



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Metronidazole	Rationale for the EUCAST clinical breakpoints, version 1.0	11th January 2010
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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. Metronidazole: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Metronidazole is an imidazole agent, available for oral and parenteral use. It is also available in the form of suppositories.

Apart from its anti-parasitic activity it is with some exceptions, active only against obligate anaerobic bacteria. Its activity against Gram-positive anaerobes such as *Propionibacterium* spp. and *Actinomyces* spp. is less pronounced and is variable. Metronidazole also appears active against *Helicobacter pylori*. Against susceptible organisms metronidazole is bactericidal. In order to be active metronidazole must be taken up by the bacterial cell and reduced intracellularly. Resistance in most anaerobic organisms is rare and occurs in specific species such as *Anaerobiospirillum succiniproducens*. Resistance mechanisms include altered permeability, and reduction of the activity of the metronidazole-modifying enzyme.

Metronidazole is widely used in the treatment of anaerobic, parasitic and *H. pylori* infections. EUCAST breakpoints have been set for Gram-positive and Gram-negative anaerobic bacteria and *H. pylori*.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	400mg x 3 oral 500mg x 3 iv	500 mg x 3 oral 500 mg x 3 iv	500 mg x 3 oral 500 mg x 3 iv	500mg x 3 oral 500mg x 3 iv	200-400 mg x 3 oral 1 g x 1 iv	400 mg x 3 oral 1 g x 1 iv
Maximum dose schedule	500mg x 3 iv	500 mg x 4 oral 500 mg x 4 iv	500 mg x 3 oral 500 mg x 3 iv	500mg x 4 oral 500mg x 4 iv	1,5 g day 1 and then 1 g x 1 iv	1,5 g day 1 and then 1 g x 1 iv
Available formulations	Iv, oral, rectal	Iv, oral	Iv, oral	Iv, oral, rectal	iv, oral, rectal	Iv, oral, rectal

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

	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	1	32	23	110	64	33	14	3	1	0	2	11	7	0	0	ND
<i>Bacteroides fragilis</i>	0	0	0	0	20	14	36	123	345	747	298	65	17	12	2	2	0	1	0	4
<i>Bacteroides fragilis</i> group	0	0	0	1	30	35	102	241	613	1411	531	120	34	19	2	12	4	0	0	4
<i>Bacteroides thetaiotaomicron</i>	0	0	0	0	5	1	5	16	66	79	11	8	3	0	0	0	0	0	0	ND
<i>Campylobacter coli</i>	0	0	0	0	0	0	0	0	15	55	33	14	12	19	34	15	1	0	0	ND
<i>Campylobacter jejuni</i>	0	0	0	0	0	0	0	0	3	19	1	1	2	5	4	10	12	0	0	ND
<i>Clostridium difficile</i>	0	0	0	2	49	282	494	358	180	28	19	1	0	0	0	0	0	0	0	1
<i>Clostridium</i> spp	0	0	0	1	4	15	21	31	49	14	8	1	1	0	0	0	0	0	0	1
<i>Fusobacterium</i> spp	0	0	0	0	17	80	22	17	16	6	4	2	2	0	0	0	0	0	0	ND
<i>Helicobacter pylori</i>	0	0	0	7	21	53	83	97	619	1390	1570	251	77	58	66	71	23	221	122	4
<i>Prevotella</i> spp	0	0	0	7	21	172	69	75	157	104	64	19	7	30	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 (IE) no epidemiological cut-off has been determined.

3. Breakpoints prior to harmonisation (mg/L) S ≤ R >							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoint							
Species specific breakpoints:							
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							
<i>Streptococcus</i> spp.							
Alpha haemolytic streptococci							
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive	8/8	4/16		4/4	4/8	4/4	8/16
Anaerobes, Gram-negative	8/8	4/16		4/4	4/8	4/4	8/16
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>			8/8		4/4	4/4	

4. Pharmacokinetics				
Dosage (mg)	400 mg oral	500mg oral	500mg iv	1000mg iv
Bioavailability	>80%	>80%		
Cmax (mg/L)	10	13	13-22	25
Cmin (mg/L)			10 (at 8h)	
Total body clearance (L/h)				
T ½ (h), mean (range)	8	7	7-8	9
AUC24h (mg.h/L)			120	227
Fraction unbound (%)	>80	85	85	
Volume of distribution (L/kg)	0.7	0.6-0.85	0.6-0.85	
Comments	<ul style="list-style-type: none"> Two values are given where references differ. Cells are left empty when data are not readily available. 			
References	<ul style="list-style-type: none"> Lau AH et al. Clin Pharmacokinet 1992; 23: 328-64 Mattila J et al. Antimicrob Ag Chemother 1983; 23: 721-5 Sprandel KA et al. Antimicrob Ag Chemother 2004; 48:4597-605 Sprandel KA et al. Diagn Microbiol Infect Dis 2006; 55:303-9 Dubreuil L. In Antimicrobial Agents 2005; Ed Bryskier A, ASM Press: 930-940 			

5. Pharmacodynamics				
%fAUC/MIC for stasis				
%fAUC/MIC for 2 log drop				
%fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> • Pharmacodynamic parameters are not available but investigations suggest that the activity of metronidazole is concentration dependent. • Cells are left empty when data are not readily available. 			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

Not available.

7. Clinical data

The bacteriological and clinical efficacy of metronidazole has been evaluated in several trials involving patients with mixed infections with facultative and obligate anaerobic infections. These data support the efficacy of metronidazole in combination therapy for treatment of infections involving obligate anaerobes with wild type susceptibility to metronidazole. Metronidazole has also been shown to be effective in the treatment of *Clostridium difficile*-associated disease caused by strains with wild type susceptibility. It is also effective in combination with other antimicrobial agents and a proton pump inhibitor for the eradication of *H. pylori*.

8. Clinical breakpoints

Non-species-related breakpoints	In the absence of pharmacodynamic data, no non-species-related breakpoints can be given.
Species-related breakpoints	Breakpoints were based on Pk data, microbiological data and clinical experience. 4/4 mg/L for Gram-positive and Gram-negative anaerobes. 4/4 for <i>H. pylori</i> .
Species without breakpoints	All bacterial groups other than anaerobes and <i>H. pylori</i> are inappropriate targets for metronidazole.
Clinical qualifications	Metronidazole is most commonly used in combination treatment of infections caused by mixtures of facultative and obligate anaerobes. Metronidazole may also be used for the eradication of <i>H. pylori</i> .
Dosage	Breakpoints apply to a metronidazole dosage of 400-500mg x 3 oral or iv.
Additional comment	

9. Metronidazole - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None