EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Guidance Document on Cefotaxime and Ceftriaxone for *Staphylococcus aureus* infection

January 2023

Background

Two third-generation cephalosporins, cefotaxime and ceftriaxone, have been used for many years in selected instances of more serious methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, such as allergy to beta-lactams, mixed infections, and in the case of ceftriaxone, as stepdown outpatient intravenous therapy. 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 because it permits once-daily dosing.

To determine if the current recommendation that *Staphylococcus aureus* susceptibility to these agents can be inferred provided that the isolates are phenotypically or genotypically negative for *mecA* or *mecC*, EUCAST has reviewed the PK/PD of these and similar parenteral cephalosporins, and, where available, the data on clinical outcomes. The review and Steering Committee proposals underwent General Consultation in 2022 [Appendix].

Outcomes of Pharmacokinetic/Pharmacodynamic Analysis

A recent EUCAST review of the pharmacokinetics and pharmacodynamics of cefotaxime and ceftriaxone and subsequent consultation showed efficacy against wild-type*. aureus* could be achieved with high-dosages of cefotaxime (2 g x 3-4 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 [1].

Clinical Outcome Studies with Cefotaxime

Aldridge summarised the outcomes for MSSA seen multiple clinical studies that were conducted on cefotaxime efficacy up to 1995 [2]. Clinical cure rates of >90% were seen 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.

Clinical Outcome Studies with Ceftriaxone

The efficacy of ceftriaxone in MSSA bloodstream infections has recently been the subject of a meta-analysis [3]. Alsowaida et al. reviewed 12 controlled studies where ceftriaxone was used to treat serious MSSA infections associated with bacteraemia. They concluded that ceftriaxone was noninferior to comparator agents on measures of clinical cure, microbiological cure, 30- and 90-day mortality. In the different 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 stepdown outpatient therapy on measures of treatment failure (repeat positive blood culture within 6 months of the original episode) or 30-day all-cause readmission [4]. In these studies ceftriaxone dosages 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 [5].

Implications for Susceptibility Testing

The current evidence supports concept that cefotaxime in high dosage will be effective in serious MSSA infections. The evidence for ceftriaxone, is conflicting. PK/PD studies suggest suboptimal activity even at the highest dosages.

The EUCAST recommendation is that for MSSA, susceptibility can be inferred for

- Cefotaxime, provided dosages of 2 g x 3-4 are used
- Ceftriaxone, provided dosages of 2 g x 2 iv or 4 g x 1 iv are used, and preferably only as stepdown therapy after initial response to other more established antistaphylococcal agents

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, is strongly discouraged.

References

[1] Heffernan AJ, Sime FB, Lim SMS, Adiraju S, Wallis SC, Lipman J, Grant GD, Roberts JA. Pharmacodynamics of ceftriaxone for the treatment of methicillin-susceptible *Staphylococcus aureus*: is it a viable treatment option? Int J Antimicrob Agents. 2022 Mar;59(3):106537.

[2] Aldridge, Kenneth E. Cefotaxime in the treatment of staphylococcal infections: Comparison of in vitro and in vivo studies. Diagnostic microbiology and infectious disease, 1995, Vol.22 (1), p.195-201

[3] Alsowaida YS , Benitez G, Saleh KB, Almangour TA, Shehadeh F, Mylonaki E. Effectiveness and Safety of Ceftriaxone Compared to Standard of Care for Treatment of Bloodstream Infections Due to Methicillin-Susceptible *Staphylococcus aureus*: A Systematic Review and Meta-Analysis, Antibiotics 2022; 11, 375.

[4] Ganguly A, de la Flor C, Alvarez K, Brown LS, Mang NS, Smartt J, King H, Perl TM, Filizola H, Bhavan KP. Safety and efficacy of ceftriaxone in the treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections: a noninferiority retrospective cohort study. Ann Pharmacother 2022 Aug 9;10600280221115460. Online ahead of print.

[5] Ibrahim LF, Hopper SM, Orsini F et al. Efficacy and safety of intravenous ceftriaxone at home versus intravenous flucloxacillin in hospital for children with cellulitis (CHOICE): a single-centre, open-label, randomised, controlled, non-inferiority trial. Lancet Infect Dis 2019; 19:477-86.

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 cetotaxime 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 [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).

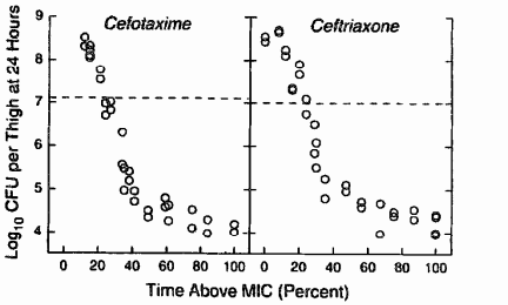

FIGURE 5 Relationship between percentage of time serum levels exceed the minimum inhibitory concentration (MIC) and the number of *Staphylococcus aureus* ATCC 25923 in the thighs of neutropenic mice after 24 h of therapy with cefotaxime (left panel) and ceftriaxone (right panel). Animals were infected 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 [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 [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%) [5]. Similar values have been observed in the mouse pneumonia mode [5,6,7].

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 [3,9]

***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 grey 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
Red line indicates highest MIC giving at least 95% target attainment with that dosing regimen

Cefazolin **[ECOFF = 2]**

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

***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 [11,12]

***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 [3,13]

***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 [3,14]

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 [3,15]

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; t½β (h): 8.1 ± 3.9 [3,14]

	f%T>MIC 55% Regimen					*f*%T>MIC 75% Regimen			
	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
0.5	87	95	91	96	0.5	80	92	87	95
1	78	91	87	95	1	66	87	80	92
2	58	80	78	91	2	43	73	66	87
4	31	55	58	80	4	20	46	43	73
8	13	25	31	55	8	8	20	20	46
14	5	10	13	25	14	3	8	8	20
32	2	4	5	10	32	2	3	3	8

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

Healthy volunteers. PB(%): 92.7 ± 3.2; Vd (L): 14.0 ± 2.1; t½β (h): 5.8 ± 1.2 [3,15]

	*f*T>MIC 55 Regimen					*f*T>MIC 75 Regimen			
	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
0.5	83	96	94	98	0.5	56	93	83	97
1	50	89	83	96	1	17	79	56	93
2	9	59	50	89	2	1	37	17	79
4	0	9	9	59	4	0	2	1	37
8	0	0	0	9	8	0	0	0	2
14	0	0	0	0	14	0	0	0	0
32	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 [3,16]

*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 [3,17]

*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 [18-24]. 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 [25]. It is suggested that the inoculum effect is associated with the type of penicillinase harboured by the infecting strain [26], and a test for the rapid detection of the inoculum effect has been developed [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)(28).

Although not studied formally, cefepime appears to work well clinically in serious *S. aureus* infections, including osteomyelitis (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* (29). Dosages in this study varied widely.

Two recent studies have examined the efficacy of ceftriaxone in methicillin-susceptible *Staphylococcus aureus* bacteraemia [23] and undifferentiated cellulitis in children [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 (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 [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 (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 (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 [32].

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