

Rationale for EUCAST clinical breakpoints

Agent	Trimethoprim-sulfamethoxazole	
Current version	1.0	5 June 2017
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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 www.eucast.org.

EUCAST rationale documents

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

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at www.eucast.org.

Citation of EUCAST documents

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Trimethoprim-sulfamethoxazole: Rationale for the clinical breakpoints, version 1.0 2015. <http://www.eucast.org>.

1. Introduction

Trimethoprim-sulfamethoxazole (co-trimoxazole) is a combination of trimethoprim, a synthetic diaminopyrimidine agent, and sulfamethoxazole, a sulphonamide agent. The combination is commonly synergistic against a wide range of organism including most aerobic Gram-positive organisms, Enterobacteriaceae, *Acinetobacter* spp. *Stenotrophomonas maltophilia*, *Haemophilus influenzae* (only trimethoprim has activity) and *Moraxella catarrhalis* (only sulfamethoxazole has activity). Co-trimoxazole has no clinically useful activity against *Pseudomonas aeruginosa* or anaerobic bacteria.

Trimethoprim inhibits bacterial dihydrofolate reductase (DHFR). Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase, competing with para-aminobenzoic acid. Thus, the two agents inhibit different steps in tetrahydrofolic acid synthesis and the sequential inhibition is the basis of the synergistic action. Resistance may be conferred by combinations of chromosomal mutations resulting in over-production or modification of the target enzymes or reduced permeability and/or efflux pumps, and different *dhfr*-genes encoding dihydrofolate reductase enzymes that are resistant to the agent. Resistance to sulfamethoxazole is conferred by sulphonamide resistance genes (*sul*), which act as competitive inhibitors of the enzyme dihydropteroate synthase, thereby blocking folate biosynthesis in the bacterial cell.

Trimethoprim-sulfamethoxazole is available as oral and iv preparations and has been used to treat a wide range of infections including urinary tract infections (UTI), respiratory infections and enteric infections. Trimethoprim-sulfamethoxazole is also used to treat infections caused by *Pneumocystis jiroveci* and *Tropheryma whippelii*.

Breakpoints for trimethoprim-sulfmethoxazole were set in 2006 but no rationale document was prepared at that time. This document relates to data available at the time breakpoints were originally set during the harmonisation process. No significant new data have been encountered while preparing this document.

2. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	160+800mg x 2	160+800 mg x 2	160+800 mg x 2	160+800 mg x 2	160+800 mg x 2	160+800 mg x 2
Maximum dose schedule	240+1200 x 2	160+800 mg x 2	320+1600 mg x 3	80+400 mg x 5	240+1200 mg x 2	1400+7000 mg/day
Available formulations	oral, iv	oral	oral, iv	oral, iv	oral, iv	oral, iv

¹Dosage given in the format trimethoprim+sulfamethoxazole

3. MIC distributions¹ 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
<i>Acinetobacter baumannii</i>	0	0	0	0	2	163	327	246	85	24	18	13	19	39	26	41	0	0	0	1
<i>Burkholderia cepacia</i>	0	0	0	0	0	0	0	4	4	2	5	2	0	0	0	0	0	0	0	ND
<i>Citrobacter braakii</i>	0	0	0	0	1	7	1	0	0	0	0	0	0	1	0	2	0	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	1	31	20	7	1	1	0	0	0	19	0	7	0	0	0	1
<i>Citrobacter koseri</i>	0	0	0	0	0	6	7	2	0	0	0	0	0	0	0	1	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	75	181	83	34	9	3	5	2	18	52	7	2	14	0	1
<i>Enterobacter cloacae</i>	0	0	0	0	4	542	1181	640	175	49	30	20	5	116	63	31	0	37	0	1
<i>Enterococcus faecium</i>	0	0	0	0	0	100	171	110	43	36	13	1	8	140	0	0	0	0	0	1
<i>Escherichia coli</i>	0	0	4	38	495	2311	1611	693	416	133	45	14	5	3	1343	601	0	0	0	1
<i>Haemophilus influenzae</i>	0	0	11	89	5553	7224	2731	1449	303	183	409	1537	1402	387	93	0	0	0	0	0.5
<i>Klebsiella oxytoca</i>	0	0	0	0	4	88	80	26	8	3	2	0	0	6	0	14	0	8	0	1
<i>Klebsiella pneumoniae</i>	0	0	0	2	19	884	1760	971	245	145	77	54	19	393	109	93	0	0	0	1
<i>Listeria monocytogenes</i>	2	0	68	52	0	0	4	2	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Mannheimia haemolytica</i>	0	0	4	5	17	24	38	17	7	6	1	8	15	4	1	0	0	0	0	ND
<i>Moraxella catarrhalis</i>	0	0	0	0	17	407	1827	1657	350	52	47	12	0	1	1	0	0	0	0	0.5
<i>Morganella morganii</i>	0	0	0	0	0	45	306	431	39	18	5	11	5	123	100	11	3	8	0	1
<i>Neisseria gonorrhoeae</i>	0	0	0	1	0	0	2	2	17	24	30	49	27	8	7	0	0	0	0	ND
<i>Neisseria meningitidis</i>	0	0	0	0	57	67	7	2	25	35	80	22	5	0	0	0	0	0	0	ND
<i>Pasteurella multocida</i>	0	0	1	2	9	16	67	11	23	22	7	1	1	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	0	0	1	361	1062	419	102	120	88	85	26	831	124	56	41	22	0	1
	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>Proteus vulgaris</i>	0	0	0	0	0	127	234	94	18	5	5	9	4	40	132	2	0	0	0	1
<i>Pseudomonas aeruginosa</i>	0	0	0	0	2	4	3	1	3	13	39	109	94	43	21	106	0	0	0	ND
<i>Salmonella enterica</i>	0	0	0	0	10	124	145	780	355	81	25	14	12	11	73	112	0	0	0	1
<i>Serratia liquefaciens</i>	0	0	0	0	0	10	34	63	41	8	3	6	1	8	143	2	0	0	0	1
<i>Serratia marcescens</i>	0	0	0	0	0	33	96	385	522	93	35	39	15	58	161	3	14	91	0	1

<i>Staphylococcus aureus</i>	0	0	0	1	84	1530	904	285	110	83	81	11	18	1	0	0	0	0	0.5
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	145	338	202	42	13	45	140	283	202	0	0	0	0	0.5
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	34	176	249	449	463	298	152	84	34	66	152	11	18	2	2
<i>Streptococcus pneumoniae</i>	0	2	1	6	22	161	2720	14060	4177	2718	1125	2412	2879	818	848	3	0	0	1
<i>Streptococcus pyogenes</i>	0	0	0	5	115	603	1031	550	201	54	14	6	1	0	10	6	0	0	0.5
<i>Yersinia enterocolitica</i>	0	0	0	0	0	102	46	23	6	1	0	0	0	0	0	0	0	0	0

¹The 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. Some combined distributions may include distributions truncated at concentrations below 512 mg/L. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

4. Breakpoints prior to harmonisation (mg/L) S ≤ R >							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoint							
	-	2/8	1/2	2/4	-	-	-
Enterobacteriaceae	2/2	2/8			2/8	2/4	2/4
<i>Pseudomonas</i> spp.							
<i>Stenotrophomonas maltophilia</i>	2/2	2/8				4/4	2/4
<i>Acinetobacter</i> spp.		2/8				2/8	
<i>Staphylococcus</i> spp.	2/2	2/8			2/8	2/8	0.5/4
<i>Streptococcus</i> spp.	2/2	2/8			0.5/2	1/2	
Viridans group streptococci	2/2	2/8			0.5/2	1/2	
<i>Streptococcus pneumoniae</i>	2/2	2/8			0.5/2	1/2	0.5/2
<i>Enterococcus</i> spp.	2/2	2/8					
<i>Haemophilus influenzae</i>	2/2	0.5/1			0.5/2	0.5/1	0.5/2
<i>Moraxella catarrhalis</i>	2/2				1/2	0.5/1	0.5/2
<i>Corynebacterium</i> spp.							
<i>Neisseria meningitidis</i>							0.12/0.5
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

¹ Breakpoints are based on the trimethoprim concentration in a 1:19 ratio of trimethoprim:sulfamethoxazole.

5. Pharmacokinetics				
Dosage	160 : 800 mg oral			
C _{max} (mg/L)	1-2 : 20-40			
C _{min} (mg/L)				
Total body clearance (L/h)				
T _½ (h), mean (range)	7-11 : 9-10			
AUC _{24h} (mg.h/L)	31 (trimethoprim)			
AUC _{0-12h,ss} (mg.h/L)				
AUC _∞ (mg.h/L)				
Fraction unbound (%)	55 : 30			
Volume of distribution (L/kg)	1-2 : 0.2-1.2			
Comments	<ul style="list-style-type: none"> • Values given are for trimethoprim:sulfamethoxazole • Two values are given where references differ. Cells are left empty when data are not readily available. 			
References	<ul style="list-style-type: none"> • Veyssier P. et al. In <i>Antimicrobial Agents</i>. Ed. Bryskier A. ASM 2005, pp 953-956. • Swedberg G et al. In <i>Antibiotic and chemotherapy</i>. Ed Finch, Greenwood, Norrby and Whitley. Churchill Livingstone 2001, pp 250-258. • Tegmark-Wisell K. J Antimicrob Chemother. 2008;62(1):35-40 			

6. Pharmacodynamics	
Comments	<ul style="list-style-type: none"> It has not been established which pharmacodynamic parameter correlates best with antimicrobial effect.
References	<ul style="list-style-type: none"> Tegmark-Wisell K et al. <i>J Antimicrob Chemother.</i> 2008; 62: 35-40

7. Monte Carlo simulations and PK/PD breakpoints

Not available.

8. Clinical data

Trimethoprim-sulfamethoxazole has been used successfully in the treatment of urinary tract infection, intra-abdominal infection, wound infection and respiratory tract (including *Pneumocystis jiroveci* and *Nocardia* spp.) infection caused by wild type organisms. Trimethoprim-sulfamethoxazole is the only agent for which there is clinical documentation of efficacy for the treatment of *S. maltophilia*. The agent is also use for treatment of *Tropheryma whipplei*.

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9. Clinical breakpoints

PK/PD breakpoints	There is insufficient evidence to set PK/PD breakpoints.			
Species-related breakpoints	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
				Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. Breakpoints are expressed as the trimethoprim concentration in the trimethoprim:sulfamethoxazole mixture at a ratio of 1:19.
	Enterobacteriaceae	2	4	
	<i>Pseudomonas</i> spp.	-	-	(1) These organisms were considered poor targets for therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints.
	<i>Stenotrophomonas maltophilia</i>	4	4	Breakpoints are based on high dose therapy.
	<i>Acinetobacter</i> spp.	2	4	Breakpoints were based on PK data, microbiological data and clinical experience.
	<i>Staphylococcus</i> spp.	2	4	
	<i>Enterococcus</i> spp.	0.03	1	The activity of trimethoprim-sulfamethoxazole is uncertain against enterococci so the wild type population is categorized as intermediate.
	Streptococcus groups A,B,C,G	2	2	
	<i>Streptococcus pneumoniae</i>	2	4	
	Viridans group streptococci	-	-	(1)
	<i>Haemophilus influenzae</i>	0.5	1	
	<i>Moraxella catarrhalis</i>	0.5	1	
	<i>Neisseria gonorrhoeae</i>	-	-	(1)
	<i>Neisseria meningitidis</i>	-	-	(1)
	Anaerobes, Gram-positive	-	-	(1)
	<i>Clostridium difficile</i>	-	-	(1)
	Anaerobes, Gram-negative	-	-	(1)
	<i>Helicobacter pylori</i>	-	-	(1)
	<i>Listeria monocytogenes</i>	0.06	0.06	
	<i>Pasteurella multocida</i>	0.25	0.25	
	<i>Campylobacter</i> spp.	-	-	(1)
	<i>Corynebacterium</i> spp.	-	-	(1)

Clinical qualifications	
Dosage	Breakpoints apply to an oral dose of trimethoprim:sulfamethoxazole 160: 800 mg x 2 to 320:1600 mg x 2.
Additional comment	<p>Dosage of trimethoprim:sulfamethoxazole in the ratio 1:5 results in serum concentrations in the approximate ratio of 1:19. Hence in vitro testing and breakpoints are based on the 1:19 ratio.</p> <p>Further information on susceptibility testing of <i>S. maltophilia</i> is given in a EUCAST guidance note (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/S_maltophilia_EUCAST_guidance_note_20120201.pdf)</p>

10. Exceptions noted for individual national committees
None.