Tetracycline	Rationale for the EUCAST clinical breakpoints, version 1.0	20th November 2009

Introduction

The natural tetracyclines, including tetracycline, chlortetracycline, oxytetracycline and demethylchlortetracycline are derived from *Streptomyces* spp. They have broad spectrum activity against many aerobic and anaerobic Gram-positive and Gram-negative bacteria.

Tetracyclines are bacteriostatic and inhibit protein synthesis by binding to the 30S ribosomal subunit. Resistance may be mediated by efflux, ribosomal protection and ribosomal modification. In *Bacteroides* spp. an inactivation mechanism has been described.

Tetracycline use is limited by poor absorption, resistance and the availability of more active and better tolerated alternatives. Tetracyclines have a wide range of potential clinical indications such as infections caused by chlamydiae, mycoplasmas and rickettsiae, and as alternative agents for respiratory tract and sexually transmitted infections, acne vulgaris, skin and skin structure infection and pelvic inflammatory disease. They are also used for treatment of brucellosis and infections with *Yersinia* spp., *Burkholderia pseudomallei* and *Leptospira* spp.

Tetracycline is available for oral administration.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	250 mg x 4	250 mg x 4	250 mg x 4	250 mg x 4	250 mg x 4	250 mg x 4
Maximum dose schedule	500 mg x 4	500 mg x 4	500 mg x 4	500 mg x 4	250 mg x 4	500 mg x 4
Available formulations	Oral	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
Acinetobacter spp	0	0	0	0	0	0	0	0	7	21	62	47	13	5	2	0	2	16	0	8
Campylobacter coli	0	0	0	0	0	1	9	41	191	56	17	11	24	36	164	184	288	258	0	2
Campylobacter jejuni	0	0	0	0	0	1	20	391	72	66	51	15	17	19	180	26	72	55	22	2
Citrobacter spp	0	0	0	0	0	0	0	0	10	90	118	13	24	1	0	2	19	3	0	8
Clostridium difficile	0	0	0	0	291	154	36	2	3	8	12	20	26	7	18	4	2	25	0	ND
Enterobacter aerogenes	0	0	0	0	0	0	0	0	0	0	10	4	7	0	0	0	0	1	0	8
Enterobacter aerogenes	0	0	0	0	0	0	0	0	0	0	24	12	0	0	0	0	0	2	0	8
Enterobacter agglomerans	0	0	0	0	0	0	0	0	56	107	13	5	1	0	0	0	0	0	0	ND
Enterobacter cloacae	0	0	0	0	0	0	0	0	0	3	50	71	31	3	3	2	1	5	0	8
Enterobacter cloacae	0	0	0	0	0	0	0	0	1	23	211	148	21	8	9	6	5	17	0	8
Enterobacter dissolvens	0	0	0	0	0	0	0	0	0	3	39	33	4	2	0	0	0	0	0	ND
Enterobacter spp	0	0	0	0	0	0	0	0	3	60	62	69	15	2	0	0	4	1	0	ND
Enterococcus faecalis	0	0	0	0	0	0	1	16	150	327	60	9	9	88	259	697	173	20	0	2
Enterococcus faecium	0	0	0	0	0	0	0	94	308	469	100	18	16	45	93	193	129	103	0	2
Enterococcus hirae	0	0	0	0	0	0	0	1	125	263	125	5	0	2	10	34	3	0	0	2
Enterococcus spp	0	0	0	0	0	0	0	21	14	1	0	2	0	2	6	10	11	1	0	2
Escherichia coli	0	0	0	0	0	0	0	1	55	1438	3670	1236	139	60	50	812	1013	778	0	8
Haemophilus influenzae	0	0	0	0	0	21	441	3514	27612	4327	329	189	340	271	58	3	1	1	0	1
Haemophilus parainfluenzae	0	0	0	0	0	0	38	100	200	41	3	9	14	9	2	0	0	0	0	1
Hafnia alvei	0	0	0	0	0	0	0	0	0	2	5	28	20	1	0	0	0	0	0	ND
Helicobacter pylori	0	0	0	4	26	85	157	86	46	10	1	0	0	0	0	0	0	0	0	1
Klebsiella oxytoca	0	0	0	0	0	0	0	0	21	156	38	10	7	0	2	0	6	5	0	8
Klebsiella pneumoniae	0	0	0	0	0	0	0	0	11	158	342	95	30	26	7	1	25	61	0	8
Klebsiella spp	0	0	0	0	0	0	0	0	1	2	11	9	1	3	0	0	0	2	0	ND
Kluyvera spp	0	0	0	0	0	0	0	0	1	17	14	7	0	1	0	0	2	0	0	ND
Listeria monocytogenes	0	0	0	0	0	2	6	20	76	12	0	0	0	0	0	0	0	0	0	1
Mannheimia haemolytica	0	0	0	0	0	0	0	3	29	23	1	1	2	16	58	11	4	0	0	2

	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
Moraxella catarrhalis	0	0	0	0	0	2	170	3872	3171	807	256	114	36	19	26	1	1	0	0	1
Morganella morganii	0	0	0	0	0	0	0	0	0	9	14	17	4	3	8	5	10	1	0	ND
Neisseria gonorrhoeae	0	0	0	1	2	10	101	94	197	162	161	46	57	101	77	76	56	17	8	ND
Neisseria meningitidis	0	0	0	0	0	0	0	1	27	28	0	0	0	0	0	0	0	0	0	ND
Pasteurella multocida	0	0	0	0	0	0	1	9	42	41	15	3	12	38	13	7	1	0	0	2
Proteus mirabilis	0	0	0	0	0	0	0	0	0	5	2	1	0	34	355	125	24	20	0	128
Proteus spp	0	0	0	0	0	0	0	0	0	3	13	3	2	8	4	2	0	15	0	ND
Raoultella spp	0	0	0	0	0	0	0	0	3	29	9	3	1	0	0	1	3	0	0	ND
Salmonella spp	0	0	0	0	0	0	0	1	126	672	4972	731	36	26	335	601	273	0	0	8
Serratia liquefaciens	0	0	0	0	0	0	0	0	0	3	8	31	23	2	0	1	0	0	0	ND
Serratia spp	0	0	0	0	0	0	0	0	0	0	2	8	82	13	6	13	13	3	0	32
Staphylococcus aureus	0	0	0	0	0	0	110	2739	2596	100	35	20	25	87	773	194	126	110	0	1
Staphylococcus aureus MRSA	0	0	0	0	0	0	0	3	161	35	1	0	0	0	3	1	1	0	0	1
Staphylococcus aureus MSSA	0	0	0	0	0	0	1	8	253	12	1	0	1	1	4	1	1	0	0	1
Staphylococcus coagulase-negative	0	0	0	0	0	0	32	130	171	15	73	21	5	7	40	5	13	16	0	1
Staphylococcus coagulase-negative MRSE	0	0	0	0	0	0	0	13	44	15	91	23	8	1	6	10	11	6	0	1
Staphylococcus epidermidis	0	0	0	0	0	0	1	28	27	23	29	4	0	2	5	5	1	1	0	ND
Staphylococcus epidermidis	0	0	0	0	0	0	0	24	30	0	42	22	1	1	0	4	3	2	0	ND
Staphylococcus haemolyticus	0	0	0	0	0	0	1	7	2	16	13	5	7	1	0	4	3	7	0	ND
Staphylococcus saprophyticus	0	0	0	0	0	0	0	2	14	2	0	0	0	0	0	0	0	0	0	ND
Stenotrophomonas maltophilia	0	0	0	0	0	0	0	0	0	0	0	5	18	30	12	1	0	0	0	ND
Streptococcus agalactiae	0	0	0	0	0	0	4	66	53	29	4	6	8	36	504	153	33	0	0	1
Streptococcus anginosus	0	0	0	0	0	0	0	20	31	5	9	6	6	2	3	1	1	1	0	ND
Streptococcus group G	0	0	0	0	0	0	0	3	61	33	10	6	18	8	9	29	11	0	0	ND
Streptococcus oralis	0	0	0	0	0	0	7	43	76	15	3	2	0	8	16	22	4	0	0	1
Streptococcus pneumoniae	0	0	0	1	4	464	10024	37732	6361	369	167	310	6274	875	6394	97	14	6	0	0.5
Streptococcus pyogenes	0	0	0	0	0	45	6478	13731	487	69	13	37	1104	249	1076	73	6	0	0	0.5
Streptococcus viridans	0	0	0	0	0	1	12	98	164	63	23	17	18	25	71	60	20	4	0	ND
Yersinia spp	0	0	0	0	0	0	0	0	0	11	37	4	0	0	0	0	1	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							
		4/8	1/4	1/4	-	2/2	
Species specific breakpoints:							
Enterobacteriaceae	1/1	4/8			4/8		4/8
Pseudomonas spp.	1/1	4/8					
Acinetobacter spp.	1/1	4/8					4/8
Staphylococcus spp.	1/1	4/8			1/2	2/2	4/8
Streptococcus spp.	1/1	4/8			2/2	2/2	2/4
Streptococcus pneumoniae	1/1	4/8			2/2	2/2	2/4
Enterococcus spp.		4/8			1/1		4/8
Haemophilus influenzae	1/1	2/4			2/2	2/2	2/4
Moraxella catarrhalis	1/1	2/4			2/2	2/2	
Corynebacteria							
Neisseria meningitidis	1/1				0.25/1		
Neisseria gonorrhoeae	1/1	1/4			0.12/1	0.12/1	0.25/1
Pasteurella multocida							
Anaerobes, Gram-positive					4/4		
Anaerobes, Gram-negative					4/4		
Campylobacter spp.		4/8					
Helicobacter pylori			4/4		2/2	2/2	

4. Pharmacokinetics

Dosage (mg)	250 mg	500 mg		
Cmax (mg/L)	2	3 - 5		
Cmin (mg/L)	-	-		
Total body clearance (L/h)	-	-		
T ½ (h), mean (range)	6 - 11	8.5		
AUC24h (mg.h/L)	-	-		
Fraction unbound (%)	36 – 45	36 – 45		
Volume of distribution (L/kG)	1.3	1.3		
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available. • The drug is 80-90% absorbed from the small intestine, and is 30% excreted in the urine • Peak serum concentrations are achieved in 1 - 3.5h			
References	• Bryskier A. In Antimicrobial Agents 2005. ASM; 642-51. • Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 469-84. • Agwuh KN, MacGowan A. J. Antimicrobial Chemotherapy 2006. 61, 1-10.			

5. Pharmacodynamics				
*f*AUC/MIC for bacteriostasis	-			
*f*AUC/MIC for 2 log reduction	-			
*f*AUC/MIC from clinical data	-			
Comments	• Free drug AUC/MIC is the dominant pharmacodynamic index; there is insufficient data to determine its size for bacteriostatic or bactericidal effects in pre-clinical models and no supporting clinical data.			
References	• Review by Agwuh KN, MacGowan A. 2006, J. Antimicrob Chemother, 61, 1-10.			

6. Monte Carlo simulations and Pk/Pd breakpoints

No data

7. Clinical data

There is little recent clinical experience with the use of tetracycline and no contemporary randomised controlled trials to support its use.

8. Clinical breakpoints	
Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on Pk data, microbiological data and clinical experience. For *Staphylococcus* spp., group A,B,C,G streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* the breakpoints are 1/2 mg/L. For *Neisseria gonorrhoeae* breakpoints are 0.5/1 mg/L. For *Pasteurella multocida* breakpoints are 2/4 mg/L.
Species without breakpoints	Enterobacteriaceae, *Pseudomonas aeruginosa, Acinetobacter* spp., *Enterococcus* spp., and *Streptococcus* spp. other than Group A,B,C,G streptococci and *S. pneumoniae* were considered poor targets for tetracycline therapy and for that reason did not receive breakpoints. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd and clinical outcome. Therefore no breakpoint is given. Breakpoints are given for *Neisseria meningitidis* only for use as an indicator of minocycline susceptibility for use in prophylaxis.
Clinical qualifications	
Dosage	Breakpoints apply to oral tetracycline dosage of 250-500 mg x4/day.
Additional comment	

9. Tetracycline - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None