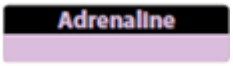
Adrenaline (Epinephrine) - Fixed concentration 2023

Newborn use only

Alert	Adrenaline **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.
Indication	Treatment of hypotensive shock with or without myocardial dysfunction
Action	Catecholamine with alpha and beta adrenergic actions. Haemodynamic effects are dose dependent: • At low doses of 0.01–0.1 microgram/kg/minute primarily stimulates cardiac and vascular beta 1- and beta 2-adrenoreceptors leading to increased inotropy, chronotropy, conduction velocity and peripheral vasodilation. • At doses greater than 0.1 microgram/kg/minute adrenaline also stimulates vascular and cardiac alpha 1-receptors causing vasoconstriction and increased inotropy. The net effects are increases in blood pressure and systemic blood flow caused by the drug-induced increases in systemic vascular resistance (SVR) and cardiac output.1
Drug type	Inotropic vasopressor.
Trade name	Adrenaline (Epinephrine) 20 microgram/mL (1000 microgram in 50mL) in sodium chloride 0.9% - No stability agreement is required with Baxter. Adrenaline (Epinephrine) 20 microgram/mL (1000 microgram in 50mL) in glucose 5% - Stability agreement is required with Baxter.
Presentation	1000 microgram of adrenaline in 50mL (20 microgram/mL) premade syringe. Adrenaline (epinephrine) is supplied as adrenaline acid tartrate. Note: This fixed strength solution contains 1800 microgram of adrenaline acid tartrate in 50 mL, which is equivalent to 1000 microgram of adrenaline in 50 mL. Identify the correct inotrope syringe by cross checking the label on the **silver** coloured overpouch:  **Note:** ANMF recommends glucose 5% as diluent with a 90-day fridge shelf life for this fixed concentration solution.[11] Baxter has no information on fridge shelf life, but 30-day shelf life at room temperature in sodium chloride 0.9%. This ANMF recommended shelf life requires signed stability agreement between the individual NICU and Baxter company as per the manufacturer.
Dose	**Low dose:** 0.05–0.1 microgram/kg/minute **High dose:** 0.1–1 microgram/kg/minute ***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 the 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	Continuous IV infusion preferably via dedicated central line. Use with caution via a peripheral line. It is recommended to infuse the drug using syringe drivers with administration increments at 2 decimal points if available.
Monitoring	Continuous heart rate, ECG and blood pressure monitoring preferable. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and extravasation.
Contraindications	Arrhythmia and tachyarrhythmia. Cardiovascular disease resulting in arterial narrowing including cerebrovascular disease, coronary artery disease and digital ischaemia. Phaeochromocytoma. Thyrotoxicosis. Glaucoma. Known hypersensitivity to sympathomimetic amines
Precautions	Ensure adequate circulating blood volume prior to commencement. Potent chronotrope and vasopressor – may cause excessive tachycardia, severe hypertension and ventricular arrhythmias. May cause lactic acidosis and hyperglycaemia.
Drug interactions	Hypotension may be observed with concurrent use of vasodilators such as glyceryl trinitrate, nitroprusside and calcium channel blockers. Concurrent use of digitalis glycosides may increase the risk of cardiac arrhythmias. Concurrent use of IV phenytoin with adrenaline may result in dose dependent, sudden hypotension and bradycardia.
Adverse reactions	Tachycardia and arrhythmia. Systemic hypertension especially at higher doses. May cause hypokalaemia. Tissue necrosis at infusion site with extravasation. Digital ischaemia.
Compatibility	Information is extrapolated from epinephrine **hydrochloride**. No specific information is available for epinephrine **acid tartrate** used in this fixed strength formulation. **Fluids at Y-site:** Glucose 5%, glucose 10%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, amino acid solution (refer to Micromedex for specific information) **Y-site:** Alfentanyl, amikacin, amiodarone, amphotericin B lipid complex, Amphtericin B liposome, anidulafungin, ascorbic acid, , atenolol, atracurium, atropine sulfate, azithromycin, aztreonam, benztropine mesylate, , bumetanide, buprenorphine HCL, calcium chloride, calcium gluconate, capreomycin, , caspofungin, cefamandole nafate, cefazolin sodium, cefoperazone, cefotaxime, cefotefan disodium, cefoxitin sodium, cefpirome sulfate, ceftazidime, ceftizoxime sodium, caftriaxone sodium, cefuroxime sodium, chloramphenicol sodium succinate, chlorothiazide sodium, cisatracurium besylate, clindamycin phosphate, clonidine HCL, cloxacillin sodium, colistimethate sodium, cyanocobalamin, cyclophosphamide, cyclosporin, , daptomycin, , dexamethasone sodium phosphate, dexmedetomidine HCL, digoxin, diltiazem, diphenhydramine, dobutamine HCL, dopamine HCL, doxycycline hyclate, enalaprilat, ephedrine sulfate, epoietin alfa, ertapenem sodium, erythromycin lactobionate, esmolol, fentanyl citrate, fluconazole, folic acid, foscarnet sodium, fosphenytoin sodium, furosemide, gentamicin sulfate, glycopyrrolate, heparin sodium, hydrocortisone sodium succinate, hydromorphone hydrochloride, ibuprofen lysine, imipenem/cilastatin sodium, isoproterenol HCL, kanamycin sulfate, ketamine HCL, labetalol HCL, leucovorin calcium, levofloxacin, lidocaine HCL, lincomycin, linezolid, lorazepam, magnesium sulfate, meropenem, metaraminol bitartrate, methadone hydrochloride, methylprednisolone sodium succinate, metoprolol tartrate, metronidazole, midazolam hydrochloride, milrinone, morphine sulfate, moxifloxacin hydrochloride, , mycophenolate mofetil hydrochloride, nafcillin sodium, naloxone HCL, netilmicin sulfate,

	nicardipine HCL, nitroglycerin, norepinephrine bitartrate, octreotide acetate, ondansetron, oxacillin, pamidronate disodium, pancuronium bromide, papaverine HCL, penicillin G potassium, penicillin G sodium, pentamidine, phentolamine mesylate, phenylephrine HCL, piperacillin sodium, piperacillin sodium/tazobactam sodium, polymyxin B sulfate, potassium acetate, potassium chloride, propranolol hydrochloride, protamine sulfate, pyridoxine, remifentanil HCL, rocuronium bromide, sildenafil citrate, sodium acetate, sodium nitroprusside, succinylcholine chloride, tacrolimus, thiamine, ticarcillin sodium, ticarcillin disodium/clavulanate potassium, tigecycline, tobramycin sulfate, tolazoline hydrochloride, urokinase, vancomycin HCL, vasopressin, vecuronium bromide, verapamil HCL, voriconazole, warfarin sodium.
Incompatibility	Information is extrapolated from epinephrine hydrochloride. No specific information is available for epinephrine acid tartrate used in this fixed strength formulation. **Y-site:** Aciclovir, amphotericin B, aminophylline, azathioprine, diazepam, diazoxide, ganciclovir sodium, indomethacin sodium, micafungin sodium, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sodium bicarbonate, sulfamethoxazole/trimethoprim, thiopental. **Caution/variable:** ampicillin sodium, fosfomycin sodium, hydralazine HCL, insulin regular, pantoprazole sodium, propofol.
Stability	**Baxter premade Adrenaline (Epinephrine) 20 microgram/mL in sodium chloride 0.9%** - Stable for 30 days in refrigerator (2-8°C) and 24 hours at room temperature. **Baxter premade Adrenaline (Epinephrine) 20 microgram/mL in glucose 5%** - Stable for 90 days in refrigerator (2-8°C) and 24 hours at room temperature (Stability agreement is required)
Storage	Protect from light.
Excipients	
Special comments	Preferably administered via "dedicated" line to avoid accidental bolus, but often the infusion volume is small (e.g. <0.5 mL/hour) and in such cases, ensure the co-administered maintenance solution is compatible with adrenaline fixed concentration solution (refer to compatibility section). Do not use as a sideline with maintenance fluids to avoid varying drug infusion rate with changing maintenance fluid infusion rate. Discard if exhibiting colour change.

Adrenaline 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	0.60	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	0.6	0.72	0.84	0.96	1.08	1.2	2.4	3.6	4.8	6

Evidence	**Efficacy** <u>Treatment of hypotension in preterm infants</u> A single study of adrenaline 0.125−0.5 microgram/kg/minute versus dopamine 2.5−10 microgram/kg/minute reported they are equally effective at treating hypotension and increasing cerebral blood flow in very preterm infants. Adrenaline is associated with worse acid base status and increased hyperglycaemia. No difference in clinical outcomes was reported. [1−3] A single study of adrenaline 0.125, 0.250, 0.375, 0.5 microgram/kg/minute versus dopamine 5, 10, 15, 20 microgram/kg/minute reported

	dopamine reduced left ventricular output (LVO) 10% compared to a 14% increase in LVO with adrenaline. Dopamine and adrenaline caused significant increases in mean BP and pulmonary artery pressure. (LOE II, GOR C) Infants and children with septic shock Early administration of adrenaline 0.1–0.3 microgram/kg/minute was associated with increased survival compared to dopamine. [4] (LOE II, GOR B) Vasopressors for hypotensive shock (newborns excluded) In treatment of hypotensive shock beyond the newborn period, there was no difference in mortality comparing adrenaline and other vasopressors (noradrenaline, noradrenaline and dobutamine, or noradrenaline and dopexamine). [5] (LOE I, GOR B) Summary: Adrenaline may be used in hypotensive neonates with vasodilatory shock with or without myocardial dysfunction, particularly those with septic shock or unresponsive to other inotropes. (LOE II, GOR B) **Safety** Adrenaline may be associated with worse acid base status and increased hyperglycaemia.[3] Adrenaline is a potent vasoconstrictor. [6] **Pharmacokinetics** The onset of action is rapid and after intravenous infusion the half-life is approximately 5−10 minutes. [7] However, the half-life of intravenous adrenaline has not been reported in sick newborn infants.
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. Pellicer A, Bravo MDC, Madero R, Salas S, Quero J, Cabañas F. Early systemic hypotension and vasopressor support in low birth weight infants: Impact on neurodevelopment. Pediatrics. 2009;123:1369- 76. 2. Pellicer A, Valverde E, Elorza MD, Madero R, Gayá F, Quero J, Cabañas F. Cardiovascular support for low birth weight infants and cerebral hemodynamics: A randomized, blinded, clinical trial. Pediatrics. 2005;115:1501-12. 3. Valverde E, Pellicer A, Madero R, Elorza D, Quero J, Cabanas F. Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. Pediatrics. 2006;117:e1213-22. 4. Ventura AMC, Shieh HH, Bousso A, Góes PF, Fernandes IDCFO, De Souza DC, Paulo RLP, Chagas F, Gilio AE. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. Critical Care Medicine. 2015;43:2292-302. 5. Havel C, Arrich J, Losert H, Gamper G, Mullner M, Herkner H. Vasopressors for hypotensive shock. The Cochrane database of systematic reviews. 2011:CD003709. 6. Noori S, Seri I. Neonatal blood pressure support: the use of inotropes, lusitropes, and other vasopressor agents. Clinics in perinatology. 2012;39:221-38. 7. Fitzgerald GA, Barnes P, Hamilton CA, Dollery CT. Circulating adrenaline and blood pressure: the metabolic effects and kinetics of infused adrenaline in man. European journal of clinical investigation. 1980;10:401-6. 8. Schwab KO, von Stockhausen HB. Plasma catecholamines after endotracheal administration of adrenaline during postnatal resuscitation. Archives of disease in childhood Fetal and neonatal edition. 1994;70:F213-7. 9. 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 10. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: November/10/2023). 11. 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

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