



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Trimethoprim

Rationale for the EUCAST clinical breakpoints, version 1.0

26th September 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. Trimethoprim: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Trimethoprim is a synthetic diaminopyrimidine agent.

Trimethoprim is a competitive inhibitor of dihydrofolate reductase (DHFR). It is active against most species of Enterobacteriaceae, aerobic Gram-positive organisms and *Haemophilus influenzae*. Resistance may be conferred by a wide variety of *dhfr*-genes encoding dihydrofolate reductase enzymes that have markedly reduced affinity for trimethoprim. In Enterobacteriaceae, these genes are mainly spread horizontally, are usually located on integrons and associated resistance to ampicillin and fluoroquinolones is very common. Resistance may also be conferred by chromosomal mutations resulting in over-production or modification of the DHFR or reduced permeability.

Trimethoprim shows synergistic activity with sulfonamides and combinations, particularly trimethoprim-sulfamethoxazole, are commonly used. Trimethoprim alone has been widely used in the oral treatment of uncomplicated urinary tract infections (UTI). Increasing resistance in Enterobacteriaceae during the last decade has, however, limited its use as empirical treatment. Breakpoints are given for bacteria causing uncomplicated UTI only.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	200mg x 2	-	300 mg x 1	150 mg x 2	160 mg x 2 or 300 mg x 1	160 mg x 2 or 300 mg x 1
Maximum dose schedule	200mg x 2	-	300 mg x 1	200 mg x 2	160 mg x 2	160 mg x 2 or 300 mg x 1
Available formulations	oral	-	Oral	oral	oral	oral

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
<i>Acinetobacter baumannii</i>	0	0	0	0	0	0	0	0	2	1	8	26	60	61	0	0	0	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	0	0	17	27	14	3	1	1	0	10	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	0	3	72	130	42	32	14	4	23	0	0	0	0	54	ND
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	10	278	617	308	76	38	28	103	0	0	0	0	64	ND
<i>Enterobacter spp</i>	0	0	0	0	0	0	0	140	308	118	37	27	11	25	0	0	0	0	80	ND
<i>Escherichia coli</i>	0	0	0	0	0	85	292	1645	2997	1111	170	67	24	214	476	716	190	6	205	2
<i>Haemophilus influenzae</i>	3	3	13	35	309	1362	2851	2140	280	78	22	24	41	170	354	418	239	17	16	0.5
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	10	49	54	18	2	1	0	17	0	0	0	0	0	ND
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	0	4	559	781	199	84	39	42	265	0	0	0	0	95	ND
<i>Listeria monocytogenes</i>	0	0	0	1	9	36	68	2	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Moraxella catarrhalis</i>	0	0	0	0	0	0	0	0	0	9	12	128	587	1001	225	121	34	2	4	ND
<i>Morganella morganii</i>	0	0	0	0	0	0	0	0	6	31	113	149	12	58	0	0	0	0	101	ND
<i>Proteus mirabilis</i>	0	0	0	0	0	0	3	24	110	476	408	198	38	646	0	0	0	0	126	ND
<i>Proteus vulgaris</i>	0	0	0	0	0	0	0	9	35	115	129	85	43	59	0	0	0	0	134	ND
<i>Salmonella spp</i>	0	0	0	0	0	0	4	2184	5914	616	180	124	146	3	15	99	750	0	0	2
<i>Serratia liquefaciens</i>	0	0	0	0	0	0	0	6	3	12	20	29	25	15	0	0	0	0	145	ND
<i>Serratia marcescens</i>	0	0	0	0	0	0	1	9	44	77	111	170	129	80	0	0	0	0	162	ND
<i>Serratia spp</i>	0	0	0	0	0	0	0	7	12	35	36	57	36	12	0	0	0	0	176	ND
<i>Staphylococcus aureus</i>	0	0	0	0	0	0	5	37	450	668	167	31	7	13	8	9	15	7	0	4
<i>Staphylococcus aureus</i> MRSA	0	0	0	0	0	0	0	119	43	7	3	2	8	7	7	1	1	7	0	ND
<i>Staphylococcus aureus</i> MSSA	0	0	0	0	0	0	0	112	140	20	2	0	0	1	1	0	0	7	0	ND
<i>Staphylococcus</i> coagulase negative	0	0	0	0	0	0	0	34	25	18	2	4	1	0	5	9	9	102	0	ND
<i>Staphylococcus</i> coagulase negative MRSE	0	0	0	0	0	0	0	25	10	4	4	3	0	0	8	7	7	160	0	ND
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	0	0	89	34	9	2	0	0	0	9	16	21	196	0	ND
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	0	1	5	6	5	1	0	0	0	1	2	45	0	ND
<i>Streptococcus anginosus</i>	0	0	0	0	0	0	0	1	2	1	0	0	0	0	0	0	0	14	0	ND

	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
<i>Streptococcus pneumoniae</i>	0	0	0	0	0	0	0	0	5	147	502	2336	1156	76	30	340	0	0	0	ND
<i>Streptococcus pyogenes</i>	0	1	4	36	132	386	324	68	7	0	1	0	0	0	3	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 to harmonisation (mg/L) S_≤ R_{>}							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints							
		4/8	1/2	2/4			
Species-related breakpoints							
Enterobacteriaceae	2/2 UTI 0.5/2 systemic	4/8			2/4	2/4	4/8
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	2/2 UTI 1/1 systemic	4/8			2/4	2/4	4/8
<i>Streptococcus</i> spp.	2/2					2/4	
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>	0.5/0.5 systemic						
<i>Moraxella catarrhalis</i>	0.5/0.5 systemic						
<i>Corynebacteria</i>							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

4. Pharmacokinetics				
Dosage (mg)	160 mg			
Cmax (mg/L)	2.3, 1.2-2.1			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	8-11, 5.5-9.3			
AUC24h (mg.h/L)				
Fraction unbound (%)	60-70			
Volume of distribution (L/kg)	1-2			
Comments	<ul style="list-style-type: none"> • Two values are given where references differ. Cells are left empty when data are not readily available. • Oral absorption >90%. Trimethoprim is eliminated mainly through glomerular filtration and tubular secretion and 40-50 % of an oral dose is found unchanged in the urine. This gives a urine concentration of 18-100 mg/L throughout 24 h (AUC approximately 500). Trimethoprim is widely distributed (in a dose proportional fashion) to tissues and body fluids. • Peak serum concentrations are achieved in 2-4h. 			
References	<ul style="list-style-type: none"> • Finch, Greenwood, Norrby and Whitley (eds). Antibiotic and chemotherapy 2001. Churchill Livingstone; 286-288 • Bryskier A. In Antimicrobial Agents 2005. ASM; 941-63 • Tegmark-Wisell K, Kahlmeter G, Giske CG. J Antimicrob Chemother. 2008; 62: 35-40 			

5. Pharmacodynamics				
fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not readily available. • It has not been established which pharmacodynamic parameter correlates best with antimicrobial effect 			
References	<ul style="list-style-type: none"> • Tegmark-Wisell K, Kahlmeter G, Giske CG. J Antimicrob Chemother. 2008; 62: 35-40 			

6. Monte Carlo simulations and Pk/Pd breakpoints

Not available.

7. Clinical data

There are some data (but not published clinical trials) indicating that the overall clinical efficacy of trimethoprim in the treatment or prophylaxis of UTI is comparable with nitrofurantoin (Brendstrup et al. *Acta Paediatr Scand* 1990; 79:1225-34, fosfomicin (Minassian MA et al. *Int Journal of Antimicrobial Agents* 1998, 10:39-47) and trimethoprim in combination with sulfamethoxazole (Brumfitt et al. *BMJ* 1972;2:673-676). The increasing resistance to trimethoprim in Enterobacteriaceae is, however, a clinical problem which now limits its use as empirical treatment in UTI. (MacNulty et al. *J Antimicrob Chemother* 2006; 58:1000-8).

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	<p>Breakpoints were based on Pk data, microbiological data and clinical experience.</p> <p>For Enterobacteriaceae and <i>Staphylococcus</i> spp. the breakpoints, which relate to UTI only, are 1/2 mg/L.</p> <p>For <i>Enterococcus</i> spp. the breakpoints, which relate to UTI only, are 0.03/1 mg/L. The activity of trimethoprim is uncertain against enterococci due to their ability to incorporate exogenously produced folates (which may be found in highly variable concentrations in the urine), so the wild type population is categorized as intermediate.</p>
Species without breakpoints	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., streptococci, <i>H. influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria gonorrhoeae</i> , <i>Neisseria meningitidis</i> and anaerobes were considered poor or inappropriate targets for trimethoprim therapy in UTI and for that reason did not receive breakpoints.
Clinical qualifications	Breakpoints are for uncomplicated UTI only.
Dosage	Breakpoints apply to an oral dose of 160 mg x 2 or 300 mg x 1 given in the treatment of UTI.
Additional comment	

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None