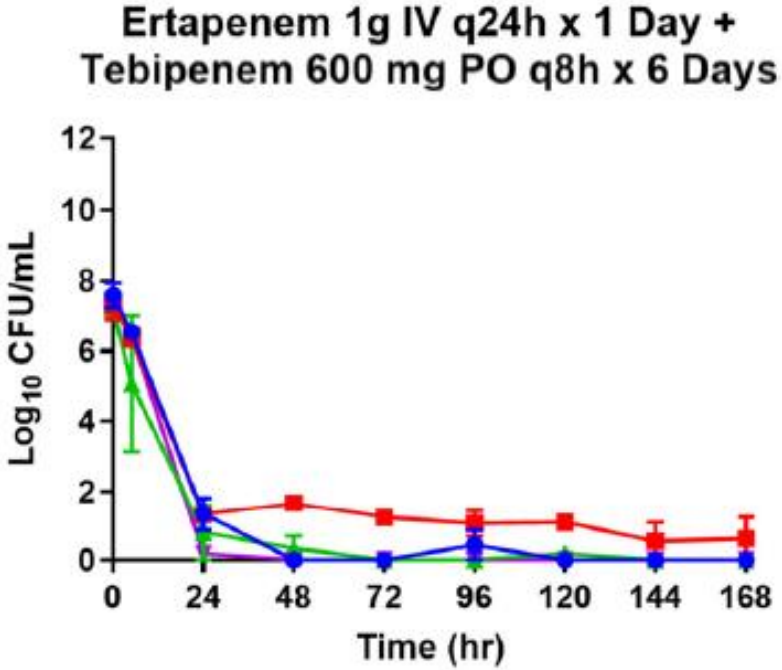
Adapted from slide by Navaneeth Narayanan

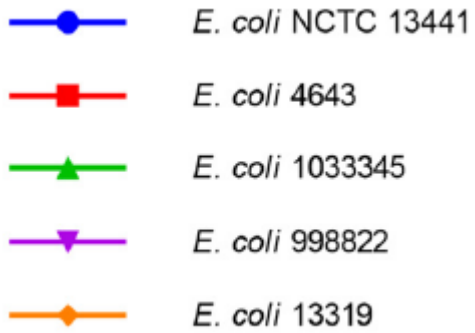
Antimicrob Agents Chemother. 2023;67(3):e0090822









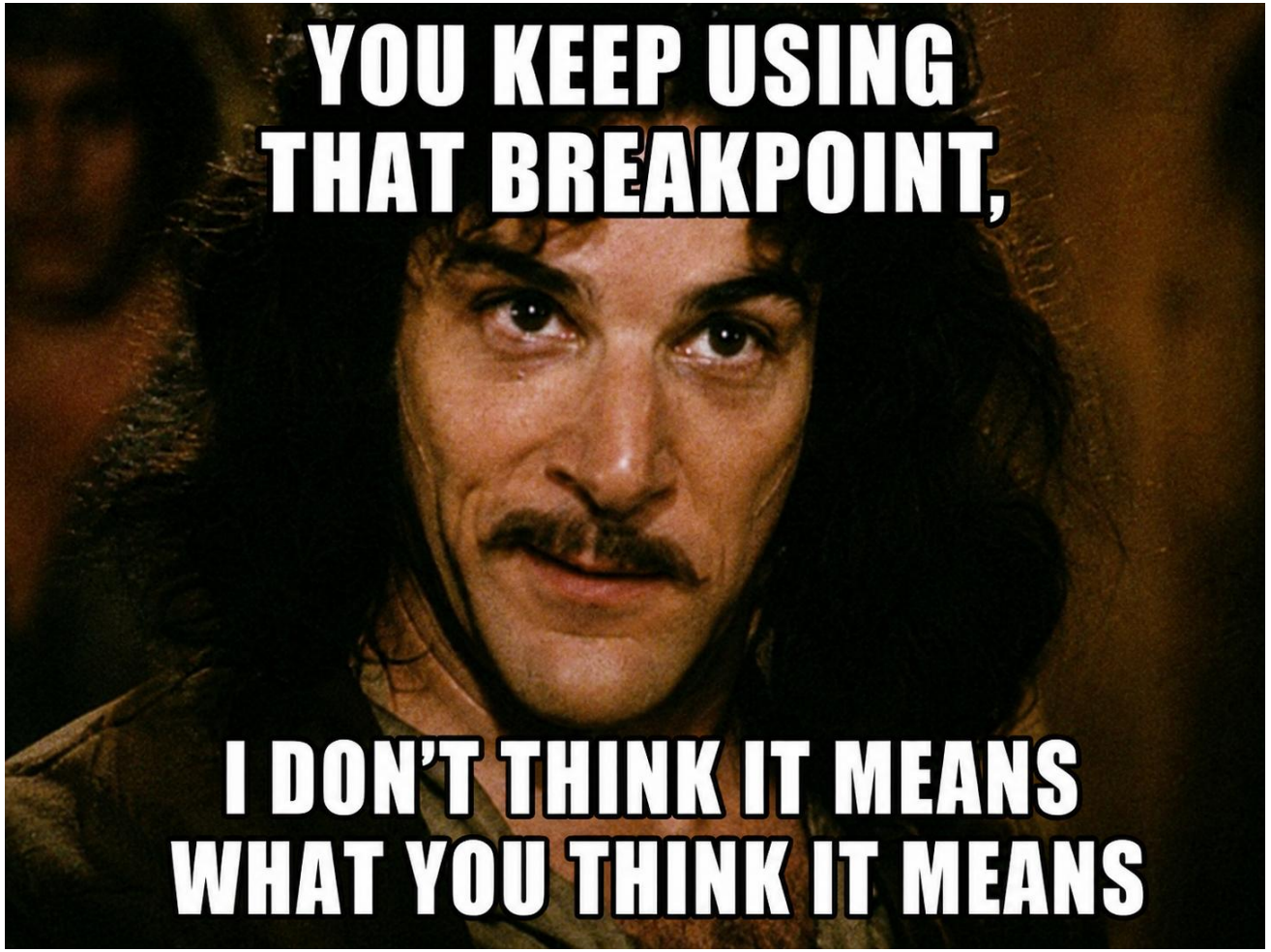


Modal MIC (mg/L)	
Tebipenem	Ertapenem
0.015	0.03
0.008	0.015
0.06	0.25
0.03	0.015
0.015	0.125

Adapted from slide by Navaneeth Narayanan

Antimicrob Agents Chemother. 2023;67(3):e0090822

Questions?


YOU KEEP USING
THAT BREAKPOINT,
I DON'T THINK IT MEANS
WHAT YOU THINK IT MEANS