



Title	<i>NHS Borders Guidance for the Administration of Intravenous Piperacillin/Tazobactam in Adults in Critical Care via Extended Infusion</i>
Document Type	<i>Guideline</i>
Version Number	<i>V1.0</i>
CGQ & RDS ID Number	<i>Clinical Governance & Quality Use only</i>
Approval/Issue date	<i>Sept 2022</i>
Review date	<i>Sept 2025</i>
Owner/Responsible Person	<i>Duguid A; anne.duguid@borders.scot.nhs.uk</i>
Developed by	<i>NHS Grampian Antimicrobial Management Group; used with permission for NHS Borders</i>
Reviewed by	<i>NHS Borders Antimicrobial Management Team</i>
Significant resource implications (financial/workload)	<i>N/A</i>
Approved by	<i>NHS Borders Antimicrobial Management Team</i>
Health Inequality Impact Assessment (HIIA) <small>(only statutory for policies)</small>	<i>N/A</i>

Uncontrolled when printed

NHS Borders Guidance for the Administration of Intravenous Piperacillin/Tazobactam in Adults in Critical Care via Extended Infusion

Piperacillin/tazobactam contains a beta-lactam penicillin, piperacillin, that exhibits time dependent bacterial killing. Free beta lactam levels do not have to remain above the minimum inhibitory concentration (MIC) for the entire dosing interval; near maximal bactericidal effect is typically observed when the concentration exceeds the MIC for 50% of the dosing interval.¹ It has been suggested that administering piperacillin/tazobactam as an infusion for longer than the conventional 30 minute infusion time produces a drug concentration in excess of the MIC for a longer period which may achieve improved outcomes in critically ill patients.^{1,2} A systematic review and meta-analysis concluded that prolonged infusion of antipseudomonal β -lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion³

Additionally, administration of a loading dose immediately prior to commencing the first extended infusion allows rapid attainment of therapeutic levels.⁴

For these reasons the NHS Borders Antimicrobial Management Team have agreed that **Infection Specialists can recommend** the use of extended infusions of piperacillin/tazobactam for patients

in critical care settings usually ITU for treatment of resistant gram-negative infections. This is an off-label method of administration for piperacillin/tazobactam. It is appreciated that this method of infusion may not be possible in certain patients depending on venous access and infusion compatibilities.

Additionally, administration of a loading dose immediately prior to commencing the first extended infusion allows rapid attainment of therapeutic levels.⁴

Piperacillin/tazobactam should be prescribed on the main medicine chart. The loading dose should be prescribed in the once-only section on the front page. The maintenance dose should be prescribed in the regular medication section, annotated 'as per extended infusion protocol' in the additional comments box.

The following patients should be **excluded** from this protocol for the administration of piperacillin/tazobactam by extended infusion: patients on haemodialysis, HDF/High flux or APD/CAPD.

The guidance below details how these infusions should be administered.^{1,2,3,4,5,6,7}

Administration Of Extended (off-label) Infusion	
All patients should receive a loading dose ⁴ over 30 minutes immediately followed by the first 3 hour extended infusion then subsequent infusions at 6, 8 or 12 hourly intervals according to renal function (as noted below).	
Loading dose ⁴ :	4.5g infusion over 30 minutes.
Usual Adult Daily Maintenance Dose:	4.5g every 6 - 8 hours in normal renal function. Each dose via 3 hour extended infusion.
Renal Impairment: ^{5,6,7}	
Not on dialysis but creatinine clearance (CrCl) 20 - 40mL/minute	Maximum dosage suggested in SPC is 4.5g every 8 hours.
Not on dialysis but CrCl <20mL/minute	Maximum dosage suggested in SPC is 4.5g every 12 hours.
CVVH or CVVHD/HDF	Dose as CrCl 20 – 40mL/minute above or calculate individual clearance rate

Hepatic Impairment:	
Patients with hepatic impairment can receive a loading dose and 3 hour extended infusions at usual adult dosage.	
Reconstitution Directions: ^{1,5,6,8}	
•	The infusions should be prepared according to the general procedures detailed in the Code of Practice for the Control of Medicines
•	Each vial of 4.5g should be reconstituted with 20mL of water for injections or 0.9% sodium chloride.
•	The contents of the vial should then be further diluted to the desired volume (50 to 100mL) with sodium chloride 0.9% or glucose 5%.
•	For loading dose – administer 50 - 100mL over 30 minutes.
•	For extended infusion - administer 50 - 100mL over 3 hours via a rate-controlled infusion device.
•	Start infusion immediately after preparation to reduce risk of microbial contamination.
•	Flush before and after administration with sodium chloride 0.9% or compatible diluent.

Glossary

HDF	intermittent haemodiafiltration
APD/CAPD	automated peritoneal dialysis / continuous ambulatory peritoneal dialysis
CVVH	continuous arteriovenous/venovenous haemofiltration
CVVHD/HDF	continuous venovenous haemodialysis/haemodiafiltration

References:

1. Thomas P, Lodise Jr et al. Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy. *Clinical Infectious Diseases*. 2007;44:357-63. <http://cid.oxfordjournals.org/content/44/3/357.full#sec-2>
2. Lee GC, Liou HL, Yee R, Quan CF and Neldner K. Outcomes of Extended-Infusion Piperacillin-Tazobactam: A retrospective Analysis of Critically Ill Patients. *Clinical Therapeutics*. 2012;34:2297-2300.
3. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G and Falagas ME. Prolonged versus short-term intravenous infusion of anti-pseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. [Lancet infect Dis 2018; 18: 108-20](#) [http://dx.doi.org/10.1016/S1473-3099\(17\)30615-1](http://dx.doi.org/10.1016/S1473-3099(17)30615-1)
4. De Waele JJ, Lipman J, Carlier M, Roberts JA. Subtleties in practical application of prolonged infusion of beta-lactam antibiotics. *International Journal of Antimicrobial Agents* 2015; 45: 461-463 <http://dx.doi.org/10.1016/j.ijantimicag.2015.01.007>
5. Summary of Product Characteristics for Tazocin 2.25g and 4.5g Powder for Solution for Infusion Pfizer Ltd Last updated on www.medicines.org.uk on 23/12/21.
6. Summary of Product Characteristics for Piperacillin/Tazobactam 4.5g Powder for Infusion. Bowmed Ibisqus Ltd. Last updated on www.medicines.org.uk on 01/08/22.
7. Roger C, Cotta MO, Muller L, Wallis SC, Lipman J, Lefrant J and Roberts JA. Impact of renal replacement modalities on the clearance of piperacillin-tazobactam administered via continuous infusion in critically ill patients. *International Journal of Antimicrobial Agents* 50 (2017) 227-231
8. Piperacillin Tazobactam monograph. NHS Injectable Medicines Guide Website – Medusa. <http://medusa.wales.nhs.uk/> Date published 14/07/22.

With thanks to NHS Grampian Antimicrobial Management Group for allowing us to use their staff protocol for the administration of intravenous Piperacillin/Tazobactam in adults via Extended Infusion (July 19).