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

Introduction

Minocycline is a semi-synthetic tetracycline, which has broad spectrum activity against many aerobic and anaerobic Gram-positive and Gram-negative bacteria, including some strains of staphylococci, streptococci and *Haemophilus influenzae* resistant to tetracycline. Minocycline is generally more active than other tetracyclines against Gram-positive organisms, and better absorbed.

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. Most efflux mechanisms confer resistance to tetracycline but not minocycline. In *Bacteroides* spp. an inactivation mechanism has been described.

Minocycline use is, as with other tetracyclines, limited primarily by resistance 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. Minocycline is also used for prophylaxis of meningococcal infection.

Minocycline is available for oral administration.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	100 mg x 2	100 mg x 1	50 mg x 2*	100 mg x 2	-	-
Maximum dose schedule	100 mg x 2	100 mg x 2	100 mg x 2	100 mg x 2	-	-
Available formulations	Oral	Oral	Oral	Oral	-	-

*Loading dose of 200 mg on first day.

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	19	12	6	3	0	1	2	1	0	0	0	0	0	0	ND
Acinetobacter spp	0	0	0	0	0	63	43	17	6	3	12	6	4	0	0	0	0	0	0	ND
Citrobacter spp	0	0	0	0	0	0	0	1	6	73	68	30	5	7	2	0	0	0	0	8
Enterobacter aerogenes	0	0	0	0	0	0	0	1	1	7	62	30	4	0	4	1	0	0	0	16
Enterobacter agglomerans	0	0	0	0	0	0	0	16	83	22	4	1	0	0	0	0	0	0	0	ND
Enterobacter cloacae	0	0	0	0	0	0	0	0	6	17	185	366	128	39	35	23	0	0	0	16
Enterobacter dissolvens	0	0	0	0	0	0	0	0	1	3	26	7	0	0	0	0	0	0	0	ND
Enterobacter spp	0	0	0	0	0	0	0	2	8	38	38	13	1	0	0	0	0	0	0	ND
Enterococcus faecalis	0	0	0	0	7	23	59	25	0	1	3	4	32	174	226	0	1	0	0	0.5
Enterococcus faecium	0	0	0	0	5	105	59	15	0	0	1	3	19	73	45	0	0	0	0	0.5
Escherichia coli	0	0	0	0	0	0	1	16	212	588	292	113	82	138	48	8	0	0	0	4
Haemophilus influenzae	0	0	0	0	4	7	115	1798	1477	322	57	11	5	0	0	0	0	0	0	2
Klebsiella oxytoca	0	0	0	0	0	0	0	0	4	135	106	24	13	4	4	0	0	0	0	8
Klebsiella pneumoniae	0	0	0	0	0	0	2	3	18	106	432	193	60	48	58	18	0	0	0	8
Moraxella catarrhalis	0	0	0	0	8	338	1295	64	2	0	0	0	0	0	0	0	0	0	0	0.25
Morganella morganii	0	0	0	0	0	0	0	0	0	0	16	39	29	23	17	6	0	0	0	ND
Neisseria meningitidis	0	0	0	0	0	3	14	184	94	5	0	0	0	0	0	0	0	0	0	1
Proteus mirabilis	0	0	0	0	0	0	0	0	1	1	3	15	109	347	318	83	0	0	0	ND
Serratia liquefaciens	0	0	0	0	0	0	0	1	2	12	6	2	0	0	0	0	0	0	0	64
Serratia spp	0	0	0	0	0	1	0	0	0	7	63	57	9	2	0	1	0	0	0	ND
Staphylococcus aureus	0	0	0	5	35	535	677	115	6	7	12	16	8	1	0	0	0	0	0	0.25
Staphylococcus aureus MRSA	0	0	0	0	0	6	300	89	6	0	1	1	1	0	0	0	0	0	0	0.5
Staphylococcus aureus MSSA	0	0	0	0	0	8	419	118	20	3	1	1	1	0	0	0	0	0	0	0.5
Staphylococcus coagulase negative	0	0	0	0	0	50	58	51	43	4	2	1	0	0	0	0	0	0	0	ND
Staphylococcus coagulase negative MRSE	0	0	0	0	0	50	149	110	196	26	5	2	0	2	4	0	0	0	0	ND
Staphylococcus epidermidis	0	0	0	0	0	63	98	98	108	5	4	0	0	0	0	0	0	0	0	ND
Staphylococcus epidermidis MSSE	0	0	0	0	0	17	32	14	20	0	0	0	1	0	0	0	0	0	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
Staphylococcus haemolyticus	0	0	0	0	0	6	8	20	20	5	2	3	1	1	0	0	0	0	0	ND
Stenotrophomonas maltophilia	0	0	0	0	0	1	45	52	32	7	1	0	0	0	0	0	0	0	0	1
Streptococcus agalactiae	0	0	0	0	3	1	27	15	8	0	2	3	8	102	137	0	0	0	0	0.5
Streptococcus anginosus	0	0	0	0	0	32	22	11	10	2	3	1	2	2	0	0	0	0	0	0.5
Streptococcus group G	0	0	0	0	8	4	61	50	9	3	4	3	8	18	20	0	0	0	0	0.5
Streptococcus oralis	0	0	0	0	1	17	46	55	23	4	2	12	19	14	3	0	0	0	0	0.5
Streptococcus pneumoniae	0	0	0	5	408	1996	1019	169	74	25	13	43	80	111	19	0	0	0	0	0.5
Streptococcus pyogenes	0	0	0	0	39	23	177	51	18	3	5	6	14	27	7	0	0	0	0	0.5
Streptococcus viridans	0	0	0	0	6	72	194	57	25	13	14	19	50	60	32	9	0	0	0	0.5

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							
				1/4			
Enterobacteriaceae	0.5/0.5	4/8					4/8
Pseudomonas spp.	0.5/0.5						
Acinetobacter spp.							4/8
Staphylococcus spp.	0.5/0.5	4/8					4/8
Streptococcus spp.	0.5/0.5						
Streptococcus pneumoniae	0.5/0.5						
Enterococcus spp.							4/8
Haemophilus influenzae	0.5/0.5						
Moraxella catarrhalis	0.5/0.5						
Corynebacteria							
Neisseria meningitidis							2/-
Neisseria gonorrhoeae							
Pasteurella multocida							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
Campylobacter spp.							
Helicobacter pylori							

4. Pharmacokinetics

Parameter				
Dosage (mg)	200 mg			
Cmax (mg/L)	3.1			
Cmin (mg/L)	-			
Total body clearance (L/h)	-			
T ½ (h), mean (range)	17			
AUC24h (mg.h/L)	44.0			
Fraction unbound (%)	24			
Volume of distribution (L/kG)	1.2			

Comments

- Two values are given where references differ. Cells are left empty when data are not readily available.
- The drug is 95% absorbed from the small intestine, and is 6-10% excreted in the urine.
- Peak serum concentrations are achieved in 2 - 3hr.

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.Chemother 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 effect 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

Recent clinical experience would indicate minocycline has useful clinical activity against wild type MRSA causing mild to moderate infection only requiring oral therapy.

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*, and *Neisseria gonorrhoeae* the breakpoints are 0.5/1 mg/L. For *Haemophilus influenzae, Moraxella catarrhalis* and *Neisseria meningitidis* breakpoints are 1/2 mg/L.
Species without breakpoints	Enterobacteriaceae, *Pseudomonas aeruginosa, Enterococcus* spp., and *Streptococcus* spp. other than Group A,B,C,G streptococci and *S. pneumoniae* were considered poor targets for minocycline therapy and for that reason did not receive breakpoints. For *Acinetobacter* spp. there is insufficient evidence that the species is a good target for therapy with minocycline. 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 in prophylaxis.
Clinical qualifications	
Dosage	Breakpoints apply to oral minocycline dosage of 100 mg x2/day.
Additional comment	

9. Minocycline - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees
None