



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

**Rifampicin**

**Rationale for the EUCAST clinical breakpoints, version 1.0**

14<sup>th</sup> April 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. Rifampicin: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

## Introduction

Rifampicin is a member of the rifamycin group, a large family of antibiotics with an aromatic ring structure.

Rifampicin is bactericidal. It inhibits DNA transcription by binding to the DNA-dependent RNA polymerase. It very active against Gram-positive organisms and some Gram-negative organisms including *Neisseria* spp. and *Haemophilus* spp. Resistance may be mediated by chromosomal modification of the DNA-dependent RNA polymerase gene. Resistance may be selected readily in vitro and rifampicin is commonly used in combination with other agents to prevent the emergence of resistance.

Rifampicin is especially relevant for staphylococcal and streptococcal skin and soft tissue infections. It is also used for prophylaxis of meningococcal infections and in combination therapy for the treatment of *Mycobacterium tuberculosis* infections and infections related to prosthetic devices. It is available for oral and parenteral use.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN<sup>1</sup></b>	<b>NWGA<sup>2</sup></b>	<b>SRGA</b>
Most common dose	600 mg x 1	600 mg x 2	300-600 mg x 2	-	450-600 mg x 1	600 mg x 1
Maximum dose schedule	600 mg x 2	600 mg x 3	600 mg x 2	-	450-600 mg x 1	450 mg x 2
Available formulations	iv/oral	iv/oral	iv/oral	-	oral	iv/oral

<sup>1</sup>In Germany, rifampicin is registered for use against *Mycobacterium tuberculosis* and for prophylaxis of meningococcal infections.

<sup>2</sup>In Norway, rifampicin is registered for use against *Mycobacterium tuberculosis*. However, the drug is also used in treating some other infections, primarily in combination with other drugs in infections related to prosthetic devices.

## 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>Clostridium difficile</i>	89	1	482	0	1	0	0	0	3	1	0	0	0	0	5	0	0	125	0	ND
<i>Enterococcus faecalis</i>	0	0	0	0	0	29	5	29	445	961	650	476	202	103	0	0	0	0	0	4
<i>Haemophilus influenzae</i>	0	0	0	0	1	28	218	465	73	2	0	0	0	0	0	0	0	0	0	0.5
<i>Mycobacterium tuberculosis</i>	0	0	0	2	7	11	24	32	14	0	0	0	0	0	0	0	0	0	0	ND
<i>Neisseria meningitidis</i>	15	67	207	230	145	98	29	14	1	0	0	0	0	0	0	0	0	30	0	ND
<i>Staphylococcus aureus</i>	1	196	588	171	2	2	1	1	0	0	0	2	0	0	1	3	8	17	2	0.016
<i>Staphylococcus aureus</i> MRSA	0	93	195	22	0	0	0	0	0	0	0	5	0	0	0	0	0	0	2	0.016
<i>Staphylococcus aureus</i> MSSA	0	84	131	175	24	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0.016
<i>Staphylococcus</i> coagulase-negative	2	54	174	275	92	13	2	0	1	0	3	1	0	1	1	2	8	54	14	0.064
<i>Staphylococcus</i> coagulase-negative MRSCN	0	50	103	115	33	5	1	0	1	2	3	7	0	0	3	0	7	10	30	0.064
<i>Staphylococcus epidermidis</i>	0	55	52	108	65	41	1	0	0	1	0	4	0	0	1	0	8	4	36	0.064
<i>Staphylococcus epidermidis</i> MSSE	0	11	24	36	12	0	0	0	0	0	0	0	0	0	0	0	0	1	0	ND
<i>Staphylococcus haemolyticus</i>	0	1	11	14	23	6	8	0	0	0	0	1	0	0	0	0	0	0	2	ND
<i>Streptococcus anginosus</i>	0	1	11	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	0	0	4	138	613	206	24	2	3	3	2	0	3	0	0	0	0	0	0	0.064

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 <sup>1</sup>
<b>General breakpoint</b>			1/1			0.5/0.5	
Enterobacteriaceae							
<i>Pseudomonas</i> spp.		4/16					
<i>Acinetobacter</i> spp.		4/16					
<i>Staphylococcus</i> spp.	0.06/0.06	0.5/16			1/1	1/1	1/2
<i>Streptococcus</i> spp.		4/16				1/1	
<i>Streptococcus pneumoniae</i>	1/1					1/1	1/2
<i>Enterococcus</i> spp.					1/1		1/2
<i>Haemophilus influenzae</i>		2/4					1/2
<i>Moraxella catarrhalis</i>		2/4					1/2
Corynebacteria							
<i>Neisseria meningitidis</i>	1/1	0.25/-				1/1	0.5/1
<i>Neisseria gonorrhoeae</i>	1/1						
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive		4/16					
Anaerobes, Gram-negative		4/16					
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<sup>1</sup>CLSI breakpoints converted to EUCAST terminology.

<b>4. Pharmacokinetics</b>				
Dosage (mg)	600 mg x 1 oral/iv			
C <sub>max</sub> (mg/L)	6-11			
C <sub>min</sub> (mg/L)				
Total body clearance (L/h)				
T <sub>1/2</sub> (h), mean (range)	1.5-4			
AUC <sub>24h</sub> (mg.h/L)	35-116			
Fraction unbound (%)	10-40			
Volume of distribution (L/kg)				
Comments	<ul style="list-style-type: none"> <li>• Two values or ranges are given where references differ. Cells are left empty when data are not readily available.</li> <li>• Published values vary widely.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Bryskier. Antimicrobial Agents 2005, 919-21.</li> <li>• Peloquin et al. Chest 199; 115: 12-18.</li> </ul>			

<b>5. Pharmacodynamics</b>				
fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> <li>• Cells are left empty when data are not readily available.</li> </ul>			
References				

## **6. Monte Carlo simulations and Pk/Pd breakpoints**

Not available.

## 7. Clinical data

Although there are increasing numbers of case reports of combination therapy with rifampicin there is little documented clinical experience and no contemporary randomised controlled trials that support its use for treatment of non-mycobacterial infections (Forrest GM and Tamura K. *Clin Microbiol Rev* 2010; 23: 14-34).

## 8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. <i>Staphylococcus</i> spp., Group A,B,C,G streptococci and <i>Streptococcus pneumoniae</i> , S $\leq$ 0.06 and R >0.5 mg/L. <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> S $\leq$ 0.5 and R >0.5 mg/L. <i>Neisseria meningitidis</i> S $\leq$ 0.25 and R>0.25 mg/L for prophylaxis only.
Species without breakpoints	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., <i>Streptococcus</i> spp. other than Group A,B,C,G streptococci and <i>S. pneumoniae</i> , <i>Neisseria gonorrhoeae</i> and anaerobes were considered poor targets for rifampicin therapy and for that reason did not receive breakpoints.
Clinical qualifications	
Dosage	Breakpoints apply to a dosage of 600 mg x 1.
Additional comment	

## **9. EUCAST clinical MIC breakpoints**

All current EUCAST clinical MIC breakpoints can be found at <http://www.eucast.org>

## **10. Exceptions noted for individual national committees**

None