UWTASP tele-antimicrobial stewardship program | echo

July 9, 2024

Applied Microbiology- ESBLs

- Zahra Kassamali Escobar, PharmD

Project ECHO

EUCAST vs. CLSI: If it's an ESBL E.coli in Europe, is it an ESBL E.coli in the US?

Agenda

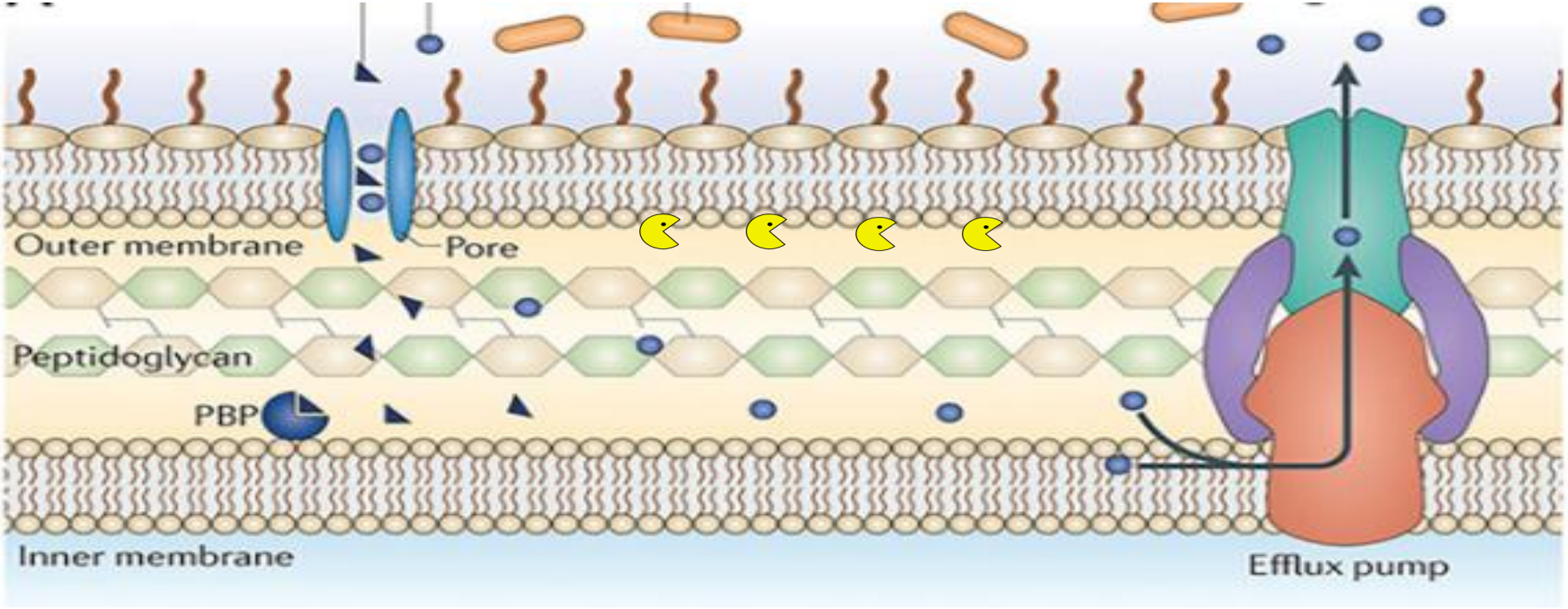
- What is an ESBL organism
- What does this mean for treatment (PK/PD 101, the fastest review)
- Interpreting MICs with an accent (European vs. US guidance)

What is an ESBL organism

citations

Multiple Mechanisms of Resistance
Defense = Survival

Gram negative bacteria



Chellat MF. 2016. Targeting antibioticresistance. Angew Chem Int Ed Engl 55:6600–6626

= beta-lactamase

Slide Credit: Frank Tverdek

citations

Beta-Lactamases

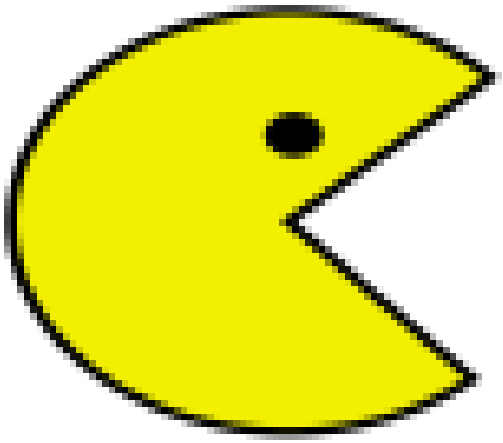
- **MOA -** Inactivate beta-lactam antibiotics by splitting the amide bond of the beta-lactam ring.
- **Heterogeneity -** More than 600 beta-lactamases have been described!!!!
- **Genetically encoded -** by either chromosomal or transferable genes located on plasmids and transposons.
- **Expression -** Can be *suppressed*, *induced*, *derepressed* or constitutively expressed (AMP-Cs)

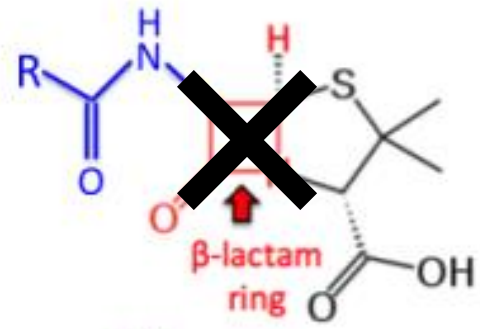
Slide Credit: Frank Tverdek

citations

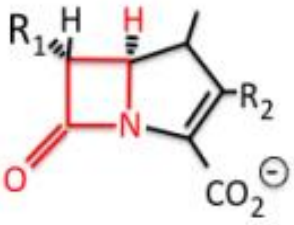
What is an ESBL?

Extended Spectrum Beta Lactamase

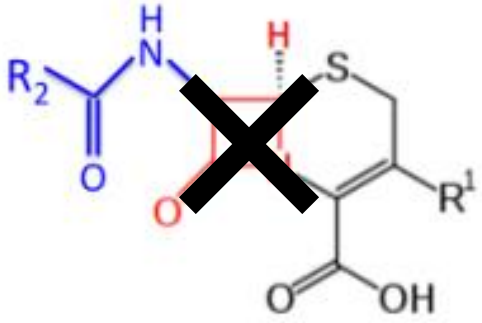




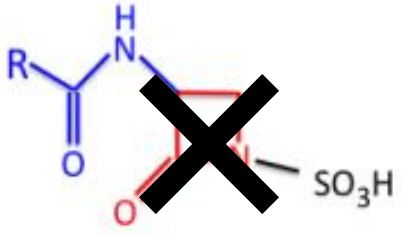
penicillins



carbapenems



cephalosporins



monobactams

Image from: https://tmedweb.tulane.edu/pharmwiki/do

What does this mean for treatment?

Specimen: Blood

Drug	MIC	Interpretation
1 gen Ceph (cefazolin)	≥ 8	R
2 gen Ceph (cefoxitin)	4	S
3 gen Ceph (ceftriaxone)	≥ 4	R
4 gen Ceph (cefepime)	≥ 16	R
Pip-tazo	16/2	S
Carbapenem	0.5	S
Aztreonam	≥ 16	R

citations

Would you treat this bacteremia with piperacillin/tazobactam?

Specimen: Blood

Drug	MIC	Interpretation
1 gen Ceph (cefazolin)	≥ 8	R
2 gen Ceph (cefoxitin)	4	S
3 gen Ceph (ceftriaxone)	≥ 4	R
4 gen Ceph (cefepime)	≥ 16	R
Pip-tazo	16/2	S
Carbapenem	0.5	S
Aztreonam	≥ 16	R

- Yes
- No
- Maybe

citations

What does this mean for treatment (PK/PD 101)

citations

Defining Terms: Pharmacokinetics

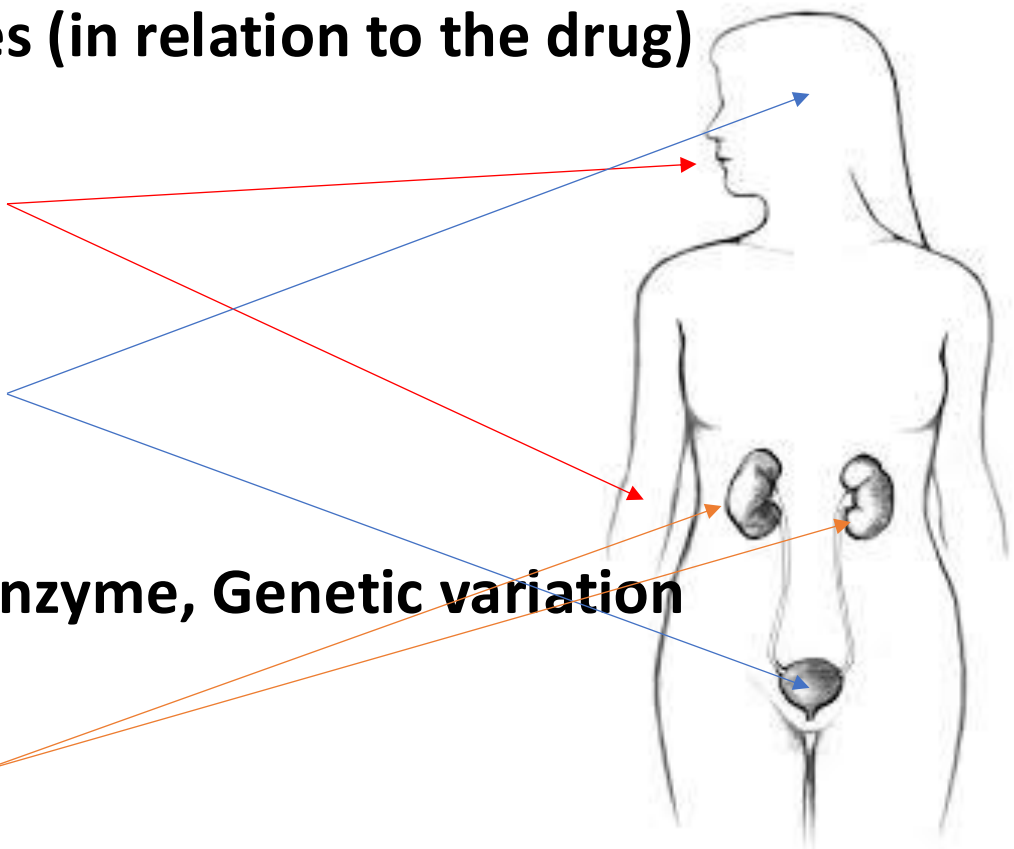
What the body does (in relation to the drug)

ABSORPTION:

DISTRIBUTION:

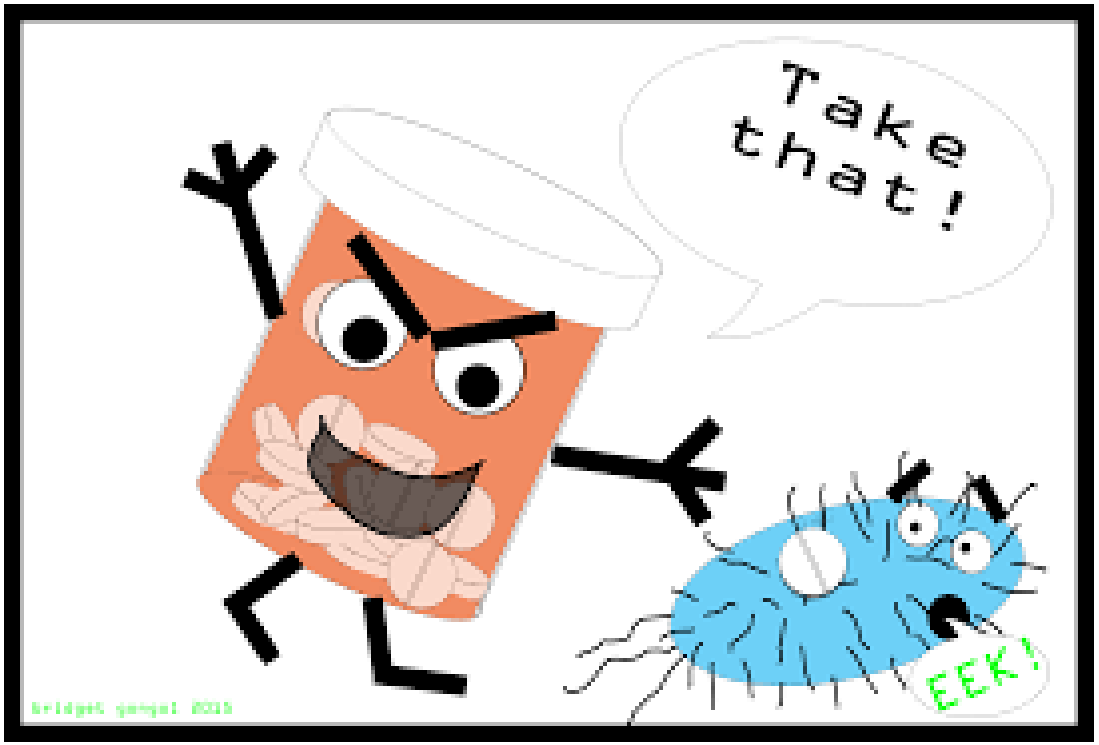
METABOLISM: **Enzyme, Genetic variation**

ELIMINATION:



Defining Terms: Pharmacodynamics

What the drug does (in relation to the body)

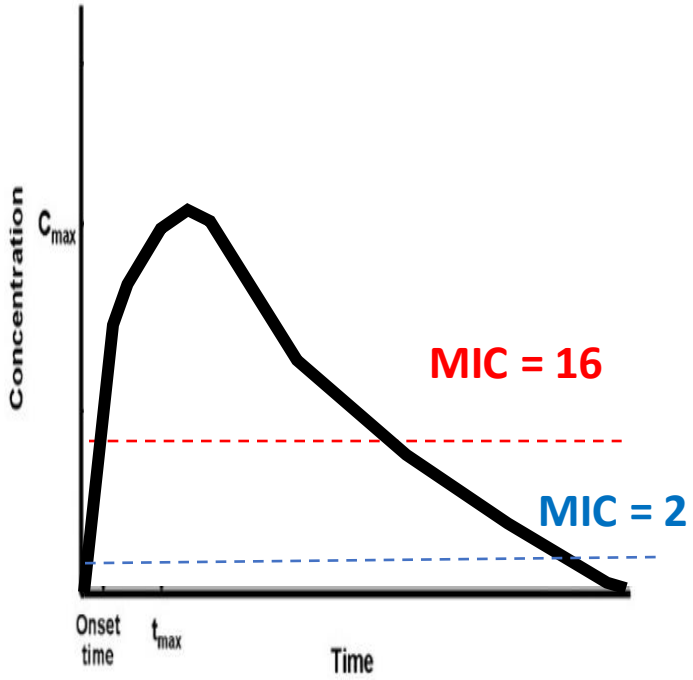


Efficacy of Antibiotics is directly related to how we dose them

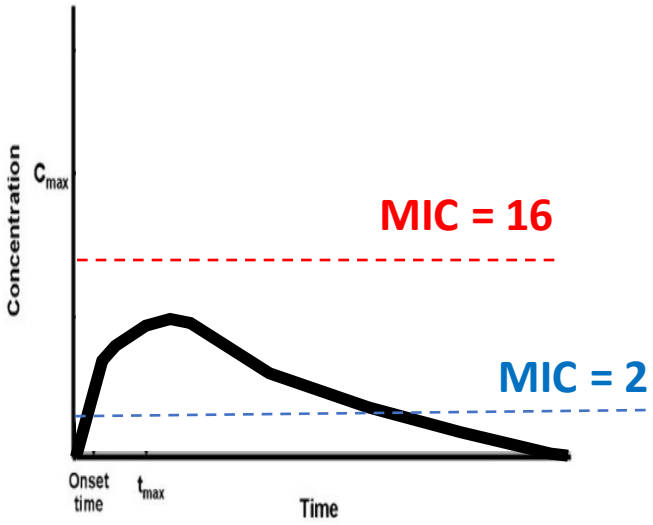
Urine is a unique compartment:

Cefazolin concentration in blood vs. urine

URINE Concentrations of Cefazolin



BLOOD Concentrations of Cefazolin



Clinical Infectious Diseases 2011;52(7):917–924

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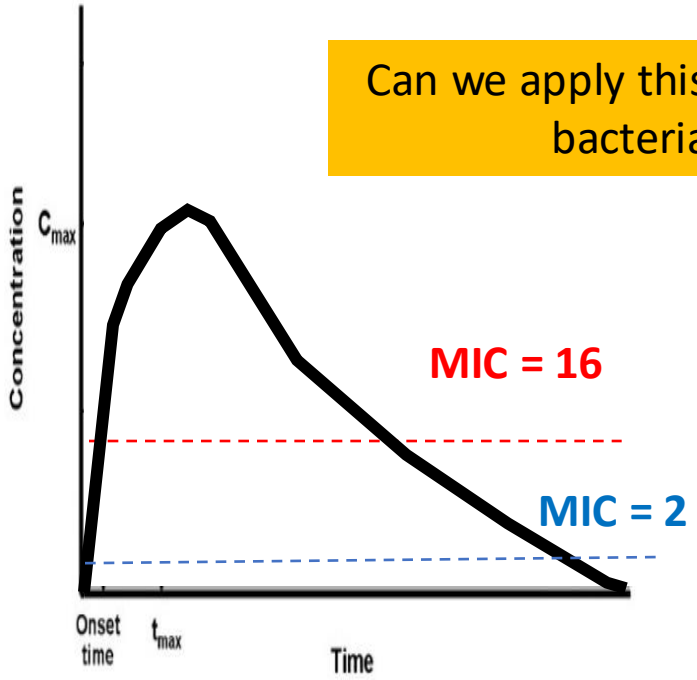

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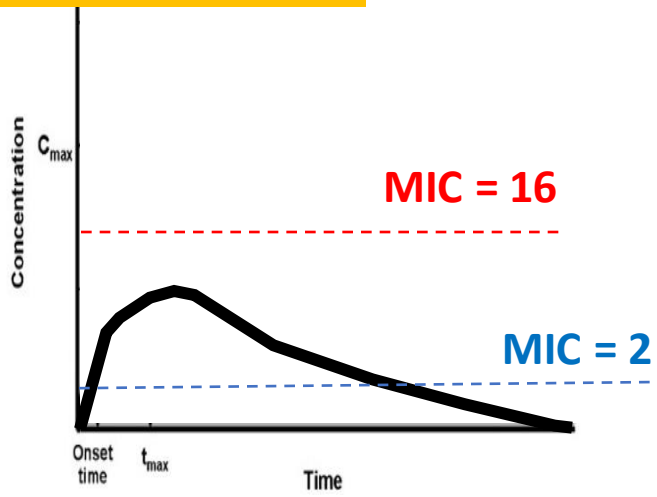


Can we apply this concept to ESBL-producing bacteria and other drugs?

Clinical Infectious Diseases 2011;52(7):917–924

Interpreting MICs

citations

Clinical Question

- Pivmecillinam FDA approved for treatment of uncomplicated UTIs in women in the US.
- Approved dose 200mg PO TID x 3-7 days.

	Clinical Study (done in Norway)	Norway	USA
Dose	200mg TID	400mg TID	200mg TID
Comments about ESBL	Associated with clinical failure for pts with ESBLs	Recommended for ESBL E.coli	Displays *in-vitro* activity against ESBL E. coli
Microbiology guidance	EUCAST	EUCAST	CLSI

J Antimicrob Chemother 2018; 73: 2503–2509 doi:10.1093/jac/dky230.

If it's an ESBL E.coli in Europe, is it an ESBL E.coli in the US?

CLSI

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

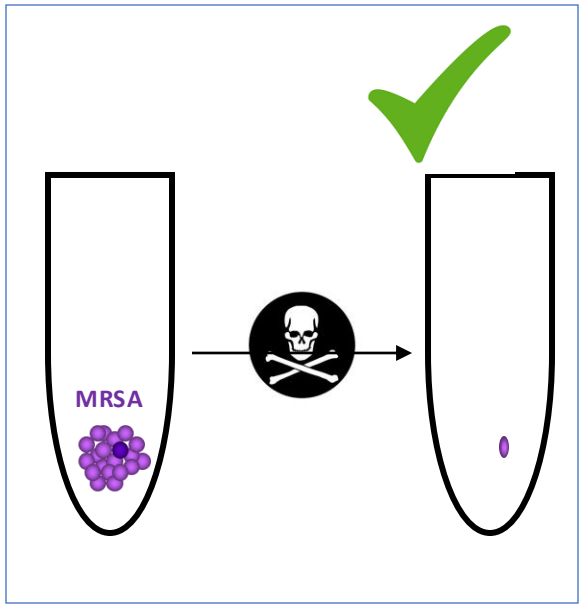
citations

MIC ≠ Breakpoint

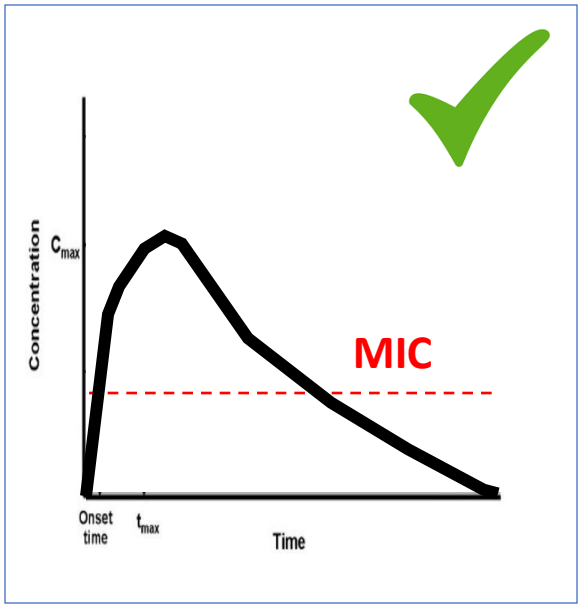
The Breakpoint:

Breakpoint setting integrates knowledge of **wild-type MICs**, assessment of antimicrobial **pharmacokinetics and pharmacodynamics**, and studies of **clinical outcomes** when the antimicrobial is used

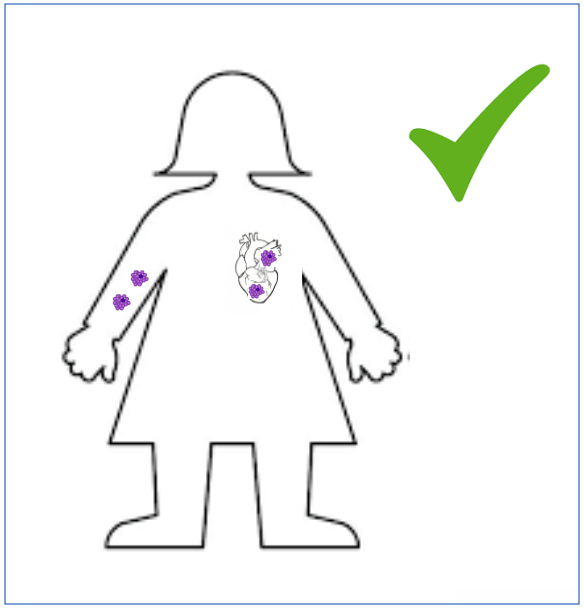
MIC



PK/PD



Clinical Outcomes



Turnidge J, Paterson DL. Setting and Revising Antibacterial Susceptibility Breakpoints. Clin Microbiol Rev 2007; 20(3):391-408.

What does CLSI say?

Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
		S	SDD	I	R	S	SDD	I	R	
PENICILLINS										
Mecillinam* (U)[b]	10 µg	≥ 15	–	12–14^	≤ 11	≤ 8	–	16^	≥ 32	**(8)** Report only on *E. coli.*

- Mecillinam = Active drug for Pivmecillinam (prodrug)
- Report for *E.coli* in Urine ONLY
- Susceptible = MIC ≤ 8

CLSI M100 ED34:2024

What does EUCAST say?

Antimicrobial wild type distributions of microorganisms

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

Search database

Method ● **MIC** ○ **Disk diffusion**

Antimicrobial

Mecillinam

Species

Species...

MIC distributions for Mecillinam, 2024-07-08

Antimicrobial: Mecillinam (Method: MIC)

Minimum inhibitory concentration

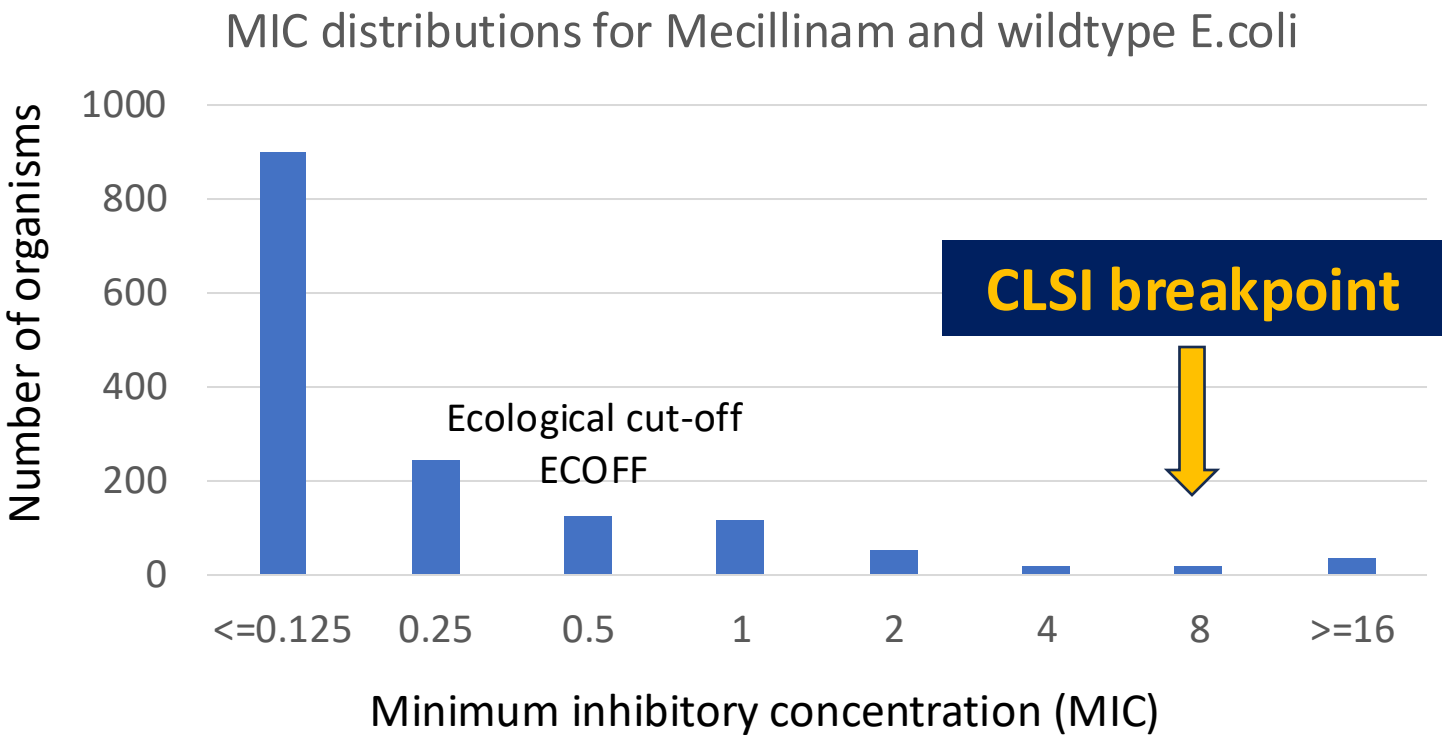
Organisms	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Citrobacter freundii	0	0	0	0	0	2	22	11	3	2	0	1	0	0	0	0	0	0	0	1	41	ID	
Citrobacter koseri	0	0	0	1	1	11	20	9	3	1	0	0	0	0	0	0	0	1	2	1	49	ID	
Enterobacter cloacae	0	0	0	0	0	2	4	17	18	3	1	0	1	0	0	0	0	0	0	1	46	ID	
Escherichia coli	0	0	0	0	7	225	667	241	125	115	51	18	17	5	5	7	6	8	5	4	1502	(0.5)	0.25 - 0.5
Klebsiella aerogenes	0	0	0	0	0	0	3	16	26	12	2	1	1	0	0	0	0	0	4	1	65	ID	

# of observations/organisms

Ecological cut-off (ECOFF)

mic.eucast.org

What does EUCAST say?



MIC distributions for Mecillinam, 2024-07-08

Antimicrobial: Mecillinam (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
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Enterobacter cloacae	0	0	0	0	0	2	4	17	18	3	1	0	1	0	0	0	0	0	0	1	46	ID	
											51	18	17	5	5	7	6	8	5	4	1502	(0.5)	0.25 - 0.5
											2	1	1	0	0	0	0	0	4	1	65	ID	

mic.eucast.org

Pivmecillinam for ESBL E.coli UTI

	ESBL N = 88		Non-ESBL N = 74		P-value
Dose selection	200mg TID	400mg TID	200mg TID	400mg TID	
	42.5%	68.5%	65.8%	34.2%	<0.01
Duration of Symptoms	5 days		3 days		<0.01
Persistent symptoms > 2 weeks after treatment	36.5%		15.3%		<0.01
2nd Antibiotic prescription	34.1%		13.9%		<0.01
Persistent bacteriuria	18.5% (15/81)		9.0% (6/67)		0.1

For patients treated with 400 mg of pivmecillinam given three times daily, there was no significant difference in the risk of treatment failure for the ESBL cases or the non-ESBL controls regardless of treatment duration

J Antimicrob Chemother 2018; 73: 2503–2509 doi:10.1093/jac/dky230.

Can we use Pivmecillinam for ESBL E.coli UTI?

YES	NO
✔ Women ✔ Cystitis, uncomplicated ✔ 400mg TID	✖ Men ✖ Pyelonephritis ✖ Prostatitis ✖ Complicated anatomy ✖ 200mg TID

ZKE's take: Yes, we can use pivmecillinam
but FIRST:

-adjudicate ASB vs. UTI
-attempt nitrofurantoin
-find out how much it costs

citations

Summary

ESBL *E.coli*

-Challenging pathogen for infections because of broad inactivation of *most* beta-lactam antibiotics

PK/PD

-High urinary concentrations allow for some antibiotics to overcome resistance (usually determined for bloodstream infections)

Application: Pivmecillinam

-Susceptibility breakpoints in Europe and US are consistent (although US breakpoint is on the high end for *E.coli*)

-Dose matters- better outcomes for ESBL with higher than FDA-approved dose = 400mg TID

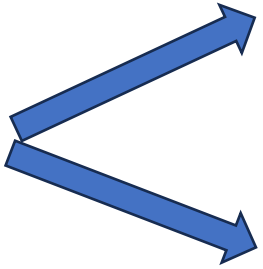
- The question: EUCAST vs. CLSI - if it's an ESBL E. coli in Europe, is it an ESBL E. coli in the US?
  The background:
  As you may have heard, pivmecillinam was given the FDA green light for treatment of uncomplicated UTIs in women in the US. The approved dose is 185mg (equal to 200mg of pivmecillinam hydrochloride) PO TID x 3-7 days. The package insert states that it has displayed in-vitro activity against ESBL E. coli; however, the reality turns out to be a bit more complicated. There are data from Norway showing an association with 200mg TID dosing for 5 days or less and clinical failure in patients with E. coli that are classified as ESBL per EUCAST. Moreover, Norway's own country-wide guidelines recommend 400mg TID x 5 days specifically for ESBL E. coli (this dosing sadly not approved here in the US). This has led me to wonder about EUCAST vs. CLSI and if these Norway data can inform US usage of the approved dosing for our own ESBLs.
- The study, in case it helps: J Antimicrob Chemother 2018; 73: 2503–2509 doi:10.1093/jac/dky230.

citations

What does this mean for treatment?

MOA	ESBL
Location	Plasmid
Inducible	*NO*
Bacteria	*E.coli, Klebsiella spp, Proteus mirabilis*
1 gen Ceph (cefazolin)	R
2 gen Ceph (cefoxitin)	S
3 gen Ceph (ceftriaxone)	R
4 gen Ceph (cefepime)	R / S
Pip-tazo	S
Carbapenem	S
Aztreonam	R

Concentration (MIC) is high



More drug needed to overcome all the ESBLs the bacteria are producing