EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Amoxicillin	Rationale for the EUCAST clinical breakpoints, version 1.0	22nd November 2010

Foreword

EUCAST
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at http://www.EUCAST.org.

EUCAST rationale documents
EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST document
All EUCAST documents are freely available from the EUCAST website at http://www.EUCAST.org.

Citation of EUCAST documents
This rationale document should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Amoxicillin: Rationale for the clinical breakpoints, version 1.0, 2010. http://www.eucast.org.

Introduction

Amoxicillin is an aminopenicillin that is available for parenteral and oral use.

Amoxicillin is active against staphylococci, streptococci (including *Streptococcus pneumoniae* and alpha-haemolytic streptococci), *Enterococcus faecalis*, *Haemophilus influenzae, Neisseria* spp. and many anaerobic bacteria. It is less active against Enterobacteriaceae and has no clinically useful activity against *Pseudomonas* spp. or *Acinetobacter* spp. Due to the production of beta-lactamases, resistance to amoxicillin is common unless it is combined with a beta-lactamase inhibitor. Resistance to amoxicillin may also be conferred by changes in penicillin-binding proteins (PBPs), the mechanism of resistance in *S. pneumoniae.*

Amoxicillin is used for therapy of uncomplicated urinary tract infections, exacerbations of chronic bronchitis and otitis media. Amoxicillin in combination with aminoglycoside is used in the treatment of endocarditis caused by streptococci or enterococci. Other clinical indications are endocarditis prophylaxis, eradication of *H. pylori* and urogenital infections caused by *Neisseria gonorrhoeae*.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	250-500 mg x 3 oral 1 g x 3 iv	500 mg x 3 oral 1 g x 2 iv	500 mg-1 g x 3 oral 1 g x 3 – 4 iv	500 mg-1 g x 3 oral	500 mg x 3 oral	500 mg-1 g x 3 oral
Maximum dose schedule	2 g x 6 iv	3 g x 6 iv	2 g x 6 iv	2 g x 6 iv	1 g x 3-4	1 g x 3-4
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral	oral

2. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Anaerobic cocci Gram-positive	0	0	0	0	40	320	130	111	34	11	9	2	8	5	1	1	2	0	0	ND
Bacteroides fragilis	0	0	0	0	1	0	0	1	5	10	7	5	30	177	176	88	144	0	0	ND
Bacteroides fragilis group	0	0	0	0	0	8	11	53	63	44	29	17	98	352	380	102	411	0	0	ND
Bacteroides thetaiotaomicron	0	0	0	0	0	2	6	12	7	2	0	5	12	49	78	17	42	0	0	ND
Campylobacter coli	0	0	0	0	0	0	0	7	37	120	204	170	153	7	10	92	0	0	0	8
Campylobacter jejuni	0	0	0	0	0	0	0	1	1	17	27	89	135	19	40	72	0	0	0	16
Citrobacter spp	0	0	0	0	0	0	0	0	0	1	2	3	5	23	13	48	63	28	34	ND
Clostridium difficile	0	0	0	0	9	14	29	42	46	12	7	4	0	1	1	1	0	0	0	ND
Clostridium perfringens	0	0	0	0	25	70	11	2	4	1	1	1	0	0	0	0	0	0	0	ND
Enterobacter aerogenes	0	0	0	0	0	0	0	0	0	0	1	0	2	3	6	16	26	15	41	ND
Enterobacter agglomerans	0	0	0	0	0	0	0	0	0	1	3	38	23	12	9	14	16	8	0	ND
Enterobacter cloacae	0	0	0	0	0	0	0	0	0	1	3	12	13	27	62	99	147	95	365	ND
Enterobacter dissolvens	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	34	0	ND
Enterobacter spp	0	0	0	0	0	0	0	0	0	4	3	17	30	1	5	3	11	31	0	ND
Enterococcus faecium	0	0	0	0	0	16	55	148	292	258	993	453	28	7	14	0	0	0	0	ND
Escherichia coli	0	0	0	0	0	0	0	0	9	96	737	1670	669	42	11	692	600	58	693	8
Fusobacterium spp	0	0	0	0	25	123	9	10	4	4	4	4	3	2	5	1	1	0	0	ND
Haemophilus influenzae	0	0	0	0	9	36	296	2614	6491	1573	702	266	272	429	542	192	46	8	1	1
Haemophilus parainfluenzae	0	0	0	0	0	0	63	148	133	21	8	3	5	7	28	0	0	0	0	1
Helicobacter pylori	0	0	0	2392	652	616	192	43	13	1	3	0	0	0	0	0	0	0	0	0.125
Klebsiella oxytoca	0	0	0	0	0	0	0	0	0	1	0	1	0	6	16	63	102	42	60	ND
Klebsiella pneumoniae	0	0	0	0	0	0	0	1	0	1	4	4	1	3	54	178	312	142	248	ND
Legionella pneumophila	0	0	0	0	0	0	1	3	18	20	25	16	12	2	3	0	0	0	0	ND
Mannheimia haemolytica	0	0	0	3	1	8	22	26	3	0	0	0	3	9	24	13	0	0	0	0.5
Moraxella catarrhalis	2	0	21	80	12	17	30	8	62	34	95	136	236	319	267	159	41	16	1	0.125
Morganella morganii	0	0	0	0	0	0	0	0	2	1	3	1	2	8	14	26	33	29	11	8
Pasteurella multocida	0	0	0	5	10	23	38	25	2	0	0	1	1	1	0	9	0	0	0	0.5

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Porphyromonas spp	0	0	0	0	1	47	5	3	1	2	0	0	0	1	0	0	0	0	0	ND
Prevotella spp	0	0	0	0	8	112	20	12	8	9	12	9	20	40	26	8	50	0	0	ND
Propionibacterium acnes	0	0	0	0	7	93	9	19	12	1	4	2	1	0	0	0	0	0	0	ND
Proteus mirabilis	0	0	0	0	0	0	0	13	228	49	5	50	2	4	18	17	5	13	107	2
Salmonella spp	0	0	0	0	0	0	0	6	2418	5791	207	6	4	2	14	1148	553	0	0	4
Serratia liquefaciens	0	0	0	0	0	0	0	0	0	0	1	2	6	6	4	2	2	0	0	ND
Serratia spp	0	0	0	0	0	0	0	0	0	0	1	5	8	9	7	45	24	13	49	ND
Streptococcus agalactiae	0	0	0	9	54	228	15	0	0	0	0	0	0	0	0	0	0	0	0	0.25
Streptococcus anginosus	0	0	0	2	4	25	27	8	0	1	0	0	0	0	0	0	0	0	0	0.25
Streptococcus group G	0	0	33	138	10	5	1	1	0	0	0	0	0	0	0	0	0	0	0	0.064
Streptococcus oralis	0	0	4	41	62	26	23	12	9	6	5	5	0	3	0	0	0	0	0	0.125
Streptococcus pneumoniae	2	150	1471	2528	272	122	118	53	117	289	47	14	5	0	0	0	0	0	0	0.064
Streptococcus pyogenes	0	3	130	224	7	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0.064
Streptococcus viridans group	0	0	4	26	54	81	81	38	21	17	10	2	0	1	0	0	0	0	0	ND

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

3. Breakpoints prior[1] to harmonisation (mg/L) S≤ R>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI[2]
General breakpoint							
		4/16	2/16	2/8		2/8	
Species specific breakpoints:							
Enterobacteriaceae	8/16	4/16			0.5/8	1/8 (*E. coli* I) 2/16 (*P. mirabils* S)	
Pseudomonas spp.							
Acinetobacter spp.	8/16						
Staphylococcus spp.						0.5/0.5 *S. saprophyticus*	
Streptococcus spp.		0.5/16			0.25/-	0.25/1	
Alpha haemolytic streptococci	1/1	0.5/16			0.25/4 *S. viridans*		
Streptococcus pneumoniae		0.5/2			0.5/2	0.064/1	2/4 non-meningitis
Enterococcus spp.					2/8	2/8	
Haemophilus influenzae	1/1		1/2		1/4	0.5/0.5	
Moraxella catarrhalis	1/1		1/2		1/4	0.5/0.5	
Corynebacteria							
Neisseria meningitidis		0.25/2			0.25/2		
Neisseria gonorrhoeae		0.25/2			0.25/2	0.12/2	
Pasteurella multocida						0.5/0.5	
Anaerobes, Gram-positive		4/16					
Anaerobes, Gram-negative		4/16					
Campylobacter spp.							
Helicobacter pylori	1/1				0.5/0.5	0.5/1	

[1]2005
[2]CLSI breakpoints converted to EUCAST terminology.

4. Pharmacokinetics

Dosage (mg)	500 x 1 oral	500 x 1 iv	1000 x 1 iv		
Bioavailability	80-85		142.7		
Cmax (mg/L)	5.9-10.8	62.5	0		
Cmin (mg/L) 6 hr		≤0.5	0.8		
Total body clearance (L/g/h)	0.2-0.3	0.2-0.3	0.2-0.3		
T ½ (h), mean (range)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1		
AUC24h (mg.h/L)	53.4 ± 8.9	-	-		
Fraction unbound (%)	80-83	80-83	80-83		
Volume of distribution (L/kG)	0.3-0.4	0.46	0.49		
Comments	• Pharmacokinetics are based on single doses. • Dosing across Europe for iv amoxicillin varies from 500 mg x 3 (1.5g/day) to 2g x 6 (12g/day). • Two values are given where references differ. Cells are left empty when data are not readily available.				
References	• Spyker et al. Antimicrob Agents Chemother 1977: 11; 132-141 • Todd, Benfield. Drugs 1990: 39; 264-307 • Bryskier. Penicillins. In Antimicrobial Agents 2005; pp113-162, Tables 37 and 47				

5. Pharmacodynamics

	Enterobacteriaceae	*Streptococcus pneumoniae*	*Haemophilus influenzae*		
*%f*T>MIC for stasis : exp	30 – 35	25 – 35	25 – 35		
*%f*T>MIC for 2 log drop : exp		35 – 45	35 - 45		
*%f*T>MIC from clinical data		40	40		
Comments	• Cells are left empty when data are not readily available.				
References	• Gerber AU et al. *J Infect Disease* 1986; 153: 90-97 • Craig WA et al. 33rd ICAAC 1993; Abstract 86 • Craig WA. In Antimicrobial Pharmacodynamics Theory and Clinical Practice 2002. Eds. C Nightingale, TT Murakawa, PG Ambrose. Marcel Dekker Inc, Basel: 1-22 • MacGowan AP. *Clin Microbiol Infect* 2004: 52: 6-11				

6. Monte Carlo simulations and PK/PD Breakpoints

The following iv amoxicillin pharmacokinetics were modelled:
Volume of distribution 18L ± 5
Serum half life 1.1±0.1h
Fraction unbound 80%.

Doses modelled were those commonly reported to be employed across Europe, namely 500 mg x 3; 750 mg x 3; 750 mg x 4; 1 g x 3; 1 g x 4; 2 g x 4 iv. The most common doses were 500 mg x 3 and 1g x 3 iv.

A fT>MIC target of 30-40% was used. For a >90% target attainment rate, pharmacodynamic breakpoints range from 2-16mg/L for all doses and 2-4 mg/L for the two most common doses.

Target Attainment Rate (%)												
Dose	500 mg x 3		750 mg x 3		750 mg x 4		1g x 3		1g x 4		2g x 4	
T>MIC(%)	30	40	30	40	30	40	30	40	30	40	30	40
MIC(mg/L)												
0.5	100	100	100	100	-	-	-	-	-	-	-	
1	100	100	100	100	100	100	100	100	-	-	-	-
2	100	90	100	99	100	100	100	100	100	100	-	-
4	75	20	98	63	100	99	100	90	100	100	100	100
8	8	1	39	6	86	39	75	20	99	75	100	100
16	0	0	2	0	11	2	8	0	34	8	99	75
32	0	0	0	0	0	0	0	0	2	0	34	8

7. Clinical data

The bacteriological and clinical efficacy of amoxicillin has been evaluated in several trials involving patients with acute bacterial sinusitis, acute otitis media, skin and skin structure infections, and community-acquired pneumonia. These trials support the efficacy of amoxicillin for treatment of respiratory tract infections. Clinical experience also indicates that amoxicillin is effective in treatment of uncomplicated urinary tract infection caused by wild type organisms and in treatment of uro-genital infections caused by wild type *N. gonorrhoeae*. Amoxicillin is also used for eradication of *H. pylori* in combination therapy.

- Addo-Yobo E et al. *Lancet* 2004; 364:1141-8
- Ball P. *Int J Antimicrob Agents* 2007 ;30 Suppl 2: S113-7
- Qasim A et al. *Fundam Clin Pharmacol* 2009; 23: 43-52
- Brocklehurst P. *Cochrane Database Syst Rev* 2002; 2: CD000098
- Shanson D. *Curr Opin Infect Dis*. 2008; 21:191-9

8. Clinical breakpoints

Non-species-related breakpoints	Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. A fT>MIC target of 30-40% and a >90% target attainment rate results in breakpoints ranging from 2-16mg/L for the range of doses used in Europe. The most common dose of 500 mg x 3 results in an S breakpoint of 2 mg/L. The R breakpoint of 8 mg/L is based on a 1g dose.
Species-related breakpoints	For Enterobacteriaceae breakpoints are S - / R >8 mg/L. The R breakpoint is >8 mg/L but an S breakpoint is not defined because dosing traditions vary considerably in Europe and the clinical efficacy is dependent on the dose and infection type. For *Enterococcus* spp. breakpoints are S ≤4 / R >8 mg/L. The S breakpoint was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution. For streptococci other than Groups A, B, C, G breakpoints are S ≤0.5 / R >2 mg/L. The S breakpoint is essentially an epidemiological cut-off and the R breakpoint was reduced to 2 mg/L since clinical outcome is uncertain in patients infected with strains with MICs greater than 2 mg/L. For *H. influenzae* breakpoints are S ≤1 / R >1 mg/L. The breakpoints are essentially epidemiological cut-off values. For *M. catarrhalis* breakpoints are S ≤1 / R >1 mg/L (currently under review). For *Neisseria meningitidis* breakpoints are S ≤0.12 / R >1 mg/L. The S breakpoint is essentially an epidemiological cut-off and the R breakpoint was reduced to 1 mg/L to meet international consensus. For Gram-negative anaerobes breakpoints are S ≤0.5 / R >2 mg/L. The S breakpoint was reduced to 0.5 mg/L to avoid reporting beta-lactamase-producing *Prevotella* spp. as susceptible. The R breakpoint was reduced to 2 mg/L to ensure that all beta-lactamase-producing *B. fragilis* are reported resistant. For Gram-positive anaerobe breakpoints are S ≤4 / R >8 mg/L. The S breakpoint was increased from 2 to 4 mg/L to avoid dividing wild type MIC distributions.

Species without breakpoints	Staphylococci are commonly resistant to amoxicillin because they are penicillinase-producers. Isolates susceptible to benzylpenicillin will be susceptible to amoxicillin. Isolates resistant to oxacillin or cefoxitin will be resistant to amoxicillin. For streptococcus Groups A, B, C, G and *N. gonorrhoeae* the susceptibility to amoxicillin is inferred from the benzylpenicillin susceptibility. For *S. pneumoniae* susceptibility is inferred from benzylpenicillin and ampicillin susceptibility (report susceptible if susceptible in oxacillin screen test, otherwise use ampicillin to categorize susceptibility to amoxicillin). *Pseudomonas* spp. and *Acinetobacter* spp. were considered poor targets for amoxicillin therapy and for that reason did not receive breakpoints.
Clinical qualifications	
Dosage	Dosing across Europe for iv amoxicillin varies from 500 mg x 3 (1.5g/day) to 2g x6 (12g/day). The non-species-related breakpoints are based on doses of at least 0.5 g x 3-4 (1.5-2 g/day).
Additional comment	

9. EUCAST clinical MIC breakpoints

These can be found at **http://www.eucast.org**

10. Exceptions noted for individual national committees

None