Table 1: Dosing for backbone antibiotics in SNAP Trial

Principles of dosing

The dosing regimens included below have been derived from the following types of studies, with preference given to clinical data ahead of pre-clinical data:

a) clinical outcome studies to define maximally effective dosing regimens
b) clinical pharmacokinetic studies to define doses that achieve pharmacodynamic targets
c) pre-clinical infection model studies that define pharmacodynamic targets or improved bacterial killing with different infusion durations or frequency of dosing

The doses below are strongly recommended for patients enrolled in the SNAP Trial, however local or patient-specific circumstances may mean that different dosing regimens are required. Second-line dosing regimens are included, where relevant, in parentheses. If using the dose for 'critically ill or IE or deep-seated infections', the dose can be reduced to standard dose with resolution of critical illness, or at 2 weeks for deep seated infections.

Indication	**Benzylpenicillin**	**Cloxacillin**	**Flucloxacillin**	**Cefazolin**	**Clindamycin**[1]
Standard dose	1.8 g (3 MU) IV 4-hourly[2,3,4] (2.4 g [4 MU] IV 6-hourly)	2 g IV 4-hourly[6,7,8]	2 g IV 6-hourly[9,10]	2 g IV 8-hourly[12,13]	600 mg IV 8-hourly
High dose Critically unwell (ie patients in ICU) or IE or CNS infection	2.4 g (4 MU) IV 4-hourly (FDA max dose 18 g/day)[4,5]	2 g IV 4-hourly[6,7,8] (FDA max dose 12 g/day)	2 g IV 4-hourly [10,11] (FDA max 12 g/day)	2 g IV 6-hourly[13,14] (FDA max dose 12 g/day)	
Renal impairment (based on Australian Therapeutic Guidelines: Antibiotic v 16 2019, unless otherwise stated)	CrCl less than 50 mL/min and above 10 mL/min: 75% of total daily dose	CrCl less than 30 min/min: no dose reduction required	CrCl less than 10 mL/min: 1 g IV 6-hourly (max 4g per day)	CrCl 20-40 mL/min: 2g IV 12-hourly	
	CrCl less than 10 mL/min: administer a single loading dose of 1.8g (standard dose) or 2.4g (for patients requiring high dose) followed by 1.2g q8h (standard dose) or 1.2g q6h (for patients requiring high dose)[15]. (TG: max 6g [10MU] per day. Renal Drug handbook: max 4.8g [8MU] /day)			CrCl less than 20 mL/min[16]: 1g q24h	

continuous renal replacement therapy	1.2 to 1.8 g (2-3 MU) IV 6-hourly[17]	no dose reduction required	2 g IV 6 to 8 hourly[18]	1 g 8-hourly or 2 g 12-hourly[19]	

ICU: intensive care unit. IE: infective endocarditis. CNS: central nervous system. IV: intravenous. MU: million units. CrCl: creatinine clearance.

1. Clindamycin dosing for virulence gene suppression. Support for 600mg q8h doses is provided by data from hollow fibre models. References: Shukla SK, Carter TC, Ye Z, Pantrangi M, Rose WE. Modeling of Effective Antimicrobials to Reduce Staphylococcus aureus Virulence Gene Expression Using a Two-Compartment Hollow Fiber Infection Model. Toxins (Basel). 2020;12(2):69-72, and Pichereau S, Pantrangi M, Couet W, Badiou C, Lina G, Shukla SK, et al. Simulated antibiotic exposures in an in vitro hollow-fiber infection model influence toxin gene expression and production in community-associated methicillin-resistant Staphylococcus aureus strain MW2. Antimicrob Agents Chemother. 2012;56(1):140-7.
2. Clinical success using benzylpenicillin 3g IV q6h (96% of patients had 50% fT>MIC with this dose, 71% had 100% fT>MIC) for IE (Obrink-Hansen et al), not a common regimen in Australia, though 1.8g IV q4h provides a similar total daily dose with pharmacokinetic advantages of shortened dosing interval.
3. At MIC 0.125 mg/L, for 50% fT>MIC for benzylpenicillin 1.8g IV q4h and 2.4g IV q6h are both PTA is >90%. At MIC 0.125 mg/L, for 100% fT>MIC, PTA with 1.8g q4h is approx. 88%, with 2.4g q6h is approx. 65%. (Bos et al)
4. Benzylpenicillin mean daily dose (MDD) for patients that got adverse effects was 13.5g/day compared to no ADRs MDD was 12.0g/day P=0.003. Also showed that as MDD decreased over time (1984-85 MDD 16.9g/d, after 1986 MDD 12g/day incidence of neutropenia decreased from 35% to 8% P=0.01. Authors recommend not exceeding 12g/day if treatment intended for longer than 2 weeks (Olaison et al 1990 and 1999).
5. Benzylpenicillin efficacy target: 2.4g IV q4h (standard dose) achieved 100% fT>MIC in Gloria Wong's 2018 paper (composite doses and pathogens, ie no MICs).
6. Cloxacillin efficacy target: at MIC 0.5 mg/L for 50% fT>MIC, 2g q6h PTA only 50%, at MIC 0.5 mg/L for 50% fT>MIC 2g IV q4h gives PTA 100% (Courjon et al).
7. Cloxacillin toxicity: concerns of nephrotoxicity with doses of 12g/day (or cloxacillin concentration above 50mg/L, Lavergne 2018 IJAA)
8. Cloxacillin 2g IV q4h has clinical efficacy data in IE (Fortun, Ribera).
9. Flucloxacillin efficacy target: at MIC 0.5mg/L for 50% fT>MIC, 2g IV q6h, PTA 100% (as did 1g IV q6h and 1g IV q4h, Ulldemolins 2010).
10. Flucloxacillin toxicity: Hepatotoxicity not generally considered dose related, one study described hepatoxicity with higher doses, defined as greater than 1.5g/day (Olssen et al), there is minimal information about nephrotoxicity related to flucloxacillin dose or concentration, and neurotoxicity was related to flucloxacillin Cmin of 125.1 mg/L (total concentration) equivalent to a free level of 7.5mg/L (Imani et al).
11. Flucloxacillin efficacy targets: ICU patients 2g IV q4h target 100% fT>MIC, for MIC 0.5 mg/L, eGFR 96 mL/min: 87% PTA; for eGFR 153 mL/min, 71% PTA—use CI or TDM. MIC 0.25 mg/L, target 100% fT>MIC, eGFR 96 mL/min or less: >90% PTA (Jager 2020). In another analysis from healthy volunteers: 2g IV q4h, 100% will get 50% fT>MIC up to MIC of 1 mg/L; for MIC 0.5mg/L, 2g IV q4h achieved approx. 88% T>MIC (Landersdorfer)
12. Cefazolin efficacy target: (1 g and 2 g q8h) achieved 100% ƒT>MIC for MIC distributions 0.5-1mg/L, though actual data wasn't presented in paper (Zelenitsky, 2018 JAC). A second study aiming for 50% fT>MIC, 97% PTA for MIC 2mg/L with 2g IV q8h (So et al 2014)
13. Cefazolin toxicity: absence of toxicity when cefazolin concentrations less than 100mg/L, in a study of CIV cefazolin for bone infection. Only 1 had pt had confusion with a level of 127mg/L (Zeller et al). Cefazolin shows neurotoxicity and nephrotoxicity in animal models, albeit at doses far above what would be used in humans (Schliamser 1991, Silverblatt 1973).

14. Efficacy targets: cefazolin penetration into ISF, for MIC 2 mg/L and ClCr of 215 mL/min, 2 g 6-hourly achieved 84% fractional target attainment. (Roberts)
15. Australian Guidelines (Therapeutic Guidelines: Antibiotic v 16 2019) recommend 25-50% of total daily dose. For 'standard dose' patients, 1.2g q8h is 33% of total daily dose (10.8g/day), and for 'high dose' patients, 1.2 q6h is 33% of total daily dose (14.4g/day).
16. For patients on haemodialysis, use a dose of 2g after each haemodialysis session (Kuypers 1998).
17. Cheng et al 2019 recommended 1.8g IV q6h for penicillin-susceptible *S. aureus* bacteraemia based on data from 2 critically unwell patients receiving prolonged intermittent renal replacement therapy.
18. Williams et al 2019 recommended flucloxacillin 2g IV q6h for critically unwell patients receiving CRRT (doses selected for continuous venovenous haemofiltration and assumed an ultra- filtration rate of 2000 mL/h). However, the committee noted that when therapeutic drug monitoring is undertaken, the dose can sometimes be reduced to 2g IV q8h, so either regimen is acceptable.
19. These doses are supported by the Pistolesi 2019 review of antimicrobial dosing in critically ill patients on CRRT.

EUCAST ECOFFs (CLSI Susceptible BP)

- Benzylpenicillin: 0.125mg/L (0.12)
- Cefazolin: 2.0mg/L (inferred from methicillin results)
- Cloxacillin: 0.5mg/L (inferred from oxacillin or cefoxitin results)
- Clindamycin: 0.5mg/L (0.5)
- Flucloxacillin: (as for cloxacillin) 0.5mg/L (not addressed)