SESLHD PROCEDURE COVER SHEET

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FUNCTIONAL GROUP(S)	Medicine Pharmacy/Pharmaceutical
KEY TERMS	Antimicrobial Stewardship, antimicrobials, medications
SUMMARY	This procedure outlines the requirements for the safe administration of antimicrobials by prolonged or continuous infusion in the inpatient setting.

1. POLICY STATEMENT

This procedure outlines the safe administration of antibiotics by prolonged or continuous infusion in the inpatient setting. The procedure has been developed for use in hospital inpatients (not HITH/PACs).

The aim of this procedure is to:
- Provide staff with evidence-based information and procedures for management of prolonged or continuous antibiotic infusions
- Ensure safety, stability, compatibility and efficacy of prolonged or continuous antibiotic infusions
- Ensure appropriate prescribing and monitoring of prolonged or continuous antibiotic infusions.

2. BACKGROUND

Administration by prolonged or continuous infusion over 24 hours can optimise the bacterial killing of some antibiotics (in particular beta-lactams) by optimising time during the dose interval that the free drug concentration exceeds the minimum inhibitory concentration (MIC) of the target organism[1] while reducing the risk for adverse drug reactions, which are often peak-dependent. Administration of antibiotics by prolonged or continuous infusion is determined by the stability of the medication. If prepared or administered incorrectly, there is potential for increased risk of patient harm due to precipitation of medication or infusion site reactions (i.e. phlebitis). Stability is limited by the concentration, diluents, admixtures and infusion device temperature[1].

The administration of beta-lactams by continuous infusion has been shown to be at least as effective as intermittent dosing[1]. Antibiotic infusion may be preferred in patients with difficult to treat infections who require pharmacokinetic optimisation of antibiotic dose. This should be discussed with Infectious Diseases and Antimicrobial Stewardship (AMS) pharmacist.

Definitions:
- **Continuous antibiotic infusion:** antibiotic infusion administered over a continuous period of time (e.g. 12 hours or 24 hours), with the next dose commenced immediately restarted at the completion of the infusion
- **eMMS**: electronic medication management system – provided by Cerner eMEDs application
- **eRIC**: electronic medical record for Intensive Care
- **PICC:** peripherally inserted central catheter
- **Prolonged antibiotic infusion**: antibiotic infusion administered over a prolonged period of time (40-50% of the dosing interval, eg. over 3-4 hours) over the course of the dosing interval
- **TDM**: therapeutic drug monitoring – measurement of drug levels in the blood to ensure therapeutic and safe doses are maintained for effective therapy.

3. RESPONSIBILITIES

Medical Officers will:
- Be familiar with policies and procedures outlined in this document prior to prescribing antibiotic infusions to patients
- Liaise with Infectious Diseases team prior to prescribing antibiotics by continuous or prolonged infusion
- Ensure patient is appropriate for the prolonged or continuous antibiotic infusion, taking into consideration availability of lines for duration of infusion, compatibility with other IV medications, and suitability of patient for prolonged infusion (e.g. mobility of patient)
- Ensure appropriate dose of antibiotic is correctly charted in the eMMS
- Document on medical treatment order fluids to be administered.

Pharmacists will:
- Be familiar with policies and procedures outlined in this document prior to dispensing antibiotics for infusion to patients
- Collaborate with medical officer(s) and nursing staff to ensure patient is appropriate for antibiotic infusion, taking into consideration availability of lines for duration of infusion, compatibility with other IV medications, and suitability of patient for prolonged infusion (e.g. mobility of patient)
- Advise on appropriate prescribing and preparation of antibiotic infusion to ensure stability of dose over duration of infusion (up to 24 hours).

Nurses will:
- Be familiar with policies and procedures outlined in this document prior to providing antibiotic infusions to patients
- Collaborate with medical officer and pharmacist to ensure patient is appropriate for antibiotic infusion, taking into consideration availability of lines for duration of infusion, compatibility with other IV medications, and suitability of patient for prolonged infusion (e.g. mobility of patient)
- Prepare antibiotic infusions according to guideline to ensure stability of medication for the prolonged or continuous infusion.

4. PROCEDURE

4.1 Indications

- Administration of an antibiotic by prolonged or continuous infusion may be indicated to optimise bacterial killing for severe infections or patients with altered pharmacokinetics e.g. critical illness, burns, cystic fibrosis which makes achieving optimal concentrations of antimicrobials challenging due to augmented renal drug clearance, abnormal fluid balance and changes in protein binding.
- Prolonged or continuous antibiotic infusions should be prescribed and administered under recommendation of Infectious Diseases or AMS Pharmacist.

4.2 Intravenous Access

- Due to the possibility of thrombophlebitis, **continuous infusions** of antibiotics should be administered via central venous catheter, PICC or midline catheter
- If the patient has no central venous access, consider administering as an intermittent infusion until central access can be achieved
- **Prolonged infusions** of antibiotics can be given via central or peripheral access.
- Patients prescribed antibiotic infusions should have a **dedicated line** for the duration of the infusion. If other IV medications are prescribed, they should be administered via a separate line.

4.3 Prescriber Guidelines

Refer to Table 1 in the appendix for dose, diluent and duration of infusion for specific antibiotic when giving as an infusion.

The medical officer must prescribe medications by generic name on the electronic medical record prior to administration. In eMEDs, this is to be done via the Continuous Antimicrobial Infusions powerplan by selecting the required antimicrobial and appropriate order sentence. For further information on prescribing via a powerplan, see the Ordering a Powerplan quick reference guide.

Transition from intermittent dosing:
If the patient is already receiving intermittent dosing of the antibiotic, schedule the infusion to start at the time the next dose is due. e.g. Vancomycin charted 2 g 12 hourly. Commence 4g (continuous infusion over 24 hours) 12 hours after the start of the last 2g dose.

New Initiation of antimicrobial?
If the patient has not been on the antibiotic prior, the patient should receive **a single or loading dose** as outlined in Table 2 in the appendix.

4.4 Preparation and administration

Registered nurses must provide a double check of intravenous medications and administer as per NSW Health Policy Directive PD2022_032 – Medication Handling and SESLHDPD/160 – Medication: Administration by Enrolled Nurses.

Reconstitute the antibiotic infusion by following the detailed guidelines in Table 1 of the appendix. Once reconstituted with water for injection, **the entire dose should be drawn up into the minimum number of syringes and added to the infusion bag**, to avoid multiple punctures of the bag. Double check the appropriate volume of sodium chloride 0.9% (either 100 mL, 250 mL or 500 mL) is used depending on the drug and dose as indicated in Table 1 of the appendix. **The antibiotic infusion should be prepared immediately prior to use.**

When preparing antibiotic infusions, staff must follow strict aseptic technique as per local Aseptic Non-Touch Technique policies, including disinfection of the vial stopper with alcohol wipe prior to drawing up medication to reduce contamination risk.

The antibiotic dose should be administered by prolonged or continuous infusion at a rate as indicated in Table 1 of the appendix. The duration of the infusion accounts for the stability of the infusion and ensures the medication is stable for the entire duration of the dose.

4.5 Monitoring requirements

Note: Refer to Table 1 in the Appendix for the list of antibiotics that are appropriate for administration via prolonged or continuous infusion, their stability, and compatibility and how to prescribe.

For continuous infusions – monitor the bag/syringe and extension line every 4 hours to detect signs of precipitation (i.e. precipitation, "clouding", crystallisation, colour change).
For intermittent infusions, monitor the bag/syringe and extension line every hour.

If an antibiotic infusion becomes cloudy, precipitates or crystallises in the bag/syringe or administration line:
- Immediately **stop** administration of the medication. **Do not flush the administration line**
- Discard all equipment including extension tubing
- Contact Medical Officer
- Identify the dose that has already been administered and how much additional dose is required. Medical Officer will need to create a new medical order for nurse to sign off.
- Prepare a new dose of the antimicrobial
- Restart infusion
- Document in the patient's medical record and ensure the incident is recorded in the Incident Information Management System (IIMS) and include medication name and batch and expiry.

4.6 Labelling
The antibiotic infusion should be labelled according to the NSW Health Policy Directive PD2022_032 – Medication Handling.

4.7 Patient Education
For safe administration of antibiotics by infusion, it is imperative that patients and their carers are provided with education. Education should include:
- What and why the patient is getting prolonged or continuous antibiotic infusion
- Ways to mobilise with continuous antibiotic infusion
- Alerting nursing staff to any pain or rash at the infusion site.

4.8 Therapeutic Drug monitoring (TDM)
4.8.1 Vancomycin
Therapeutic drug monitoring is recommended for all patients receiving intravenous vancomycin for greater than 48 hours. This is done to ensure patients are not being under dosed and to minimise the risk of toxicity from high levels of vancomycin.

Vancomycin levels can be taken at any time whilst patients are on continuous infusions. However, it must be more than 24 hours post initiation of infusion or after a change in dose.

The target level for continuous infusion may differ from intermittent dosing and is usually 20-25 mg/L. Higher doses may be required in some cases (up to 30mg/L). Seek advice from ID.

4.8.2 Beta-lactams
Therapeutic drug monitoring for beta-lactams is currently done in laboratories outside of SESLHD. Please speak to Infectious Diseases and AMS pharmacist for advice on indication for TDM, timing of samples and target levels for beta lactams.

5. DOCUMENTATION
Electronic Medication chart (eMEDS)
Electronic Record Intensive Care (eRIC)
Fluid chart (fluid volumes)

6. AUDIT
Number of IIMS related to antibiotic infusions for inpatients.

7. REFERENCES
1. Gilbert DN, Chambers HF, Eliopoulos EG, Saag MS, Pavia AT, Black D, Freedman DO, Kim K, Schwartz BS, editors. The Sanford Guide to Antimicrobial Therapy 2019. 50th ed. Sperryville, VA: Antimicrobial Therapy Inc; 2019. P.129.
2. NSW Health Policy Directive PD2022_032 – Medication Handling
3. SESLHDPD/160 – Medication: Administration by Enrolled Nurses
4. eTG complete [digital]. Melbourne: Therapeutic Guidelines Limited; 2022 August. https://www.tg.org.au
5. Symons K, Ermer J, editors. The Australian Injectable Drugs Handbook. Eighth ed. Melbourne: The Society of Hospital Pharmacists of Australia: 2020.

8. Appendices
Appendix 1: Antibiotic infusion doses, preparation and stability

9. REVISION AND APPROVAL HISTORY

Date	Revision No.	Author and Approval
May 2020	DRAFT	Adriana Chubaty, Senior Pharmacist Antimicrobial Stewardship, Prince of Wales Hospital. Ellie Butina, Senior Pharmacist Antimicrobial Stewardship, The Wollongong Hospital. Danica Furtula, Senior Analyst Antimicrobial Stewardship Lead. Antimicrobial Stewardship Clinical Application Advisory Group, SESLHD/ISLHD.
November 2020	DRAFT	Draft for Comment

January 2021	0	Final draft approved by Executive Sponsor.
		Processed by Executive Services prior to submission to Quality Use and Medicines Committee.
February 2021	0	Approved by Quality Use of Medicines Committee
April 2021	0	Approved at March 2021 Clinical and Quality Council
March 2023	1	Minor review. Updates to Sections 4.1, 4.4 and 4.6. Updated links.
		Daniel Chieng, Senior Pharmacist Antimicrobial Stewardship, Prince of Wales Hospital. Suman Adhikari, Senior Pharmacist Antimicrobial Stewardship, St George Hospital. Ellie Butina, Senior Pharmacist Antimicrobial Stewardship, The Wollongong Hospital. Kerry Watts, Senior Production Pharmacist, The Wollongong Hospital. Samantha Li-Yan-Hui, Senior Analyst Antimicrobial Stewardship Lead.
		Antimicrobial Stewardship Clinical Application Advisory Group, SESLHD/ISLHD.
		Approved by Executive Sponsor.
April 2023	1	Approved at SESLHD Drug and Therapeutics Committee.

Appendix

Table 1: Antibiotic infusion doses, preparation and stability

Antibiotic	Equivalent Intermittent Daily Dose	Dose to prescribe	Dose to prepare	Infusion Duration	Reconstitution volume	Additive Volume	Volume of Sodium Chloride 0.9%	Approximate final concentration	Stability
Benzylpenicillin	2.4g 4 hourly (14.4g in 24 hours)	4.8g infused over 8 hours, 8 hourly	4.8 g	Infuse over 8 hours	Reconstitute 1.2 g vials with 3.2 mL water for injection[6] (=300mg/mL)	4 vials Withdraw 16mL and add to bag	100 mL	41mg/mL	8 to 12 hours at 26°C[5,6] For continuous infusions, split the dose into three, 8 hour infusions
	1.8g 4 hourly (10.8g in 24 hours)	3.6g infused over 8 hours, 8 hourly	3.6 g	Infuse over 8 hours		3 vials Withdraw 12mL and add to bag	100 mL	32mg/mL	
	2.4g 6 hourly or 1.6g 4 hourly (9.6g in 24 hours)	3.2 g infused over 8 hours, 8 hourly	3.2 g	Infuse over 8 hours		3 vials Withdraw 10.6mL and add to bag	100 mL	29mg/mL	
Cefazolin	2g 6 hourly (8g in 24 hours)	4g infused over 12 hours	4 g	Infuse over 12 hours	Reconstitute 1g vials with 2.5mL water for injection[6] (=330mg/mL)	4 vials Withdraw 12mL and add to bag	100 mL	36mg/mL	Infusion solution: stable for 24 hours below 25 °C[5,6] For continuous infusions, split the dose into two, 12 hour infusions.
	2g 8 hourly (6g in 24 hours)	3g infused over 12 hours	3 g	Infuse over 12 hours		3 vials Withdraw 9mL and add to bag	100 mL	28mg/mL	

| Flucloxacillin | 2 g 4 hourly (12 g in 24 hours) | 6 g infused over 12 hours, 12 hourly | 6 g | Infuse over 12 hours | Reconstitute 1g vial with 2.5 mL water for injection[6]

(=333mg/mL) | 6 vials

Withdraw 18mL and add to bag | 100 mL | 50mg/mL | Unbuffered solutions of 50 mg/mL in sodium chloride are stable for 24 hours at 31 °C. For continuous infusions split the dose into two 12 hour infusions.[6] |
|---|---|---|---|---|---|---|---|---|---|
| | 2 g 6 hourly (8 g in 24 hours) | 4 g infused over 12 hours, 12 hourly | 4 g | Infuse over 12 hours | | 4 vials

Withdraw 12mL and add to bag | 100 mL | 36mg/mL | |
| Meropenem | 2 g 8 hourly (6g in 24 hours) | 2 g infused over 3 hours, 8 hourly | 2 g | Infuse over 3 hours | Reconstitute 1g vials with 20mL of water for injection*

(=50mg/mL) | 2 vials

Withdraw 40mL and add to bag | 250 mL | 7mg/mL | Infusion solutions of 1–20 mg/mL in sodium chloride 0.9%- 3-8hrs[5,6]

APO Brand – 3 hours GH, Kabi, Ranbaxy Brand – 8 hours |
| | 1 g 8 hourly (3g in 24hours) | 1 g infused over 3 hours, 8 hourly | 1 g | Infuse over 3 hours | | 1 vials

Withdraw 20mL and add to bag | 250 mL | 4mg/mL | |
| Piperacillin/ Tazobactam (Tazocin®) | 4.5g 6 hourly (18 g in 24 hours) | 18 g infused over 24 hours, 24 hourly | 18g | Infuse over 24 hours | Reconstitute 4.5g vials with 17 mL water for injection*

(=225mg/mL) | 4 vials

Withdraw 80mL and add to bag | 500 mL | 31mg/mL | 24hrs at all concentrations[5,6] |
| | 4.5g 8 hourly (13.5g in 24 hours) | 13.5g infused over 24 hours, 24 hourly | 13.5g | Infuse over 24 hours | | 3 vials

Withdraw 60mL and add to bag | 500 mL | 24mg/mL | |
| Vancomycin | | >1250mg to 5000mg | >1250mg to 5000mg | Infuse over 24 hours | Reconstitute the 500 mg vial with 10 mL of water for injections and the 1 g vial with 20 mL of | Calculate volume 1 ÷ 50 x mg needed = mL to withdraw. | 500 mL | 2-9mg/mL | Infusion solution: stable for 24 hours below 25 °C[5,6] |
| | | > 500mg to 1250mg | >500mg to 1250mg | Infuse over 24 hours | | | 250 mL | 2-5mg/mL | |

		≤ 500 mg	≤500mg	Infuse over 24 hours	water for injections* (=50mg/mL)	E.g. 1000mg = 20mL	100 mL	≤ 5mg/mL Do not exceed 10mg/mL	

Table 2: Antibiotic dose initiation (if patient not previously on antibiotics)

Antibiotic	Initiation dose/load	Infusion dose
Benzylpenicillin	2.4 g stat, then immediately begin infusion as per table 1	4.8g infusion over 8 hours, 8 hourly
	1.8 g stat, then immediately begin infusion as per table 1	3.6g infusion over 8 hours, 8 hourly
	2.4g stat then immediately begin infusion as per table 1	3.2g infusion over 8 hours, 8 hourly
Cefazolin	2 g stat then immediately begin infusion as per table 1	4 g infusion over 12 hours, 12 hourly
		3 g infusion over 12 hours, 12 hourly
Flucloxacillin	2 g stat then immediately begin as per table 1	6 g infusion over 12 hours, 12 hourly
		4 g infusion over 12 hours, 12 hourly
Meropenem	Commence prolonged infusion from first dose	1 or 2 g infusion over 3 hours, 8 hourly
Tazocin	4.5 g stat then immediately being infusion as per table 1	18 g infusion over 24 hours, 24 hourly
		13.5 g infusion over 24 hours, 24 hourly
Vancomycin	15-20mg/kg loading dose then immediately begin infusion as per table 1	