ANTICOAGULANT THERAPY OF VENOUS THROMBOEMBOLISM (VTE) - SCH

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Patients at high risk of thromboembolism may benefit from prophylaxis with low molecular weight heparin (LMWH).
- Baseline FBC, APTT, PT must be performed to exclude the presence of an underlying coagulation disorder and platelet count should be checked after 3 to 4 days of therapy to monitor for the development of heparin induced thrombocytopenia. Prophylactic anti-Xa levels should be performed.
- **Planned treatment of Venous Thromboembolism must be discussed with a haematologist before commencement**.
- Neonates are managed with initial anticoagulation at treatment doses of Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) for 3 to 5 days followed by LMWH or radiological monitoring with treatment being instituted if progression of thrombosis.
- Children receive initial anticoagulation at treatment doses of LMWH or UFH (for 5 to 10 days) followed by either Warfarin or LMWH.
  - Baseline tests including FBC, APTT, PT and renal function should be performed and dose adjusted accordingly.
  - LMWH requires monitoring of anti-Xa levels; UFH requires monitoring of APTT
  - Protamine may be used for reversal of anticoagulation based on the timing of the previous dose of LMWH or UFH. Senior Staff should be informed prior to the administration of Protamine.
  - Caution must be used when administering protamine as there may be serious side effects (e.g Hypotension, Bradycardia, Anaphylaxis).
  - Warfarin treatment is complex and may be difficult to manage. Patient and family education is of vital importance. Dose adjustment is necessary based on INR results.

Approved by:	Director of Clinical Governance	
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CHANGE SUMMARY

- The document replaces C.20.25 Anticoagulant Treatment of Venus Thromboembolism and includes:
  - Update of references and formatting
  - Addition of precautions in renal impairment and caution in heparin vial selection
  - Information on appearance of warfarin tablets
  - Changes to management of prolonged INRs
  - Standard heparin infusion to be used for all patients at a concentration of 100 units/mL
  - Standard premixed heparin bags are available at SCH.
- **9/07/21**: Minor review, updated pg8 to align with the implementation of B Braun pumps to SCH.

READ ACKNOWLEDGEMENT

- The following staff should read and acknowledge they understand the contents of this document:
  - Medical Staff prescribing anticoagulants
  - Nursing staff administering anticoagulants and particularly preparing heparin infusions
  - All Pharmacists

TABLE OF CONTENTS

Anticoagulant Therapy of Venous Thromboembolism (VTE)

Guidelines for established indications for prophylaxis and treatment of paediatric thromboembolism can be found online:

- Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition).
- See also:
  - SCHN Central Venous Access Device (CVAD) Practice Guideline
  - SCH Enoxaparin Administration Drug Protocol

1 Anti-Coagulant Prophylaxis

1.1 Indications

- Patients at high risk of thromboembolism may benefit from prophylaxis with low molecular weight heparin (LMWH).
- In the adult population patients are routinely administered prophylactic anti-coagulation following major surgery and orthopaedic procedures. Venous thromboembolism occurs much less commonly in the paediatric setting with no established evidence in favour of prophylaxis. However there may be clinical circumstances in which prophylaxis is clinically indicated, particularly in patients who have underlying risk factors and:
  - **i.** Undergoing major surgery where there is the likelihood for long periods of inactivity.
  - **ii.** Experience major trauma and who are expected to be immobilized for an extended period of time.
- Prophylactic therapy may be instituted on request by a surgeon in consultation with a haematologist to discuss dosing and duration of therapy.

1.2 Precautions[2]

In patients with renal failure prophylactic heparin injections may result in therapeutic anticoagulation.

As with other anticoagulant medications, consideration must be given to the management of prophylactic heparin injections prior to invasive procedures such as lumber punctures and surgery.

Concurrent use of non-steroidal anti-inflammatories (NSAIDs) e.g. Aspirin /diclofenac should NOT be allowed in patients receiving anticoagulants or those who have an epidural insitu.

For patients with a history of coagulation disorders, be it thrombosis or bleeding or currently taking anticoagulant therapy, a Haematology consult is mandatory.

1.3 Prophylactic Enoxaparin Dose

Children under 2 months of age:	0.75 mg/kg/dose	12-hourly subcutaneously
Children 2 months of age or older: Maximum 40mg daily.	0.5 mg/kg/dose	12 hourly subcutaneously;

1.4 Administration and Monitoring

1. Obtain baseline FBC, APTT, PT to exclude the presence of an underlying coagulation disorder.
2. Administer via rotating injection sites.
3. Platelet count should be checked after 3-4 days of therapy to monitor for the development of heparin induced thrombocytopenia.
4. Prophylactic Anti-Xa levels: 0.1 – 0.3 Units/mL measured 4 hours post dose.

2 Treatment of Deep Vein Thrombosis and/or Pulmonary Embolus

The following are guidelines for the dosing and monitoring of heparin. It may be necessary to modify this protocol according to individual patient requirements.

Planned treatment must be discussed by a haematologist before commencement.

2.1 Monitoring and duration

Neonates

Initial anticoagulation at treatment doses of Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) for 3-5 days followed by LMWH or radiological monitoring with treatment being instituted if progression of thrombosis.

UFH:	Target APTT 60-85 seconds.
LMWH:	Target Anti-Xa level 0.5-1.0 Units/mL; Level taken 4 hours post dose.[3]

- The optimal duration of anticoagulation treatment is controversial and is a complex decision. The usual timeframe is approximately 3 months. The decision should be taken after consultation between the treating Doctor and Haematologist.
- Central Venous Catheter (CVC) or Umbilical Venous Catheters (UVC) associated with thrombosis should be removed, if possible, after 3 to 5 days of anticoagulation.[1]
- If CVC remains in situ after completion of treatment period, prophylactic LMWH (target anti-Xa level 0.1 to 0.3 Units/mL) should be instituted until the CVL has been removed.

Children

Initial anticoagulation at treatment doses of LMWH or UFH (for 5 to 10 days) followed by either Warfarin or LMWH.

UFH :	Target APTT 60 to 85 seconds
LMWH:	Target anti-Xa level 0.5 to 1 Units/mL; Level taken 4 to 6 hours after dose

- The optimal duration of anticoagulation treatment is controversial and is a complex decision. The usual timeframe is approximately 3 months. The decision should be taken after consultation between the treating Doctor and Haematologist.
- For children with CVC related thrombosis where the CVC is non-functioning or no longer required it should be removed after 5 days of anticoagulation. If the CVC cannot be removed, after the initial therapeutic treatment course (approximately 3 months), patients should receive prophylaxis with either warfarin (target INR 1.5 to 1.9) or LMWH (target anti-Xa Level 0.1 to 0.3 Units/mL) until the CVC is removed.
- Where there are other ongoing risk factors (other than CVC), longer therapy with prophylactic or treatment doses may be necessary.
- Children with recurrent idiopathic VTE should receive indefinite treatment with warfarin to achieve a target INR of 2 to 3.

For other indications that may not be covered above please contact the Haematologist on call.

2.2 Dosing

Low Molecular Weight Heparin (LMWH)

In Neonates and Children the LMWH of choice is Enoxaparin (Clexane®).

Practice Points

- Weigh patient
- Obtain baseline Full Blood Count (FBC)
- Administer via subcutaneous route, either via an Insuflon catheter, or by rotating sites of subcutaneous injections. See: SCH Enoxaparin Administration Drug Protocol.
- Timing of commencement of therapy (especially post-procedural) should be individualised.
- Duration of therapy is determined on an individualised basis, based upon indication for treatment.

2 doses should be withheld before invasive procedures (eg Lumbar Punctures)

Treatment Dose[1]

- Infants under 2 months of age: 1.5 mg/kg/dose 12-hourly subcutaneously.
- Children 2 months of age and older: 1 mg/kg/dose 12-hourly subcutaneously.

Monitoring[1]

- Avoid the use of aspirin unless clearly directed by the senior medical officer to take the 2 drugs concurrently.

- Avoid IM injections and arterial punctures if possible during treatment with LMWH.
- APTT is irrelevant in LMWH monitoring.
- Anti-Xa level is to be taken 4 to 6 hours post subcutaneous administration of LMWH.
- Sample NOT to be taken from a line contaminated with standard heparin. It must be a venous sample placed in a coagulation tube. Do not overfill or underfill tube

Dose adjustment of LMWH at treatment dosages

Anti-Factor Xa level (Units/mL)	Hold Next Dose	Dose Adjustment	Repeat anti-Xa level
Below 0.35	No	Increase by 25%	4 hours after next a.m. dose.
0.35 – 0.49	No	Increase by 10%	4 hours after next a.m. dose.
0.5 – 1	No	No change	Weekly - 4 hours after next a.m. dose.
1.1 – 1.5	No	Decrease by 20%	4 hours after next a.m. dose.
1.6 – 2	Delay next dose for 3 hours	Decrease by 30%	Trough level before next dose, then 4 hours after next a.m. dose.
Above 2	Until ant-Xa level is below 0.5 Units/mL	Decrease by 40%	Trough level pre next dose and if not below 0.5 Units/mL, repeat twice daily.

Reversal of LMWH[2]

Senior Staff should be informed prior to the administration of Protamine. When reversal of LMWH is required (e.g. for bleeding) the antidote is **Protamine Sulphate**. Caution must be used when administering Protamine as there may be serious side effects (e.g. hypotension, bradycardia, anaphylaxis).

Dosage:

Note: Maximum dose is 50mg except for reversal of Cardiopulmonary Bypass.

- *If less than 8 hours since LMWH administration*: 1 mg Protamine per 100 Units (1 mg) LMWH given in the last dose.
- *If greater than 8 hours since LMWH administration:* 0.5 mg Protamine per 100 Units (1mg) LMWH given in the last dose.

Protamine sulphate is usually administered undiluted (10 mg/mL) over at least 10minutes and not exceeding 5 mg/minute. If administration is too rapid cardiopulmonary collapse may be precipitated.

Intravenous Unfractionated Heparin

A common cause of fatal heparin induced bleeding is accidental overdose, especially in neonates. The most common cause of this is drug error, with 5,000 Units/mL or similar concentration vials being erroneously selected instead of 50 Units/mL vials.

Care should be taken to ensure the appropriate strength is selected when prescribing and administering heparin.

Administration:

- Obtain baseline FBC, APTT and PT (INR) and assess renal function.
- Any patient with a low platelet count, abnormal APTT or PT must be discussed with a Haematologist prior to commencing heparin.
- Obtain patient's weight:

  i. **Infants and children under 20 kg**

  1. Heparin should be given via syringe pump

  2. Prepare heparin to a concentration of 100 Units/mL.

  i.e. Combine heparin (5,000 Units/5mL) with 45mL compatible fluid to make 5,000 Units in 50mL **OR** withdraw 50mL from standardised premixed 25,000 Unit/250mL bag.

  Heparin is compatible with and 0.9% sodium chloride and 5% glucose.

  ii. **Patients 20kg or greater**

  1. Heparin may be given via infusion pump.

  2. Prepare heparin to a concentration of 100 Units/mL.

  i.e Use standardised premixed heparin 25,000Unit/250mL (in 0.9% sodium chloride)

  - *If using a large volume infusion pump, the pump must be locked.*
  - *Infusion Line and pump must be labelled with appropriate labels:*

The ICU consultant may individualise drug concentration of heparin to meet patient requirements. Where necessary, this must be clearly documented in the medical notes.

Dosages[1]:

- Initial loading dose of 75 Units/kg (maximum dose 5,000 Units) should be given over 10 minutes.
- Maintenance doses are based on patient age:
  - Under 1 year of age: 28 Units/kg/hour.
  - 1 year of age or older: 20 Units/kg/hour (Maximum of 1,500 Units/hour).
- Patients with Renal Impairment may require an altered dose regime.

Heparin Dose adjustment to maintain APTT 60 to 85 seconds

APTT (seconds)	Bolus (Units/kg)	Hold (minutes)	Rate change (Units/hr)	Repeat APTT
Below 50	50	Nil	Increase by 20%	4 hours
50 – 59	Nil	Nil	Increase by 10%	4 hours
60 – 85	Nil	Nil	No change	24 hours
86 – 95	Nil	Nil	Reduce by 10%	4 hours
96 – 120	Nil	30	Reduce by 10%	4 hours
Above 120	Nil	60	Reduce by 15%	4 hours

Note: *Target APTT may be different with different clinical indications.*

Monitoring of Therapy

- Avoid IM injections and arterial stabs and lumbar punctures during anticoagulant therapy. When such procedures are clinically necessary, ensure adequate external pressure is applied post-procedure.
- Avoid aspirin and other antiplatelet medications during heparin therapy.
- APTT should be taken 4 hours from the completion of the loading dose.
- Adjust heparin infusion to maintain APTT between 60 to 85 seconds or at a level determined by the treating medical team.
- APTT results across laboratories cannot be reliably compared.
- APTT blood samples can NOT be drawn from the same line as the heparin infusion. Coagulation tubes must be filled exactly to the specified mark to avoid erroneous results.
- Heparin is usually monitored by APTT. However, this may be inaccurate in certain clinical circumstances. An alternative is an anti-Xa assay. Haematology consult is recommended if there are any concerns. Therapeutic range for standard heparin using APTT corresponds to an anti-Xa assay of 0.3 to 0.7 Units/mL.
- The duration of heparin therapy is dependent upon the primary problem. Please consult the Haematology department for guidelines.

Twice weekly FBC are required. If there is an abrupt decrease in platelet count, (e.g. 50%) consider Heparin Induced Thrombocytopaenia (HIT) and arrange an immediate Haematology consult. Consideration then needs to be given to stopping heparin and changing to a different anticoagulant.

Reversal of Heparin

- If anticoagulation with heparin is to be discontinued, stopping the infusion will usually suffice.
- If reversal is needed (e.g. for major bleeding, immediate need for invasive procedure) consider protamine sulphate
- Senior Staff should be informed prior to the administration of protamine.

Considerations:

- Caution must be used when administering protamine as there may be serious side effects (e.g. Hypotension, Bradycardia, Anaphylaxis). See Table: Protamine Dose.
- Protamine sulphate is usually administered in a concentration of 10mg/mL at a rate not to exceed 5mg/minute. If administration is too rapid cardiopulmonary collapse may be precipitated.
- Dosage of protamine is based on the dose of Heparin infused within the last 2 hours.
- Maximum protamine dose is 50mg except for reversal of Cardiopulmonary Bypass.
- Obtain blood for APTT and PT 15 minutes after the administration of protamine.
- Patients with known hypersensitivity reactions to fish, and those who have received protamine containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.

Protamine Dose

Time since last Heparin Dose	Protamine Dose (Maximum total dose 50mg)
Less than 30 minutes	1mg per 100 Units of heparin received in the last 2 hours
30 to 60 minutes	0.5 mg to 0.75 mg per 100 Units of heparin received in the last 2 hours
60 to 120 minutes	0.375 mg to 0.5 mg per 100 Units of heparin received in the last 2 hours
Greater than 120 minutes	0.375 mg to 0.5 mg per 100 Units of heparin received in the last 2 hours

2.3 Warfarin

Warfarin treatment is complex and may be difficult to manage.

It is vital that there is adequate patient education regarding the possible side effects (e.g. bleeding, teratogenicity), drug interactions and need for monitoring prior to commencing warfarin treatment. Adequate patient and family education protocols have been reported to be a major factor in reducing adverse bleeding events in children on warfarin.[1]

Contact your pharmacist for patient information and medication counselling before discharge.

- Adequate follow up of patients is also essential.
- There are *2 brands of warfarin*: Coumadin® (dispensed at SCH) and Marevan®. It is not advisable to interchange the 2 brands as the active warfarin component may differ from brand to brand.[4]
  - **Coumadin®**: Light tan (1mg), Lavender(2mg) and Green (5mg) tablets
  - **Marevan®**: Brown(1mg), Blue (3mg) and Pink (5mg) tablets
- Tablets must be taken as whole preparations (i.e. not halved) as the active warfarin component may not be evenly distributed within the tablet. Alternate day regimes (i.e. 2mg one day, 3mg the next) may be needed to achieve the desired INR.[2]

Before commencing warfarin

- Vitamin K intake must be considered before commencing warfarin. e.g. multivitamins, Total Parenteral Nutrition(TPN), nutritional supplements.
- TPN may need Vitamin K to be discontinued or the concentration of Vitamin K altered.
- Patients who are breastfed may need 1 to 2 bottle feeds (30 to 60mL of formula) per day to ensure constant intake of Vitamin K. Bottle fed babies may be more resistant to warfarin due to the relative higher intake of Vitamin K.[1]
- Target INR to clinical indication. If unsure please consult Haematologist on call.
- A full medication history must be taken, including complementary medicines e.g. ginger. As there are multiple interactions with warfarin, doses may need to be altered accordingly.
- Patients must have a baseline FBC, APPT and INR prior to commencement of warfarin.

Dosage

Loading of Warfarin is usually performed over 4 days:

- **Loading dose on Day 1** should be 0.2mg/kg (maximum dose of 5mg) if the baseline INR is between 1 to 1.3.
- Dose may need to be altered according to condition e.g. impaired liver or renal function, concomitant interacting drugs, and if baseline INR above 1.3. Loading dose should be 0.1mg/kg (maximum dose of 5mg) in this setting.[2, 6]
- **Loading doses on days 2 to 4** are dependent on the INR response of the initial day 1 loading dose. Adjustment should be made according to the Table: Warfarin loading dose adjustments.

  Note: Target INR may differ with differing clinical indications.
- Most children will take between 3 to 5 days for the INR to become therapeutic.
- LMWH or UFH should be continued until the INR has been therapeutic for 2 consecutive days.[4]

Warfarin Loading Dose adjustments Days 2 to 4

Adjustment recommendations aim to maintain INR between 2 and 3.[1]

INR	Warfarin Adjustment
1.1 to 1.3	Repeat initial loading dose
1.4 to 1.9	50% initial loading dose
If the INR is below 1.5 on day 4 then the loading dose may need to be increased on an individual patient basis.	
2 to 3	50% initial loading dose
3.1 to 3.5	25% initial loading dose
Above 3.5	Withhold dose until INR is below 3.5 and then recommence at 50% initial loading dose

Monitoring of INR

Once the patient has been adequately loaded there is still need for close monitoring of INR:

- Recheck INR within 3 days of achieving therapeutic INR.
- Recheck INR within 5 days of any dose adjustment, commencement of any new medication or any significant change in diet that may affect INR.
- When the INR is stable, monitoring may become less frequent, but must be performed at least once a month.
- Target INR may differ with different clinical indications

Warfarin *Maintenance* Dose adjustments

INR	Dose Adjustment
1.1 to 1.4	Increase dose by 20%
1.5 to 1.9	Increase dose by 10%
2 to 3	No change in dose
3.1 to 3.5	Decrease dose by 10%
Above>3.5	Withhold dose until INR below 3.5. Restart at 20% less than the previous dose.

***Reversal of Warfarin*[6]**

Vitamin K and/or Fresh Frozen Plasma are used to reverse the effect of Warfarin depending on clinical indication.

- Vitamin K formulations:
  - Konakion 10 mg tablet,
  - Konakion MM Paed 2 mg/0.2 mL (oral or subcutaneous)
  - Konakion 10mg/mL intravenous injection

Konakion MM Adult differs only from Konakion MM Paediatric Solution in the filling volume, not in formulation.

NOTE: In complex situations eg balancing the dangers of bleeding against the risk of clot forming on a prosthetic valve, consultation with the treating Consultant and the Haematologist is necessary.

Depending on the site of bleeding consider the possibility that there may be an underlying anatomical lesion from which the patient is bleeding (eg underlying gut pathology) which requires investigation in its own right. The same holds true for unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology.

For prolonged INR with major bleeding:

- Urgent Haematology consult.
- Stop warfarin.
- Administer phytomenadione (vitamin K1) 2 mg to 5 mg by slow intravenous injection and prothrombin complex concentrate (Prothrombinex®) 25 to 50 Units/kg IV.[7]
- Where Prothrombinex® is not available Fresh Frozen Plasma (FFP) 15 to 20 mL/kg IV should be used.

For INR greater than 8 with minor bleeding

- Stop warfarin.
- Give phytomenadione (vitamin K1) 1 to 3 mg by slow intravenous injection; repeat dose of phytomenadione if INR still too high after 24 hours;
- Restart warfarin when INR is below 5.

For INR greater than 8 with no bleeding

- Stop warfarin.
- Give phytomenadione (vitamin K1) 1 to 5mg by mouth; repeat dose of phytomenadione if INR still too high after 24 hours;
- Restart warfarin when INR below 5.

For INR between 5 and 8 with minor bleeding

- Stop warfarin.
- Give phytomenadione (vitamin K1) 1 to 3mg by slow intravenous injection; restart warfarin when INR is below 5.

For INR between 5 and 8 with no bleeding

- Withhold 1 or 2 doses of warfarin and reduce subsequent maintenance dose.

3 References

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