Noradrenaline (Norepinephrine) 2019

Newborn use only

<table>
<tr><td>Alert</td><td>Prescribe as noradrenaline base. Noradrenaline acid tartrate 2 mg/mL is equivalent to noradrenaline base 1 mg/mL (1:1,000)</td></tr>
<tr><td>Indication</td><td>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]</td></tr>
<tr><td>Action</td><td>Catecholamine with strong vascular alpha and cardiac beta-adrenergic action, moderate cardiac alpha-adrenergic 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]</td></tr>
<tr><td>Drug Type</td><td>Inotrope and vasopressor.</td></tr>
<tr><td>Trade Name</td><td>Hospira Levophed Noradrenaline 1:1,000, Noradrenaline BNM 1:1000, Noradrenaline MYX 1:1000. All contain Noradrenaline acid tartrate.</td></tr>
<tr><td>Presentation</td><td>Noradrenaline acid tartrate 8 mg/4 mL is equivalent to noradrenaline base 4 mg/4 mL (1:1000)</td></tr>
<tr><td>Dosage / Interval</td><td>0.05-1.0 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 FiO2, and reduced lactate.
(b) Consider starting at higher dose particularly in term infants with respiratory failure and hypotension refractory to other treatments.</td></tr>
<tr><td>Route</td><td>Continuous IV infusion.</td></tr>
<tr><td>Preparation/Dilution</td><td>LOW CONCENTRATION IV infusion (for =>1kg)
<table>
<tr><th>Infusion dose</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 0.05 microgram/kg/minute</td><td>150 microgram/kg noradrenaline base and make up to 50 mL</td></tr>
</table>
Draw up 150 micrograms/kg (0.15 mL/kg) with 5% glucose or sodium chloride 0.9%[6] to make a 50 mL solution [i.e., 3 micrograms/kg/mL]. Infusing at a rate of 1 mL /hour = 0.05 microgram/kg/minute.

HIGH CONCENTRATION IV infusion
<table>
<tr><th>Infusion dose</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 0.2 microgram/kg/minute</td><td>600 microgram/kg noradrenaline base and make up to 50 mL</td></tr>
</table>
Draw up 600 micrograms/kg (0.6 mL/kg) with 5% glucose or sodium chloride 0.9%[6] to make a 50 mL solution [i.e., 12 micrograms/kg/mL]. Infusing at a rate of 1 mL / hour =0.2 microgram/kg/minute.

For infants requiring fluid restriction consider:
VERY HIGH CONCENTRATION continuous IV infusion
<table>
<tr><th>Infusion dose</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 0.4 microgram/kg/minute</td><td>1,200 microgram/kg noradrenaline base and make up to 50 mL</td></tr>
</table>
Draw up 1,200 microgram/kg (1.2 mL/kg) with 5% glucose or sodium chloride 0.9%[6] to make a 50 mL solution [i.e., 24 micrograms/kg/mL]. Infusing at a rate of 1 mL / hour = 0.4 microgram/kg/minute.</td></tr>
<tr><td>Administration</td><td>Noradrenaline should be given via a central venous catheter (UVC or PICC) using a continuous infusion. Infuse through a dedicated line where possible.</td></tr>
<tr><td>Monitoring</td><td>Continuous heart rate, ECG and blood pressure.
Assess urine output and peripheral perfusion frequently.
Observe IV site closely for blanching and extravasation.</td></tr>
<tr><td>Contraindications</td><td>Infants with hypovolaemia until blood volume replaced - may cause severe peripheral and visceral vasoconstriction.</td></tr>
</table>

	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] 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: Glucose 5%, sodium chloride 0.9% with glucose 5%, sodium chloride 0.9%, lactated Ringer's solution. Y-site: Amiodarone, anidulafungin, bivalirudin, caspofungin, ceftaroline fosamil, cisatracurium, dexmedetomidine, dobutamine, dopamine, doripenem, esmolol, ethanol, haloperidol lactate, heparin sodium, hydrocortisone sodium succinate, labetalol, midazolam, milrinone, morphine sulfate, mycophenolate mofetil, potassium chloride, remifentanil, sodium nitroprusside, tigecycline.
Incompatibility	Fluids: No information. 10% Dextrose not tested. Y-site: aminophylline, azathioprine, benzylpenicillin, folic acid, foscarnet, ganciclovir, indomethacin, insulin (short-acting), iron salts, phenobarbitone, sodium bicarbonate, thiopentone. Incompatible with alkalis and oxidising agents. No information: Adrenaline HCL is compatible with noradrenaline bitartrate but no stability data is available for Adrenaline acid tartrate and noradrenaline acid tartrate.
Stability	Diluted solution stable for 24 hours.
Storage	Ampoule: Store below 25°C. Protect from light. Discard unused portion. Do not freeze.
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.
Evidence summary	**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 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 0.5–1.0 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:** Two case series report 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 (0.4–1.0) 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 FiO_2, and reduction in other inotrope support. Mortality was 33.3%, 5 of 16 survivors assessed had cerebral palsy and developmental delay.[7] [LOE IV, no recommendation]. **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]
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. Micromedex online. Accessed on 23 February 2017.

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