

## Ceftriaxone: Rationale for EUCAST Clinical Breakpoints

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Previous versions	–	–

### Introduction

The cephalosporins are a large group of compounds with a 6-membered dihydrothiazine ring fused to a beta-lactam ring. They are derivatives of 7-aminocephalosporanic acid with various modifications to several ring positions resulting in differences in activity, beta-lactamase stability, and pharmacokinetic properties. Ceftriaxone is a 3rd generation cephalosporin with potent antimicrobial activity and resistance to hydrolysis by many beta-lactamases. It is bactericidal at concentrations close to the MIC. Ceftriaxone is available only for parenteral administration and the long serum half-life permits once daily dosing.

Ceftriaxone is used for therapy of septicaemia, meningitis, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin and soft tissue infections caused by *Enterobacterales*, *Streptococcus* spp. (including *S. pneumoniae*) and *Haemophilus influenzae*. Ceftriaxone is not considered to have useful activity against *Enterococcus* spp. or Gram-negative anaerobic bacteria and is poorly active against *Pseudomonas* spp.

Ceftriaxone resistance in *S. pneumoniae* may be conferred by alterations in penicillin-binding proteins. In *Enterobacterales* resistance to cefotaxime may be conferred by several mechanisms alone or in combination, including the production of some beta-lactamases (ESBLs, AmpC and others), porin loss and alteration in efflux pumps.

### Dosages related to clinical breakpoints

**Standard dosage:** 2 g x 1 iv  
**High dosage:** 2 g x 2 or 4 g x 1 iv

### MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

## Pharmacokinetics

PK parameter	Pharmacological studies			
	1 g x 1 iv	1 g x 1 im	1 g x 1 iv [2]	
Dosage	1 g x 1 iv	1 g x 1 im	1 g x 1 iv [2]	
C <sub>max</sub> (mg/L)	199 ± 154	80.5 ± 31.7		
Total body clearance (L/h)	0.83 ± 0.83	0.57 ± 0.58	1.2 ± 0.3	
T <sub>1/2</sub> (h), mean (range)	8.1 ± 3.9	17.7 ± 9.3	5.8 ± 1.2	
Fraction unbound (%)				7.3 ± 3.2
Volume of distribution <sub>ss</sub> (L)	7.8 ± 5.4	11.8 ± 2.2	14.0 ± 2.1	
Reference	Goonetilleke et al., 1996	Goonetilleke et al., 1996	Meyers et al., 1983	Craig & Suh, 1986

\* Values expressed as median and [interquartile range]

## Pharmacodynamics

Index*	In vitro PD	Neutropenic mouse thigh		
	<i>S. aureus</i>	<i>Enterobacterales</i>	<i>S. aureus</i>	<i>S. pneumoniae</i>
	Value	Range	Range	Range
f%T>MIC for bacteriostasis	55	34-42	23-27	38-41
f%T>MIC for 1-log <sub>10</sub> kill	75	~50	~30	–
Reference	Zelenitsky et al, 20018	Craig, 1995	Craig, 1995	Craig, 1995

## Monte Carlo simulations

Monte Carlo simulations applying PK parameters from Goonetilleke et al (1996) and protein binding data from Craig and Suh (1986)

Target attainment rates: <i>Enterobacterales</i>					Target attainment rates: <i>S. aureus</i> (Craig target)					Target attainment rates: <i>S. aureus</i> (Zelenitsky target)				
f%T>MIC 40%					f%T>MIC 25%					f%T>MIC 55%				
	1 g x 1	1 g x 2	2 g x 1	2 g x 2		1 g x 1	1 g x 2	2 g x 1	2 g x 2		1 g x 1	1 g x 2	2 g x 1	2 g x 2
<b>0.125</b>	96%	97%	96%	98%	<b>0.125</b>	97%	98%	98%	98%	<b>0.125</b>	94%	97%	95%	97%
<b>0.25</b>	95%	97%	96%	97%	<b>0.25</b>	97%	98%	97%	98%	<b>0.25</b>	92%	96%	94%	97%
<b>0.5</b>	91%	96%	94%	97%	<b>0.5</b>	95%	97%	96%	98%	<b>0.5</b>	87%	95%	91%	96%
<b>1</b>	86%	93%	92%	96%	<b>1</b>	92%	95%	95%	97%	<b>1</b>	78%	91%	87%	95%
<b>2</b>	71%	85%	86%	93%	<b>2</b>	82%	90%	92%	95%	<b>2</b>	59%	80%	78%	91%
<b>4</b>	43%	64%	70%	85%	<b>4</b>	58%	72%	82%	90%	<b>4</b>	32%	56%	58%	80%
<b>8</b>	18%	31%	44%	64%	<b>8</b>	28%	38%	57%	72%	<b>8</b>	12%	25%	32%	56%
<b>16</b>	7%	12%	19%	31%	<b>16</b>	10%	15%	27%	38%	<b>16</b>	5%	10%	13%	25%
<b>32</b>	3%	5%	8%	12%	<b>32</b>	5%	6%	11%	15%	<b>32</b>	2%	4%	5%	10%

Red lines indicate highest MIC at which the proportion of target attainment is at least 95%

## Clinical studies

Clinical trials have shown the efficacy of ceftriaxone treatment of patients with septicaemia, meningitis, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, complicated skin- and soft tissue infections and gonococcal infections caused by micro-organisms categorized as wild type.

The efficacy of ceftriaxone in serious infections caused by methicillin-susceptible strains of *Staphylococcus aureus* (MSSA) is controversial. In recent studies, ceftriaxone was inferior to cefazolin in the treatment of bacteraemia in one study [4], but was as effective as intravenous flucloxacillin in another study of children with cellulitis, although in the latter study the proportion of patients with staphylococcal versus streptococcal infection was not known. The ECOFF of MSSA is 8 mg/L, and Monte Carlo simulations using either of two identified targets suggest that even at the highest dosage of 2 g x 2, it is not possible to cover the wild type.

## Clinical breakpoints

The clinical breakpoints for ceftriaxone can be found in the most recent version of the Breakpoint tables: [https://www.eucast.org/clinical\\_breakpoints](https://www.eucast.org/clinical_breakpoints)

Note: The ECOFF of *S. aureus* is 8 mg/L, but the PK/PD breakpoint is 1 or 2 mg/l (high dosage). Clinical experience supports the use of ceftriaxone in high dosage, preferably only as stepdown therapy after initial response to other more established agents. Susceptibility is inferred from the cefoxitin screen.

## References

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