Heparin (unfractionated heparin) Intravenous for Adults

Who can administer

May be administered by registered competent doctor or nurse/midwife

Important information

- Use the Green cardboard administration guidelines available on all wards
- See **'Monitoring'** - below
- Vials may be poorly labelled. - ie some brands are not labelled as 25,000 units per 5mL (instead they state 5,000 units/mL, and vials contain 5mL - **errors have occurred**)
- **Double check total volume/strength** before administration
- **Invert** the bag 6 times when adding heparin to ensure that the drug is evenly distributed - there are reports of most of the heparin being given during the start of an infusion due to pooling [ref 1]
- Refer to heparin on main drug chart (by prescribing as 'Heparin- see Heparin prescription sheet', so that all practitioners are aware that the patient is receiving heparin
- Vials are for **single use** only. Discard after opening
- See under Further information for guidance on use of unfractionated heparin with **spinal/epidural catheters**
- For Y-site compatibility see below

Available preparations

Route	Preparation		Manufacturer
For infusion	Heparin sodium 5,000 units in 5mL	Vial	Wockhardt
For flushing	Heparin sodium 50 units in 5mL (preservative free)	Ampoule	Wockhardt
For Dialysis unit and Cardiac Angio, Critical care	Heparin sodium 25,000 units in 5mL	Vial	Wockhardt
For cardiothoracic theatre	Heparin sodium 20,000 units in 20mL (preservative free)	Ampoule	Wockhardt
For paediatric use (line locks)	Heparin sodium 1,000 units in 1mL (preservative free)	Ampoule	Wockhardt
For subcutaneous use-prophylaxis	Heparin sodium 5,000 units in 0.2mL (preservative free)	Ampoule	Wockhardt

Note: Heparin 25,000 units in 5mL (5,000 units per mL) is no longer to be routinely stocked in GUH (but it is supplied to Dialysis unit, Cardiac Angio and Critical care)

Reconstitution

Already in solution

Ampoules: Draw up using a 5 micron filter needle

Infusion fluids

Sodium chloride 0.9% or Glucose 5%

Methods of intravenous administration

Slow intravenous injection (loading dose and bolus doses only)

- Administer undiluted injection solution over at least 3 minutes [ref 1]

Continuous intravenous infusion (maintenance dose) (administer using an electronically controlled infusion device) [ref 2]

- Add 25,000 units (25mL of 1,000 units/mL) to 225mL infusion solution to produce an infusion containing 100 units per mL
- Invert the bag six times to ensure adequate mixing - see 'Important information'
- Set up as a continuous infusion, and adjust rates according to body weight and aPTT

Dose in adults

1: Venous Thromboembolism (VTE)

Important

- Check baseline APTT - if elevated, APTT may not be suitable for monitoring heparin therapy. Haematology consult may be required as Factor Xa monitoring may be required [ref 3]

Loading dose (by slow intravenous injection)

- Give 80units/kg (round to nearest 500 units), followed by an initial maintenance infusion

Initial maintenance dose for infusion

- Give 18 units per kg per hour - then adjust according to APTT (see simplified dosing table on GUH Heparin prescription sheet)
- Check APTT every 4 to 6 hours until stable. Check 4 to 6 hours after a rate change or bolus dose.
- Once three consecutive APTT are in required range, can monitor APTT once daily
- Adjust doses as per the table on the green prescription sheet
- See Intravenous Heparin prescription (Green prescription) for dosage adjustments to achieve APTT within the therapeutic range - see under 'monitoring' for more details

2: Intra-aortic balloon pump

- As directed by cardiologist or intensivist

3: For use as a flush solution

- For doses please refer to relevant policies: Intravenous Drug administration CLN-NM-093 Policy for nurses/midwives and procedure for the administration of drugs and TPN via peripheral cannulae and CVC for Health Care Professionals

Monitoring

- Check baseline APTT - and see under maintenance dose above for required frequency thereafter
- Patient's baseline APTT can vary - aim for APTT two to three times baseline value
- An optimum target **APTT** of between 55 and 80 is suggested based on a mean average aPTT of 28 in GUH [ref 4]

- The mean **aPTT is specific to each laboratory**, and is reagent and analyser specific
- **High baseline aPTT** may be possible in e.g. Lupus, Factor XII deficiency - in these situations aPTT cannot be used to monitor efficacy. Consider LMWH or haematology consult as Factor Xa monitoring may be required [ref 3]
- Monitor patient for signs of **bleeding**
- All patients receiving intravenous unfractionated heparin should have **baseline platelet counts** and repeat measurements on alternate days
- For patients who have received unfractionated heparin within the **last 100 days,** a repeat platelet count should be taken within 24 hours of starting heparin
- **Hyperkalaemia** can occur - plasma potassium levels should be measured regularly. Patients particularly at risk include those with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium, or those on potassium-sparing drugs

Further information

- The blood sample for aPTT should be taken from a site separate to that at which heparin is being infused (and not immediately 'downstream' of it) [ref 2]
- Antidote : Protamine Sulphate
- Caution is recommended in spinal and epidural anaesthesia. **Heparin infusion must be stopped** for a minimum of four hours, and the aPTT should be normal before attempting a block or removing spinal or epidural catheters. This is due to the risk of **spinal haematoma and paralysis** [ref 4] - see prescription sheet for details. After neuraxial puncture and catheter removal, heparin infusion must not be restarted until after one hour (and normal aPTT) [ref 4]
- **Surgery:** stopping heparin infusion for 4 to 6 hours should result in a 'normal' aPTT. However, this **must be confirmed** by laboratory analysis.

Heparin Induced Thrombocytopenia [ref 6]

Introduction

- Heparin induced thrombocytopenia (HIT), with or without thrombosis, is a recognised devastating immune-mediated complication of heparin therapy. HIT may arise in up to 3% of patients on unfractionated heparin (UFH) with a lower prevalence in patients who receive low molecular weight heparin (LMWH) (<1%).
- The platelet count typically begins to fall 5 to 10 days after starting heparin, although in patients who have received heparin in the previous 3 months it can have a rapid onset due to pre-existing antibodies.
- If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of heparin-induced thrombocytopenia (HIT) between days 4 and 14 of heparin administration, HIT should be considered and a clinical assessment made
- Occasionally, the onset can occur after more than 10 days of heparin exposure but it is rare after 15 days
- Early diagnosis is crucial and therefore, all patients receiving heparin should have baseline platelet counts and repeat measurements on alternate days. For patients who have received UFH within the last 100 days, a repeat platelet count should be taken within 24 hours of starting heparin.

What to do when a diagnosis of HIT is suspected

- The 4T's are key to assessing the probability that a patient is developing HIT: **T**hrombocytopenia, **T**iming of platelet count fall, **T**hrombosis, o**T**her causes for thrombocytopenia. Reassessment should be done periodically as new information can change pre-test probability (e.g. positive blood culture). Table

1 below outlines the '4T's' criteria to determine the pretest probability of HIT.
- If HIT is suspected, all sources of UFH and LMWH should be discontinued. It is important to note that no heparin should be given through arterial lines or indwelling cannulas. Central lines with heparin-coated tips (e.g. some Swan-Ganz catheters) should be removed.

Table 1 Estimating the Pretest Probability of HIT: The "Four T's"

	Pre-test Probability Score Criteria Points (0,1,2 for each of 4 Categories)		
	2 points	**1 point**	**0 points**
Thrombocytopenia	>50% fall and platelet nadir 20 x 10^9/L or greater	30 - 50% fall or platelet nadir 10 -19 x 10^9/L	Fall <30% or platelet nadir less than 10 x 10^9/L
Timing*of platelet count fall or other sequelae	Clear onset between days 5 and 10; or 1 day or less (if heparin exposure within past 30 day)	Consistent with immunisation but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10; or fall 1 day or less (if heparin exposure 30 -100 days ago)	Platelet count fall 4 days or less (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post- heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
O**t**her cause for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
***First day of immunising heparin exposure considered day 0**			
6 to 8 High	**Alternative anticoagulant required**	**If pretest probability score is high or intermediate contact Consultant Haematologist for advice.**	
4 to 5 Intermediate	**Consider alternative anticoagulant**		
0 to 3 Low	**Do not test. No alternative anticoagulant required**		

Laboratory Testing for HIT

- There are two major types of assays used to detect HIT antibodies; activation assays (functional) and antigen-dependent assays.
- Antigen assays detect antibodies that recognize platelet-factor 4 bound to heparin. There are a number of commercially available assays available. Antigen assays may detect antibodies that are not clinically significant. They should be interpreted in combination with the result of the activation assay and the clinical setting, hence the importance of the 4T score
- These tests need to be confirmed with an ELISA (Enzyme Linked Immunosorbent Assay) assay and a functional assay (Heparin Induced Platelet Aggregation (HIPA))due to the high false positive rate.
- The strength of positivity (optical density) of the ELISA result correlates with the clinical presentation
- Two serum sample are required and a completed 4T score must be sent to the Haematology lab or the sample will not be processed

How to manage a patient with HIT

- **Haematology should be consulted if HIT is suspected or confirmed**
- UFH and LMWH should not be used in these patients. LWMH rarely results in HIT. However, once this complication has developed, there is cross reactivity to LMWH in almost 100% of cases. Cessation of heparin alone is not sufficient to prevent the thrombotic complications of HIT. The choice of an alternative agent should be discussed with the Consultant Haematologist.Â·For patients receiving warfarin at the time of diagnosis of HIT, the anticoagulant effects should be reversed with vitamin K (5mg to 10 mg IV). **Warfarin should be discontinued.**
- **Treatment strategies to be considered include:**
  - For patients with strongly suspected (or confirmed HIT) whether or not complicated by thrombosis, therapeutic anticoagulation with an alternative agent should be commenced.
  - The **initial** drug of choice is argatroban
  - Patients will switch to a DOAC once the platelet count has normalised. Initiation,duration and choice of therapy will be decided by the Consultant Haematologist
  - Given the high mortality and morbidity associated with HIT, the Consultant Haematologist may decide to commence treatment in the absence of the laboratory assay.
  - Vigilant follow up is required as up to 50% of patients may subsequently develop a thrombotic event within the next month, even when the platelet count has returned to normal
  - It is important to note that **argatroban use in the absence of HIT is associated with a high risk of bleeding**. Hence the importance of calculating the 4T score in all patients with suspected HIT (ref 4)

Storage

- Store below 25^{0}C
- Vials are for use on one patient only
- The high strength formulation (**25,000 units in 5mL**) must be stored in **Controlled Drug press** in Critical care areashttps://pubmed.ncbi.nlm.nih.gov/24930477/

References

1.Injectable Medicines Administration Guide Medusa - downloaded 21st Oct 2021

2. Intravenous Heparin Prescription sheet November 2016

3: Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology Br J Haematol. 2014 Sep;166(6):830-41

4. Expert opinion. Dr Ruth Gilmore, Consultant Haematologist, November 23rd, 2021

5. GUH Bridging guideline 2017

6: Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition Henry Watson,Simon Davidson,David Keeling British Society of Haematology

Therapeutic classification

Anticoagulant