

## Cefazolin: Rationale for EUCAST Clinical Breakpoints

<b>Current version</b>	<b>1.0</b>	<b>February 2026</b>
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### 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.

Cefazolin is a 1st generation cephalosporin with moderate antimicrobial activity, moderate resistance to hydrolysis by staphylococcal beta-lactamase and readily hydrolysed by many enterobacterial beta-lactamases. It is bactericidal at concentrations close to the MIC. Cefazolin is available only for parenteral administration.

Cefazolin has been used for therapy of infections caused by a range of Gram-positive and Gram-negative organisms that do not produce beta-lactamases but has been largely replaced by compounds that are more active and more resistant to beta-lactamases. It is used extensively as surgical prophylaxis.

Cefazolin has some activity against species of Enterobacterales that do not possess intrinsic cephalosporinases: *Escherichia coli*, *Klebsiella pneumoniae* and *K. oxytoca*

In staphylococci, MICs are raised by the production of beta-lactamase and strains that produce PBP2a (methicillin resistant) are resistant to cefazolin. In Enterobacterales resistance to cefazolin may be conferred by several mechanisms alone or in combination, including the production of beta-lactamases, porin loss and alteration in efflux pumps.

### Dosages related to clinical breakpoints

**Standard dosage:** 1 g x 3 iv  
**High dosage:** 2 g x 3 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		
	1000 <sup>a</sup>	1000 <sup>b</sup>	1000 <sup>c</sup>
Dosage	38.8-75.7		94.5 ± 30.3
C <sub>max</sub> (mg/L)			15.0 ± 7.4
C <sub>min</sub> (mg/L)		4.55 ± 1.16	3.72 ± 2.16
Total body clearance (L/h)		2.18 ± 0.20	3.51 ± 0.99
T ½ (h), mean (range)	1.80 ± 0.38		
AUC <sub>0-12</sub> (mg.h/L)			
AUC <sub>0-24</sub> (mg.h/L)			
AUC <sub>0-∞</sub> (mg.h/L)			
Fraction unbound (%)	16-27		14.9 ± 1.1
Volume of distribution <sub>ss</sub> (L)	8.47 ± 2.01 (L)	0.19 ± 0.06	0.17 ± 0.07 (L/Kg)

a Nightingale et al. J Pharm Sci 1975; 64: 1899-1926

b Scheld et al, Antimicrob Agents Chemother 1981; 19:613-9

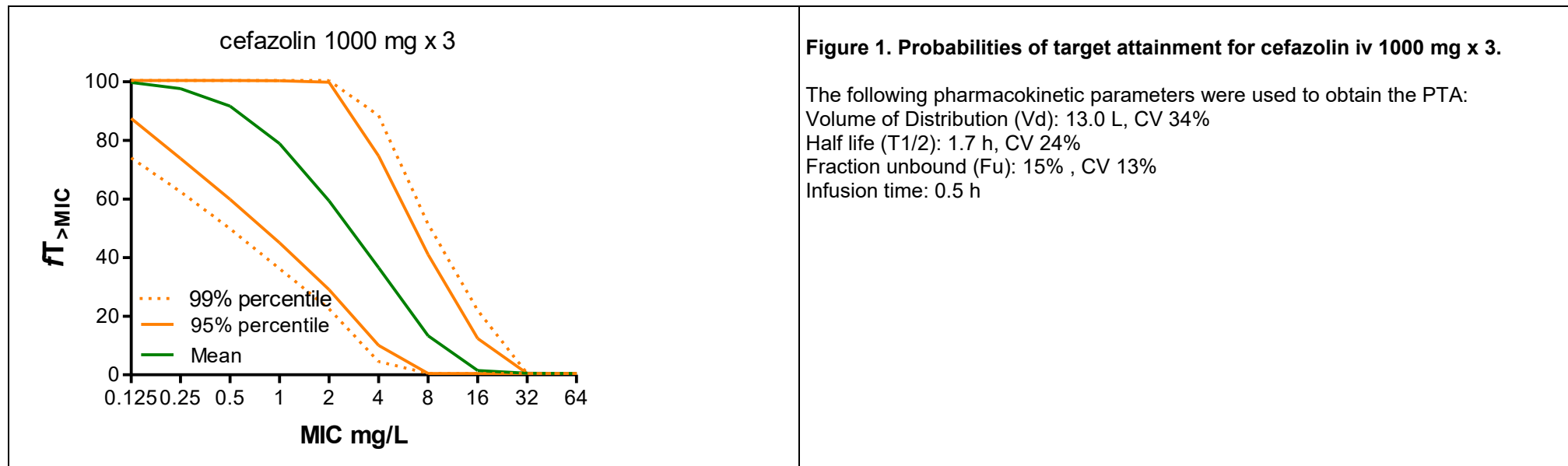
c Bhalodi et al, Antimicrob Agents Chemother 2013; 57:5679-83

## Pharmacodynamics

Index*	Enterobacteriales	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>
f%T>MIC for bacteriostasis	35-40	35-40	20-30
f%T>MIC for 2-log <sub>10</sub> kill	40-50		

Ref: Craig. Diagn Microbiol Infect Dis 22; 89: 1995

## Monte Carlo simulations



**Target attainment rates published by Turnidge et al. 2011 based on Nightingale et al. 1975 and Scheld et al. 1981; analyses performed by Michael Dudley**

MIC (µg/mL)	Percentage of Target Attainment (50% T > MIC) (Nightingale et al [11])				Percentage of Target Attainment (50% T > MIC) (Scheld et al [12])			
	1 g q8h	1 g q6h	1.5 g q6h	2 g q8h	1 g q8h	1 g q6h	1.5 g q6h	2 g q8h
0.5	100	100	100	100	100	100	100	100
1	94	99	100	100	100	100	100	100
2	64	88	98	94	83	97	100	100
4	18	42	74	65	22	51	85	84
8	1	4	19	18	0	3	24	22
16	0	0	1	1	0	0	1	0

Target attainment rates published by So et al., 2014 (patients with complicated skin/skin structure infections)

MIC (mg/L)	1 g q8h			2 g q8h		
	30% fT > MIC	50% fT > MIC	100% fT > MIC	30% fT > MIC	50% fT > MIC	100% fT > MIC
(a) Serum						
0.125	1.00	0.99	0.96	1.00	0.99	0.96
0.25	0.99	0.99	0.93	1.00	0.99	0.96
0.5	0.99	0.98	0.84	0.99	0.99	0.93
1	0.99	0.97	0.66	0.99	0.98	0.84
2	0.98	0.79	0.41	0.99	0.97	0.66
4	0.77	0.61	0.08	0.98	0.79	0.41
8	0.33	0.09	0.01	0.77	0.61	0.08
16	0.03	0.01	0.00	0.34	0.09	0.01

## Clinical studies

A summary of uncontrolled studies (n=9) in a range of infections, but with relatively small patient numbers, was published in Turnidge et al., 2011. These were summaries of published studies up to the time of publication. Dosage regimens vary considerably in these studies, but since 1995 the regimens most common used were either 1 or 2g every 8 hours, and these for studies in acute pyelonephritis.

The revision of CLSI breakpoints for Enterobacterales in 2011 (whereby breakpoints were lowered) has led to four retrospective analyses of efficacy in gram-negative infections including three in bacteraemia.

Wang et al. and Chuang et al. were back-to-back studies from the same institution in Taiwan on the efficacy in *E. coli* and *K. pneumoniae* bacteraemia respectively. Excluding patients whose dosing regimen was adjusted due to impaired renal function, clinical cures by MIC were as follows:

Study	Species	Regimen	0.25	0.5	1	≤ 1	2	4	8
Wang et al.	<i>E. coli</i>	1g x 4 iv				13/13	6/6	3/3	2/2
		1g x 3 iv				6/6	3/3	1/1	
Chuang et al.	<i>K. pneumoniae</i>	1g x 4 iv		1/1	40/40		8/10		
		1g x 3 iv	0/1		29/30		6/6	2/2	1/1

95% of *E. coli* isolates originated from the urinary tract. For *K. pneumoniae*, two-thirds came from intra-abdominal infections, with urinary tract infections and unknown sources being seen with equal frequency in the remainder.

In a study from a different group in Taiwan (Hsieh et al., 2016), clinical outcomes of community-onset bacteraemia treated empirically with either cefazolin or extended spectrum cephalosporins were compared matched by propensity score. The species involved were *E. coli*, *Klebsiella* spp. and *Proteus mirabilis*, and 90% of bacteraemias treated with cefazolin originated from urinary tract infections. Only patients with patients infected with strains susceptible to the treating agent according to 2015 CLSI criteria (for cefazolin: ≤ 2 mg/L) were included in the propensity score-matched groups. In those cohorts (n=121 in each group), there was no significant difference in time to defervescence, late clinical failures or 28-day crude mortality. Cefazolin dosing followed recommendations found in the Sanford Guide but specific details were not provided.

A large retrospective US study compared cefazolin and ceftriaxone in acute pyelonephritis (Hobbs et al., 2016). In the cefazolin arm (n=92), 64% of patients had *E. coli* as the documented cause; there were very low numbers of other Gram-negative pathogens. Susceptibility/resistance to the treating agent was not examined in the analysis and dosing regimens were not described other than as 'physician choice'. Despite these limitations, there was no difference in symptom resolution, time to defervescence, length of stay or 30-day readmission rates between the two agents.

In a Japanese paediatric study, Abe et al. demonstrated that empirical cefazolin 50mg/kg x 3 per day (equivalent to 2g x 3 in adults) was effective in 85% of children admitted with their first upper urinary tract infection (n=75). Of note, none of the cefazolin-treated patients were bacteraemic.

There has been renewed interest in the role of cefazolin in the treatment of *Staphylococcus aureus* bacteraemia in recent years. Weis et al., 2019, have summarised the findings of 14 studies that compared cefazolin to anti-staphylococcal penicillins for this condition. All but one was a retrospective analysis. These authors found that "Cefazolin treatment may be associated with lower 30-day mortality rates (RR 0.70 (0.54, 0.91), low quality of evidence) and less nephrotoxicity (RR 0.36 (0.21, 0.59), (low quality of evidence). We are uncertain whether cefazolin and ASP differ regarding treatment failure/ relapse as the quality of the evidence has been assessed as very low (RR of 0.84 (0.59, 1.18)). For patients with endocarditis (RR 0.71 (0.12, 4.05)) or abscesses (RR 1.17 (0.30, 4.63)), cefazolin treatment may be associated with equal 30-

day and 90-day mortality (low quality of evidence). "Cefazolin appears to be at least as effective as anti-staphylococcal penicillins in *S. aureus* bacteraemia. These results allay to some extent the concerns about cefazolin's in vitro susceptibility to certain types of penicillinase and to the inoculum effect (Saeki et al). Susceptibility to cefazolin would be inferred from tests designed to rule out methicillin-resistance.

## Clinical breakpoints

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

## References

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