EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Guidance Document on Cephalosporins for *Staphylococcus aureus* Infection

27 April 2026

Limitations

This document is limited to oral and parenteral cephalosporins with either documented clinical effect on infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA), or that are widely used in the treatment of such infections. Cephalosporins with proven activity on methicillin-resistant *S. aureus* (MRSA) can be interpreted according to their respective clinical breakpoints and will not be discussed further. For other cephalosporins not covered by this document, generally considered inferior as antistaphylococcal agents, care should be taken when reporting susceptibility or utilizing these agents for treating infections caused by *S. aureus*.

Most clinical studies addressing oral cephalosporins are done on uncomplicated or non-severe skin and soft tissue infections ((u)SSTI). Generally, the high placebo response rate in these infections, as described by Rajendran et al., suggest some caution should be applied when conclusions are drawn from the clinical studies referred to below (1).

Background

Various cephalosporins have been used for many years for treatment of a variety of infections caused by MSSA. The third-generation cephalosporins, cefotaxime and ceftriaxone, have been used in selected instances of more serious MSSA infections, such as allergy to penicillins, mixed infections, and in the case of ceftriaxone, as follow-on outpatient parenteral antimicrobial therapy (OPAT). Their use in these settings is controversial given their ecological impact on the gut microbiome and their resistance selection pressure. Ceftriaxone has become widely used in some countries for outpatient intravenous therapy because it permits once-daily dosing.

EUCAST has reviewed the PK/PD of the intravenous agents and the data on clinical outcomes for both oral and intravenous agents to determine if the current recommendation that *S. aureus* susceptibility to these agents can be inferred provided that the isolates are phenotypically (cefoxitin susceptible) or genotypically negative for the presence of *mecA* or *mecC*.

Outcomes of Pharmacokinetic/Pharmacodynamic Analysis

A recent EUCAST review of the pharmacokinetics and pharmacodynamics of the intravenous agents and subsequent consultation showed efficacy against wild-type *S. aureus* could be achieved with high-dosages of cefazolin (2 g x 3 iv), cefotaxime (2 g x 3-4 iv), and cefepime (2 g x 3 iv), but not with the highest dosages of ceftriaxone (2 g x 2 iv or 4 g x 1 iv) [See Appendix]. In the hollow fibre model, using a single strain of MSSA with a modal

MIC of 4 mg/L, simulated ceftriaxone dosages of less than 2 g x 2 iv over a 168-hour interval showed little or only short-term activity, and even at 2 g x 2 iv only bacteriostasis was achieved (2).

ORAL CEPHALOSPORINS:

Cefalexin

Cefalexin has been compared to various other antimicrobials (trimethoprim-sulfamethoxazole, clindamycin, azithromycin, ofloxacin, and moxifloxacin) for treatment of non-severe skin and soft tissue infections (SSTI) caused by *S. aureus* and coagulase-negative staphylococci (CoNS) in more than 700 adults (3-7). Overall, the conclusion found that cefalexin was equally effective as the comparators, and that treatment failures were mostly related to MRSA. The dosages used, where stated, were 500 mg x 2-4. In a small RCT from 1983, cefalexin was compared and found non-inferior to dicloxacillin for *S. aureus* impetigo in children (<14 years) (8). Only 78 children were included, and the dosage used was 25 mg/kg x 2.

Cefadroxil

Cefadroxil was found equally effective as azithromycin in an RCT of 296 adults with uncomplicated SSTI (9). In another RCT of 499 paediatric patients with uSSTI comparing cefadroxil and linezolid (10), clinical cure rates were similar and both treatments effective. Cefadroxil was also evaluated in a large RCT of 1685 cases of uSSTI, comparing cefadroxil to oral cefuroxime and cefditoren (11). Cefadroxil had similar cure rates as the comparators.

Cefaclor

The *in vitro* activity of cefaclor might be greater than that of cefalexin against staphylococci based on differences in MIC-values and protein binding, however, cefaclor is less stable to staphylococcal penicillinase (12, 13). There are several clinical studies evaluating cefaclor in the treatment of SSTI, where *S. aureus* has been the most common pathogen. Overall, the results support the use of cefaclor in both adults and children (14-17). However, in an RCT comparing cefaclor to cefpodoxime in 196 patients with uSSTI, mainly caused by *S. aureus*, cefaclor had a higher, though not significant, failure rate (18).

Cefuroxime oral

There are hardly any clinical studies evaluating the use of oral cefuroxime in the treatment of *S. aureus* infections. Bucko et al. compared oral cefditoren (200 mg x 2 and 400 mg x 2) to cefuroxime (250 mg x 2) and cefadroxil (500 mg x 2) in an RCT (11). In this study, 1685 patients with various uSSTI were included, and in half of the cases *S. aureus* was found to be the causative pathogen. Clinical cure rates were similar among all four treatments, at 83 – 88%.

Cefpodoxime

Clinical trials evaluating cefpodoxime against *S. aureus* are very scarce. Cefpodoxime was compared to cefaclor in an RCT including 196 patients with uSSTI (18). Clinical cure rate was 99% for the 139 patients in the cefpodoxime arm.

PARENTERAL CEPHALOSPORINS:

Cefazolin (and Cephalothin)

Cefazolin is the only intravenous agent for which there are reasonable number of publications on efficacy, mostly supportive of it's use as a primary or supportive therapy for MSSA bacteraemia (19-25). A lingering issue with this agent is the inoculum effect: a recent clinical study showed increased 30-day all-cause mortality associated with strains possessing a demonstrable inoculum effect *in vitro* (26). It is suggested that the inoculum effect is associated with the type of penicillinase harboured by the infecting strain (27), and a test for the rapid detection of the inoculum effect has been developed (28). The clinical study found an inoculum effect in 54.5% of the 77 patients included (26). A recent French study showed that cefazolin was as effective as oxacillin or cloxacillin in the treatment of *S. aureus* infective endocarditis, an infection where the presence of an inoculum effect would be expected to be a problem (the authors did not test for it) (29).

One large multicentre Finnish RCT from 1983-2005 included a total of 189 children (<16 years) with *S. aureus* osteoarticular infections (30, 31). This trial compared first-generation cephalosporin (IV with oral follow-on) to clindamycin. Both regimens were found to be equally effective, but they concluded that a high dose of both agents were needed (150 mg/kg/day, q6h). The papers evolving from this study are the main basis of the ESPID recommendation for the bone and joint infections.

Cefuroxime iv

The efficacy of intravenous cefuroxime is unclear, and there is a lack of RCTs to draw a definitive conclusion. Three Danish retrospective studies have compared cefuroxime to benzylpenicillin/dicloxacillin, dicloxacillin or piperacillin-tazobactam, respectively. Nissen et al. compared cefuroxime iv to benzylpenicillin or dicloxacillin in penicillin-susceptible *S. aureus* bacteraemia and found a significantly higher mortality with cefuroxime (32). In this study a dosage of 750 mg x 3 was regarded as an optimal dosage of cefuroxime. Rasmussen et al. compared cefuroxime iv with dicloxacillin in bacteraemic *S. aureus* infections, reporting that cefuroxime was associated with significantly greater 90-day mortality (33). Unfortunately, neither cefuroxime dosages nor duration of antimicrobial therapy were examined in this study. Bigseth et al. looked at empirical therapy with cefuroxime or piperacillin-tazobactam in *S. aureus* bacteraemia and found no difference in mortality or relapse between the two regimens (34). Dosages were not registered in this study either, however, it stated that most patients received 1.5 g x 3. The need for a high dose is supported by a further Danish study using PK determined in healthy volunteers, where Monte Carlo simulations showed that a dosage of at least 1.5 g x 3 was required to reach the *S. aureus* ECOFF of 4 mg/L (35).

Cefotaxime

Aldridge summarised the outcomes for MSSA infections in multiple clinical studies that were conducted on cefotaxime efficacy up to 1995 (36). Clinical cure rates of >90% were seen in cases of bacteraemia, pneumonia, skin and skin structure infections, and bone and joint infections. Microbiological eradication was also >90% for these conditions, apart from skin and structure infections, where the eradication was 85%. Dosages were not addressed in this review. Similarly, although not studied formally, cefotaxime appears to be effective in lower respiratory infections caused by *S. aureus* (37). Dosages in this study varied widely.

Ceftriaxone

The efficacy of ceftriaxone in MSSA bloodstream infections has recently been the subject of a meta-analysis (38). Alsowaida et al. reviewed 12 controlled studies where ceftriaxone was used to treat serious MSSA infections associated with bacteraemia. The authors concluded that ceftriaxone was noninferior to comparator agents on measures of clinical cure, microbiological cure, 30- and 90-day mortality. In the separate studies, comparators included cefazolin most commonly, but also isoxazoylpenicillins and nafcillin. A further study of MSSA bacteraemia, published after the

meta-analysis, reached similar conclusions, with ceftriaxone being noninferior to cefazolin as follow-on outpatient therapy on measures of treatment failure (repeat positive blood culture within 6 months of the original episode) or 30-day all-cause readmission (39). Ceftriaxone dosages in these studies were not commonly reported, but when they were, the commonest dosage way 2 g x 1 iv. Comparable efficacy has also been seen in paediatric outpatient when ceftriaxone at a dosage of 50 mg/kg daily was compared to flucloxacillin (40).

Cefepime

Although not studied formally, cefepime appears to work well clinically in serious *S. aureus* infections, including osteomyelitis (41). The cefepime dosage used in this study was 2 g x 2.

Implications for Susceptibility Testing

The current evidence supports concept that parenteral cephalosporins in high dosage will be effective in serious MSSA infections. However, the evidence for cefuroxime is conflicting. PK/PD studies suggest suboptimal activity even at the highest dosages. The clinical evidence for the use of cefuroxime is also unclear but a dosage of 1.5 g x 3 is most likely effective even in severe infections.

The EUCAST recommendation is that for MSSA, susceptibility can be inferred for the following parenteral agents:

- Cefazolin, provided a dosage of 2 g x 3
- Cefuroxime iv, provided a dosage of 1.5 g x 3
- Cefotaxime, provided dosages of 2 g x 3-4
- Ceftriaxone, provided dosages of 2 g x 2 iv or 4 g x 1 iv are used, and preferably only as follow-on therapy after initial response to other more established agents
- Cefepime, provided a dosage of 2 g x 3

There are no specific staphylococcal breakpoints for these agents, and testing of individual isolates for clinical purposes, including MIC determination by e.g. gradient diffusion should not be performed. If these agents are reported for MSSA, they should be reported as “Susceptible, increased exposure” (I).

Further, for MSSA in less severe infections or as oral follow-on therapy, susceptibility can be inferred for the following oral agents:

- Cefalexin and Cefadroxil
- Cefaclor
- Cefpodoxime
- Cefuroxime oral

“For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised.”

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APPENDIX

Staphylococcus spp. and Parenteral Cephalosporin Breakpoints

General Consultation

26 September 2022

Please send comments to the EUCAST Scientific Secretary at jturnidge@gmail.com by **November 7, 2022**

Current "breakpoints"

Cephalosporins[1]	MIC breakpoints (mg/L)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.	Linked dosages
	S ≤	R >	ATU		
Cefazolin	Note[1]	Note[1]		**1/A.** Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. If cefotaxime and ceftriaxone are reported for methicillin-susceptible staphylococci, these should be reported "Susceptible, increased exposure" (I). Some methicillin-resistant *S. aureus* are susceptible to ceftaroline and ceftobiprole**, see Notes 5/D and 7/F.** **2.** See table of dosages.	S: 1 g x 3, H 2 g x 3
Cefepime	Note[1]	Note[1]			S: 1 G x 3 or 2 g x 2; H: 2 g x 3
Cefotaxime[2]	Note[1]	Note[1]			S: 1 g x 3, H 2 g x 3 *S. aureus;* high dose only
Ceftriaxone[2]	Note[1]	Note[1]			S: 2 g x 1; H: 2 g x 2 or 4 g x 1
Cefuroxime iv	Note[1]	Note[1]			S: 0.75 g x 3; H: 1.5 g x 3 *S. aureus:* high dose only

Proposals

Cephalosporins[1]	MIC breakpoints (mg/L)		
	S ≤	R >	Special situations
Cefazolin	Note[1]	Note[1]	*S. aureus* high dosage only
Cefepime	Note[1]	Note[1]	*S. aureus* high dosage only
Cefotaxime	Note[1]	Note[1]	*S. aureus* high dosage only
Ceftriaxone	Note[1]	Note[1]	*S. aureus* high dosage and non-serious infection only
Cefuroxime iv	Note[1]	Note[1]	*S. aureus* high dosage only

Note 1/A modified to:

1/A. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. If cefazolin, cefepime, cefotaxime, ceftriaxone or cefuroxime are reported for methicillin-susceptible *Staphylococcus aureus*, these should be reported “Susceptible, increased exposure” (I) and ceftriaxone should additionally be reported as "suitable only for non-serious infection" . Some methicillin-resistant *S. aureus* are susceptible to ceftaroline and ceftobiprole, see Notes 5/D and 7/F.

Background

EUCAST does not list breakpoints for *Staphylococcus* spp. and most cephalosporins. Instead, susceptibility/resistance is inferred from the cefoxitin susceptibility test result as described in Note 1/A.

Note 1/A. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections. For agents given orally, care to achieve sufficient exposure at the site of infection should be exercised. If cefotaxime and ceftriaxone are reported for methicillin-susceptible staphylococci, these should be reported as “Susceptible, increases exposure” (I).

Breakpoints are provided for two cephalosporins that have specifically developed and marketed for the treatment of methicillin-resistant *S. aureus*. EUCAST suggests that methicillin-susceptible *Staphylococcus* spp. can be reported without testing specifically for these agents.

In reviewing the Dosages tab in the Breakpoint Tables v11.0, questions have arisen about whether the currently listed cephalosporin High dosages are approriate for staphylococcal infection. These doages are:

Breakpoints for *Staphylococcus aureus* have already been set for two cephalosporins with activity against methicillin-resistant strains; ceftobiprole and ceftaroline.

Cephalosporins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Cefaclor	0.25-0.5 g x 3 oral depending on species and/or infection type	1 g x 3 oral		***Staphylococcus* spp.:** Minimum dose 0.5 g x 3 oral
Cefadroxil	0.5-1 g x 2 oral	None	0.5-1 g x 2 oral	
Cefalexin	0.25-1 g x 2-3 oral	None	0.25-1 g x 2-3 oral	
Cefazolin	1 g x 3 iv	2 g x 3 iv		
Cefepime	1 g x 3 iv or 2 g x 2 iv	2 g x 3 iv		
Cefiderocol	2 g x 3 iv over 3 hours	None		
Cefixime	0.2-0.4 g x 2 oral	None	0.2-0.4 g x 2 oral	**Uncomplicated gonorrhoea:** 0.4 g oral as a single dose
Cefotaxime	1 g x 3 iv	2 g x 3 iv		**Meningitis:** 2 g x 4 iv ***S. aureus*:** High dose only
Cefpodoxime	0.1-0.2 g x 2 oral	None	0.1-0.2 g x 2 oral	
Ceftaroline	0.6 g x 2 iv over 1 hour	0.6 g x 3 iv over 2 hours		***S. aureus* in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv		
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours			
Ceftibuten	0.4 g x 1 oral	None		
Ceftobiprole	0.5 g x 3 iv over 2 hours	None		
Ceftolozane-tazobactam (intra-abdominal infections and UTI)	(1 g ceftolozane + 0.5 g tazobactam) x 3 iv over 1 hour	None		
Ceftolozane-tazobactam (hospital acquired pneumonia, including ventilator associated pneumonia)	(2 g ceftolozane + 1 g tazobactam) x 3 iv over 1 hour	None		
Ceftriaxone	2 g x 1 iv	2 g x 2 iv or 4 g x 1 iv		**Meningitis:** 2 g x 2 iv or 4 g x 1 iv ***S. aureus*:** High dose only **Uncomplicated gonorrhoea:** 0.5-1 g im as a single dose
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv		
Cefuroxime oral	0.25 g x 2 oral	0.5 g x 2 oral	0.25 g x 2 oral	

This consultation focusses only on those cephalosporins which have no formal breakpoints but are used by some or all clinicians in the treatment of staphylococcal infections, namely the intravenous agents:

Cefazolin, cefepime, cefotaxime, ceftriaxone and cefuroxime

MIC distributions for *Staphylococcus aureus*

AGENT	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	(T)ECOFF
Cefazolin	0	0	0	0	0	18	359	3277	7870	4718	878	250	181	157	1343	0	0	0	201	5	2
Cefepime	0	0	1	12	10	4	8	34	180	548	2043	854	98	33	13	64	8	12	0	38	8
Cefotaxime	0	0	2	0	1	3	18	103	383	2174	2383	400	92	25	242	10	6	15	0	41	4
Ceftriaxone	0	0	0	0	0	0	0	0	0	4	119	211	8	9	1	3	1	1	0	3	(8)
Cefuroxime	0	0	0	2	3	2	55	363	1265	7230	1429	234	124	890	247	1	0	8	0	8	4

Pharmacokinetics and pharmacodynamics

Animal model data show that the determinant of efficacy in vivo is *f*% T>MIC [Appendix-1]. For two extended-spectrum cephalosporins, cefotaxime and ceftriaxone, the *f*% T>MIC values for bacteriostasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill are approximately 25%, 30% and 35% respectively (Figure).

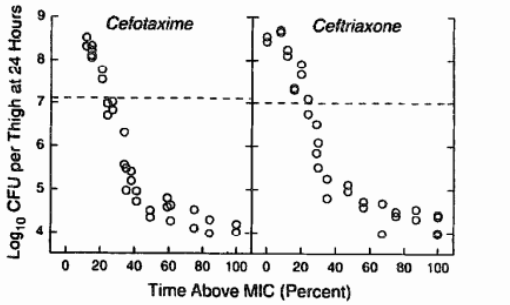

FIGURE 5 Relationship between percentage of time serum levels exceed the minimum inhibitory concentration (MIC) and the number of *Staphylococcus aureus* ATCC 25923 in the thighs of neutropenic mice after 24 h of therapy with cefotaxime (left panel) and ceftriaxone (right panel). Animals were infected by thigh injection 2 h before treatment. The dotted lines reflect the number of bacteria at the initiation of therapy. Free, unbound concentrations were used for ceftriaxone as estimated from protein binding measurements in murine serum.

Similar values have been found in an *in vitro* PK/PD model for ceftaroline [Appendix-2]: 24.5 ± 8.9% for bacteriostasis, 27.8 ± 9.5% for 1-$\log_{10}$ kill and 32.1 ± 8.1% for 2-$\log_{10}$ kill, suggesting that these values may apply across the whole class. Different targets were identified in an *in vitro* PD model by Zelenitsky et al. for cefazolin and ceftriaxone: 55% for bacteriostasis, 75% for 1-$\log_{10}$ kill and 100% for 3-$\log_{10}$ kill [Appendix-4]. The reason for the differences between these values and those observed in previous studies is not clear.

For ceftobiprole bacteriostasis targets in the mouse thigh model were 21% (range 14- 24%), with 2-log kill targets of 29% (range 24-39%) [Appendix-5]. Similar values have been observed in the mouse pneumonia model [Appendix-5,Appendix-6,Appendix-7].

In a recent *in vitro* model, different target values were obtained for ceftriaxone. Zelenitsky et al. found a bacteriostatic *f*T>MIC target of 55%, and a value of 75% for a 1-$\log_{10}$ kill [8]

Monte Carlo Simulations

Original PK publications were sought where available. Protein binding was sourced mostly from Reference [3]. Dosage regimens explored with those listed in the Dosages tab of Breakpoint Tables v11.0. Additional (higher) regimens were examined to determine whether these might provide better PTAs for some agents. Simulations were performed using the RiskAMP add-in (2020) for MS Excel.

Cefazolin **[ECOFF = 2]**

Healthy volunteers. PB(%): 91.6 ± 6.7; Vd (L): 6.94 ± 2.2; t½β (h): 1.45 ± 0.15 [Appendix-3,Appendix-9]

f%T>MIC 25%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	99	99	100	100
2	99	99	99	99
4	94	97	99	99
8	68	82	94	97

f%T>MIC 30%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	99	99	100	100
2	98	99	99	99
4	90	95	98	99
8	53	74	90	95

f%T>MIC 35%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	100	100	100
1	99	99	99	100
2	97	99	99	99
4	83	93	97	99
8	37	64	84	93

Red text and shading represent the ECOFF and the wild type respectively of ***Staphylococcus aureus***
Purple dosages are those already listed as either Standard or High on the Dosages tab

Cefazolin **[ECOFF = 2]**

Patients. PB(%): 91.6 ± 6.7; Vd (L): 13.01 ± 4.4; t½β (h): 1.8 ± 0.38 [Appendix-3,Appendix-10]

f%T>MIC 25%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	99	99	99	99
2	95	97	99	99
4	79	87	96	97
8	34	47	79	87

f%T>MIC 30%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	99	99	99	99
2	93	96	98	99
4	71	82	93	97
8	24	38	71	83

f%T>MIC 35%

	Regimen			
	1 g x 3	1 g x 4	2 g x 3	2 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	99	100	100
1	98	99	99	99
2	89	95	97	99
4	61	77	90	95
8	17	31	60	77

Cefepime **[ECOFF = 8]**

Patients. PB(%): 20.0 ± 5.0; Vd (L): 21.3 ± 6.5; $t_{½\beta}$ (h): 2.4 ± 0.7 [Appendix-11,Appendix-12]

f%T>MIC 25%

	Regimen		
	1 g x 3	2 g x 2	2 g x 3
0.5	100	100	100
1	100	100	100
2	100	100	100
4	100	99	100
8	98	98	99
16	76	92	98
32	13	46	76

f%T>MIC 30%

	Regimen		
	1 g x 3	2 g x 2	2 g x 3
0.5	100	100	100
1	100	100	100
2	100	99	100
4	99	99	100
8	96	96	99
16	64	84	96
32	9	31	64

f%T>MIC 35%

	Regimen		
	1 g x 3	2 g x 2	2 g x 3
0.5	100	100	100
1	100	99	100
2	99	99	100
4	99	98	100
8	93	93	98
16	52	73	93
32	6	20	52

Cefotaxime **[ECOFF = 4]**

Healthy volunteers. PB(%): 36.6 ± 5.9; Vd (L): 16.6 ± 8.1; $t_{½\beta}$ (h): 1.1 ± 0.4 [Appendix-3,Appendix-13]

f%T>MIC 25%

	Regimen			
	1 g x 3	2 g x 3	1 g x 4	2 g x 4
0.25	98	99	99	99
0.5	98	98	99	99
1	97	98	98	99
2	94	97	97	98
4	88	94	94	97
8	65	88	82	94
16	25	65	42	82

f%T>MIC 30%

	Regimen			
	1 g x 3	2 g x 3	1 g x 4	2 g x 4
0.25	98	98	99	99
0.5	97	98	98	99
1	95	97	97	98
2	91	95	96	98
4	80	91	91	95
8	51	80	73	91
16	17	51	31	72

f%T>MIC 35%

	Regimen			
	1 g x 3	2 g x 3	1 g x 4	2 g x 4
0.25	97	98	98	99
0.5	95	97	98	98
1	92	95	96	97
2	86	92	94	96
4	71	86	86	93
8	38	71	62	86
16	12	38	22	62

Ceftriaxone (Craig targets [1]) [ECOFF = 8]

Patients. PB(%): 92.7 ± 3.2; Vd (L): 7.8 ± 6.4; $t_{½\beta}$ (h): 8.1 ± 3.9 [Appendix-3,Appendix-14]

f%T>MIC 25%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	95	97	96	98
1	92	95	95	97
2	83	90	92	95
4	58	71	82	90
8	27	38	58	72
14	11	15	25	38
32	5	6	10	15

f%T>MIC 30%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	94	97	96	97
1	90	95	94	97
2	79	88	90	95
4	53	69	79	88
8	24	35	53	69
14	9	14	23	35
32	4	6	9	14

f%T>MIC 35%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	93	96	95	97
1	88	94	93	96
2	75	87	88	94
4	48	66	75	86
8	21	33	48	56
14	8	13	20	33
32	4	5	8	13

Ceftriaxone (Craig targets [1]) [ECOFF = 8]

Healthy volunteers. PB(%): 92.7 ± 3.2; Vd (L): 14.0 ± 2.1; $t_{½\beta}$ (h): 5.8 ± 1.2 [Appendix-3,Appendix-15]

f%T>MIC 25%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	96	98	98	98
1	91	95	96	98
2	65	83	90	95
4	13	40	65	83
8	0	1	13	41
14	0	0	0	2
32	0	0	0	0

f%T>MIC 30%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	96	97	98	98
1	87	94	95	97
2	54	80	86	94
4	7	33	55	80
8	0	1	7	34
14	0	0	0	1
32	0	0	0	0

f%T>MIC 35%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	94	97	97	98
1	83	93	94	97
2	43	77	82	93
4	3	27	43	78
8	0	0	3	28
14	0	0	0	0
32	0	0	0	0

Ceftriaxone **(Zelenitsky targets [8]) [ECOFF = 8]**

Patients. PB(%): 92.7 ± 3.2; Vd (L): 7.8 ± 6.4; $t_{½\beta}$ (h): 8.1 ± 3.9 [Appendix-3,Appendix-14]

f%T>MIC 55%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	87	95	91	96
1	78	91	87	95
2	58	80	78	91
4	31	55	58	80
8	13	25	31	55
14	5	10	13	25
32	2	4	5	10

f%T>MIC 75%

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	80	92	87	95
1	66	87	80	92
2	43	73	66	87
4	20	46	43	73
8	8	20	20	46
14	3	8	8	20
32	2	3	3	8

Ceftriaxone **(Zelenitsky targets [8]) [ECOFF = 8]**

Healthy volunteers. PB(%): 92.7 ± 3.2; Vd (L): 14.0 ± 2.1; $t_{½\beta}$ (h): 5.8 ± 1.2 [Appendix-3,Appendix-15]

*f*T>MIC 55

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	83	96	94	98
1	50	89	83	96
2	9	59	50	89
4	0	9	9	59
8	0	0	0	9
14	0	0	0	0
32	0	0	0	0

*f*T>MIC 75

	Regimen			
	1 g x 1	1 g x 2	2 g x 1	2 g x 2
0.5	56	93	83	97
1	17	79	56	93
2	1	37	17	79
4	0	2	1	37
8	0	0	0	2
14	0	0	0	0
32	0	0	0	0

Cefuroxime [ECOFF = 4]

Patients. PB(%): 37.5 ± 10.6; Vd (L): 11.4 ± 2.6; t½β (h): 1.32 ± 0.36 [Appendix-3,Appendix-16]

*f*T>MIC 25

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	100	100	100	100
2	99	100	100	100
4	98	99	99	100
8	89	98	97	99

*f*T>MIC 30

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	100	100	100	100
1	99	100	100	100
2	98	99	99	100
4	95	98	99	99
8	78	95	93	98

*f*T>MIC 35

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	100	100	100	100
0.25	100	100	100	100
0.5	99	100	100	100
1	99	99	99	100
2	97	99	99	100
4	91	97	97	99
8	62	91	97	97

Cefuroxime [ECOFF = 4]

Healthy volunteers. PB(%): 37.5 ± 10.6; Vd (L): 13.4 ± 4.5; t½β (h): 1.41 ± 0.47 [Appendix-3,Appendix-17]

*f*T>MIC 25

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	99	100	100	100
0.25	99	99	100	100
0.5	99	99	100	100
1	99	99	99	100
2	98	99	99	99
4	95	98	98	99
8	81	95	92	98

*f*T>MIC 30

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	99	99	100	100
0.25	99	99	99	100
0.5	99	99	99	99
1	98	99	99	99
2	96	98	98	99
4	91	96	96	98
8	69	91	86	96

*f*T>MIC 35

	Regimen			
	0.75 g x 3	1.5 g x 3	0.75 g x 4	1.5 g x 4
0.125	99	99	99	100
0.25	99	99	99	99
0.5	98	99	99	99
1	97	98	98	99
2	94	97	97	99
4	86	94	94	97
8	55	85	78	94

Clinical data

Cefazolin is the only agent for which there are reasonable number of publications on efficacy, mostly supportive of its use as a primary or supportive therapy for MSSA bacteraemias [Appendix-18-Appendix-24]. A lingering issue with this agent is the inoculum effect. A recent clinical study showed increased 30-day all-cause mortality associated with strains possesing a demonstrable inoculum effect *in vitro* [Appendix-25]. It is suggested that the inoculum effect is associated with the type of penicillinase harboured by the infecting strain [Appendix-26], and a test for the rapid detection of the inoculum effect has been developed [Appendix-27]. A recent French study showed that cefazolin was as effective as oxacillin or cloxacillin in the treatment of *S. aureus* infective endocarditis, an infection where the presence of an inoculum effect would be expected to be a problem (the authors did not test for it)(Appendix-28).

Although not studied formally, cefepime appears to work well clinically in serious *S. aureus* infections, including osteomyelitis (Appendix-30) The cefepime dosage used in this study was 2 g x 2. Similarly, although not studied formally, cefotaxime appears to be effective in lower respiratory infections caused by *S. aureus* (Appendix-29). Dosages in this study varied widely.

Two recent studies have examined the efficacy of ceftriaxone in methicillin-susceptible *Staphylococcus aureus* bacteraemia [Appendix-23] and undifferentiated cellulitis in children [Appendix-31]. In the first, ceftriaxone, mostly at a once-daily dose of 2 g, was demonstrably inferior to cefazolin, mostly at a dose 2 g x 3. The authors attributed the poorer efficacy to the high protein binding of ceftriaxone. In the latter study, ceftriaxone as outpatient therapy at a dose of 50 mg/kg daily (equivalent to an adult dose of 2g x 1), was as efficacious as inpatient flucloxacillin (Appendix-32). This study did not seek the causative pathogen, and the frequency with which *S. aureus* was the cause was unknown. Furthermore, a recent meta-analysis suggested non-inferiority of ceftriaxone in MSSA bacteraemia compared to standard of care, although the studies were somewhat heterogeneous [Appendix-33]

The efficacy of intravenous cefuroxime is unclear. In a recent Danish study comparing cefuroxime iv with dicloxacillin in bacteraemic *S. aureus* infections, cefuroxime was associated with significantly greater 30-day mortality (Appendix-34). Unfortunately, cefuroxime dosages were not examined in this study. A further Danish study, using PK determined in healthy volunteers, showed using Monte Carlo simulation that a dosage of at least 1.5 g x 3 was required to reach the *S. aureus* ECOFF of 4 mg/L (Appendix-35),

Conclusions

Available clinical data and PK/PD analyses support the use of cefazolin and cefepime with the currently listed dosage regimens. PK/PD analysis support the use of cefuroxime iv, but published experience with its use is limited and high dosages are required. PK/PD analyses suggest that cefotaxime may not be a reliable agent, especially in serious infections. This is also the case for ceftriaxone, although there is ongoing controversy in the literature about is role and efficacy [Appendix-32].

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