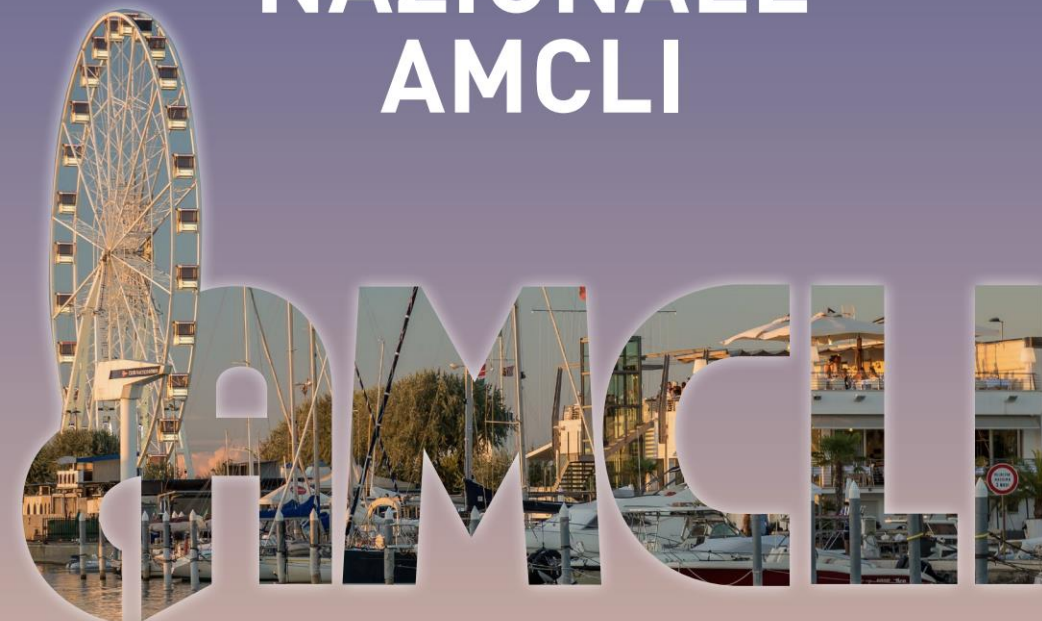


51° CONGRESSO NAZIONALE AMCLI



8-11 MARZO 2024
PALACONGRESSI RIMINI

CORSO PRECONGRESSUALE D
Antibiogramma 2024: “*Quo vadis?*”

EUCAST 2024: novità e ripasso delle regole recenti

Giulia De Angelis

Università Cattolica del Sacro Cuore

Fondazione Policlinico Universitario A. Gemelli IRCCS

Roma



Clinical breakpoints and dosing of antibiotics

Organization

Consultations

EUCAST News

New definitions of S, I and R

Clinical breakpoints and dosing

About "Clinical breakpoints".

Rationale documents

Splitting MIC wild type distributions

When there are no breakpoints?

Breakpoints in brackets

EUCAST setting breakpoints.

Rapid AST in blood cultures

Expert rules and expected phenotypes

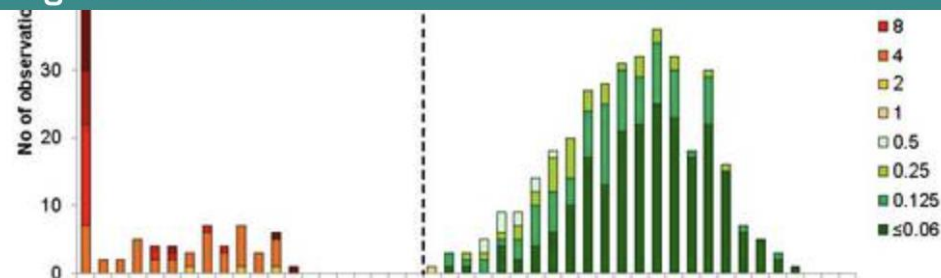
Resistance mechanisms

Guidance documents

SOP

MIC and zone distributions and ECOFFs

AST of bacteria



Clinical breakpoints - breakpoints and guidance

January 2, 2023

- [Clinical breakpoints \(v 14.0\)](#) - file for printing (1 Jan, 2024)
- [Clinical breakpoints \(v 14.0\)](#) - file for screen (1 Jan, 2024)
- [Clinical breakpoints - fungi](#)
- [Dosages \(v 14.0\)](#) - file for printing and screen (1 Jan, 2024)

The major changes between the 2023 and 2024 breakpoint tables are:

- Fosfomycin iv breakpoints revised
- Cefiderocol ATUs revised, and zone diameter breakpoint for Enterobacterales adjusted
- Ciprofloxacin breakpoints for staphylococci revised
- Breakpoint for C. difficile and fidaxomicin added
- Breakpoints for Bacillus anthracis added
- Breakpoints for Brucella melitensis added
- PK-PD breakpoints removed from the table (see explanation in the PK-PD tab) and "When there are no breakpoints"

Clinical breakpoints and dosing of anti

Breakpoint tables

- [Breakpoints bacteria \(print\)](#)
- [Breakpoints bacteria \(screen\)](#)
- [Breakpoints fungi](#)
- [Dosing table](#)

Make sure the device you are using for the presentation of tables can correctly display footnotes (Note₁, Note₂) and other typographical tools.

Cefiderocol

- injectable siderophore cephalosporin
- indicated for the treatment of infections due to aerobic gram-negative bacteria in adult patients with limited treatment options
- activity of cefiderocol occurs by inhibition of Gram-negative bacterial cell wall synthesis by binding to penicillin binding proteins
- stable to hydrolysis by both serine- and metallo- β -lactamases from all four Ambler classes
- in addition to entering the bacterial cell passively through outer membrane porin channels, cefiderocol also binds to free ferric iron (Fe-III) via a catechol group and is actively taken up via iron transport proteins.

Cefiderocol

Enterobacterales

2023, v. 13.1

Cephalosporins ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor (uncomplicated UTI only)	IE	IE			IE	IE	
Cefadroxil (uncomplicated UTI only)	16	16		30	12	12	
Cefalexin (uncomplicated UTI only)	16	16		30	14	14	
Cefazolin (infections originating from the urinary tract), <i>E. coli</i> and <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>)	0.001 ²	4 ²		30	50 ^A	20 ^A	
Cefepime	1	4		30	27	24	
Cefiderocol	2 ³	2 ³		30	22	22	18-22
Cefixime (uncomplicated UTI only)	1	1		5	17	17	
Cefotaxime (indications other than meningitis)	1	2		5	20	17	
Cefotaxime (meningitis)	1	1		5	20	20	
Cefoxitin (screen only) ⁴	Note ⁴	Note ⁴		30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1		10	21	21	
Ceftaroline	0.5	0.5		5	23	23	22-23
Ceftazidime	1	4		10	22	19	
Ceftazidime-avibactam	8 ⁵	8 ⁵		10-4	13	13	
Ceftibuten (infections originating from the urinary tract)	1	1		30	23	23	
Ceftobiprole	0.25	0.25		5	23	23	
Ceftolozane-tazobactam ⁶	2 ⁷	2 ⁷		30-10	22	22	19-21
Ceftriaxone (indications other than meningitis)	1	2		30	25	22	
Ceftriaxone (meningitis)	1	1		30	25	25	
Cefuroxime iv, <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	0.001	8		30	50	19	
Cefuroxime oral (uncomplicated UTI only), <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8		30	19	19	

Pseudomonas

2023, v. 13.1

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor	-	-			-	-	
Cefadroxil	-	-			-	-	
Cefalexin	-	-			-	-	
Cefazolin	-	-			-	-	
Cefepime	0.001	8		30	50	21	
Cefiderocol, <i>P. aeruginosa</i>	2 ¹	2 ¹		30	22	22	14-22
Cefixime	-	-			-	-	
Cefotaxime	-	-			-	-	
Cefoxitin	-	-			-	-	
Cefpodoxime	-	-			-	-	
Ceftaroline	-	-			-	-	
Ceftazidime	0.001	8		10	50	17	
Ceftazidime-avibactam, <i>P. aeruginosa</i>	8 ²	8 ²		10-4	17	17	16-17
Ceftibuten	-	-			-	-	
Ceftobiprole	IE	IE			IE	IE	
Ceftolozane-tazobactam ³ , <i>P. aeruginosa</i>	4 ⁴	4 ⁴		30-10	23	23	
Ceftriaxone	-	-			-	-	
Cefuroxime iv	-	-			-	-	
Cefuroxime oral	-	-			-	-	

Media and methods for cefiderocol testing

Unsolved warning on Sensititre BMD panel

- Cefiderocol MIC by broth microdilution on freeze dried panels from Thermofisher - the manufacturer has issued a warning against all current batches of MH broth when used together with any freeze dried Sensititre BMD panel.
- The following plates are listed as containing cefiderocol, MDRGNX2F, CAN2MSTF, GNARUM6F, THAMDR1F, CMP3QLN, DEURUB1, SWEEDL1, EUSHION8, FRCNRP4 and the manufacturer issues the following recommendation: "If you have bought any of these lots, then please ignore results for Cefiderocol".
- EUCAST recommendation: If uncertain confirm directly with the manufacturer (January, 2022).
- **There is as yet no news of a solution to the problem (November, 2023).**

Media and methods for cefiderocol testing

Disk diffusion is the gold standard

- **Laboratories are recommended to start testing cefiderocol with disk diffusion.**
- Disk diffusion, when correctly performed and calibrated using quality material and recommended quality control guidelines, is predictive of susceptibility and resistance outside the ATU.
- Inside the ATU, and as long as there is no alternative method to resolve interpretative uncertainties (eg MIC-testing in the routine laboratory or assistance from a reference laboratory), EUCAST recommends colleagues to **ignore the ATU and interpret using the zone diameter breakpoints in the breakpoint table.**

<https://www.eucast.org/ast-of-bacteria/warnings>

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/2022_manuals/Cefiderocol_disk_diffusion_training.pdf

Media and methods for cefiderocol testing

- For cefiderocol, using a cross-over protocol, **disks from three manufacturers** (Liofilchem, Mast and Oxoid) and **Mueller-Hinton media from five manufacturers** (BBL, bioMérieux, Bio-Rad, Liofilchem and Oxoid) were evaluated.
- If care is taken to ensure that the EUCAST QC criteria for the two strains, E. coli ATCC 25922 and P. aeruginosa ATCC 27853, are met, i.e. with the mean of at least 5 repeated tests is within ± 1 mm of the target values, disk diffusion using EUCAST breakpoints performed well.
- When the mean value was more than ± 1 mm from the target, an increasing proportion of results were erroneous. This was particularly problematic for *Pseudomonas aeruginosa*.
- Among the evaluated cefiderocol 30 µg disks (Liofilchem, Mast and Oxoid) and Muller-Hinton agars (BBL, bioMérieux, Bio-Rad, Liofilchem and Oxoid), **disks from Oxoid and MH agar from Bio-Rad produced larger than acceptable zone diameters for both QC strains and clinical isolates. Combining Oxoid disks with Bio-Rad MH agar increased the problem further.**

Update correlation MIC-zone diameter 2024



EUCAST News

Organization

Consultations

EUCAST News

New definitions of S, I and R

Clinical breakpoints and dosing

Rapid AST in blood cultures

Expert rules and expected phenotypes

Resistance mechanisms

Guidance documents

SOP



EUCAST News

Here you can find the latest news and updates from EUCAST.

09 Jan 2024

Files correlating MIC and zone diameters updated

The files demonstrating the correlation between broth microdilution MIC-values and inhibition zone diameters are now updated. The files are organised by species or species group and agent. [\[more\]](#)

Enterobacterales

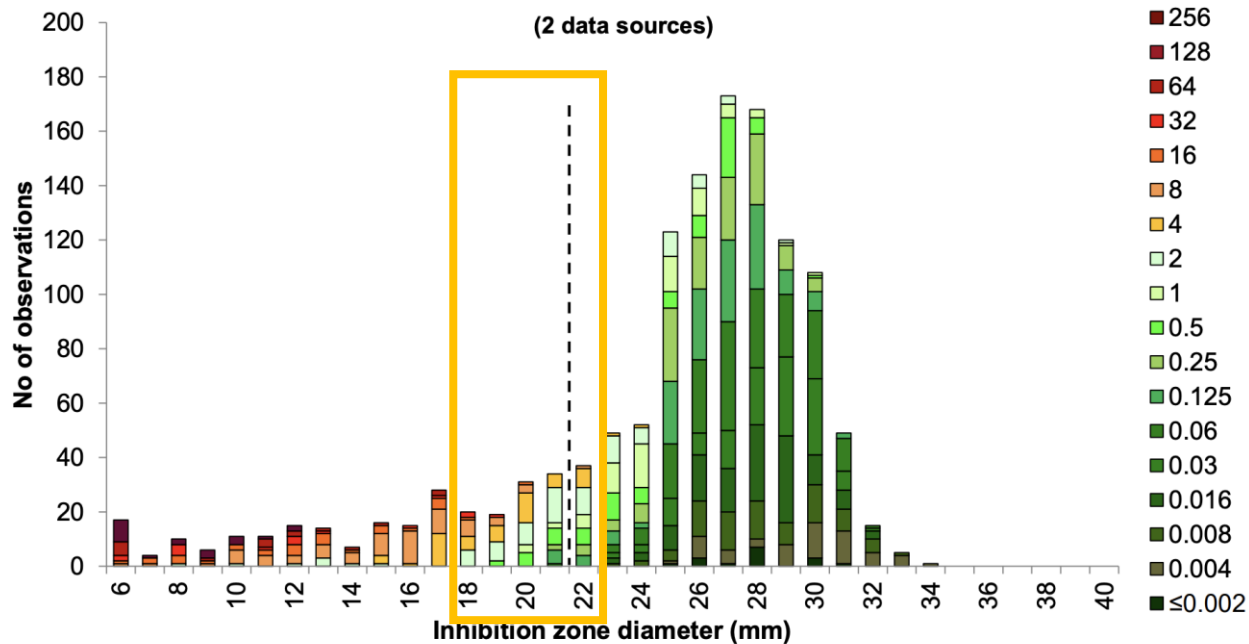
Calibration of zone diameter breakpoints to MIC values

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_criteria/Validation_2024/Enterobacterales_v_12.0_January_2024.pdf

Version 12.0
January 2024

2023

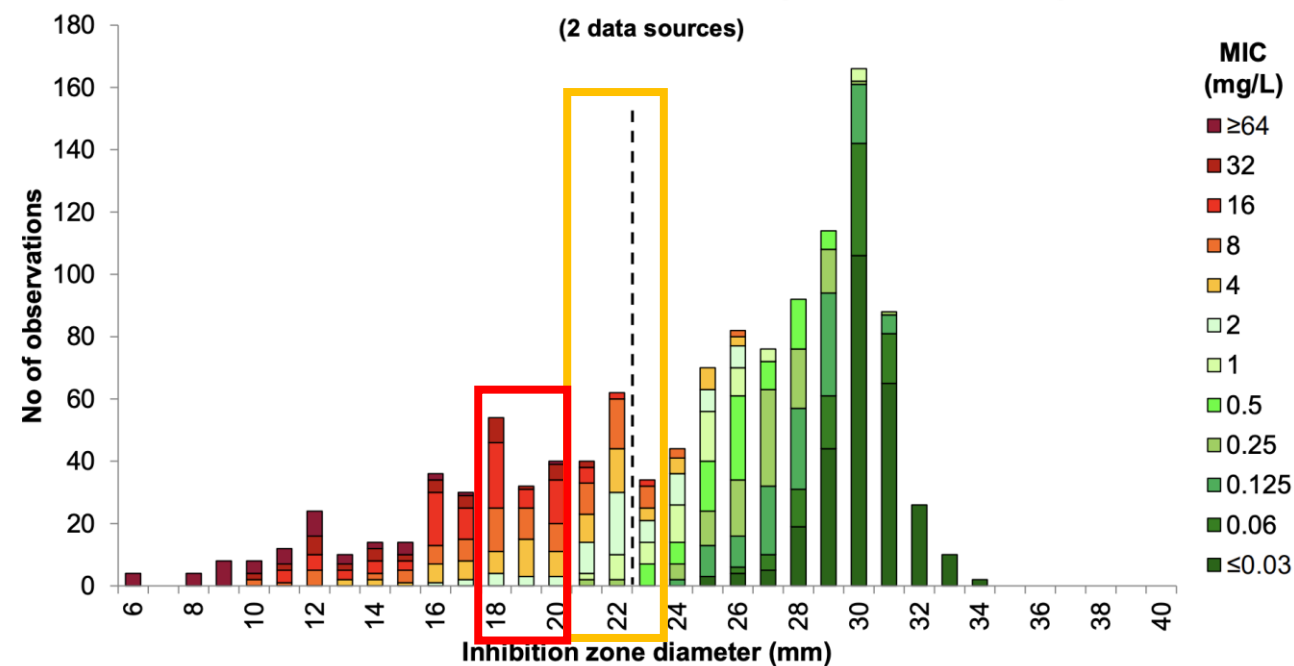
Cefiderocol 30 µg vs. MIC
***Enterobacterales*, 382 isolates (1302 correlates)**



ATU 18-22

2024

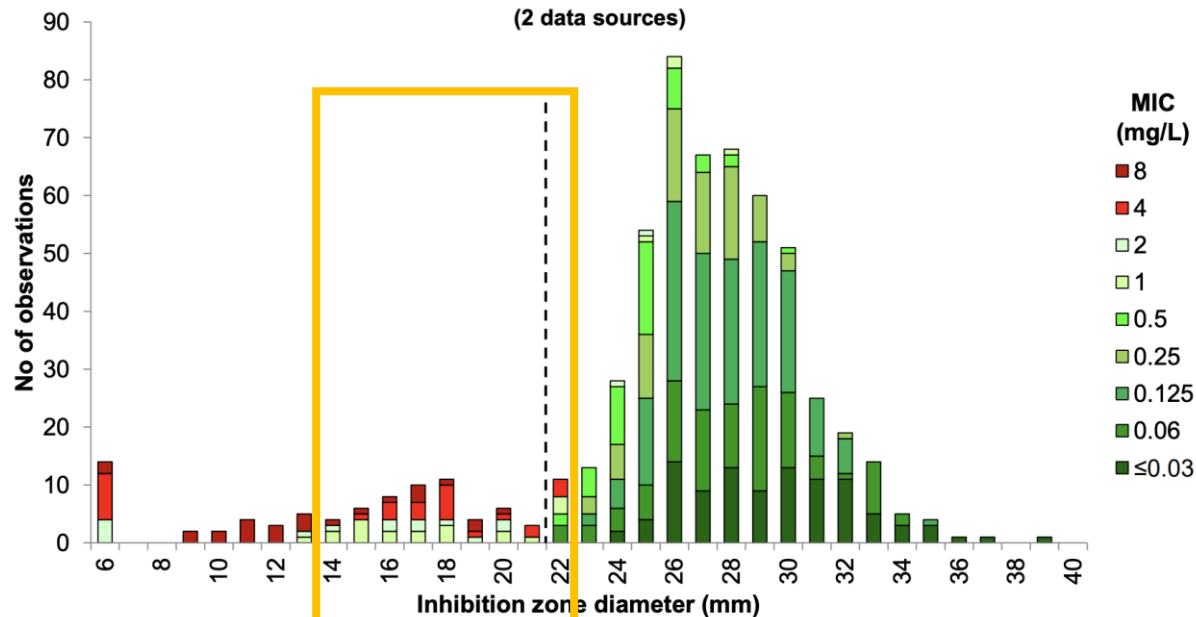
Cefiderocol 30 µg vs. MIC
***Enterobacterales*, 299 isolates (1196 correlates)**



ATU 21-23

2023

Cefiderocol 30 µg vs. MIC
P. aeruginosa, 152 isolates (588 correlates)
 (2 data sources)

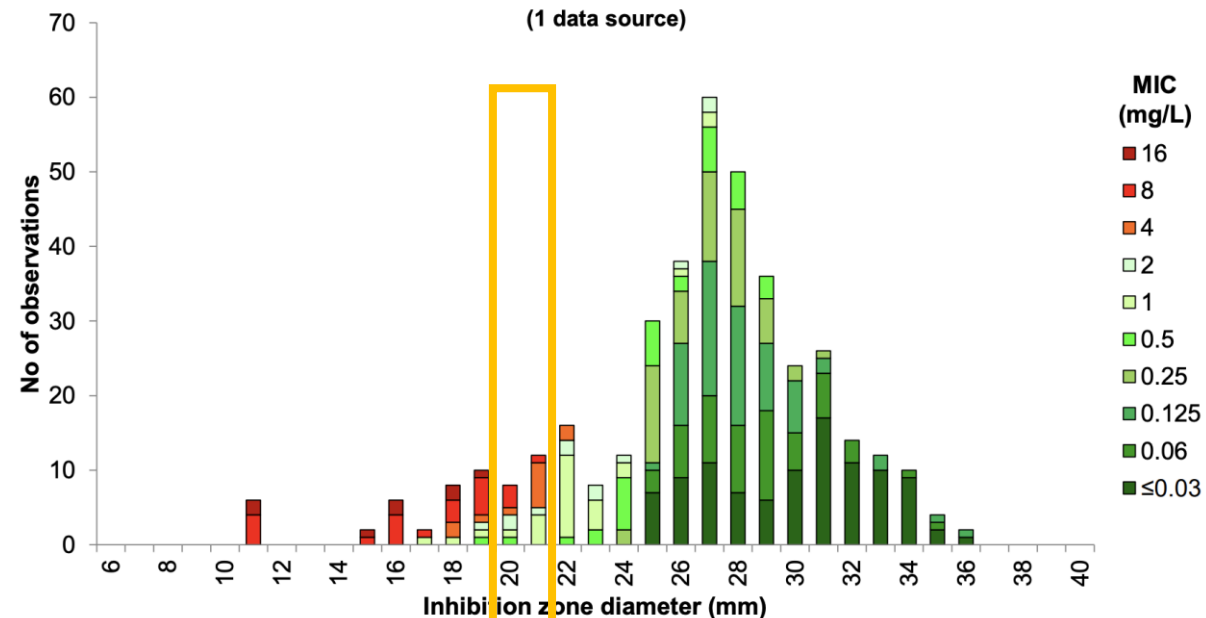


Breakpoints
 MIC S≤2, R>2 mg/L
 Zone diameter S≥22, R<22 mm

ATU 14-22

2024

Cefiderocol 30 µg vs. MIC
P. aeruginosa, 99 isolates (396 correlates)
 (1 data source)



Breakpoints
 MIC S≤2, R>2 mg/L
 Zone diameter S≥22, R<22 mm

ATU 20-21



Enterobacterales

Cefiderocol zone diameter and ATU revised

2023, v. 13.1

Cephalosporins ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor (uncomplicated UTI only)	IE	IE			IE	IE	
Cefadroxil (uncomplicated UTI only)	16	16		30	12	12	
Cefalexin (uncomplicated UTI only)	16	16		30	14	14	
Cefazolin (infections originating from the urinary tract), <i>E. coli</i> and <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>)	0.001 ²	4 ²		30	50 ^A	20 ^A	
Cefepime	1	4		30	27	24	
Cefiderocol	2 ³	2 ³		30	22	22	18-22
Cefixime (uncomplicated UTI only)	1	1		5	17	17	
Cefotaxime (indications other than meningitis)	1	2		5	20	17	
Cefotaxime (meningitis)	1	1		5	20	20	
Cefoxitin (screen only) ⁴	Note ⁴	Note ⁴		30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1		10	21	21	
Ceftaroline	0.5	0.5		5	23	23	22-23
Ceftazidime	1	4		10	22	19	
Ceftazidime-avibactam	8 ⁵	8 ⁵		10-4	13	13	
Ceftibuten (infections originating from the urinary tract)	1	1		30	23	23	
Ceftobiprole	0.25	0.25		5	23	23	
Ceftolozane-tazobactam ⁶	2 ⁷	2 ⁷		30-10	22	22	19-21
Ceftriaxone (indications other than meningitis)	1	2		30	25	22	
Ceftriaxone (meningitis)	1	1		30	25	25	
Cefuroxime iv, <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	0.001	8		30	50	19	
Cefuroxime oral (uncomplicated UTI only), <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8		30	19	19	

2024, v. 14.0

Cephalosporins ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor (uncomplicated UTI only)	IE	IE			IE	IE	
Cefadroxil (uncomplicated UTI only)	16	16		30	12	12	
Cefalexin (uncomplicated UTI only)	16	16		30	14	14	
Cefazolin (infections originating from the urinary tract), <i>E. coli</i> and <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>)	0.001 ²	4 ²		30	50 ^A	20 ^A	
Cefepime	1	4		30	27	24	
Cefiderocol	2 ³	2 ³		30	23	23	21-23
Cefixime (uncomplicated UTI only)	1	1		5	17	17	
Cefotaxime (indications other than meningitis)	1	2		5	20	17	
Cefotaxime (meningitis)	1	1		5	20	20	
Cefoxitin (screen only) ⁴	Note ⁴	Note ⁴		30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1		10	21	21	
Ceftaroline	0.5	0.5		5	23	23	22-23
Ceftazidime	1	4		10	22	19	
Ceftazidime-avibactam	8 ⁵	8 ⁵		10-4	13	13	
Ceftibuten (infections originating from the urinary tract)	1	1		30	23	23	
Ceftobiprole	0.25	0.25		5	23	23	
Ceftolozane-tazobactam ⁶	2 ⁷	2 ⁷		30-10	22	22	19-21
Ceftriaxone (indications other than meningitis)	1	2		30	25	22	
Ceftriaxone (meningitis)	1	1		30	25	25	
Cefuroxime iv, <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	0.001	8		30	50	19	
Cefuroxime oral (uncomplicated UTI only), <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8		30	19	19	

Pseudomonas aeruginosa

Cefiderocol ATU revised

2023, v. 13.1

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor	-	-			-	-	
Cefadroxil	-	-			-	-	
Cefalexin	-	-			-	-	
Cefazolin	-	-			-	-	
Cefepime	0.004	8		30	50	24	
Cefiderocol, <i>P. aeruginosa</i>	2 ¹	2 ¹		30	22	22	14-22
Ceftazidime							
Cefotaxime	-	-			-	-	
Cefoxitin	-	-			-	-	
Cefpodoxime	-	-			-	-	
Ceftaroline	-	-			-	-	
Ceftazidime	0.001	8		10	50	17	
Ceftazidime-avibactam, <i>P. aeruginosa</i>	8 ²	8 ²		10-4	17	17	16-17
Ceftibuten	-	-			-	-	
Ceftobiprole	IE	IE			IE	IE	
Ceftolozane-tazobactam ³ , <i>P. aeruginosa</i>	4 ⁴	4 ⁴		30-10	23	23	
Ceftriaxone	-	-			-	-	
Cefuroxime iv	-	-			-	-	
Cefuroxime oral	-	-			-	-	

2024, v. 14.0

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor	-	-			-	-	
Cefadroxil	-	-			-	-	
Cefalexin	-	-			-	-	
Cefazolin	-	-			-	-	
Cefepime	0.004	8		30	50	24	
Cefiderocol, <i>P. aeruginosa</i>	2 ¹	2 ¹		30	22	22	20-21
Ceftazidime							
Cefotaxime	-	-			-	-	
Cefoxitin	-	-			-	-	
Cefpodoxime	-	-			-	-	
Ceftaroline	-	-			-	-	
Ceftazidime	0.001	8		10	50	17	
Ceftazidime-avibactam, <i>P. aeruginosa</i>	8 ²	8 ²		10-4	17	17	16-17
Ceftibuten	-	-			-	-	
Ceftobiprole	IE	IE			IE	IE	
Ceftolozane-tazobactam ³ , <i>P. aeruginosa</i>	4 ⁴	4 ⁴		30-10	23	23	
Ceftriaxone	-	-			-	-	
Cefuroxime iv	-	-			-	-	
Cefuroxime oral	-	-			-	-	

Media and methods for cefiderocol testing

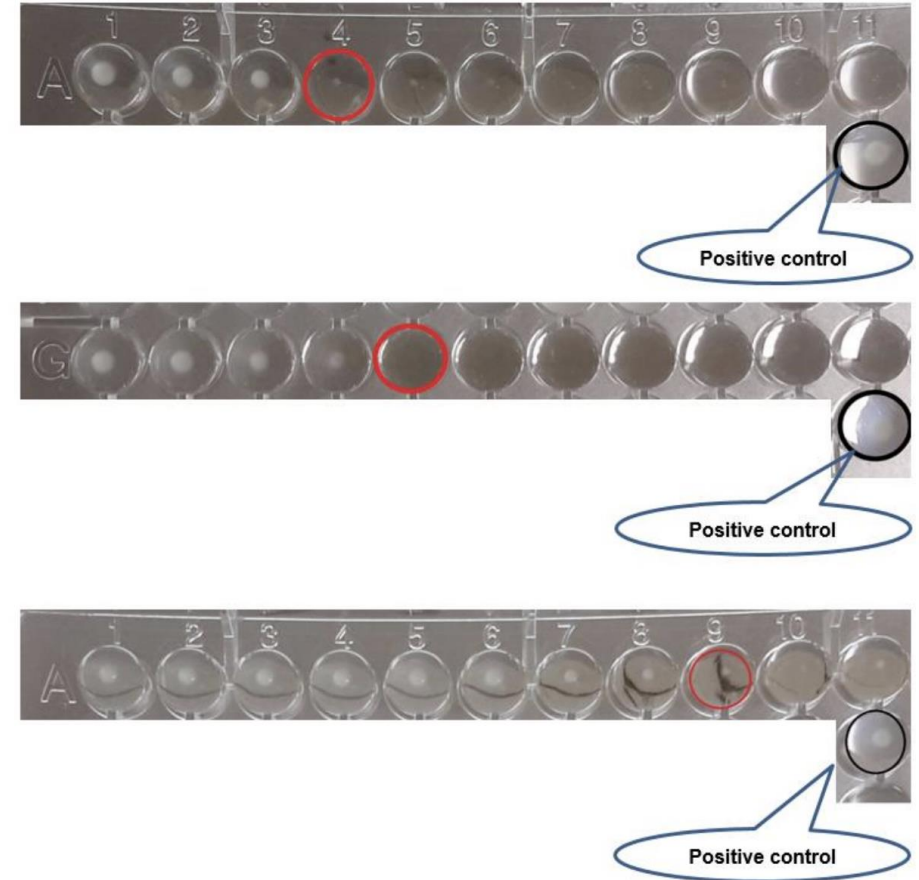
Guidance document on broth microdilution testing of cefiderocol

Preparation of iron-depleted cation-adjusted Mueller Hinton Medium (ID-CAMHB)¹

1. Add 100 g Chelex100® (Bio-Rad) to 1 L of autoclaved Mueller Hinton broth (other cation-binding resin can be used in place of Chelex)
2. Stir at room temperature for approximately 6 hours
3. Filter using 0.2 micron filter (The cation concentration of Mg, Ca, Zn and Fe should be below detection limit by these treatments.)
4. Add calcium (final concentration 20-25 µg/mL), magnesium (final concentration 10-12.5 µg/mL) and zinc (final concentration 0.5-1.0 µg/mL) into the Chelex-treated medium
5. Adjust pH to 7.2-7.4 by using HCl
6. Filter using 0.2 micron filter (optional)

Defined cation concentration in ID-CAMHB

Ca	20-25 µg/mL
Mg	10-12.5 µg/mL
Zn	0.5-1.0 µg/mL
Fe	0.03 µg/mL or less



Media and methods for cefiderocol testing

Two MIC commercial products currently under investigation

UMIC Cefiderocol



- Essential agreement between 78.4% (*Acinetobacter*) and 91.7% (*Enterobacterales*)
- Categorical agreement between 89% (*Acinetobacter*) and 95% (*non-fermenters*)

Media and methods for cefiderocol testing

Two commercial products currently under investigation

- ComASP



- Essential agreement between 81.4% (*Acinetobacter*) and 84% (*all Gram-negatives*)
- Categorical agreement between 88% (*Acinetobacter*) and 95.9% (*Acinetobacter*)

Fosfomycin iv

- organic phosphonate agent
- broad-spectrum agent which is particularly active against *Escherichia coli* and some other *Enterobacterales*. It also shows good activity against *Staphylococcus aureus*, including methicillin resistant *S. aureus* and most coagulase-negative staphylococci.
- resistance rates in clinical isolates are still relatively low
- re-emerged as a valuable tool in the treatment of multi-drug resistant (MDR) and extensively drug-resistant (XDR) infections, because of its broad spectrum of antibacterial action and pharmacokinetic characteristics, **frequently in combination with other active agents.**

Enterobacterales

Fosfomycin iv breakpoint and zone diameter revised

2023, v. 13.1

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	Note ¹	Note ¹			Note ^A	Note ^A		<p>Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.</p> <p>1/A. Efficacy for this order is uncertain. Screening cut-off values can be used to distinguish wild-type isolates from isolates with acquired resistance (MIC >16 mg/L : zone diameter <17 mm for the chloramphenicol 30 µg disk). For chloramphenicol treatment in meningitis, see table of dosages.</p> <p>2. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (<i>E. coli</i> ATCC 25922 or <i>P. aeruginosa</i> ATCC 27853) and the colistin resistant <i>E. coli</i> NCTC 13846 (<i>mcr-1</i> positive).</p> <p>3. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.</p> <p>4. Breakpoints for fosfomycin iv are currently under review.</p> <p>5. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.</p> <p>6. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.</p> <p>B. Use an MIC method (broth microdilution only).</p> <p>C. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate.</p> <p>D. Zone diameter breakpoints apply to <i>E. coli</i> only. For other <i>Enterobacterales</i>, use an MIC method.</p> <p>E. Ignore isolated colonies within the inhibition zone (see pictures below).</p>
Colistin ²	(2) ³	(2) ³			Note ^B	Note ^B		
Daptomycin	-	-			-	-		
Fosfomycin iv ⁴	32 ⁵	32 ⁵		200 ^C	21 ^{D,E}	21 ^{D,E}		
Fosfomycin oral (uncomplicated UTI only), <i>E. coli</i>	8 ⁵	8 ⁵		200 ^C	24 ^E	24 ^E		
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only), <i>E. coli</i>	64	64		100	11	11		
Nitroxoline (uncomplicated UTI only), <i>E. coli</i>	16	16		30	15	15		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	4	4		5	15	15		
Trimethoprim-sulfamethoxazole ⁶	2	4		1.25-23.75	14	11		

Enterobacterales

Fosfomycin iv breakpoint and zone diameter revised

2024, v. 14.0

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	Note ¹	Note ¹			Note ^A	Note ^A		1/A. Efficacy for <i>Enterobacterales</i> is uncertain. Screening cut-off values can be used to distinguish wild-type isolates from isolates with acquired resistance (MIC >16 mg/L; zone diameter <17 mm for the chloramphenicol 30 µg disk). For chloramphenicol treatment in meningitis, see table of dosages. 2. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (<i>E. coli</i> ATCC 25922 or <i>P. aeruginosa</i> ATCC 27853) and the colistin resistant <i>E. coli</i> NCTC 13846 (<i>mcr-1</i> positive). 3. f 4. / me 5/E 6/E En 7. B. C. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate. D. Zone diameter breakpoints apply to <i>E. coli</i> only. For other <i>Enterobacterales</i> , use an MIC method. D. Ignore isolated colonies within the inhibition zone (see pictures below).
Colistin ²	(2) ³	(2) ³			Note ^B	Note ^B		
Daptomycin	-	-			-	-		
Fosfomycin iv (infections originating from the urinary tract), <i>E. coli</i>	8 ⁴	8 ⁴		200 ^C	24 ^D	24 ^D		
Fosfomycin iv (other indications), <i>E. coli</i>	Note ⁵	Note ⁵			Note ^E	Note ^E		
Fosfomycin iv, other <i>Enterobacterales</i>	Note ⁶	Note ⁶			Note ^F	Note ^F		
Fosfomycin oral (uncomplicated UTI only), <i>E. coli</i>	8 ⁴	8 ⁴		200 ^C	24 ^D	24 ^D		
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only), <i>E. coli</i>	64	64		100	11	11		5/E: lack of <u>clinical evidence</u> to support breakpoints 6/E: <u>susceptibility testing discouraged</u>
Nitroxoline (uncomplicated UTI only), <i>E. coli</i>	16	16		30	15	15		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	4	4		5	15	15		
Trimethoprim-sulfamethoxazole ⁷	2	4		1.25-23.75	14	11		

Pseudomonas

Fosfomycin iv

Miscellaneous agents 2023, v. 13.1	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	-	-			-	-		1. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (<i>E. coli</i> ATCC 25922 or <i>P. aeruginosa</i> ATCC 27853) and the colistin resistant <i>E. coli</i> NCTC 13846 (<i>mcr-1</i> positive). 2. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/ .
Colistin ¹	(4) ²	(4) ²			Note ^A	Note ^A		
Daptomycin	-	-			-	-		3. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems. Infections caused by wild-type isolates (ECOFF: MIC 128 mg/L; corresponding zone diameter 12 mm using the disk potency and reading instructions for <i>E. coli</i>) have been treated with fosfomycin in combination with other agents. The ECOFF is 256 mg/L.
Fosfomycin iv ³	Note ³	Note ³			-	-		
Fosfomycin oral ³	-	-			-	-		A. Use an MIC method (broth microdilution only).
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-		
Nitroxoline (uncomplicated UTI only)	-	-			-	-		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	-	-			-	-		
Trimethoprim-sulfamethoxazole	-	-			-	-		

Miscellaneous agents 2024, v. 14.0	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	-	-			-	-		1. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (<i>E. coli</i> ATCC 25922 or <i>P. aeruginosa</i> ATCC 27853) and the colistin resistant <i>E. coli</i> NCTC 13846 (<i>mcr-1</i> positive). 2. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/ .
Colistin ¹	(4) ²	(4) ²			Note ^A	Note ^A		
Daptomycin	-	-			-	-		3/E: <u>susceptibility testing discouraged</u>
Fosfomycin iv	Note ³	Note ³			Note ^B	Note ^B		
Fosfomycin oral	-	-			-	-		A. Use an MIC method (broth microdilution only).
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-		
Nitroxoline (uncomplicated UTI only)	-	-			-	-		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	-	-			-	-		
Trimethoprim-sulfamethoxazole	-	-			-	-		

Staphylococcus

Fosfomycin iv

Miscellaneous agents 2023, v. 13.1	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	IE	IE			IE	IE		1. The clinical efficacy of chloramphenicol in meningitis has been questioned and breakpoints are currently under review. For chloramphenicol treatment in meningitis, see table of dosages. 1. Resistant isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory. 2. Daptomycin MICs must be determined in the presence of Ca ²⁺ (50 mg/L in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturers' instructions for commercial systems. 3. Breakpoints for fosfomycin iv are currently under review. 4. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems. 5. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration. A. Use an MIC method.
Colistin	-	-			-	-		
Daptomycin ¹	1 ²	1 ²			Note ^A	Note ^A		
Fosfomycin iv ³	32 ⁴	32 ⁴			Note ^A	Note ^A		
Fosfomycin oral	-	-			-	-		
Fusidic acid	1	1		10	24	24		
Lefamulin, <i>S. aureus</i>	0.25	0.25		5	23	23		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only), <i>S. saprophyticus</i>	64	64		100	13	13		
Nitroxoline (uncomplicated UTI only), <i>S. saprophyticus</i>	IE	IE			IE	IE		
Rifampicin, <i>S. aureus</i>	0.06	0.06		5	26	26		
Rifampicin, Coagulase-negative staphylococci	0.06	0.06		5	30	30		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	4	4		5	14	14		
Trimethoprim-sulfamethoxazole ⁵	2	4		1.25-23.75	17	14		

Miscellaneous agents 2024, v. 14.0	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol	IE	IE			IE	IE		1. Resistant isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory. 2. Daptomycin MICs must be determined in the presence of Ca ²⁺ (50 mg/L in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturers' instructions for commercial systems. 3/B. / https:// 4. Tri A. Use an MIC method.
Colistin	-	-			-	-		
Daptomycin ¹	1 ²	1 ²			Note ^A	Note ^A		
Fosfomycin iv	Note ³	Note ³			Note ^B	Note ^B		
Fosfomycin oral	-	-			-	-		
Fusidic acid	1	1		10	24	24		
Lefamulin, <i>S. aureus</i>	0.25	0.25		5	23	23		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only), <i>S. saprophyticus</i>	64	64		100	13	13		
Nitroxoline (uncomplicated UTI only), <i>S. saprophyticus</i>	IE	IE			IE	IE		
Rifampicin, <i>S. aureus</i>	0.06	0.06		5	26	26		
Rifampicin, Coagulase-negative staphylococci	0.06	0.06		5	30	30		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	4	4		5	14	14		
Trimethoprim-sulfamethoxazole ⁴	2	4		1.25-23.75	17	14		

3/E: susceptibility testing discouraged

MIC distribution and ECOFF

MIC distributions for Fosfomycin, 2024-02-13

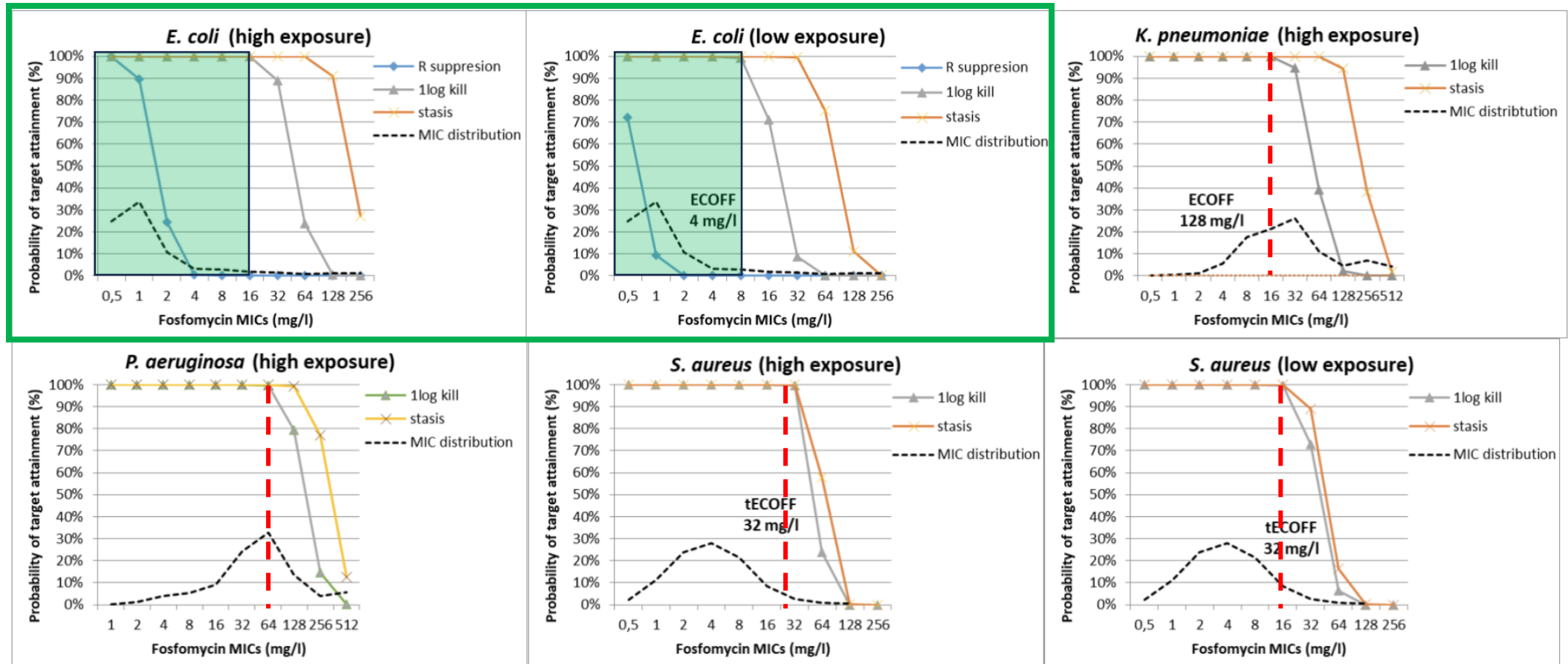
Antimicrobial: Fosfomycin (Method: MIC)

	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
<i>Acinetobacter baumannii</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	10	174	70	8	4	263	(512)
<i>Citrobacter freundii</i>	0	0	0	0	0	0	1	17	74	6	4	2	0	0	0	0	0	0	0	1	104	ID
<i>Citrobacter koseri</i>	0	0	0	0	0	0	0	1	41	50	9	0	0	1	0	0	0	0	0	1	102	ID
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	0	0	13	14	10	19	42	41	26	18	11	6	4	2	204	ID
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	2	2	0	2	19	111	1191	802	107	13	15	10	2264	128
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	1	0	0	0	0	4	82	498	81	0	1	3	667	(128)
<i>Escherichia coli</i>	0	0	0	0	0	0	73	349	588	791	253	77	68	45	38	18	25	24	2	11	2351	4
<i>Klebsiella aerogenes</i>	0	0	0	0	0	0	0	1	1	0	4	31	47	26	15	5	1	3	1	2	135	ID
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	0	0	0	1	2	1	13	27	18	7	7	2	1	1	79	ID
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	0	0	0	2	7	19	81	244	299	365	154	65	100	60	12	1396	128
<i>Proteus mirabilis</i>	0	0	0	0	0	0	5	10	14	69	78	54	18	15	18	14	14	3	5	3	317	(8)
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	0	0	0	0	2	9	29	37	63	169	229	95	28	40	7	701	256
<i>Serratia marcescens</i>	0	0	0	0	0	0	0	0	4	11	28	75	65	58	11	9	4	0	0	3	265	(32)
<i>Staphylococcus aureus</i>	0	0	0	0	0	0	0	0	14	67	144	168	130	51	16	6	3	2	3	6	604	32
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	0	0	0	51	124	148	98	146	105	33	47	183	1	6	3	942	ID
	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
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	0	0	0	0	0	0	14	28	5	3	0	0	0	0	1	50	ID



Monte Carlo simulations

Probability of target attainment



Based on low exposure Monte Carlo simulations, a PK/PD cut-off of 8 mg/l was determined for *E. coli*. For the other species, PK/PD cut-offs split the WT population even with high exposure

Clinical data

Fosfomycin iv

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Background. ZTI-01 (fosfomycin for injection) is an epoxide antibiotic with a differentiated mechanism of action (MOA) inhibiting an early step in bacterial cell wall synthesis. ZTI-01 has broad in vitro spectrum of activity, including multidrug-resistant Gram-negative pathogens, and is being developed for treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) in the United States.

Methods. Hospitalized adults with suspected or microbiologically confirmed cUTI/AP were randomized 1:1 to 6 g ZTI-01 q8h or 4.5 g intravenous (IV) piperacillin-tazobactam (PIP-TAZ) q8h for a fixed 7-day course (no oral switch); patients with concomitant bacteremia could receive up to 14 days.

Results. Of 465 randomized patients, 233 and 231 were treated with ZTI-01 and PIP-TAZ, respectively. In the microbiologic modified intent-to-treat (m-MITT) population, ZTI-01 met the primary objective of noninferiority compared with PIP-TAZ with overall success rates of 64.7% (119/184 patients) vs 54.5% (97/178 patients), respectively; treatment difference was 10.2% (95% confidence interval [CI]: -0.4, 20.8). Clinical cure rates at test of cure (TOC, day 19–21) were high and similar between treatments (90.8% [167/184] vs 91.6% [163/178], respectively). In post hoc analysis using unique pathogens typed by pulsed-field gel electrophoresis, overall success rates at TOC in m-MITT were 69.0% (127/184) for ZTI-01 versus 57.3% (102/178) for PIP-TAZ (difference 11.7% 95% CI: 1.3, 22.1). ZTI-01 was well tolerated. Most treatment-emergent adverse events, including hypokalemia and elevated serum aminotransferases, were mild and transient.

Conclusions. ZTI-01 was effective for treatment of cUTI including AP and offers a new IV therapeutic option with a differentiated MOA for patients with serious Gram-negative infections.

Clinical Trial Registration. NCT02753946

Keywords. ZTI-01; fosfomycin; complicated urinary tract infection; acute pyelonephritis.

Table 2. Overall, Clinical, and Microbiological Response by Analysis Populations

Population	Without PFGE (Uropathogen Identity Based on Species Name)			With PFGE (post hoc analysis) (Uropathogen Identity Based on Molecular Typing)		
	ZTI-01, n (%)	PIP-TAZ, n (%)	Treatment Difference ^a (95% CI)	ZTI-01, n (%)	PIP-TAZ, n (%)	Treatment Difference ^a (95% CI)
TOC (m-MITT)						
Primary endpoint—overall response						
N	184	178	10.2 (−0.4, 20.8)	184	178	11.7 (1.3, 22.1)
Success	119 (64.7)	97 (54.5)		127 (69.0)	102 (57.3)	
Failure	54 (29.3)	73 (41.0)		46 (25.0)	68 (38.2)	
Indeterminate	11 (6.0)	8 (4.5)		11 (6.0)	8 (4.5)	
Secondary endpoint—clinical endpoint response						
Clinical response, N	184	178		NA	NA	NA
Cure	167 (90.8)	163 (91.6)	−0.8 (−7.2, 5.6)			
Failure	9 (4.9)	12 (6.7)				
Indeterminate	8 (4.3)	3 (1.7)				
Secondary endpoint—microbiological endpoint response						
N	184	178		184	178	
Eradication	121 (65.8)	100 (56.2)	9.6 (−1.0, 20.1)	130 (70.7)	107 (60.1)	10.5 (0.2, 20.8)
Persistence	50 (27.2)	69 (38.8)		41 (22.3)	62 (34.8)	
Indeterminate	13 (7.1)	9 (5.1)		13 (7.1)	9 (5.1)	
Overall response in patients with AP						
Overall response, N	99	94		99	94	
Success	67 (67.7)	62 (66.0)	1.7 (−12.6, 16.0)	71 (71.7)	62 (66.0)	5.8 (−8.3, 19.9)
Failure	25 (25.3)	29 (30.9)		21 (21.2)	29 (30.9)	
Indeterminate	7 (7.1)	3 (3.2)		7 (7.1)	3 (3.2)	
Overall response in patients with cUTI						
Overall response, N	85	84		85	84	
Success	52 (61.2)	35 (41.7)	19.5 (3.5, 35.5)	56 (65.9)	40 (47.6)	18.3 (2.4, 34.1)
Failure	29 (34.1)	44 (52.4)		25 (29.4)	39 (46.4)	
Indeterminate	4 (4.7)	5 (6.0)		4 (4.7)	5 (6.0)	
Overall response in patients with bacteremia at baseline						
Overall response, N	19	13		19	13	
Success	9 (47.4)	5 (38.5)	8.9 (−32.3, 50.1)	9 (47.4)	5 (38.5)	8.9 (−32.3, 50.1)
Failure	7 (36.8)	8 (61.5)		7 (36.8)	8 (61.5)	
Indeterminate	3 (15.8)	0 (0)		3 (15.8)	0 (0)	

Clinical data

Fosfomycin iv

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

Table 1. Patient Demographics: Primary Analysis Population (Microbiologic Modified Intent-to-Treat)

	ZTI-01 (N = 184)	PIP-TAZ (N = 178)
Age, y, mean (SD)	49.9 (20.92)	51.3 (20.71)
Sex, n (%), Female:Male	119 (64.7):65 (35.3)	111 (62.4):67 (37.6)
Race		
White	184 (100)	178 (100)
BMI, kg/m ² , mean (SD)	25.75 (5.26)	26.64 (5.84)
Primary diagnosis		
AP	100 (54.3)	96 (53.9)
cUTI	84 (45.7)	82 (46.1)
SIRS at baseline	62 (33.7)	52 (29.2)
Bacteremia at baseline	19 (10.3)	13 (7.3)
Estimated Charlson comorbidity index, mean (SD)	2.2 (2.63)	2.5 (2.93)
CrCl, mL/min, mean (SD)	83.6 (32.85)	84.7 (32.25)
CrCl, ≥20–50 mL/min	26 (14.1)	20 (11.2)
Baseline pathogen		
No prior short acting antibiotics	168 (91.3)	169 (94.9%)
Gram-negative Enterobacteriaceae	177 (96.2)	169 (94.9)
<i>Escherichia coli</i>	133 (72.3)	133 (74.7)
<i>Klebsiella pneumonia</i>	27 (14.7)	25 (14.0)
<i>Enterobacter cloacae</i> species complex	9 (4.9)	3 (1.7)
<i>Proteus mirabilis</i>	9 (4.9)	5 (2.8)
<i>Klebsiella oxytoca</i>	3 (1.6)	2 (1.1)
<i>Citrobacter amalonaticus/farmeri</i>	1 (0.5)	0
<i>Raoultella ornithinolytica</i>	1 (0.5)	1 (0.6)
<i>Serratia marcescens</i>	1 (0.5)	1 (0.6)
<i>Morganella morganii</i>	0	1 (0.6)
Gram-negative aerobes other than Enterobacteriaceae	10 (5.4)	9 (5.1)
<i>Pseudomonas aeruginosa</i>	8 (4.3)	9 (5.1)
<i>Acinetobacter baumannii-calcoaceticus</i> species complex	2 (1.1)	0
Gram-positive aerobes	4 (2.2)	8 (4.5)
<i>Enterococcus faecalis</i>	3 (1.6)	7 (3.9)
<i>Staphylococcus aureus</i>	1 (0.5)	0
<i>Staphylococcus saprophyticus</i>	0	1 (0.6)

Table 3. Clinical and Microbiological Outcomes by Baseline Pathogen at Test of Cure (Microbiologic Modified Intent-to-Treat, Post Hoc Pulsed-field Gel Electrophoresis Analysis*)

Baseline Pathogen	Clinical Cure		Microbiologic Eradication	
	ZTI-01, n/N (%)	PIP-TAZ, n/N (%)	ZTI-01, n/N (%)	PIP-TAZ, n/N (%)
<i>Escherichia coli</i>	120/133 (90.2)	120/133 (90.2)	97/133 (72.9)	84/133 (63.2)
<i>Klebsiella pneumoniae</i>	25/27 (92.6)	25/25 (100)	18/27 (66.7)	14/25 (56.0)
<i>Proteus mirabilis</i>	8/9 (88.9)	3/5 (60.0)	8/9 (88.9)	1/5 (20.0)
<i>Enterobacter cloacae</i> species complex	8/9 (88.9)	3/3 (100)	6/9 (66.7)	3/3 (100)
<i>Klebsiella oxytoca</i>	2/3 (66.7)	2/2 (100)	2/3 (66.7)	2/2 (100)
<i>Raoultella ornithinolytica</i>	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
<i>Serratia marcescens</i>	1/1 (100)	1/1 (100)	1/1 (100)	0/1 (0)
<i>Morganella morganii</i>	0/0 (...)	1/1 (100)	0/0 (...)	1/1 (100)
<i>Citrobacter amalonaticus/farmer</i>	1/1 (100)	0/0 (...)	1/1 (100)	0/0 (...)
<i>Pseudomonas aeruginosa</i>	8/8 (100)	9/9 (100)	3/8 (37.5)	4/9 (44.4)
<i>Acinetobacter baumannii-calcoaceticus</i> species complex	2/2 (100)	0/0 (...)	2/2 (100)	0/0 (...)
<i>Enterococcus faecalis</i>	2/3 (66.7)	6/7 (85.7)	1/3 (33.3)	4/7 (57.1)
<i>Staphylococcus aureus</i>	1/1 (100)	0/0 (...)	1/1 (100)	0/0 (...)
<i>Staphylococcus saprophyticus</i>	0/0 (...)	1/1 (100)	0/0 (...)	1/1 (100)

Clinical data

Fosfomycin iv

Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial

ZEUS Trial: Microbiological Eradication Including Molecular Microbiology Data at TOC Visit by Baseline Pathogen and MIC to Study Drug Received (Population: Microbiologic Modified Intent-to- Treat)

Baseline Pathogen	ZTI-01			Piperacillin/Tazobactam		
	MIC	(N=184)		MIC	(N=178)	
	(µg/mL)	n/N1	(%)	(µg/mL)	n/N1	(%)
Gram-negative Enterobacteriaceae						
<i>Escherichia coli</i>	0.25	1/ 2	(50.0)	1	29/ 42	(69.0)
	0.5	42/ 59	(71.2)	2	41/ 67	(61.2)
	1	46/ 61	(75.4)	4	7/ 9	(77.8)
	2	8/ 8	(100.0)	8	5/ 7	(71.4)
	4	0/ 1	(0.0)	16	0/ 3	(0.0)
	32	0/ 1	(0.0)	32	1/ 1	(100.0)
				64	1/ 1	(100.0)
				>64	0/ 2	(0.0)
<i>Klebsiella pneumoniae</i>	4	0/ 3	(0.0)	1	2/ 3	(66.7)
	8	3/ 3	(100.0)	2	2/ 4	(50.0)
	16	6/ 8	(75.0)	4	3/ 4	(75.0)
	32	4/ 6	(66.7)	8	3/ 6	(50.0)
	128	3/ 3	(100.0)	16	1/ 1	(100.0)
	512	1/ 1	(100.0)	64	1/ 1	(100.0)
	>512	0/ 2	(0.0)	>64	2/ 5	(40.0)
<i>Enterobacter cloacae</i> species complex	4	1/ 1	(100.0)	≤0.5	1/ 1	(100.0)
	8	1/ 1	(100.0)	64	1/ 1	(100.0)
	16	4/ 5	(80.0)	>64	1/ 1	(100.0)
	64	0/ 1	(0.0)			
	>512	0/ 1	(0.0)			
<i>Proteus mirabilis</i>	0.5	2/ 2	(100.0)	≤0.5	0/ 2	(0.0)
	1	1/ 1	(100.0)	1	0/ 2	(0.0)
	2	1/ 2	(50.0)			
	8	2/ 2	(100.0)			
	32	1/ 1	(100.0)			
	64	1/ 1	(100.0)			
<i>Klebsiella oxytoca</i>	4	0/ 1	(0.0)	2	1/ 1	(100.0)
	8	1/ 1	(100.0)	>64	1/ 1	(100.0)

- Microbiological outcomes by pathogen and MIC from the ZEUS trial were kindly provided
- For *E. coli*, there were few study isolates with MICs above 2 mg/L.
- For *Klebsiella pneumoniae* there did not appear to be a relationship between MIC and outcome.

Clinical data

Fosfomycin iv

Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant *Escherichia coli* Bacteremic Urinary Tract Infections

A Randomized Clinical Trial

DESIGN, SETTING, AND PARTICIPANTS This multicenter, randomized, pragmatic, open clinical trial was conducted at 22 Spanish hospitals from June 2014 to December 2018. Eligible participants were adult patients with bacteremic urinary tract infections due to MDR *E coli*; 161 of 1578 screened patients were randomized and followed up for 60 days. Data were analyzed in May 2021.

INTERVENTIONS Patients were randomized 1 to 1 to receive intravenous fosfomycin disodium at 4 g every 6 hours (70 participants) or a comparator (ceftriaxone or meropenem if resistant; 73 participants) with the option to switch to oral fosfomycin trometamol for the fosfomycin group or an active oral drug or parenteral ertapenem for the comparator group after 4 days.

CONCLUSIONS AND RELEVANCE This study found that fosfomycin did not demonstrate noninferiority to comparators as targeted treatment of bUTI from MDR *E coli*; this was due to an increased rate of adverse event-related discontinuations. This finding suggests that fosfomycin may be considered for selected patients with these infections.

Table 2. Patients Reaching CMC and Reasons for Not Reaching It

	Patients, No./total No. (%)		Risk difference (1-sided 95% CI) ^a	P value, 1-sided
	Receiving fosfomycin	Receiving comparator		
CMC at TOC among MITT (measures of success)				
All patients	48/70 (68.6)	57/73 (78.0)	−9.4 (−21.5 to ∞)	.10
Patients with ceftriaxone-susceptible isolates ^b	25/31 (80.6)	27/31 (87.0)	−6.4 (−21.7 to ∞)	.24
Patients with ceftriaxone-resistant isolates ^b	23/39 (59.0)	30/42 (71.4)	−12.4 (−29.8 to ∞)	.12
Reasons for not reaching CMC at TOC among MITT (measures of failure)				
Clinical or microbiological failure				
All patients	10/70 (14.3)	14/73 (19.7)	−5.4 (−∞ to 4.9)	.19
Patients with ceftriaxone-susceptible isolates ^b	3/31 (9.7)	4/31 (12.9)	−3.2 (−∞ to 10.0)	.34
Patients with ceftriaxone-resistant isolates ^b	7/39 (17.9)	10/42 (23.8)	−8.9 (−∞ to 6.9)	.25
Other reasons				
Withdrawn because of adverse events	6/70 (8.5) ^c	0/73 (0)	8.5 (−∞ to 13.9)	.006
Missed assessment at TOC	3/70 (4.2)	2/73 (2.7)	1.5 (−∞ to 6.5)	.31
TOC assessed but urine culture at TOC not available	3/70 (4.2)	0/73 (0) ^d	4.2 (−∞ to 8.1)	.03

EUCAST guidance on use of fosfomycin i.v. breakpoints

- The currently revised breakpoint of fosfomycin applies only to *E. coli* in infections originating from the urinary tract and is 8 mg/L, which includes the entire wild type population. The breakpoint is supported by PK/PD and clinical data.
- No breakpoints have been determined for other species, as most of them are inherently less susceptible and so have higher ECOFFs, have preclinical PK/PD targets which are not attained, and because there is limited clinical data to support the use of the agent in monotherapy.
- It has not been possible to assess the added value of fosfomycin in combination therapy so far, and available data show no evidence to suggest that MICs are predictive of clinical efficacy. Thus, EUCAST will not issue guidance on how susceptibility testing would add value in the planning of combination therapy.

EUCAST General Consultation on Fosfomycin IV breakpoints

Consultation period 14 May to (extension) 15 July 2022

EUCAST General Consultation on iv Fosfomycin Breakpoints

Consultation period: 12 July to 12 September 2023

There is a dilemma between lack of fosfomycin data according to EUCAST standards, which is focused on monotherapy, and the lack of an established methodology to set breakpoints for substances primarily used in combination. Simply extinguishing established breakpoints does not provide proper guidance to the clinician and the microbiologist how to deal with this situation.

I am deeply concerned regarding the modified proposal on IV fosfomycin breakpoints. The lack of data on the use of *E. coli* does not allow for a reliable assessment of the combination therapy. Therefore, I consider the proposed modification problematic with respect to the clinical practice. Such an important issue, to which all stakeholders should be involved in the management of the infection, should be properly arranged. The concern that this will indirectly lead to the use of quinolones, which can have many unfavorable consequences, is justified. Therefore, I would like to ask you to pay attention to this aspect during the work on modifying EUCAST.

fundamental changes proposed, in my humble opinion; rather, they are studies that would establish the breakpoints. Academic and clinical reports and

there being no statement which

mitigates the possible discouragement in use caused by the lack of breakpoints. Suggest "Despite the limited breakpoints available and poor predictive value in some species this agent is a useful treatment in combination"

lead to usage discontinuation of this important antibiotic in clinical practice.

EUCAST response:

- **There is insufficient evidence to state anything about MICs in relation to efficacy in combination therapy.**
- **There is insufficient evidence to state whether AST is useful to guide combination therapy.**
- None of the recommendations pertain to the use of fosfomycin in combination therapy. It is not known whether MICs can predict efficacy in combination therapy.
- None of these breakpoints contradict the usage of fosfomycin in combination therapy. These are guidelines for antimicrobial susceptibility testing, not treatment recommendations. **Nowhere is it stated that the use in combination therapy is questioned or discouraged.**

Pharmacokinetics and pharmacodynamics (PK/PD) are important tools in the process of setting and revising breakpoints, and for discussion of target attainment and exposure at the site of the infection in relation to daily dose, mode of administration, and the frequency of dosing. The calculated “PK/PD breakpoints” are mostly based on data and simulations involving a limited number of species. We have come to recognize the limitations of these. A common misunderstanding is that PK/PD breakpoints are overarching in relation to species-specific breakpoints and that these can be used when species-specific breakpoints are lacking. This is not the intention. Instead EUCAST has developed guidance on “When there are no breakpoints” ([See EUCAST guidance documents](#)) and removed the PK/PD breakpoints from the table. This is to underline that these should never be considered when breakpoints are lacking. During 2024 a document on the usefulness and limitations of PK/PD breakpoints will be developed.

ent and
stly based on
reakpoints are
stead EUCAST
o underline
developed.

2023, v. 13.1

These breakpoints are used only when there are no species-specific breakpoints or other recommendations (a dash or a note) in the species-specific tables.

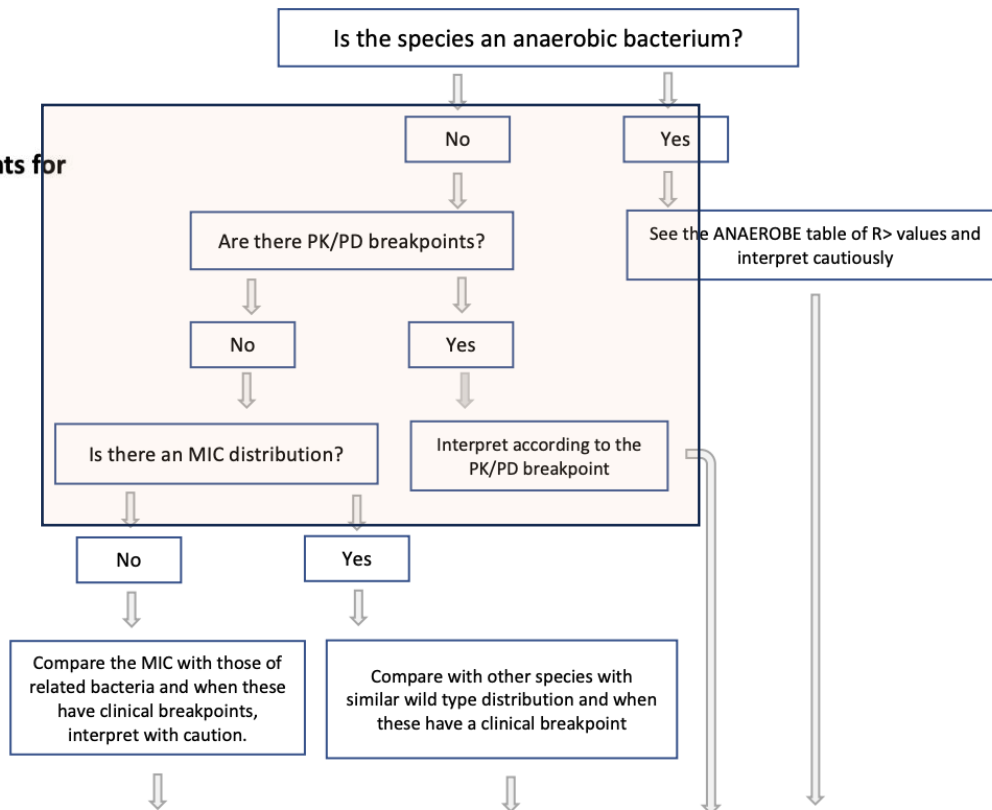
If the MIC is greater than the PK-PD resistant breakpoint, advise against use of the agent.

If the MIC is less than or equal to the PK-PD susceptible breakpoint, suggest that the agent can be used with caution. The MIC may also be reported although this is not essential. Include a note that the guidance is based on PK-PD breakpoints only, and include the dosage on which PK-PD breakpoint is based.

[More information is available in the EUCAST Guidance Document on how to test and interpret results when there are no breakpoints.](#)

Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints

Updated 1 December 2021



If no recommendation can be achieved, report:

- Categorising the susceptibility of the organism is not possible. There is no approved method and breakpoints have not been determined.
- Categorising the susceptibility of the organism is not possible. The MIC is X mg/L.

If the aim is to discourage the use of an agent, you may or may not want to add an R to the report with a comment:

- Formal categorising of the susceptibility of the organism is not possible. The MIC (of X mg/L) suggests that the agent should not be used for therapy.

If the aim is to encourage the use of an agent, you can add a comment:

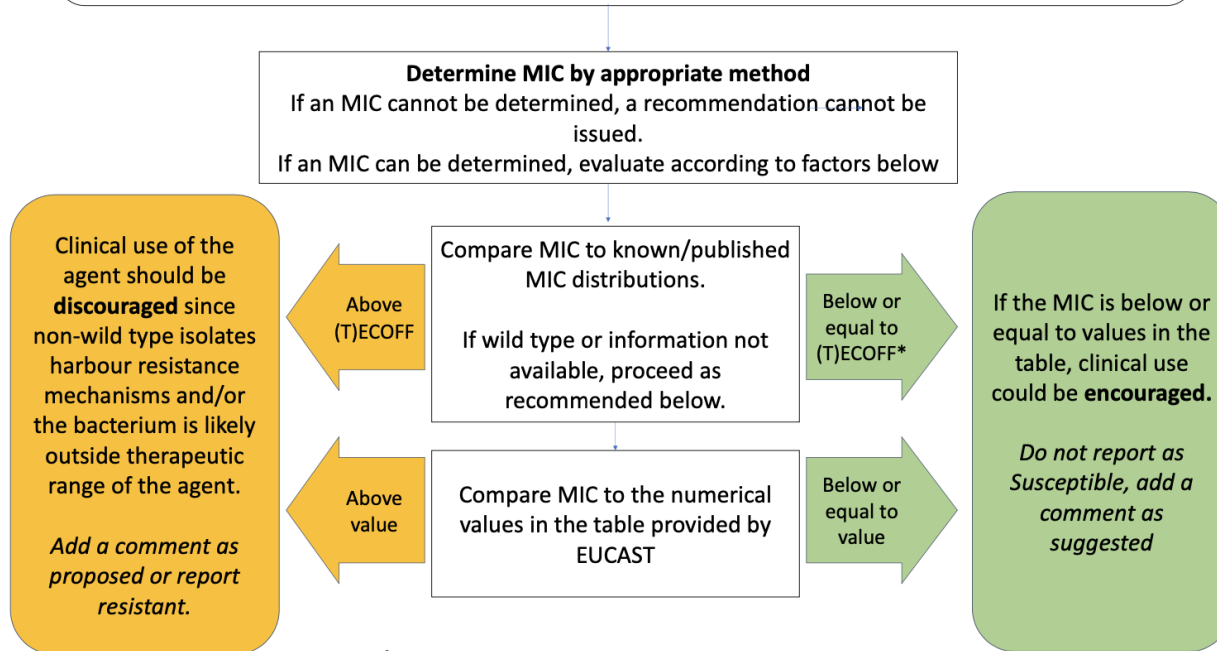
- Formal categorising of the susceptibility of the organism is not possible. The MIC (of X mg/L) suggests that the agent may be used for treatment.

EUCAST guidance on When there are no breakpoints in breakpoint tables?

2023-06-30

The isolate has been identified and it is possible to search relevant literature to determine:

- a) Significance / clinical importance of the species in question
- b) Which antimicrobials to test and for which agents to expect a successful outcome
- c) Growth characteristics to assist in choosing a suitable medium for testing



1. ECOFF available, non wild-type -> discourage
2. ECOFF available, wild-type -> TABLE
3. ECOFF not available -> TABLE

*Isolates belonging to the wild type cannot automatically be considered available for therapy

The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) the PK/PD breakpoint.

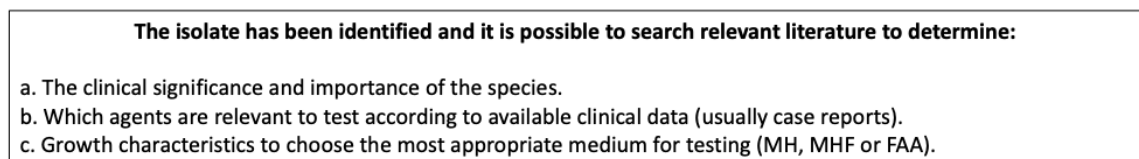
	MIC-values above which therapy with the agent should be discouraged		
Agents and notes for aerobic bacteria	Gram-positive organisms	Gram-negative organisms	Notes
Benzylpenicillin	0.25	0.5	If a beta-lactamase is detected, report resistant without further testing.
Ampicillin, Amoxicillin, Ampicillin-sulbactam, Amoxicillin-clavulanic acid (IV only)	0.5	8	The breakpoint of 8 mg/L pertains to intravenous high dose administration. If a beta-lactamase is detected, the value is only valid for amoxicillin-clavulanic acid and ampicillin-sulbactam.
Piperacillin-tazobactam	1	8	Species specific breakpoints for gram-positive organisms are 0.25 – 1 mg/L, and for gram-negative organisms 8 – 16 mg/L
Cefotaxime	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftriaxone	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftazidime	-	4	This is the Enterobacterales R-breakpoint.
Imipenem	2	2	Species specific breakpoints are often 2 mg/L.
Meropenem	2	2	Species specific breakpoints are 0.25 – 2 mg/L
Ciprofloxacin	0.25	0.25	Species specific breakpoints are 0.25 – 1 mg/L.
Levofloxacin	0.5	0.5	Species specific breakpoints are 0.25 – 1 mg/L.
Moxifloxacin	0.25	0.25	Species specific breakpoints are 0.125 – 0.5 mg/L
Clindamycin	0.5	NA	Species specific breakpoints are 0.25 – 0.5 mg/L.
Tetracycline (test tetracycline, report doxycycline, minocycline)	2	2 For Gram-negative organisms other than Enterobacterales	Tetracycline (as a representative for tetracycline, doxycycline, and minocycline) species specific breakpoints are 0.5 – 2 mg/L.
Trimethoprim-sulfamethoxazole	1	1	Species specific breakpoints are 0.5 – 2 mg/L.
Tigecycline	0.5	NA	Species specific breakpoints are 0.125 – 0.5 mg/L.
Rifampicin	0.125	NA	Species specific breakpoints are 0.06 – 0.125 mg/L.
Linezolid	2	NA	Species specific breakpoints are 2 - 4 mg/L
Vancomycin	2	NA	Species specific breakpoints are 2 mg/L.
Dalbavancin	0.125	NA	Species specific breakpoints are 0.125 mg/L.
Daptomycin	1	NA	Species specific breakpoints are 1 mg/L.

Agents and notes for anaerobic bacteria	MIC-values above which therapy with the agent should be discouraged	
Benzylpenicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin-clavulanic acid	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Ampicillin-sulbactam	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Piperacillin-tazobactam	2	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 – 2 mg/L.
Meropenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L.
Imipenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L
Ertapenem	0.25	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L
Clindamycin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 mg/L.
Metronidazole	4	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 - 4 mg/L.
Vancomycin (Gram-positive)	2	Only relevant for a few gram-positive anaerobic bacteria. A breakpoint of 2 mg/L is common for targeted species.
Rifampicin (Gram-positive)	0.125	Breakpoints for species already in the EUCAST breakpoint tables are 0.06 – 0.125 mg/L.
Linezolid (mixed infections)	Pending	Linezolid has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.
Moxifloxacin (mixed infections)	Pending	Moxifloxacin has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.

EUCAST guidance on When there are no breakpoints in breakpoint tables?

2024-02-29

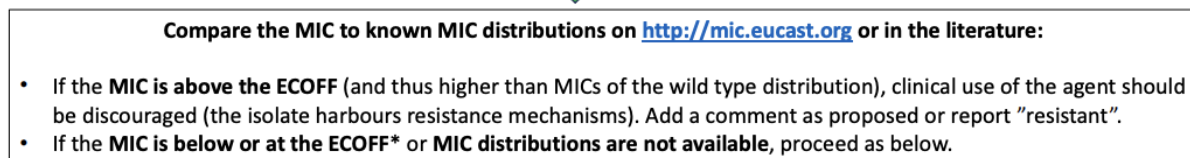
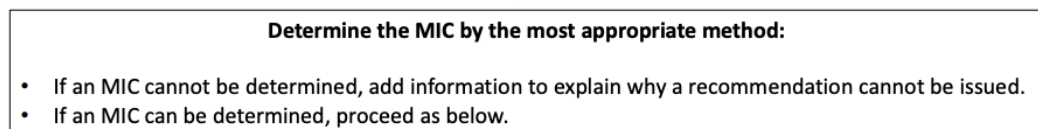
Flowchart:



the clinical relevance has been established and a decision to perform antimicrobial susceptibility testing (AST) is taken

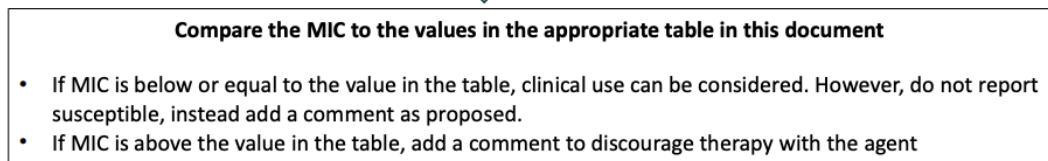


determine the MIC using reference methods or validated surrogate methods



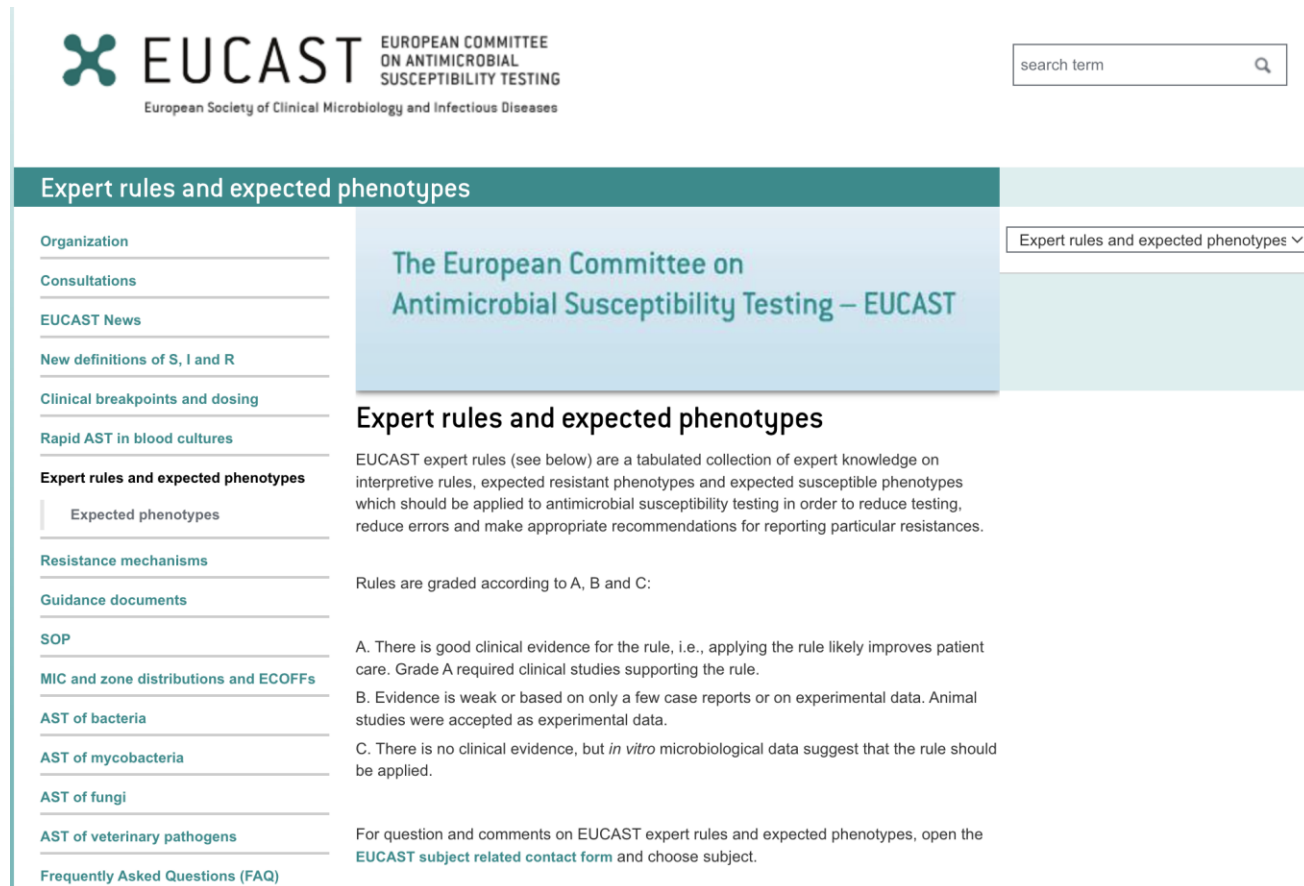
When the agent for use is not in the tables, and the last part of the flowchart cannot be applied, a decision can still be reached if a reliable MIC can be determined. Consult the literature for data to suggest a positive clinical outcome related to the MIC of this or a closely related species. Issue a cautious recommendation for use of the agent in the form of a comment, as proposed above, rather than a susceptibility category.

*Isolates belonging to the wild type cannot automatically be considered suitable for therapy.



Expert rules

News 2023



The screenshot shows the EUCAST website header with the logo and name 'EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING' and 'European Society of Clinical Microbiology and Infectious Diseases'. A search bar is present. The main navigation menu on the left includes: Organization, Consultations, EUCAST News, New definitions of S, I and R, Clinical breakpoints and dosing, Rapid AST in blood cultures, Expert rules and expected phenotypes (selected), Resistance mechanisms, Guidance documents, SOP, MIC and zone distributions and ECOFFs, AST of bacteria, AST of mycobacteria, AST of fungi, AST of veterinary pathogens, and Frequently Asked Questions (FAQ). The main content area has a teal header 'Expert rules and expected phenotypes' and a dropdown menu with the same text. Below this, the title 'The European Committee on Antimicrobial Susceptibility Testing – EUCAST' is displayed. The section 'Expert rules and expected phenotypes' contains a paragraph: 'EUCAST expert rules (see below) are a tabulated collection of expert knowledge on interpretive rules, expected resistant phenotypes and expected susceptible phenotypes which should be applied to antimicrobial susceptibility testing in order to reduce testing, reduce errors and make appropriate recommendations for reporting particular resistances.' Below this, it states 'Rules are graded according to A, B and C:' followed by three bullet points: 'A. There is good clinical evidence for the rule, i.e., applying the rule likely improves patient care. Grade A required clinical studies supporting the rule.', 'B. Evidence is weak or based on only a few case reports or on experimental data. Animal studies were accepted as experimental data.', and 'C. There is no clinical evidence, but *in vitro* microbiological data suggest that the rule should be applied.' At the bottom, it says 'For question and comments on EUCAST expert rules and expected phenotypes, open the EUCAST subject related contact form and choose subject.'

- *Enterobacterales* (Jan 2023)
- *Enterococcus spp.* (Jan 2023)
- *Staphylococcus spp.* (Feb 2023)

https://www.eucast.org/expert_rules_and_expected_phenotypes

Expert rules

January 2023

Enterobacterales

IF susceptible in vitro to cefotaxime, ceftriaxone or ceftazidime, THEN EITHER add a note that monotherapy with cefotaxime, ceftriaxone or ceftazidime as well as combination therapy of these agents with an aminoglycoside should be discouraged owing to risk of selecting resistance, OR suppress the susceptibility testing results for these agents

IF susceptible to cefotaxime, ceftriaxone or ceftazidime, THEN note that monotherapy with cefotaxime, ceftriaxone or ceftazidime may infrequently select resistant mutants

IF resistant to any 3rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4th generation (cefepime) cephalosporin and susceptible to another 3rd or 4th generation cephalosporin THEN report each as tested and enclose a warning on uncertain therapeutic outcome for infections other than urinary tract infections.

Enterococcus spp.

IF high-level resistant to streptomycin THEN report with a warning that combinations of this aminoglycoside with beta-lactams are no longer synergistic

IF vancomycin resistant AND teicoplanin susceptible THEN report with a warning of resistance development to teicoplanin during therapy;

IF vancomycin susceptible but *vanB* is detected by molecular methods THEN report resistant to vancomycin and add a warning of resistance development to teicoplanin during therapy

Staphylococcus spp.

IF resistant in norfloxacin screening test, THEN report individual agents as tested, and IF susceptible to either of ciprofloxacin, levofloxacin or moxifloxacin, THEN report agent as tested with a warning of risk for development of resistance during therapy with quinolones.

Take-home messages

- Table 14.0 includes important changes that will affect the practice
 - cefiderocol and fosfomycin iv
 - PK/PD breakpoints removes
- There are changes in the breakpoint tables every year. Some may be difficult to understand or accept without having followed the development of and the consultations
- Expert rules did not change since 2023.
- Both help to produce a clear antibiogram report for the clinicians
- More uniformity in warnings and notes?