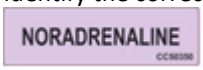
Noradrenaline (Norepinephrine) - Fixed concentration

Newborn use only

2023

Alert	Noradrenaline fixed concentration preparation is designed to be used in emergencies to manage the delay in the preparation of in-house solution. It is recommended to change over to in-house inotrope preparations as and when the situation permits. As per the drug infusion policy in New South Wales, solution needs to be changed every 24 hours. It is recommended to infuse the drug using syringe drivers with administration increments at 2 decimal points if available. **Prescribe as noradrenaline base.** Noradrenaline acid tartrate 2 mg/mL is equivalent to noradrenaline base 1 mg/mL (1:1000) The antidote for extravasation ischaemia is phentolamine. Phentolamine is only available via the Special Access Scheme.
Indication	Treatment of hyperdynamic shock secondary to sepsis.(1) Second line inotrope for treatment of fluid-refractory hypotensive shock in the setting of low systemic vascular resistance (SVR).(1) Circulatory failure in the setting of pulmonary hypertension refractory to nitric oxide.(2)
Action	Catecholamine with strong vascular alpha and cardiac beta-adrenergic action, moderate cardiac alphaadrenergic actions.(3) Noradrenaline increases blood pressure, urine output and reduces lactate in newborns with septic shock refractory to volume expansion and other inotropes.(4) Noradrenaline increases systemic and pulmonary pressures, increases pulmonary blood flow and improves systemic oxygen saturation in newborn infants with pulmonary hypertension and circulatory failure.(2)
Drug type	Inotrope and vasopressor
Trade name	Noradrenaline (Norepinephrine) 20 microgram/mL (1000 microgram in 50mL Glucose 5%)
Presentation	1000 microgram of noradrenaline in 50mL (20microgram/mL) premade syringe. Noradrenaline is supplied as noradrenaline acid tartrate. Note: This fixed strength solution contains 2000 microgram of noradrenaline acid tartrate in 50 mL, which is equivalent to 1000 microgram of noradrenaline in 50 mL. Identify the correct inotrope syringe by cross checking the label on the **Black coloured** overpouch:  **Note:** ANMF recommends glucose 5% as diluent with a 60-day fridge shelf life for this fixed concentration solution.[13] Baxter's recommended fridge shelf life is 30 days. This ANMF recommended shelf life requires signed stability agreement between the individual NICU and Baxter company as per the manufacturer.
Dose	**0.05-1 microgram/kg/minute of noradrenaline base.*** (a) Suggested starting dose of 0.1 microgram/kg/minute and titrate up to achieve not only normotensive range of blood pressure but also improved tissue perfusion manifested by good urine output, improved FiO_2, and reduced lactate. (b) Consider starting at higher dose particularly in term infants with respiratory failure and hypotension refractory to other treatments. ***NOTE:** The time from the initiation of infusion to the entry of the drug into blood stream may influence the time it takes to see the clinical effect. This lag time can be reduced by (a) starting temporarily at a higher dose by increasing the infusion rate, and/or (b) priming the line as close to the entry point as possible to reduce the dead space – however, care should be taken not to deliver excess volume that may result in tachycardia and hypertension. **Prescriber to:** 1. order the dose in microgram/kg/minute, and 2. calculate in mL/hr using the formula:

	mL/hr = dose required (microgram/kg/min) x patient's weight (kg) x 3 **Example:** A baby weighing 0.8 kg needing 0.05 microgram/kg/minute will need the 20 microgram/mL fixed concentration solution infusing at: mL/hr = 0.05 x 0.8 x 3 = 0.12 mL/hr
Dose adjustment	Therapeutic hypothermia – No specific information. ECMO – No specific information. Titrate dose to clinical response. Renal impairment – No dose adjustment is required. Hepatic impairment – No dose adjustment is required.
Maximum dose	
Total cumulative dose	
Route	Continuous IV infusion
Preparation	Ready to use syringe - No preparation is required.
Administration	Noradrenaline should be given via a central venous catheter (UVC or PICC) using a continuous infusion. Infuse through a dedicated line where possible.
Monitoring	Continuous heart rate, ECG and blood pressure. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and extravasation.
Contraindications	Infants with hypovolaemia until blood volume replaced - may cause severe peripheral and visceral vasoconstriction. Infants with mesenteric or peripheral thrombosis. Known hypersensitivity to sodium metabisulfite
Precautions	Use with caution in preterm infants and infants with poor myocardial contractility as a sole inotrope/vasopressor. Thyrotoxicosis – may cause severe hypertension. Ensure adequate circulating blood volume prior to commencement. Avoid in hypertension. Overdosage may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation into the tissues which may cause local necrosis. Do not cease infusion abruptly
Drug interactions	Should be given with close monitoring to patients exposed to monoamine oxidase inhibitors because severe, prolonged hypertension may result.
Adverse reactions	Systemic hypertension especially at higher doses. Reflex bradycardia and arrhythmia. Tissue necrosis at infusion site with extravasation. **See special comments for treatment**. Renal and digital ischaemia may occur. Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy.
Compatibility	**Fluids via Y-site:** Glucose 5%, sodium chloride 0.9% with glucose 5%, sodium chloride 0.9%(variable),[8] lactated Ringer's solution, amino acid solution (refer to Micromedex for specific information) **Y-site:** Amikacin sulfate, atropine, anidulafungin, aztreonam, bivalirudin, bumetanide, buprenorphine hydrochloride, calcium chloride, calcium gluconate, caspofungin, cefazolin sodium, cefoperazone, cefotaxime sodium, ceftazidime, ceftriaxone sodium, clindamycin phosphate, clonidine hydrochloride, cloxacillin sodium, colistimethate sodium, ceftaroline, fosamil, cisatracurium, cyclophosphamide, cyclosporine, daptomycin, dexamethasone sodium phosphate, dexmedetomidine, digoxin, dobutamine, dopamine, doripenem, esmolol, ethanol, fentanyl citrate, fluconazole, fosfomycin sodium, gentamicin sulfate, glycopyrrolate, granisetron hydrochloride, heparin sodium, hydrocortisone sodium succinate, hydromorphone hydrochloride, imipenem/cilastatin sodium, ketorolac tromethamine, labetalol, levetiracetam, lidocaine hydrochloride, lincomycin hydrochloride, linezolid, lorazepam,

	magnesium sulphate, meropenem, metaraminol bitartrate, methadone hydrochloride, methylprednisolone sodium succinate, metoprolol tartrate, metronidazole, micafungin sodium, midazolam, milrinone, morphine sulfate, moxifloxacin hydrochloride, mycophenolate, mofetil, nitroglycerine, octreotide acetate, ondansetron hydrochloride, pamidronate disodium, pancuronium bromide, penicillin G sodium, pentoxifylline, piperacillin/tazobactam sodium, potassium chloride, propranaolol hydrochloride, propofol, protamine sulfate, pyridoxine, remifentanil, sildenafil citrate, sodium nitroprusside, succinylcholine chloride, sufentanyl citrate, tigecycline, tobramycin sulfate, vancomycin hydrochloride, vasopressin, vecuronium bromide, voriconazole.
Incompatibility	**Fluids via Y-site:** No information. Glucose 10% not tested. **Y-site:** Aminophylline, amphotericin B, amphotericin B lipid complex, azathioprine, diazepam, diazoxide, folic acid, foscarnet, ganciclovir, indomethacin, phenobarbitone, phenytoin, sodium bicarbonate, sulfamethoxazole/trimethoprim, thiopentone. Incompatible with alkalis and oxidising agents. **Caution/Variable:** Amiodarone (variable), ampicillin, furosemide, haloperidol lactate, pantoprazole. No information: Adrenaline HCl is compatible with noradrenaline bitartrate but no stability data is available for Adrenaline acid tartrate and noradrenaline acid tartrate.
Stability	Noradrenaline (Norepinephrine) 20 microgram/mL (1 mg in 50mL Glucose 5%) is stable for 60 days in refrigerator (2-8°C) and 24 hours at room temperature.[13]
Storage	Store in refrigerator (2-8°C), Protect from light.
Excipients	Glucose 5%
Special comments	Do not administer with blood products. Glucose solutions (10%, 5%) are protective against the oxidation of noradrenaline. Discard if exhibiting colour change (oxidation). The antidote for extravasation ischaemia is phentolamine. Phentolamine is only available via the Special Access Scheme

Noradrenaline 20 microgram/mL fixed concentration premade solution

Dose microg/kg/min		0.05	0.06	0.07	0.08	0.09	0.1	0.2	0.3	0.4	0.5
		Rate mL/hour									
weight (Kg)	0.5	0.08	0.09	0.11	0.12	0.14	0.15	0.3	0.45	0.6	0.75
	1	0.15	0.18	0.21	0.24	0.27	0.3	0.6	0.9	1.2	1.5
	1.5	0.23	0.27	0.32	0.36	0.41	0.45	0.9	1.35	1.8	2.25
	2	0.3	0.36	0.42	0.48	0.54	0.6	1.2	1.8	2.4	3
	2.5	0.38	0.45	0.53	0.6	0.68	0.75	1.5	2.25	3	3.75
	3	0.45	0.54	0.63	0.72	0.81	0.9	1.8	2.7	3.6	4.5
	3.5	0.53	0.63	0.74	0.84	0.95	1.05	2.1	3.15	4.2	5.25
	4	0.60	0.72	0.84	0.96	1.08	1.2	2.4	3.6	4.8	6

Evidence	**Background** Norepinephrine is an endogenous catecholamine which is released from adrenergic nerve endings. It has strong stimulating effects on α and β1 receptors and weaker effects on β2 receptors. Noradrenaline has more potent α mediated effects compared to adrenaline. This results in vascular constriction with a subsequent increase in systemic vascular resistance (SVR) and blood pressure (BP). It may be useful in septic shock, in order to correct the low SVR.[(10)] **Efficacy** Norepinephrine is the first inotrope of choice in septic shock in adults.[(1)] Norepinephrine is also

recommended as an inotrope in children with septic shock.[2] However, there are no randomised trials comparing noradrenaline to other vasopressors in newborn infants. Noradrenaline was equivalent to other vasopressors in patients with hypotensive shock (newborns excluded) and resulted in less arrhythmia than dopamine.[3](LOE I, GOR B).

Term newborns with septic shock: Noradrenaline 0.2−0.5 microgram/kg/minute increased blood pressure, urine output and reduced lactate in newborns with septic shock refractory to volume expansion and dopamine/dobutamine.[4](LOE IV, GOR C).

Term newborns with pulmonary hypertension and circulatory failure refractory to fluid resuscitation: Noradrenaline 0.5–1 microgram/kg/minute improved lung function in newborn infants with PHN through a decrease in pulmonary/systemic artery pressure ratio and improved cardiac performance.[5] (LOE IV, GOR C).

Preterm newborns with refractory hypotension: A few studies reported the effects of noradrenaline in preterm infants. Rowcliff et. al. reported noradrenaline [starting dose 0.4 (0.2–0.5) µg/kg/min; maximum dose 0.7 (0.4–1) µg/kg/min] in 48 hypotensive infants born ≤32 weeks' gestation with a primary diagnosis of sepsis (63%) or pulmonary hypertension (23%) refractory to other interventions. Normotension was achieved in all but one infant at a median dose of 0.5 µg/kg/min. The increased blood pressure did not lead to immediate improvement of pH, lactate or urine output. Tachycardia was common (31%). Mortality was 46% and morbidity high.[6] Rizk et. al. reported noradrenaline (starting dose 0.1 µg/kg/min; maximum dose 0.24 ± 0.15 µg/kg/min) in 30 hypotensive preterm infants with septic shock. Noradrenaline infusion was associated with improvements in blood pressure, urine output and FiO2, and reduction in other inotrope support. Mortality was 33.3%, 5 of 16 survivors assessed had cerebral palsy and developmental delay.[7] Nissimov et al compared the clinical effectiveness of dopamine (DA) versus norepinephrine (NE) as first-line therapy for sepsis-related hypotension in preterm infants.[11] In this retrospective cohort study, preterm infants born < 35 weeks were included. A total of 156 infants were included, 113 received DA and 43 NE. The mean ± SD PMA at birth and at treatment for the DA and NE groups were 25.8 ± 2.3 vs. 25.2 ± 2.0 weeks and 27.7 ± 3.0 vs. 27.1 ± 2.6 weeks, respectively (p > 0.05). Authors found NE was more effective than DA in these infants. NE was associated with lower episode-related mortality [adjusted odds ratio (95% CI) 0.55 (0.33, 0.92)], pre-discharge mortality [0.60 (0.37, 0.97)], post-illness new diagnosis of significant neurologic injury [0.32 (0.13, 0.82)], and subsequent occurrence of NEC/sepsis among the survivors [0.34, (0.18, 0.65)].[11] Gupta et al, reported a retrospective cohort study describing the clinical responses in neonates in shock treated with NE infusion. Fifty infants received NE with mean (SD) gestational age of 34.3 (4.3) weeks and a mean birth weight of 2215 (911) g. Treatment began at a median age of 36 (IQR: 15.2, 67.2) hours of life and lasted 30.5 (IQR: 12.7, 58) hours. NE was administered at 0.1– 0.4 mcg/kg/min. Mean BP improved from 34.4 mm Hg (SD: 6.6) at baseline to 39.4 mm Hg (SD: 10.5, p <0.001) at 6 h, to 39.6 mm Hg (SD: 12.1, p = 0.002) at 12 h and to 40.4 mm Hg (SD: 15.5, p = 0.004) at 24 h after NE initiation. Urine output improved within 24 h [1.5 ml/kg/h (0.5, 2.3) at baseline to 3 (1.9, 4.3) at 24 h; p = 0.04]. Oxygen requirement decreased after NE initiation.
ANMF group consensus: The above studies, and the clinical experience gained from the current clinical practice in Australian settings support the use of norepinephrine for the treatment of hypotension, in particular refractory vasodilatory hypotension (LOE IV, GOR C).

Safety

In non-newborn patients, noradrenaline is associated with less arrhythmia compared to patients treated with dopamine. Overdose may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. Cohort studies show that delay in the use of inotropic therapies is associated with major increases in mortality risk. This delay is often related to difficulty in attaining central access. Inotropes can be given peripherally until central venous access can be attained in children who are not responsive to fluid resuscitation.[1]

Pharmacokinetics

	The onset of action is rapid after intravenous infusion. The half-life of intravenous noradrenaline has not been reported in sick newborn infants.[8]
Practice points	Fixed concentration preparations are designed to be used in emergencies to manage the delay in the preparation of in-house solution. As per the drug infusion policy in New South Wales, solution needs to be changed every 24 hours. It is recommended to change over to in-house inotrope preparations as and when the situation permits.
References	1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive care medicine. 2013 Feb 1;39(2):165-228. 2. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, Han YY, Hanson J, Hazelzet J, Hernan L, Kiff J, Kissoon N, Kon A, Irazuzta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, Schnitzler E, Shanley T, Kache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Zimmerman J, Zuckerberg A. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009;37:666-88. 3. Havel C, Arrich J, Losert H, Gamper G, Mullner M, Herkner H. Vasopressors for hypotensive shock. The Cochrane database of systematic reviews. 2011:CD003709. 4. Tourneux P, Rakza T, Abazine A, Krim G, Storme L. Noradrenaline for management of septic shock refractory to fluid loading and dopamine or dobutamine in full-term newborn infants. Acta paediatrica. 2008;97:177-80. 5. Tourneux P, Rakza T, Bouissou A, Krim G, Storme L. Pulmonary circulatory effects of norepinephrine in newborn infants with persistent pulmonary hypertension. The Journal of pediatrics. 2008;153:345- 9. 6. Rowcliff K, de Waal K, Mohamed AL, Chaudhari T. Noradrenaline in preterm infants with cardiovascular compromise. Eur J Pediatr. 2016;175:1967-73. 7. Rizk MY, Lapointe A, Lefebvre F, Barrington KJ. Norepinephrine infusion improves haemodynamics in the preterm infants during septic shock. Acta paediatrica. 2018;107:408-13. 8. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: November/29/2023). 9. Noradrenaline Juno. Accessed via MIMS online on 12 March 2023. 10. Dempsey E, Rabe H. The use of cardiotonic drugs in neonates. Clinics in perinatology. 2019 Jun 1;46(2):273-90. 11. Nissimov S, Joye S, Kharrat A, Zhu F, Ripstein G, Baczynski M, Choudhury J, Jasani B, Deshpande P, Ye XY, Weisz DE. Dopamine or norepinephrine for sepsis-related hypotension in preterm infants: a retrospective cohort study. European Journal of Pediatrics. 2022 Dec 22:1-0. 12. Gupta S, Agrawal G, Thakur S, Gupta A, Wazir S. The effect of norepinephrine on clinical and hemodynamic parameters in neonates with shock: a retrospective cohort study. European Journal of Pediatrics. 2022 Jun;181(6):2379-87. 13. Rita Marina Heeb*, Bettina Stollhof, Julia Reichhold, Judith Thiesen and Irene Krämer. Stability of ready-to-administer and ready-to-use epinephrine and norepinephrine injection solutions. Pharm. Technol. Hosp. Pharm. 2017; 2(4): 159–171

VERSION/NUMBER	**DATE**
Original 1.0	7/12/2023
Current 1.0 (minor errata)	29/02/2024
REVIEW	7/12/2028

Authors Contribution

Author/s	Mohammad Irfan Azeem, Srinivas Bolisetty
Evidence Review	Srinivas Bolisetty

Expert review	
Nursing Review	Eszter Jozsa
Pharmacy Review	Susanah Brew, Mohammad Irfan Azeem
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, Rebecca Barzegar, Rebecca O'Grady, Martin Kluckow, Michelle Jenkins, Thao Tran, Stephanie Halena, Simarjit Kaur, Helen Huynh, Renae Gengaroli, Benjamin Emerson-Parker
Final editing	Srinivas Bolisetty
Electronic version	Thao Tran, Helen Huynh, Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty

Citation for the current version
Azeem MI, Bolisetty S, Brew S, Phad N, Mehta B, Barzegar R, O'Grady R, Kluckow M, Jozsa E, Tran T, Huynh H, Jenkins M, Halena S, Chen C, Kaur S, Gengaroli R, Emerson-Parker B. Noradrenaline (Norepinephrine) Fixed concentration. Consensus formulary by the Australasian Neonatal Medicines Formulary group. Version 1, dated 30 November 2023. www.anmfonline.org