



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

**Colistin**

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

27<sup>th</sup> May 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. Colistin: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

## Introduction

Colistin (polymyxin E) is a member of the polymyxin group, which comprises basic polypeptide antibiotics with a side chain terminated by characteristic fatty acids. Polymyxin B and colistin have been developed for clinical use. All polymyxins have a similar antibacterial spectrum. They are highly active against most Enterobacteriaceae, excluding Proteae and *Serratia* spp. They are also active against *Acinetobacter* spp. and *Pseudomonas aeruginosa*. Colistin is administered as an inactive pro-drug, colistin methanesulphonate (CMS), which is converted in vivo to its active form, colistin.

Colistin acts by displacing magnesium and calcium (ions that normally stabilize the lipopolysaccharide molecules) from the negatively charged lipopolysaccharide in the bacterial cell membrane, leading to a loss of integrity of the membrane and an increase in the permeability of the cell envelope, leakage of cell contents, and subsequently, cell death. Acquired resistance to colistin occurs in Enterobacteriaceae, *Acinetobacter* spp. and *P. aeruginosa*, and is mainly due to lipopolysaccharide modifications. There is complete cross-resistance between the polymyxins. Stable acquired resistance is rare.

Colistin is used in treatment of infections caused by organisms resistant to less toxic antimicrobial agents. It is also used as an inhaled therapy in patients with chronic bronchopulmonary colonization by *P. aeruginosa*, mainly patients with cystic fibrosis or bronchiectasis. EUCAST has defined clinical breakpoints for colistin for parenteral use.

## 1. Dosage

	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>
Most common dose	2MU x 3 initial 2 MU x 2	2 MU x 3	2 MU x 2	1-2 MU x 3	1-2 MU x 3	3 MU x 3 <sup>1</sup>
Maximum dose schedule	2MU x 3	3 MU x 3	2 MU x 3	1-2 MU x 3	2 MU x 3	3 MU x 3
Available formulations	iv/nebulised	iv/nebulised	nebulised	iv	iv/nebulised	iv/nebulised

<sup>1</sup> A loading dose of 9 MU x 1 is administered.

## 2. MIC distributions 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	0	0	0	1	3	23	6	0	0	1	1	0	0	0	0	ND
<i>Acinetobacter</i> spp	0	0	0	0	0	0	0	0	2	35	24	0	0	0	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	4	1	12	93	40	10	2	2	3	0	0	0	0	0	2
<i>Enterobacter cloacae</i>	0	0	0	0	0	30	7	37	234	132	48	15	37	73	0	0	0	0	0	2
<i>Enterobacter</i> spp	0	0	0	0	0	0	0	0	0	22	12	0	0	1	1	0	0	7	0	ND
<i>Escherichia coli</i>	0	0	0	0	0	243	66	952	2814	696	136	16	6	52	6	0	0	0	0	2
<i>Klebsiella oxytoca</i>	0	0	0	0	0	16	3	28	293	142	20	4	1	9	2	0	0	0	0	2
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	50	13	58	700	409	119	16	8	28	10	0	0	0	0	2
<i>Klebsiella</i> spp	0	0	0	0	0	0	0	0	0	26	13	3	0	0	0	0	0	0	0	ND
<i>Morganella morganii</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	ND
<i>Proteus mirabilis</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	1	118	0	0	0	0	ND
<i>Pseudomonas aeruginosa</i>	0	0	0	0	1	5	13	74	771	1478	953	93	19	46	5	0	0	0	0	4
<i>Serratia marcescens</i>	0	0	0	0	0	0	0	0	0	2	0	0	0	0	106	0	0	6	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	1	3	5	4	15	14	5	36	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 no epidemiological cut-off has been determined (ND).

### 3. Breakpoints prior to harmonisation (S<sub>≤</sub>/R> mg/L)

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoint</b>			4/8				
Enterobacteriaceae	4/4	2/2				2/2	
<i>Pseudomonas</i> spp.	4/4	2/2			4/4	2/2	
<i>Acinetobacter</i> spp.	4/4	2/2				2/2	2/2
<i>Staphylococcus</i> spp.							
<i>Streptococcus</i> spp.							
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<b>4. Pharmacokinetics</b>				
Dosage (mg)	<b>3 MU</b>			
C <sub>max</sub> (mg/L)	2.3 (steady state)			
C <sub>min</sub> (mg/L)				
Total body clearance (L/h)				
T <sub>1/2</sub> (h), mean (range)	14			
AUC <sub>24h</sub> (mg.h/L)	50-60			
Fraction unbound (%)				
Volume of distribution (L/kg)	0.3			
Comments	<ul style="list-style-type: none"> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> <li>• All values relate to colistin and not the inactive pro-drugs.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Plachouras D et al. <i>Antimicrob Agents Chemother</i> 2009; 53: 3430–3436</li> </ul>			

<b>5. Pharmacodynamics</b>				
	<i>P. aeruginosa</i>			
fAUC/MIC for bacteriostasis	16-23			
fAUC/MIC for 2 log reduction	37-46			
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> <li>• A recent study of neutropenic thigh infection and lung infection in mice suggest that fAUC/MIC is the index best correlating with clinical efficacy.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Dudhani RV et al. <i>Antimicrob Agents Chemother</i> 2010; 54: 1117-24.</li> </ul>			

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

Not available.

## 7. Clinical data

A retrospective cohort study of 258 patients with microbiologically documented infections caused by multidrug-resistant Gram-negative bacteria showed successful treatment in 79% of the patients (Falagas ME et al. *Int J Antimicrob Agents* 2010; 35: 194–199). The most frequently isolated pathogens were *Acinetobacter baumannii*, *P. aeruginosa* and *Klebsiella pneumoniae*.

## 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. Enterobacteriaceae (excluding <i>Proteus</i> spp., <i>Morganella morganii</i> , <i>Providencia</i> spp. and <i>Serratia</i> spp.) and <i>Acinetobacter</i> spp. S $\leq$ 2 / R >2 mg/L For <i>Pseudomonas aeruginosa</i> the breakpoints were set at S $\leq$ 4 / R >4 mg/L to avoid splitting the wild type MIC distribution.
Species without breakpoints	<i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., streptococci, <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> spp. and anaerobes were considered poor targets or inappropriate for colistin therapy and for that reason did not receive breakpoints.
Clinical qualifications	
Dosage	Breakpoints apply to colistin dosage of 2-3 MU x 3. A loading dose (9 MU) may be needed.
Additional comment	

## 9. Colistin - EUCAST clinical MIC breakpoints

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

## 10. Exceptions noted for individual national committees

None