



European Society of Clinical Microbiology and Infectious Diseases

# Fosfomycin and aminopenicillins

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# Why do we change breakpoints?

- Data-driven
- Professional pride
- Patient safety
  
- And yes:
  - We always consider clinical data
  - We always consider practical implications

# Revision of fosfomycin breakpoints

This is a general consultation on proposed breakpoints for fosfomycin. Breakpoints are proposed for systemic infections caused by *Enterobacterales* primarily *Escherichia coli* and *Staphylococcus aureus*. The fact that fosfomycin retains activity against the majority of extended-spectrum-beta-lactamase (ESBL) producing and other multidrug resistant (MDR) isolates has led to an increased interest in the drug. However, fosfomycin was administered mostly as combination therapy with  $\beta$ -lactams or aminoglycosides against CRE and other MDR pathogens.

The proposed species related breakpoints apply only for *E. coli* for a total daily dose 16-18 g.  
S  $\leq$  8 mg/L / R > 8 mg/L for *Escherichia coli*

The draft rationale document below outlines the reasons for the selection of proposed breakpoints.

Fosfomycin	Current MIC Breakpoint (mg/L)		Proposed MIC Breakpoint (mg/L)	
	S $\leq$	R >	S $\leq$	R >
<i>Enterobacterales</i>	32	32		
<i>E. coli</i>			8	8
<i>E. cloacae</i>			IE	IE
<i>E. faecium</i>			IE	IE
<i>E. faecalis</i>			IE	IE
<i>K. pneumoniae</i>			Note <sup>1</sup>	Note <sup>1</sup>
<i>P. aeruginosa</i>			-	-
<i>S. aureus</i>	32	32	Note <sup>1</sup>	Note <sup>1</sup>

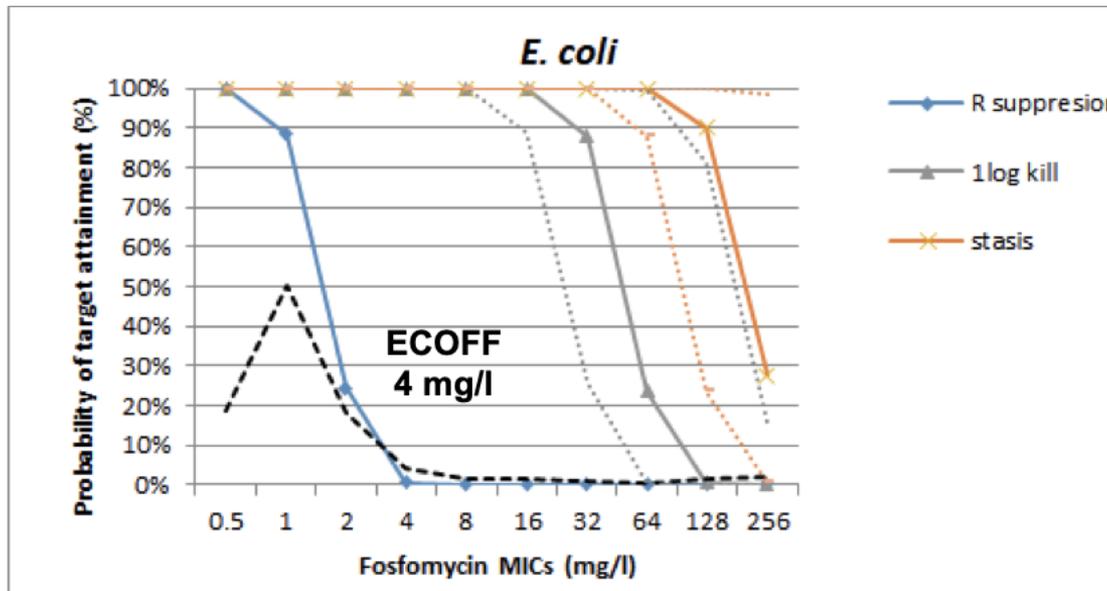
<sup>1</sup>For *K. pneumoniae* and *S. aureus* there is clinical experience with use in combination therapy. The ECOFFs are 128 and 32 mg/L, respectively, and can be used to separate strains with and without acquired resistance mechanisms. It is not known whether the ECOFF can be used to predict efficacy in combination therapy.

# Revision of fosfomycin breakpoints (II)

**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)

# Revision of fosfomycin breakpoints (IV)



# Revision of fosfomycin breakpoints (III)

- The EUCAST breakpoints proposed for *E. coli* pertain to the use of intravenous fosfomycin in monotherapy for infections originating in the urinary tract.
- The proposed breakpoints do not contradict, fail to acknowledge, or discourage from the use of intravenous fosfomycin in combination therapy for other infections. However, the correlation between the in vitro susceptibility of a pathogen to fosfomycin and the efficacy of adding fosfomycin to combination therapy has not been formally studied. **Consequently, it is not possible to propose a breakpoint for use in any combination regimen.**
- ECOFFs can be used to determine if a strain belongs to the wild type, **although this information does not predict efficacy in combination therapy.** For *S. aureus* the ECOFF is 32 mg/L, for *K. pneumoniae* it is 128 mg/L, for *P. aeruginosa* it is 256 mg/L, and for *P. mirabilis* it is 8 mg/L. For other species: insufficient data

# Aminopenicillins - *Enterobacterales*

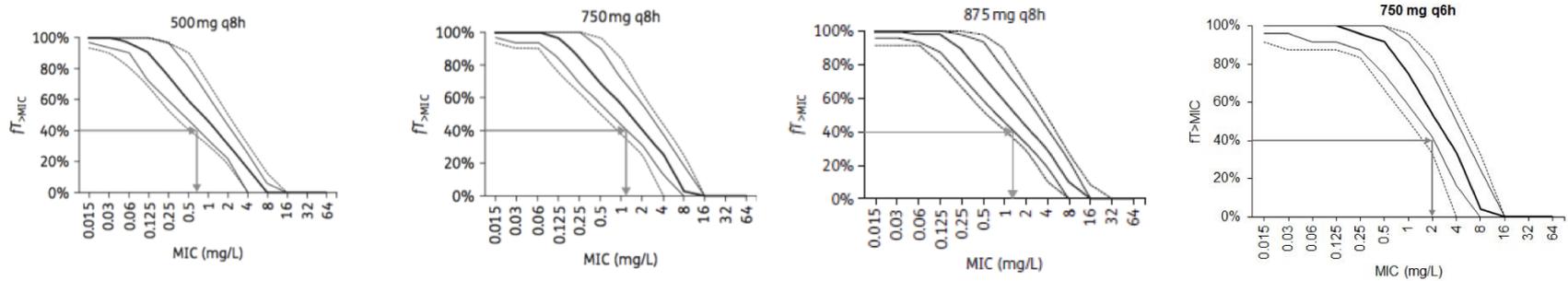
Penicillin	MIC breakpoints (mg/l)		
	S ≤	R >	ATU
<b>Ampicillin iv</b>	8	8	
<b>Ampicillin oral, uncomplicated UTI only</b>	8	8	
<b>Ampicillin-sulbactam iv</b>	8	8	
<b>Ampicillin-sulbactam oral, uncomplicated UTI only</b>	8	8	
<b>Amoxicillin iv</b>	8	8	
<b>Amoxicillin oral, complicated UTI</b>	<0.001	8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

Penicillin	MIC breakpoints (mg/l)		
	S ≤	R >	ATU
<b>Ampicillin</b>	8	8	
<b>Ampicillin-sulbactam</b>	8	8	
<b>Amoxicillin</b>	8	8	
<b>Amoxicillin-clavulanic acid</b>	8	8	
<b>Amoxicillin-clavulanic acid (uncomplicated UTI only)</b>	32	32	

# Aminopenicillins - *Enterobacterales*

Figure 1: Monte Carlo simulations for different oral doses of amoxicillin [3]



	<b>f%T&gt;MIC 40%</b>				<b>f%T&gt;MIC 50%</b>			
	<b>1 g x 3</b>	<b>1 g x 4</b>	<b>2 g x 3</b>	<b>2 g x 4</b>	<b>1 g x 3</b>	<b>1 g x 4</b>	<b>2 g x 3</b>	<b>2 g x 4</b>
<b>0.5</b>	100	100	100	100	100	100	100	100
<b>1</b>	100	100	100	100	100	100	100	100
<b>2</b>	100	100	100	100	99	100	100	100
<b>4</b>	98	100	100	100	61	100	99	100
<b>8</b>	33	98	98	100	1	56	60	100
<b>16</b>	0	6	34	98	0	0	0	57
<b>32</b>	0	0	0	7	0	0	0	0

I.V.

# Aminopenicillins - *Enterobacterales*

## Amoxicillin-clavulanic acid

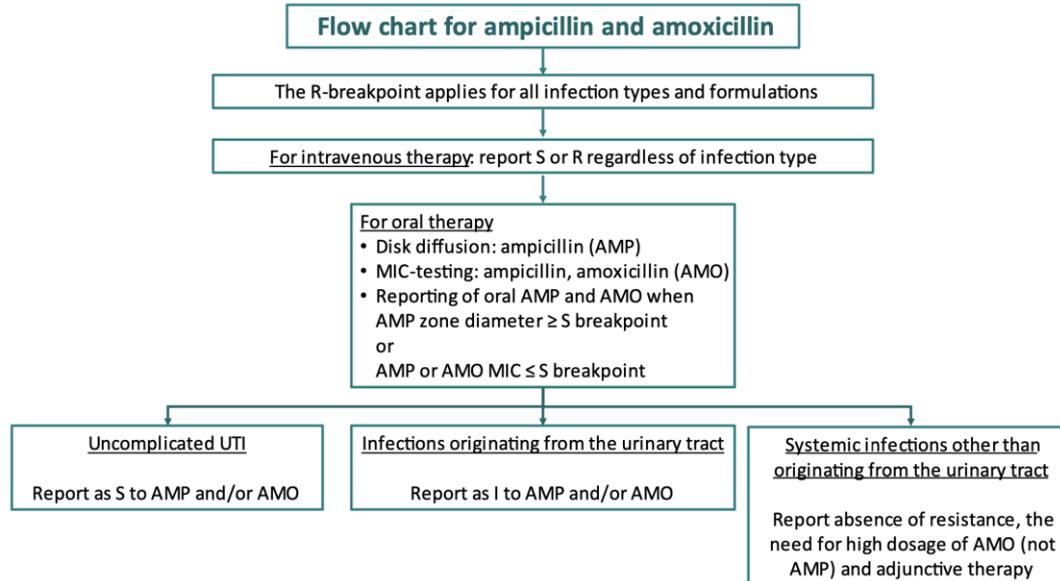
### Summaries of oral amoxicillin-clavulanic acid in non-UTI clinical trials

Infection type	Design	Outcome measure	Results	Interpretation
Drained dental abscess <sup>1</sup>	A/C + MTZ IV x 1-2 doses, then A/C 500 q 8 alone or combined with oral MTZ	Clinical cure	12/30 A/C patients had regimen changed b/c poor response; 6 MTZ added, 6 A/C changed to another drug	A/C alone failures
Drained/resected CIAI <sup>2</sup>	IV Pip/tazo vs. IV moxiflox x 3-5 d; followed by oral A/C 800q12 vs moxiflox x 5-14 d	Clinical and microbiologic	Overall no difference 80-90% cured. Moxi superior for HAI, in elderly and those with mild-mod illness. 656 patients	Unclear if A/C beneficial b/c initial IV Rx for 3-5 d (duration current guidelines)
Anaerobic lung abscess <sup>3</sup>	A/C 2g IV q8 x ~10 d, then oral <b>A/C 875-1 g q8</b> x ~30 d	clinical	All 35 patients had good outcomes. No Enterobacteriaceae. No MICs reported.	Possible role oral A/C at high dose after prolonged IV therapy
SSTI <sup>4</sup>	A/C 1g IV q8 x ~3d, then oral A/C 500 q8 x 7-21d vs. Moxi IV x 3d, then oral moxi	Clinical @ 2 wks	No differences ~80% cured. A/C arm 27 E. coli, 12 P. mirab, 5 E. cloacae, 8 P. aerug, 3 K. pneum. Most infect S. aureus. 210 each arm. No MICs reported	Possible role high dose A/C after IV therapy. Duration guidelines ~5 d. Assess not using current FDA guidance
Outpatient SSTI <sup>5</sup>	A/C 500 q8 vs. A/C 250 q8 vs. cefaclor 5-10 d	Clinical at EOT	No differences ~70% cured. Most S aureus 12 GNRs – all suscept; treatment arm unstated. 80 total pts. No MICs	A/C suitable outpatient cellulitis.

1. Br J Oral Max Fac Surg 53:18, 2. Ann Surg 244:204, 3. EJCMI 22:185, 4. Infect 37:407, 5. AAC 24:856

# Aminopenicillins - *Enterobacterales*

## Guidance on the Implementation of Revised Aminopenicillin Breakpoints for *Enterobacterales* January 2023



# Thank you for your attention!



Karolinska Institutet, South Campus



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