



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Bracketed breakpoints

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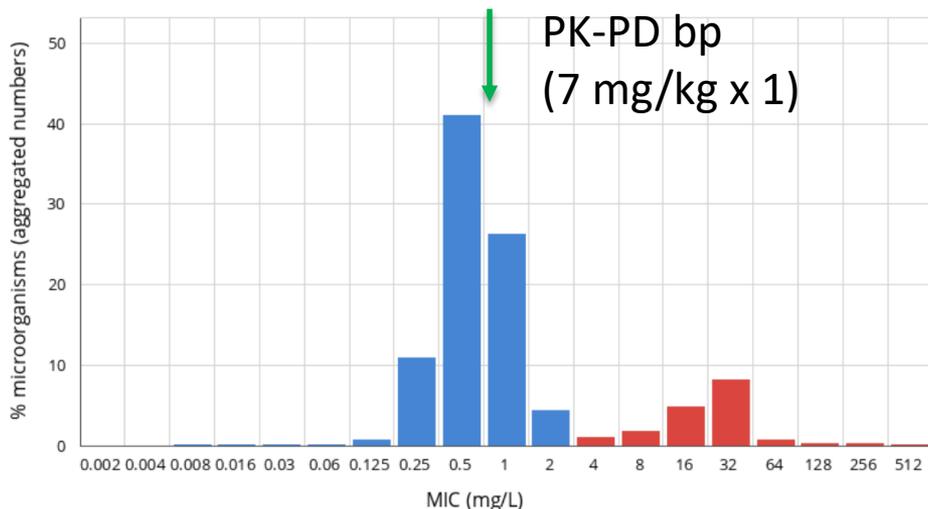
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The issue at stake

Gentamicin / Escherichia coli
International MIC distribution - Reference database 2022-05-22
Based on aggregated distributions

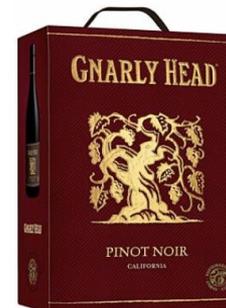
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 2 mg/L
Wildtype (WT) organisms: ≤ 2 mg/L

Confidence interval: 1 - 2
78136 observations (82 data sources)

- Possible solutions
 - Split WT: NO (reproducibility)
 - Increase dosage: NO (toxicity)
 - Remove bp: NO (good data remain for urinary focus)
 - Place the WT in the I-group: NO (contradicts new def.)
- A new tool for expressing breakpoint caveats
- BiB



Mentimeter question

- How are you dealing with breakpoints in brackets?
 - Avoid reporting
 - Report as ATU
 - Report S with a comment
 - Report as I
 - Report S with an asterisk or similar plus a comment
 - Report only a comment

Possible strategies

- Report only a comment about absence of acquired resistance and in which situations susceptibility can be expected
- Other possibilities (your LIS is usually the limitation)

Gentamicin **S***

*Gentamicin can be used in combination therapy with other active therapy or in monotherapy of infections emanating from the urinary tract

Gentamicin **(S)**

(S)= Gentamicin can be used in combination therapy with other active therapy or in monotherapy of infections emanating from the urinary tract

In which situations are BiB used?

Bracketed breakpoints

1. Aminoglycosides ([see guidance document](#))
 - a. *Enterobacterales*
 - i. Amikacin, gentamicin and tobramycin for systemic infections
 - b. *Pseudomonas* spp.
 - i. Amikacin and tobramycin for systemic infections
 - c. *Acinetobacter* spp.
 - i. Amikacin, gentamicin and tobramycin for systemic infections
 - d. *Staphylococcus* spp.
 - i. Amikacin, gentamicin and tobramycin for systemic infections

2. Colistin ([see guidance document](#))
 - a. *Enterobacterales*
 - b. *Pseudomonas* spp
 - c. *Acinetobacter* spp

Isolates with **resistance** (MIC above or zone diameter below the R-breakpoint in bracket) can be reported R (resistant) but reporting S or I should be avoided and if considered necessary, there should be a comment to explain the need for adjunctive measures as mentioned above.

3. Clindamycin
 - a. *Bacteroides* spp
Many *Bacteroides* species when without resistance mechanisms have clindamycin MIC-values of 1, 2 and 4 and some species even higher MICs. All other species with breakpoints for clindamycin have wild type MIC values and breakpoints on or below 0.5 mg/L (for example staphylococci, streptococci, *S. pneumoniae*).
Most infections with *Bacteroides* involve aerobic and anaerobic bacteria and therapeutic traditions mostly call for combination therapy.

Bracketed breakpoints for colistin

Tab	Current listing Breakpoint Tables v11.0		Proposed listing Breakpoint Tables 12.0	
	S ≤	R >	S ≤	R >
<i>Enterobacterales</i>	2	2	(2)	(2)
<i>Pseudomonas</i> spp.*	2	2	(4)	(4)
<i>Acinetobacter</i> spp.	2	2	(2)	(2)

* Note: increase of breakpoint from 2 to 4 mg/L is already approved

- Less than 50% of patients with normal renal function achieve proper drug exposure, and it is associated with high risk of nephrotoxicity.
- Even in patients achieving adequate drug exposure, this level of exposure is still insufficient to achieve bacterial stasis in pneumonia
- Randomized and observational studies consistently demonstrate increased mortality for polymyxins compared with alternative agents, when polymyxins are used in monotherapy

Bracketed breakpoints for colistin cont.

Enterobacterales

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Chloramphenicol ¹	8	8		30	17	17		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. 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. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastquidancedocuments/ .
Colistin ²	(2) ³	(2) ³			Note ^A	Note ^A		
Daptomycin	-	-			-	-		
Fosfomycin iv	32 ⁴	32 ⁴		200 ^B	21 ^{C,D}	21 ^{C,D}		
Fosfomycin oral	8 ⁴	8 ⁴		200 ^B	24 ^D	24 ^D		

P. aeruginosa

Miscellaneous agents	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/eucastquidancedocuments/ .
Colistin ¹	(4) ²	(4) ²			Note ^A	Note ^A		
Daptomycin	-	-			-	-		

Acinetobacter spp.

Miscellaneous agents	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/eucastquidancedocuments/ .
Colistin ¹	(2) ²	(2) ²			Note ^A	Note ^A		
Daptomycin	-	-			-	-		

Bracketed breakpoints for *Bacteroides*

Bacteroides spp.

Antimicrobial agent	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Piperacillin-tazobactam	8 ¹	8 ¹		30-6	20	20		1. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L. 2/A. The meropenem zone diameter breakpoint will detect all <i>cfiA</i> gene mediated carbapenem resistance in <i>Bacteroides fragilis</i> . Some isolates with an MIC of 1 mg/L may harbour the <i>cfiA</i> gene.
Piperacillin-tazobactam, <i>B. thetaiotaomicron</i>	IE	IE			IE	IE		
Meropenem	1 ²	1 ²		10	28 ^A	28 ^A		3/B. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/ .
Clindamycin	(4) ³	(4) ³		2	(10) ^{B,C}	(10) ^{B,C}		
Metronidazole	4	4		5	25	25		C. Examine zones carefully for colonies within zones. Colonies should be taken into account when reading.

PK of clindamycin:

-600 mg gives Cmax of around 10 mg/L, 300 mg gives around 5 mg/L

-Protein binding is 90-95%

-Intracellular concentration is high, but regardless: 4 mg/L is far beyond what can be achieved

-It is not known what the driver of killing efficacy is for clindamycin

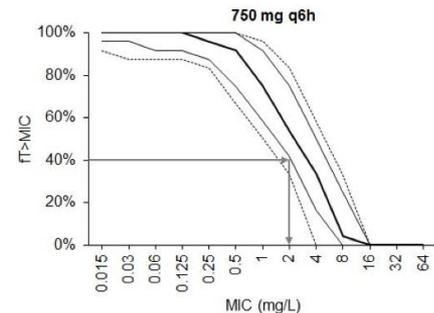
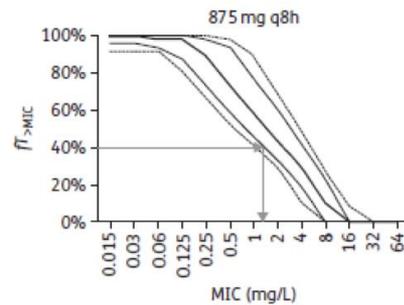
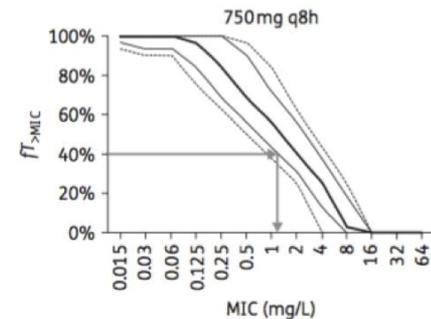
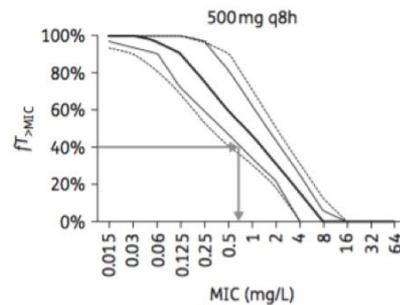
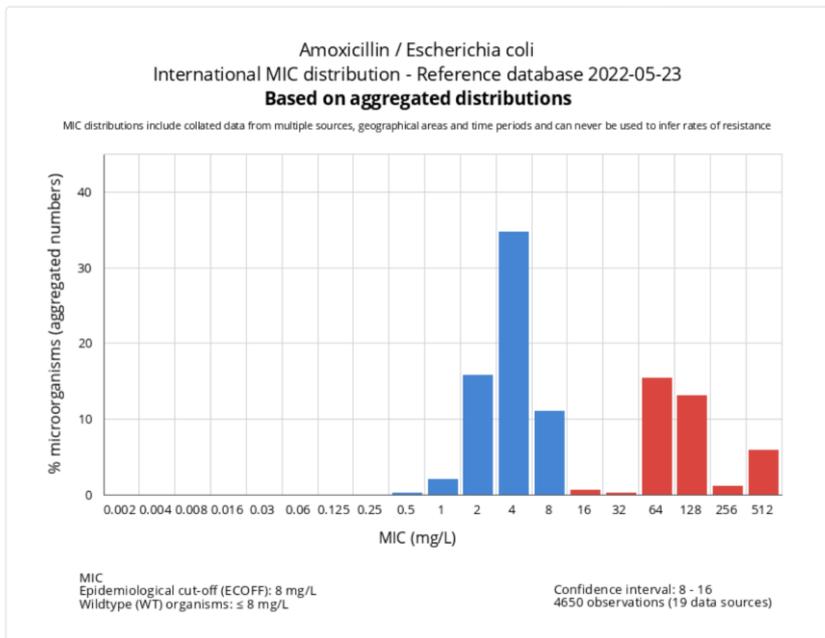
Upcoming bracketing, amino-PC

Penicillin	MIC breakpoints (mg/l)		
	S ≤	R >	ATU
Ampicillin iv	8	8	
Ampicillin oral, uncomplicated UTI only	8	8	
Ampicillin-sulbactam iv	8	8	
Ampicillin-sulbactam oral, uncomplicated UTI only	8	8	
Amoxicillin iv	8	8	
Amoxicillin oral, complicated UTI	<0.001	8	
Amoxicillin oral, uncomplicated UTI only	8	8	
Amoxicillin oral, other indications	(8) ¹	(8) ¹	
Amoxicillin-clavulanic acid iv	8	8	
Amoxicillin-clavulanic acid oral, complicated UTI	<0.001	8	
Amoxicillin-clavulanic acid oral, (uncomplicated UTI only)	32	32	
Amoxicillin-clavulanic acid oral, other indications	(8)	(8)	

Aminopenicillin	Route of administration	Standard dosage	High dosage
Ampicillin	iv	2 g x 3	2 g x 4
Ampicillin	oral	Not listed	Not listed
Ampicillin-sulbactam	iv	(2 g + 1 g) x 3	(2 g + 1 g) x 4
Ampicillin-sulbactam	oral	Not listed	Not listed
Amoxicillin	iv	1 g x 3-4	2 g x 6
Amoxicillin	oral	0.5 g x 3	0.75-1 g x 3
Amoxicillin-clavulanic acid	iv	1 g + 0.2 g x 3-4	(2 g + 0.2 g) x 3
Amoxicillin-clavulanic acid	oral	(0.5 g + 0.125 g) x 3	(0.875 g + 0.125 g) x 3

Oral, complicated UTI: report as I
 Oral, uncomplicated UTI: report as S
 Oral, other infections: report comment only
 I.v.: report as S

Why bracketing for oral amoxicillin?



Upcoming bracketing, fosfomycin

	Current MIC Breakpoint (mg/L)		Proposed MIC Breakpoint (mg/L)		
<i>Enterobacterales</i>	32	32	<i>E. coli</i>	8	8
			<i>K. pneumoniae</i>	Note ¹	Note ¹
			Enterobacterales other than <i>E. coli</i> and <i>K. pneumoniae</i>	IE ²	IE
			<i>Enterococcus</i>	-	-
			<i>P. aeruginosa</i>	-	-
			<i>A. baumannii</i>	-	-
<i>S. aureus</i>	32	32	<i>S. aureus</i>	(32)	(32)

() indicate that for systemic infections, fosfomycin IV should be used in combination with other active therapy. In this circumstance, the value in brackets can be used to distinguish between wild type organisms and organisms with acquired resistance mechanisms

¹ For *K. pneumoniae* there is clinical experience with use in combination therapy and to a limited extent use in treatment of pyelonephritis in monotherapy.

There is however insufficient data to define an ECOFF.

²For other *Enterobacterales* there is both insufficient clinical data and MIC-data to define either a clinical breakpoint or an ECOFF.

Fosfomycin emerging as a treatment alternative (combination) for difficult-to-treat *S. aureus*

For most *Enterobacterales* the MIC-data are very poor

PK-PD breakpoint is either 8 or 16 mg/L

Other situations where brackets might be used in the future

- Azithromycin vs *Salmonella* and *Shigella* (?)
- Azithromycin vs *N. gonorrhoeae*
- Moxifloxacin and enterococci (endocarditis)
- Fosfomycin and non-*E. coli* *Enterobacterales*

Conclusions

- Breakpoints in brackets are used increasingly often
- Laboratories need to find a strategy for communicating results
- Reporting a regular “S” with a comment will not be sufficient
- Reporting either a comment only is possible
- Reporting as S with an asterisk or S in brackets, in both cases accompanied by a comment, can be a viable strategy if the LIS allows this