Heparin
Newborn use only

2022

Alert	High risk medication in A PINCH Medicines list under New South Wales Clinical Excellence Commission. Also known as unfractionated heparin (UFH). Not equivalent to low molecular weight heparin (LMWH). Use in consultation with haematologist for treatment of thrombosis. Many concentrations of heparin are available. Accidental overdose can occur when multiple concentrations are kept in the unit. In neonatal settings: recommend to store the following preparations only: heparinised saline 50 units/5 mL and heparin sodium injection ampoule 1000 units/1 mL. DBL Heparin sodium injection in ***vials*** **is not recommended** in neonates as it contains benzyl alcohol. However, DBL Heparin sodium injection in ***ampoules*** does **not** contain benzyl alcohol.
Indication	Primary or secondary antithrombotic prophylaxis. Maintenance of arterial and central venous catheter patency.
Action	Heparin binds to antithrombin III (ATIII), potentiating ATIII's activity by at least 1000-fold. ATIII predominantly inactivates factor Xa and thrombin (other proteases/clotting factors to lesser degree), which in turn inhibits conversion of fibrinogen to fibrin. Also possesses anti-complementary activity, inhibiting both the classic and alternative pathways.
Drug type	Anticoagulant
Trade name	Heparin Sodium Injection (Pfizer), DBL Heparin Sodium Injection BP Heparinised Saline Injection (Pfizer)
Presentation	**Antithrombotic prophylaxis** Pfizer Heparin Sodium Injection Ampoule: 5000 units/5 mL DBL Heparin Sodium Injection BP Ampoule: 1000 units/1 mL DBL Heparin Sodium BP Vials – ***Not to be used in neonates as it contains benzyl alcohol.*** **Maintenance of catheter patency** Heparinised Saline Injection Ampoule: 50 units/5 mL (10 units/mL) Also available as premixed infusions (Heparin (1 unit/mL) in sodium chloride 0.9% in 50 mL syringe)
Dose	**Antithrombotic prophylaxis**[1,2,3] Loading dose: 75 (50-100) units/kg over 30 minutes. Initial maintenance dose: 30 (20-40) units/kg/hour as continuous IV infusion. **Adjustment of Heparin dose** Anti-Xa is preferred to assess the effect of heparin and guide dosing (Table 1).

Table 1. Heparin dosing based on anti-Xa levels (therapeutic range 0.3-0.7 unit/mL)(modified from O'Meara et al)[3]

Anti-Xa level (unit/mL)	Dose adjustment
<0.2	Increase infusion by 5 units/kg/hour
0.2-0.29	Increase infusion by 5 units/kg/hour
0.3-0.7	No change
>0.7≤1.0	Decrease infusion by 2 unit/kg/hr
>1	Seek advice from haematologist
Measure anti-Xa levels 6 hours after commencing heparin and then 6 hourly until two consequent values are within therapeutic range. After every heparin adjustment or a blood product administration, the anti-Xa level should be checked again in 6 hours and discuss with haematologist on frequency of further monitoring. PT/INR, PTT, fibrinogen, platelet count, and ATIII levels are measured daily or as advised by the haematologist.	

If anti-Xa levels are not available, APTT can be used to guide heparin dosing (Table 2).

Table 2. Heparin dosing based on APTT levels (therapeutic range 60-85 seconds).[1,4]

APTT (seconds)	Bolus (units/kg)	Hold (min)	Rate change (%)	Time until repeat APTT
<50	50	0	+10	6 h
50-59	0	0	+10	6 h

	<table><tr><td>60-85</td><td>0</td><td>0</td><td>No change</td><td>Next day or as per haematologist advice</td></tr><tr><td>86-95</td><td>0</td><td>0</td><td>-10</td><td>6 h</td></tr><tr><td>96-120</td><td>0</td><td>30</td><td>-10</td><td>6 h</td></tr><tr><td>>120</td><td>0</td><td>60</td><td>-10</td><td>6 h</td></tr><tr><td colspan="5">Obtain blood for APTT 6 hours after administration of loading dose and 6 hours after every change. When APTT values are therapeutic, blood count and APTT daily or as per the advice of haematologist.</td></tr><tr><td colspan="5"></td></tr></table> APTT: Activated partial thromboplastin time **Venous catheter patency maintenance.**[1,2,5-7,18-21] 0.5 unit/mL of heparinised saline to run at 0.5 –1 mL/hour.(Refer to evidence section) **Arterial catheter patency maintenance.**[1,2,5-7,18-21] 1 unit/mL of heparinised saline to run at 0.5 – 1 mL/hour.(Refer to evidence section) **Heparin Lock for Central Venous Access Device (CVAD)** Heparinised saline **10units/mL** with **0.5 to 1 mL** instilled per lumen as per the priming volume.
Dose adjustment	Therapeutic hypothermia – No information. ECMO – Refer to local ECMO protocols for anticoagulation. Renal impairment – Dose adjustment may be required in severe renal impairment. Discuss with haematologist. Hepatic impairment – No dose adjustment is required.[8]
Maximum dose	
Total cumulative dose	
Route	IV, intra-arterial
Preparation	**Antithrombotic prophylaxis** Dilute 1.25mL (1250units)/kg of heparin with glucose 5% or sodium chloride 0.9% to make a final volume of 50mL with a concentration of 1mL/hr = 25units/kg/hr.* *More concentrated strengths (for example 1mL/hr = 50units/kg/hr) can be prepared if fluid restriction is required. **Venous catheter patency** Add 25 units (2.5 mL) of **heparinised saline** to 47.5 mL of sodium chloride 0.9% or 0.45% to make a final volume of 50 mL with a concentration of 0.5 unit/mL. **Arterial catheter patency** Add 50 units (5 mL) of **heparinised saline** to 45 mL of sodium chloride 0.9% or 0.45% to make a final volume of 50 mL with a concentration of 1 unit/mL. Commercial premade syringe – 50 mL syringe containing heparin (1 unit/mL) in sodium chloride 0.9%.
Administration	**Systemic antithrombotic therapy** Loading dose: Administer over 30 minutes. Maintenance: Continuous IV infusion. **Vascular catheter patency** Continuous IV infusion.
Monitoring	**Antithrombotic prophylaxis** Six hours after initiating therapy, measure anti-Xa (or APTT if anti-Xa is not available), then adjust dose to achieve anti-Xa level of 0.3 to 0.7 unit/mL (equivalent to APTT of 60 to 85 seconds) – Refer to tables 1 and 2 in the dosing section. Platelet count before the commencement and then weekly. Assess for signs of bleeding and thrombosis. **Vascular catheter patency** Standard observations for intravascular catheters.
Contraindications	Known hypersensitivity to heparin, uncontrolled bleeding. Intraventricular haemorrhage, gastrointestinal haemorrhage, thrombocytopenia < 50 x 10^9/L, severe hypertension.

<table>
<tr><td></td><td>Eye, brain or spinal cord surgery – Surgeons to give clearance regarding when to start heparin.[7]</td></tr>
<tr><td>Precautions</td><td>Bleeding disorders – Discuss with haematologist.
Store heparinised saline ampoules separately from other heparin products and sodium chloride 0.9% ampoules to reduce the risk of selection errors.</td></tr>
<tr><td>Drug interactions</td><td>Paracetamol, non-steroid anti-inflammatory drugs, alprostadil, thrombolytic agents, vitamin A may increase the risk of bleeding.</td></tr>
<tr><td>Adverse reactions</td><td>Haemorrhage and haematoma formation.
Heparin-induced thrombocytopenia (HIT).
Osteoporosis.
Cholestatic liver reaction and elevation of transaminases.
Hyperaldosteronism can occur after prolonged administration.[8]

Treatment of Heparin-Induced Bleeding: (1) cease heparin and (2) if immediate reversal is required, administer protamine sulfate. The required dose of protamine sulfate is based on the amount of UFH received in the previous 2 hours as follows:[1]

<table><tr><th>Time Since Last Heparin Dose</th><th>Protamine dose per 100 units of heparin received in the last 2 hours</th></tr><tr><td><30 min</td><td>1 mg</td></tr><tr><td>30-60 min</td><td>0.5-0.75 mg</td></tr><tr><td>60-120 min</td><td>0.375-0.5 mg</td></tr><tr><td>>120 min</td><td>0.25-0.375 mg</td></tr></table>Maximum dose of 50 mg. Infusion rate of a 10 mg/mL solution should not exceed 5 mg/min.
Hypersensitivity reactions to protamine sulfate may occur in patients with known hypersensitivity reactions to fish or those previously exposed to protamine therapy or protamine-containing insulin. For more information, refer to Protamine formulary.</td></tr>
<tr><td>Compatibility</td><td>Fluids: Glucose 5%, Sodium chloride 0.9%, sodium chloride 0.45%.[8,9]
Y-site: Aciclovir, ampicillin, atropine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefotaxime, clindamycin, dexamethasone, dexmedetomidine, digoxin, dopamine, ephedrine sulfate, fentanyl, fluconazole, folic acid (sodium salt), furosemide, hydrocortisone sodium succinate, levetiracetam, linezolid, magnesium sulfate, meropenem, metronidazole, midazolam hydrochloride, morphine sulfate, naloxone hydrochloride, noradrenaline, pancuronium bromide, paracetamol, piperacillin/tazobactam, phenobarbital sodium, pipercillin-tazobactam, potassium chloride, rocuronium bromide, suxamethonium, vecuronium, zidovudine.</td></tr>
<tr><td>Incompatibility</td><td>Fluids: Fat emulsion.
Y-site: Benzylpenicillin, ciprofloxacin, cisatracurium, dobutamine, erythromycin, gentamicin, ketamine, tobramycin.</td></tr>
<tr><td>Stability</td><td></td></tr>
<tr><td>Storage</td><td>Ampoule and vial: Store below 25°C.
Bag: Store below 30°C.</td></tr>
<tr><td>Excipients</td><td>Pfizer ampoule: Water for injection
DBL ampoule: Hydrochloric acid, sodium hydroxide.
DBL vial: Benzyl alcohol. Do not give products that contain benzyl alcohol to neonates.
Heparinised saline: Hydrochloric acid, sodium chloride, sodium hydroxide.</td></tr>
<tr><td>Special comments</td><td>Protamine sulfate is the reversal agent to correct the anticoagulant effect of heparin.</td></tr>
<tr><td>Evidence</td><td>Efficacy
<u>Systemic antithrombotic therapy/prophylaxis</u>
<u>Arterial thrombosis:</u> Spontaneous arterial thrombosis is rare in neonates and the evidence around its management using heparin is limited to case reports only. De Godoy et al reported complete disappearance of an aortic thrombus and clinical improvement in a neonate following 15 days anticoagulation with heparin.[11] Similarly, anticoagulation with heparin following initial thrombolysis of a major aortic thrombus is found to be helpful in improving clinical outcomes of neonates.[12]

<u>Venous thrombosis:</u> In a cohort of 53 neonates who received heparin, Moharir et al found significant reduction in propagation of cerebral sino-venous thrombosis (2 vs 30%; P < 0.001). However, no difference</td></tr>
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	was noted in thrombus recanalisation, mortality and long-term disability.[13] Non-life threatening bleeding was seen in 5-6% of neonates. In two retrospective reviews involving 100 neonates who received heparin therapy for renal vein thrombosis with or without inferior vena cava involvement, there was no difference in irreversible renal damage and renal atrophy at long term follow up.[14, 15] In a cohort of 128 neonates with portal vein thrombosis the incidence of lobar atrophy of liver and risk of portal hypertension was not altered by the use of anticoagulants.[16] No clinical outcome studies have determined the therapeutic range for heparin in neonates and the APTT therapeutic range and monitoring is extrapolated from adults. One prospective cohort study used a weight-based nomogram to address dosing of heparin in paediatric patients required to achieve adult therapeutic APTT values. Bolus doses of 75 to 100 units/kg resulted in therapeutic APTT values in 90% of children at 4-6 hours after bolus.[17] **Maintenance of patency of central vascular catheters[1,2, 5-7]** Low dose heparin administered as a continuous infusion or regular flushes significantly increases the duration of peripheral catheter patency and reduces the episodes of infusion failure.[5,6] A systematic review involving 267 neonates reported significant reduction in occlusion of peripherally placed percutaneous central venous catheters and higher rates of completion of therapy if heparin is infused at a dose of 0.5unit/kg/hr.[7] Administration of heparin in low doses does not significantly alter the risk of sepsis or intraventricular haemorrhage.[1,5-7] However, Lesko et. al. reported a 4-fold, but statistically not significant, increase in IVH in low-birthweight infants in a case control study (OR, 3.9; 95% CI, 1.4-11.0).[10] **Maintenance of patency of peripheral arterial catheters** Heparin is shown to significantly reduce clot formation and maintain patency of peripheral arterial catheter for a longer period.[18] Compared with 1 unit/mL, heparin concentration of 5 units/mL is more effective in keeping arterial catheters patent for longer time.[19] Studies found heparinised normal saline superior to heparinised glucose solution, and continuous infusion of heparin in normal saline better compared to intermittent flushing to improve arterial catheter patency.[20,21] **ANMF consensus on the strength and infusion rate of heparinised IV fluid for catheter patency is a simplified pragmatic recommendation from the evidence.** **Heparin Lock for Central Venous Access Device (CVAD)** The 'lock' is the intraluminal injection of a limited volume of fluid, after the catheter flush, in the intervals of time when the catheter is not in use, with the purpose of preventing lumen occlusion and/or bacterial colonization. The most appropriate lock solution for central venous access devices is still to be defined. The data available from the literature are still not conclusive and no recommendation is offered by most guidelines.[25] The recommended regimen suggested by the ANMF group is reflective of the current practice in neonatal units. **Safety** Major bleeding has been reported in children treated for deep vein thrombosis/pulmonary embolism. There are case reports of osteoporosis. Given the adverse effects, and the availability of alternative anticoagulants, long term use of heparin can be avoided. Heparin-induced thrombocytopenia (HIT) has been reported in neonates. Following exposure to heparin for at least 5 days, Schmugge et al reported antibodies against HPF4 in 2.3% children who developed thrombocytopenia and thrombosis.[23] In a systematic review, Avila et. al. reported seroconversion for anti-PF4/H antibodies in 0-1.7% neonates but no neonate fulfilled the combined clinical and laboratory criteria used for the diagnosis of HIT.[24] **Pharmacokinetics** Studies of heparin in newborns are limited but show that the clearance is faster than for older children because of a larger volume of distribution. It is metabolised by liver and excreted renally within 6 hours but may be delayed. Half-life is dose-dependent but averages 1 to 3 hours. Efficacy in neonates may be low due to low antithrombin plasma concentrations.[1]
Practice points	**General** There are no data from randomised controlled trials to recommend or refute the use of heparin for treatment of neonatal thrombosis.[2] **Dose** Antithrombotic prophylaxis

	Loading doses and maintenance doses have been adapted from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 2012,[1] which were based on paediatric data from a prospective cohort study.[22] (LOE IV GOR D) Loading dose is safer to be infused over 30 minutes in neonates. (ANMF haematology expert group opinion) Initial maintenance dose is easier to be administered at 30 units/kg/hr, rather than 28 units/kg/hr. (ANMF haematology expert group opinion) <u>Central vascular catheters</u> Heparin infusions at 0.5 units/kg per hour are recommended to maintain CVAD patency.[1,7] (LOE I, GOR B) <u>Peripheral arterial catheters</u> Heparin infusions at 0.5 units/mL at 1 mL/hour are recommended.[1] (LOE II, GOR B) ANMF consensus on the strength and infusion rate of heparinised IV fluid for catheter patency is a simplified pragmatic recommendation from the evidence. <u>Heparin Lock for Central Venous Access Device (CVAD)</u> The recommended regimen suggested by the ANMF group is reflective of the current practice in neonatal units. **Dose adjustment** Anti-Xa therapeutic range: While O'Meara study suggests 0.4 – 0.8 unit/mL, range of 0.3 – 0.7 unit/mL is adequate for most indications, and most commonly used. Table 1 is a modified regimen of O'Meara study,[3] which was performed in ECMO patients where very tight anticoagulation is required, managed by staff very experience in managing anticoagulation for ECMO circuits; hence, the repeat boluses were recommended by O'Meara et. al. when anti-Xa was below the target range. Repeat boluses are not required in the majority of non-ECMO patients. Regarding dose adjustment for anti-Xa > 1, advice from the haematologist should be sought as the anti-Xa can be very high and simply reducing the infusion rate may not be appropriate.[3] (ANMF haematology expert group opinion) The frequency of testing at 2 hourly intervals is the practice in ECMO circuits but not indicated for routine anti-coagulation for non-ECMO patients. Testing too early & too frequently, lends to inappropriate dose adjustments. Testing 6 hours after starting infusion and dose changes is adequate as a general guide, and to check with the haematologist on further monitoring. (ANMF haematology expert group opinion) Dose adjustments using APTT monitoring have been adapted from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 2012,[1] which were based on paediatric data from a prospective cohort study.[22] (LOE IV GOR D) For consistency, using APTT monitoring, testing 6 hours after starting infusion and dose changes is suggested as a general guide, and to check with the haematologist. (ANMF haematology expert group opinion)
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