

Introduction

Doxycycline is a semi-synthetic tetracycline with broad spectrum activity against many aerobic and anaerobic Gram-positive and Gram-negative bacteria. Doxycycline is generally more active than tetracycline, and better absorbed orally.

Doxycycline is bacteriostatic and inhibits 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.

Doxycycline use is limited primarily by resistance and the availability of more active tetracyclines against some pathogens. 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.

Doxycycline is available for oral administration and has the advantage of once-daily administration.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	100 mg x 1*	100 mg x 1*	100 mg x 1*	100 mg x 1*	100 mg x 1*	100 mg x 1*
Maximum dose schedule	200 mg x 1	200 mg x 1	300 mg x 1	200 mg x 1	200 mg x 1	200 mg x 2
Available formulations	Oral	Oral, iv	Oral, iv	Oral, iv	Oral, iv	Oral, iv

*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
<i>Acinetobacter baumannii</i>	0	0	0	0	0	0	74	25	4	1	1	0	0	0	0	0	0	0	0	ND
<i>Campylobacter coli</i>	0	0	0	0	1	4	107	47	37	16	17	66	222	215	76	0	0	0	0	0.5
<i>Campylobacter jejuni</i>	0	0	0	0	12	22	180	20	28	6	10	14	38	63	22	0	0	0	0	0.5
<i>Citrobacter freundii</i>	0	0	0	0	0	0	0	1	8	73	133	53	18	49	20	1	0	0	0	8
<i>Enterobacter aerogenes</i>	0	0	0	0	0	0	0	1	5	47	86	16	8	14	0	0	0	0	0	8
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	4	4	8	81	458	271	47	70	11	4	0	0	0	8
<i>Enterobacter spp</i>	0	0	0	0	0	0	0	0	2	2	2	19	16	1	0	0	0	1	0	8
<i>Enterococcus faecalis</i>	0	0	0	0	0	4	72	115	50	4	1	10	105	346	162	0	1	0	0	0.5
<i>Enterococcus faecium</i>	0	0	0	0	0	4	254	161	11	14	16	11	228	815	641	35	0	0	0	0.5
<i>Escherichia coli</i>	0	0	0	0	0	0	1	25	192	675	713	286	685	585	422	65	3	1	0	4
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	2	3	113	342	79	43	18	47	8	0	0	0	0	4
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	0	0	1	39	158	139	38	23	35	47	1	0	0	0	4
<i>Klebsiella spp</i>	0	0	0	0	0	0	0	0	1	2	10	9	3	1	3	0	0	0	0	ND
<i>Moraxella catarrhalis</i>	0	0	0	0	0	0	16	89	160	19	1	2	0	0	0	0	0	0	0	1
<i>Morganella morganii</i>	0	0	0	0	0	0	0	0	8	15	12	9	5	5	8	17	0	0	0	8
<i>Mycobacterium marinum</i>	0	0	0	0	0	0	0	0	0	2	2	19	10	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	7	2	0	15	ND
<i>Proteus spp</i>	0	0	0	0	0	0	0	0	0	1	8	10	12	2	0	2	3	12	0	ND
<i>Proteus vulgaris</i>	0	0	0	0	0	0	0	1	2	6	21	32	28	5	15	3	0	0	0	ND
<i>Salmonella spp</i>	0	0	0	0	0	0	0	1	7	243	3404	1817	633	302	313	119	0	0	0	8
<i>Serratia marcescens</i>	0	0	0	0	0	0	0	1	1	4	20	48	50	38	11	1	0	0	0	ND
<i>Staphylococcus aureus</i>	0	0	0	20	195	1195	1933	725	134	115	243	196	57	37	14	3	1	1	0	0.5
<i>Staphylococcus coagulase negative</i>	0	0	0	0	0	3	13	2	6	1	1	3	4	3	4	0	0	0	0	ND
<i>Staphylococcus haemolyticus</i>	0	0	0	0	0	0	40	12	107	84	2	2	3	37	0	0	0	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	1	15	2	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	2	12	41	94	63	31	7	2	0	0	0	0	8
<i>Streptococcus agalactiae</i>	0	0	0	0	0	0	1	3	2	1	3	0	8	2	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
<i>Streptococcus pneumoniae</i>	0	0	0	2	8	271	2475	1204	182	50	61	170	183	47	7	3	0	0	0	0.5
<i>Streptococcus pyogenes</i>	0	0	0	3	18	166	879	739	105	11	3	2	46	154	65	12	1	2	0	0.5
<i>Streptococcus viridans</i>	0	0	0	0	2	3	9	3	0	1	0	2	2	3	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.

4. Pharmacokinetics

Dosage (mg)	100 mg	200 mg		
Cmax (mg/L)	2.0 ± 1.0	5.2 ± 1.5		
Cmin (mg/L)	-	-		
Total body clearance (L/h)	-	-		
T ½ (h), mean (range)	12 ± 3	13 ± 5		
AUC24h (mg.h/L)	37 – 40	90 ± 16		
Fraction unbound (%)	7 - 18	7 - 18		
Volume of distribution (L/kg)	-	0.7 ± 0.1		
Comments	<ul style="list-style-type: none">• Two values are given where references differ. Cells are left empty when data are not readily available.• The drug is >90% absorbed from the small intestine, and is 35-60% excreted in the urine.• Peak serum concentrations are achieved in 1 – 4h.			
References	<ul style="list-style-type: none">• 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 Chemother 2006, 61, 1-10.			

5. Pharmacodynamics

fAUC/MIC for bacteriostasis	-			
fAUC/MIC for 2 log reduction	-			
fAUC/MIC from clinical data	-			
Comments	<ul style="list-style-type: none">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	<ul style="list-style-type: none">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 doxycycline has useful clinical activity against wild type bacteria causing community-acquired pneumonia, exacerbation of COPD and mild to moderate MRSA infection requiring only 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 <i>Staphylococcus</i> spp., group A,B,C,G streptococci, <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> the breakpoints are 1/2 mg/L.
Species without breakpoints	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., and <i>Streptococcus</i> spp. other than Group A,B,C,G streptococci and <i>S. pneumoniae</i> were considered poor targets for doxycycline therapy and for that reason did not receive breakpoints. For <i>Neisseria gonorrhoeae</i> there is insufficient evidence that the species is a good target for therapy with doxycycline. 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.
Clinical qualifications	
Dosage	Breakpoints apply to oral doxycycline dosage of 100-200 mg x1/day.
Additional comment	

9. Doxycycline - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees
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None
