NHS
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Anticoagulation protocols for Birmingham Children's Hospital

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Purpose of the Guideline	*Rationalise and update anticoagulation and thrombolysis policies and guidelines within the Trust. Introduce thromboprophylaxis guidance.*
Who should use the Guideline?	*All Clinical Staff*
How was the Guideline developed?	*Developed through Thrombosis group using evidence base where possible. Cardiac guidelines incorporated with changes to laboratory monitoring. BCH pilot site for Thromboprophylaxis.*
How will the Guideline be monitored?	*Annual audit of acute venous thrombosis in BCH. Annual audit of patients on long term warfarin. IR1 will record complications of anticoagulation of thrombolysis. Annual audit of Thromboprophylaxis in adolescents.*
Approved By:	*BCH Thrombosis Group*
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Anticoagulation protocols for Birmingham Children's Hospital.

Executive Summary.

This summary is to be read together with the Full Guidance described in sections 1-8.

A). Unfractionated heparin (UFH). [See Section 1].

i) The anticoagulant effect of UFH is monitored using the **plasma anti-Xa level**. The APTT is **not routinely** used for therapeutic dosing of UFH at BCH.

ii).The therapeutic anti-XA level for UFH is **0.35 – 0.7 units/ml**

iii) UFH preparation:

- Use only heparin 1000 units/ml in the preparation of infusions.
- For patients <40kg, dilute 500units/kg of heparin (1000units/ml) with 0.9% sodium chloride to a total volume of 50 mls (1ml/hour = 10units/kg/hour).
- For patients 40kg and over, draw up 30000 units (30 mls of 1000units/ml) of heparin. No further dilution is required

iv) The initial maintenance dose of UFH is age and weight based:

<1 year of age = 28 units/kg/hour

=/>1 year of age = 20 units/kg/hour

40-49 kg = 800 units/hour

Over 50 kg = 1000 units/hour

Maximum initial infusion rate: 1000units/hour

v) The nomogram for dose change is:

Anti Xa (units/ml)	**Hold (minutes)**	**Dose change**	**Repeat anti Xa**
<0.20 **Consider drug administration problem**	no	Increase by 20%	4 hours after change
0.20-0.35	no	Increase by 10%	4 hours after change
0.36-0.7	no	No change	Once daily
0.71-1.0	no	Decrease by 10%	4 hours after change
1.1-1.4	30 minutes	Decrease by 10%	4 hours after restarting heparin
>1.4 **Consider sample contamination**	60 minutes	Decrease by 20%	4 hours after restarting heparin

See Section 1 for prophylactic use of UFH.

B). Low Molecular Weight Heparin (LMWH). [See section 2].

i) Enoxaparin (Clexane) is the only LMWH used at BCH. It is given subcutaneously.

ii) Anticoagulant effect is monitored using the plasma **anti-Xa** level **taken 4 hours** after Enoxaparin dose.

iii) Therapeutic range for anti-Xa is **0.5-1.0 units/ml**

iv) The (therapeutic) starting dose of enoxaparin is age based:

Age: neonate : 1.8 mg/kg/dose 12 hourly

Age: 1 - 12months : 1.5 mg/kg/dose 12 hourly

Age: >12 months : 1.0 mg/kg/dose 12 hourly

v) Dose adjustments are made using the nomogram :

Anti Xa (units/ml)	**Hold next dose**	**Dose Change**	**Repeat anti Xa**
<0.35 **Consider drug administration problem**	No	Increase by 25%	4 hours after next morning dose
0.35-0.49	No	Increase by 10%	4 hours after next morning dose
0.5-1.0	No	No change	Once daily or less frequently if anti Xa and patient stable (4 hours after morning dose)
1.1-1.5	Omit next dose	Decrease by 20%	4 hours after next morning dose
1.6-2.0	Omit next 2 doses	Decrease by 30%	4 hours after next morning dose
>2.0 **Consider sample contamination with UFH from line or cannula**	Until anti-Xa <0.5units/ml	Decrease by 40%	Trough level before next dose and if not <0.5 repeat 12 hourly, ie before next due enoxaparin dose.

vi) If surgery is required for patient receiving LMWH, it is recommended that 2 doses of LMWH are omitted prior to surgery, i.e. the morning dose is given on the day before surgery, with LMWH then being restarted post-surgery, if surgeons happy.

vii) The anti-Xa level for prophylaxis is 0.1-0.3 units/ml. The prophylactic staring dose for Enoxaparin is age and weight-based:

< 12 months old 0.75mg/kg 12 hourly

>12 months and less than 40kg: 0.5 mg/kg 12 hourly

>40 kg : 20 mg once daily for low risk Thromboprophylaxis, or 40 mg once daily for high risk Thromboprophylaxis.

See sections 2, 3, 8 for more information on Thromboprophylaxis.

C) Warfarin

The use of warfarin is described in section 5. See section 4 for use in cardiac patients.

i) Loading and maintenance dosing to maintain an INR of 2-3 are described below:

Day 1: If the baseline INR is 1.0 to 1.3: **Dose 0.2 mg/kg**

Halve loading dose if liver function tests abnormal

If INR >1.3, discuss dosage with haematologist

If weight > 45 Kg, give 9 mg warfarin.

Days 2-4: If the INR is:

INR	Action
1.1-1.3	Repeat initial loading dose
1.4-1.9	50% of initial loading dose
2.0-3.0	50% of initial loading dose
3.1-3.5	25% of loading dose
>3.5	Withhold until INR < 3.5 then restart at 50% decreased dose.

Post loading doses are always undertaken by the anticoagulation team.

ii) Overcoagulated or bleeding patients require reversal of their warfarin. **For non-urgent reversal**, use the following:

INR	TARGET 2-3	TARGET 4-5
4-5	Dose reduction	Dose reduction
5-6	Dose omission	Dose reduction
6-7	Dose omission	Dose omission
7-8	Dose omission	Dose omission
>8	Dose omission+ Vitamin K	Dose omission+ Vitamin K

The dose of vitamin K is 30 micrograms/kg oral or IV.

iii) **Emergency reversal** of warfarin should be undertaken using Prothrombin Complex Concentrate **(Beriplex) and not** Fresh Frozen Plasma/Octaplas. Always discuss usage with haematologist. There is an emergency supply of Beriplex in the Satellite Fridge in Blood Bank.

D). The specific anticoagulation of post cardiac patients is described in Section 4,

E) Thrombolysis [see Section 7].

The use of thrombolysis should be the result of a multidisciplinary discussion, and requires informed consent from the child's parents/carers. It requires expertise and careful monitoring of the patient, both clinically and through the use of a combination of laboratory and radiological tests. **Do not** undertake thrombolysis if you have no previous experience of using thrombolytic drugs.

F) The Anticoagulation Service and referral pathways are described in Section 6.

FULL GUIDANCE

Anticoagulation is used extensively at Birmingham Children's Hospital, either to prevent thrombosis in high risk patients or to treat established thrombosis. The current drugs used to anticoagulate patients consist of unfractionated heparin (UFH), Low Molecular Weight Heparin (LMWH) and warfarin. At the present time, Enoxaparin (Clexane) is the only LMWH used at BCH.

Thrombolysis describes therapeutic measures used to lyse established thrombus. At present, tissue plasminogen activator (tPA) is used preferentially to achieve thrombolysis in specific circumstances.

This document contains guidance on the use of the above drugs; there is an extensive guideline for children undergoing cardiac surgery, for line related limb ischemia and advice about Thromboprophylaxis. It should be used to guide practice: if clinical teams use a different strategy then this must be recorded in the patient's notes together with the rationale for using that particular strategy.

Early haematological consultation should be obtained for any difficulty in achieving anticoagulation or for advice on any other aspect of anticoagulation covered by this document.

CONTENT

Section 1. Unfractionated heparin in the treatment of thrombosis

Continuous infusion unfractionated heparin is used both as prophylaxis and treatment of thrombosis. It has a short half-life and its anticoagulant effects can be rapidly reversed. It is therefore used in children who require anticoagulation but are at high risk of bleeding, or where multiple surgical interventions may be necessary. Such children for example will include post-operative cardiac and other PICU patients. Usage of UFH is associated with bleeding, even at therapeutic levels of heparin; the response to UFH can be very variable, so that a wide range of dosages may be required to maintain therapeutic anticoagulation.

The laboratory monitoring of UFH can be difficult and is usually done using the APTT ratio or anti-Xa level: the correlation between the two tests (and with plasma heparin levels) is not good. The APTT can be influenced by a number of factors which are responsible for fluctuations in clotting factor levels, which then tend to reduce the APTT. For this reason, **laboratory monitoring of UFH at BCH is done using the plasma anti-XA level**: the APTT ratio should **not** be used and the dosing nomograms described in this document do not use the APTT.

1. To start treatment with UFH:

a) Check base line full blood count, coagulation screen, serum urea and creatinine before starting heparin. Maintain platelet count >50 $x10^9$/l and fibrinogen >1g/l for full dose heparin to be given. Additionally, if PT and/or APTT abnormal, or renal impairment, then discuss heparinisation with haematologist. **Inform haematology laboratory that commencing patient on unfractionated heparin and anti-Xa monitoring required.**

b) **Loading dose**: **75units/kg** over 10 minutes. **Omit** loading dose if perceived increased bleeding risk, central nervous system pathology, arterial ischaemic stroke or cerebral sinus vein thrombosis. **Omit if patient returned form cardiac surgery (see cardiac protocol).**

c) **Maximum loading dose 5000 units**.

d) **Initial maintenance dose** :

<1 year of age = 28 units/kg/hour

=/>1 year of age = 20 units/kg/hour

40-49 kg = 800 units/hour

Over 50 kg = 1000 units/hour

Maximum initial infusion rate : 1000 units/hour

e) Obtain a venous blood sample in citrate tube for **anti-Xa** level 4 hours after starting heparin. Also check PT, APTT, TT (prolonged TT will indicate heparin contamination of blood sample and invalidate results). **Check FBC once daily** or more frequently if clinically indicated.

f) **Therapeutic Range**

Anti Xa Therapeutic range = 0.35-0.70 units/ml

g) **Nomogram for dose changes**

Anti Xa (units/ml)	**Hold (minutes)**	**Dose change**	**Repeat antiXa**
<0.20 **Consider drug administration problem**	No	Increase by 20%	4 hours after change
0.20-0.35	No	Increase by 10%	4 hours after change
0.36-0.7	No	No change	Once daily
0.71-1.0	No	Decrease by 10%	4 hours after change
1.1-1.4	30 minutes	Decrease by 10%	4 hours after restarting heparin
>1.4 **Consider sample contamination**	60 minutes	Decrease by 20%	4 hours after restarting heparin

- Discuss problems of persistent under- or over-coagulation with haematology consultant or registrar. The commonest example of such a problem is that of a lack of response to increasing doses of heparin: "heparin resistance" may be due to physiological antithrombin deficiency as seen in neonates, or as a secondary event in children with protein losing conditions such as nephrotic syndrome, and may require consideration of antithrombin supplementation.
- Heparin undergoes renal clearance: impaired renal function will often necessitate reduced doses of heparin therapy.

2. Prescribing guidance for UFH:

- Use only heparin 1000 units/ml in the preparation of infusions.
- For patients <40kg, dilute 500 units/kg of heparin (1000 units/ml) with 0.9% sodium chloride to a total volume of 50 mls (1ml/hour = 10units/kg/hour).
- For patients 40kg and over, draw up 30000 units (30 mls of 1000 units/ml) of heparin. No further dilution is required.

3. Reversal of UFH.

If anticoagulation needs to be discontinued for clinical reasons, termination of heparin infusion will usually be sufficient because of the rapid clearance of heparin.

If immediate reversal of heparin is required, consider protamine sulphate infusion.

For **post cardiac surgery patients who present with bleeding on their return to PICU,** the reversal of excess heparin should be discussed with the surgical team and be based on repeated ACT values and the dose of protamine administered in theatre.

Nomogram for protamine infusion (see aapendix for further details)

Time since last heparin dose, minutes	Protamine dose, mg
<30	1mg/100 units of heparin received
30-60	0.75 mg/100 units heparin received
61-120	0.5 mg/100 units heparin received
>120	0.25 mg/100 units heparin received

- **Maximum dose of protamine sulphate is 50 mg (except for cardiopulmonary bypass).**
- Usual concentration is 10mg/ml. Give over at least 10 minutes, with rate not exceeding 5mg/minute. Hypersensitivity can occur (particularly if known fish hypersensitivity, previous protamine therapy).

4. Audit.

Audit of patients heparinised for treatment of thrombosis to be undertaken regularly by haematology.

Section 2. Low Molecular Weight Heparin

Low Molecular Weight Heparins (LMWH) has become widely used in adult medicine and their use has increased greatly in paediatrics over the last 10-15 years. LMWHs are administered subcutaneously, have a relatively long half-life and in adults give reliable therapeutic results with standard doses without laboratory monitoring. In children, there are variations in pharmacokinetics between individuals, often age-related, which have led to laboratory monitoring to achieve therapeutic anticoagulant levels being standard practice. Most children will need twice daily injections of LMWH because of shorter drug half-lives and increased clearance compared with the once daily injections given to adults.

Enoxaparin (Clexane) is the only LMWH in use at BCH currently. Laboratory monitoring is done using the **plasma anti Xa level.**

In general, LMWH delivers more reliable anticoagulation than UFH but its long duration of action may also be a disadvantage if reversal of anticoagulation is required. In addition there is no good reversal agent, though protamine sulphate can be given and will reverse some of the anticoagulant effect. Patient selection is therefore important, with UFH probably being more appropriate for children at high risk of bleeding or who require multiple procedures

1. To start treatment with LMWH:

a) Check base line full blood count and coagulation screen before starting heparin. Maintain platelet count >50 $x10^9$/l and fibrinogen >1g/l for full dose heparin to be given. Inform haematology laboratory that commencing patient on LMWH and email anticoagulation referral form to coagulation laboratory.

b) Enoxaparin (Clexane) is administered subcutaneously or through a subcutaneous cannula (Insufflon cannula). If using an Insufflon cannula, inspect at each injection for signs of cutaneous inflammation or infection. Remember the dead space of the Insufflon particularly if using in neonates and infants. Change cannula after a maximum of 3 days.

c) Starting dose of enoxaparin :

Age: neonate : 1.8 mg/kg/dose 12 hourly

Age: 1 - 12months : 1.5 mg/kg/dose 12 hourly

Age: >12 months : 1.0 mg/kg/dose 12 hourly

d) Obtain a capillary/venous blood sample in citrate for anti-Xa level 4 hours after starting LMWH. Also check PT, APTT, and TT (prolonged TT will indicate heparin contamination of blood sample and invalidate results). Check FBC once daily or more frequently if clinically indicated.

e) Anti Xa Therapeutic range = 0.50 - 1.00 units/ml

f) Use nomogram for dose changes:

Anti Xa (u/ml)	Hold next dose	Dose Change	Repeat anti Xa
<0.35 **Consider drug administration problem**	No	Increase by 25%	4 hours after next morning dose
0.35-0.49	No	Increase by 10%	4 hours after next morning dose
0.5-1.0	No	No change	Once daily or less frequently if anti Xa and patient stable (4 hours after morning dose)
1.1-1.5	Omit next dose	Decrease by 20%	4 hours after next morning dose
1.6-2.0	Omit next 2 doses	Decrease by 30%	4 hours after next morning dose
>2.0 **Consider sample contamination with UFH from line or cannula**	Until anti-Xa <0.5units/ml	Decrease by 40%	Trough level before next dose and if not <0.5 repeat 12 hourly, i.e. before next due enoxaparin dose.

- Discuss problems of under or over- heparinisation with haematology consultant or registrar. The commonest example of such a problem is that of a lack of response to increasing doses of heparin : "heparin resistance" may be caused by physiological antithrombin deficiency as seen in neonates or in protein-losing conditions such as nephrotic syndrome, or may be due to increased clearance of heparin. Antithrombin supplementation may be required in such circumstances. Heparin undergoes renal clearance: impaired renal function will often necessitate reduced doses of heparin therapy.
- Protamine sulphate reverses most but not all the effects of LMWH. If protamine is given within 8 hours of LMWH, give 1mg protamine/mg of LMWH given in last dose. If protamine given > 8 hours of LMWH, give 0.5mg protamine/mg of LMWH given in last dose. D**o not use same regimen as for UFH.**
- **If surgery is required for patient receiving LMWH, it is recommended that 2 doses of heparin are omitted prior to surgery, i.e. the morning dose is given on the day before surgery, with heparin then being restarted post-surgery.**
- Audit of patients heparinised for **t**reatment of thrombosis to be undertaken regularly by haematology.

Section 3. Prophylactic use of heparin

1. Low Dose continuous infusion of Unfractionated heparin as prophylaxis

This is used to maintain line patency and for patients with Blalock Tausig shunts (see cardiac guidance).

The dose used is **10 units/kg/hour in patients < 40 kg.** No heparin monitoring is required but the platelet count should be checked daily.

2. Prophylactic use of Low Molecular Weight Heparin (Enoxaparin)

Enoxaparin can be used as prophylaxis against venous thrombosis in patients considered to be at risk of this complication. Such patients include immobile, post-operative patients (particularly adolescents) as well as particular medical conditions, such as sickle cell crisis and nephrotic syndrome. In all cases a risk-benefit exercise should be undertaken to evaluate risk of bleeding against risk of thrombosis prior to the use of prophylactic LMWH (see section 8).

Dose:

<12 months old 0.75mg/kg 12 hourly

>12 months and less than 40kg : 0.5 mg/kg 12 hourly

>40 kg : 20 mg once daily for low risk Thromboprophylaxis, or 40 mg once daily for high risk Thromboprophylaxis.

3. Monitoring

Prophylactic anti-Xa level: 0.1 - 0.3 units/ml 4 hours after dose of LMWH.

Repeat once weekly, in an otherwise stable patient and check full blood count at least once weekly whilst patient on heparin.

Section 4. Anticoagulation Therapy for Post-operative and Post-interventional Cardiac Patients (Excluding ECLS)

1. Rationale/Purpose/Objective

• To allow standardised anticoagulation practice in post-operative cardiac surgical patients and post interventional cardiac patients on the paediatric intensive care unit (PICU) and Wards 11 and 12 at Birmingham Children's Hospital (BCH).

• To provide a factual evidence base for staff administering or prescribing anticoagulation therapy to cardiac patients on the PICU and Wards 11 and 12 at BCH.

2. Scope

This guideline applies to any post-operative cardiac patient being prescribed or administered anticoagulation therapy in PICU and the cardiac wards.

3. Roles and responsibilities

All healthcare professionals prescribing, supplying or administering anticoagulation therapy should be aware of this guideline.

The anticoagulation/antiplatelet policy forms an integral part of the hand-over process when transferring a patient from theatre to ICU. It is the surgical team's responsibility to ensure that a plan is agreed and communicated to the ICU team at that time. It is the PICU team's responsibility to seek guidance from the surgical team if this has not been made clear at the handover, prior to commencing any anticoagulation. The plan may often include a review based on the bleeding/anticoagulation profile in the early hours post-surgery. A more definitive plan will therefore be agreed at the evening/midnight round.

These are general guidelines and surgeons should be consulted regularly about unusual/individual cases. Certain patients may be at higher risk of developing thrombi e.g. low cardiac output, poor ventricular function, chyle losses, and septic, known pro-thrombotic condition. Under such circumstances the use of prophylactic heparin may be inappropriate. These patients should be considered on an individual basis for targeted anticoagulation.

The guidelines for cardiac patients were produced and ratified in 2016, and updated in 2017 and re-updated in 2018 and 2019. Given the lack of evidence, expert local opinion has been used to formulate these guidelines and consultation took place with experts in the following disciplines: intensive care, cardiology, cardiac surgery, haematology and pharmacy.

Common Arterial Trunk Repair – Gore-Tex conduit	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding, Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	3 months

4. Summary of Anticoagulation Therapy for Post-operative and Post-interventional Cardiac Patients

Cardiac Procedure -	Early Post-operative Anticoagulation	Notes	Longer Term Anticoagulation/ Antiaggregation	Notes
Blalock-Tausig Shunt (BTS) / central shunt	Yes	If no bleeding concern – Heparin 10 units/kg/h starting 4 hours after arrival on PICU (check with surgical team). It is unusual to target a specific anti-xa level though some surgeons may request such a level.	Once feeding Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1) + Dipyridamole 1 mg/kg/dose BD	Until next operation
Fontan	No	If no bleeding concern - 10 units/kg/h heparin after LA line removal (in standard Fontan this will be on day 1, after early extubation) - see note 2	Warfarin Target INR range 2-3 (for conversion see note 1)	Lifelong
Norwood Stage 1 - BTS or RV-PA conduit	Yes	If no bleeding concern – 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding Aspirin 5 mg/kg/day, max.75 mg/day (for conversion see note 1) + Dipyridamole 1mg/kg/dose BD	Until cavo-pulmonary shunt
CP shunt – no PA patch	No		Usually no – discuss with surgical team	
CP Shunt - PA patch	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	3-6 months
Common Arterial Trunk repair – homograft or Contegra	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding, Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	3 months

Tetralogy of Fallout (TOF) repair: standard with transannular Patch	No		No	
TOF Repair - with extensive PA reconstruction or Contegra as a conduit	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding, Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	3 months
Arterial Switch with usual Coronary transfer (patients with abnormalcoronary transfer to be discussedwith the surgeons)	No		No	
Ross Procedure	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	3 months
Coarctation of the Aorta	No		No	
Septal defects closed with patch	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day) for 6 months	3-6 months
Aortic Arch procedures / Damus-Kaye-Stansel (DKS)	No		No	
Double Switch procedure/Atrial Switch	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding Aspirin 5mg/kg/day, max. 75 mg/day (or conversion see note 1)	6 months
Rastelli procedure	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	Lifelong
TAPVD repair	No		No	
RV-PA conduit replacement – Standard	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	Lifelong
RV-PA conduit replacement – extensive PA reconstruction	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	Lifelong
PA reconstruction using Gore-Tex tube	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Warfarin with target INR 2-3	3 months

Pulmonary valve reconstruction using Gore-Tex leaflets	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Warfarin with target INR 2-3	6 months
Maze-type procedure	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Warfarin with target INR range 2-2.5 (for conversion see notes 1, 3)	6 months
Hybrid Norwood	Yes	If no bleeding concern - 10 units/kg/h heparin starting 4 hours after arrival on PICU (check with the surgical team).	Once feeding Aspirin 5 mg/kg/day, max. 75 mg/day (for conversion see note 1)	Until next stage
Mechanical AVR – see note 4	Yes	If no bleeding concern - start Heparin at 10units/kg/h 4 hours after arrival on ICU (check with surgical team) Check anti-Xa level 4 hours after infusion started, then increase to achieve therapeutic anti Xa level : see guidance on heparin dosage. **AVOID LOADING DOSE OF HEPARIN – (DISCUSS WITH SURGEONS if antiXa level not achieved with two dose increments of heparin.)**	Warfarin INR range: 2-3 (for conversion see notes 1,3)	Long term Enoxaparin should be considered, particularly in infants in whom warfarinisation may not be appropriate
Mechanical MVR – see note 5	Yes	If no bleeding concern - start Heparin at 10units/kg/hr. 4 hours after arrival on ICU (check with surgical team) Check anti-Xa 4hrs after infusion started, then increase to achieve therapeutic antiXa level the morning after surgery - see guidance on heparin dosage **AVOID LOADING DOSE OF HEPARIN – (DISCUSS WITH SURGEONS IF APTT NOT BEING ACHIEVED)**	Warfarin INR range: 2.5-3.5 (for conversion see notes 1,3)	Long term Enoxaparin should be considered, particularly in infants in whom warfarinisation may not be appropriate
Valve Repair / Plasty	Discuss with the surgical team	Discuss with the surgical team	Discuss with the surgical team	Discuss with surgical team
Tissue Valves :-bioprostheses e.g. Carpentier-Edwards (see note 6)	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	Lifelong
Homograft Valves (Aortic OR Pulmonary)	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	Lifelong
Valve Sparing Aortic Surgery	No		Once feeding Aspirin 5 mg/kg/day (max. 75 mg/day)	6 months

Post Cardiac Intervention

Cardiovascular Event	Post-procedure Anticoagulation/ Antiaggregation	Notes	Longer Term Anticoagulation/ Antiaggregation	Long Term Notes
Post-cardiac catheterisation vascular thrombosis (usually arterial, sometimes venous)	Yes	Heparin bolus of 50 units/kg IV followed by Heparin 20 units/kg/hr. If targeted anti-Xa then follow table in Heparin guidelines **If limb threatened, refer to: *"Management of arterial line associated reduced limb perfusion" protocol***	May require a period of once daily Aspirin or Enoxaparin following major vascular thrombosis	Cardiology team to decide
RVOT/pulmonary artery stent	Yes	Aspirin 5 mg/kg once daily (max. 75 mg OD)	Yes	Until operation
Atrial septal stent	Yes	Aspirin 5 mg/kg once daily (max. 75 mg OD) + Dipyridamole 1 mg/kg twice daily	Yes	Until operation
Fontan fenestration stent	Yes	Establish Warfarin as per ***"Postoperative Care of Fontan" protocol***	Yes	Lifelong
Pulmonary vein stent	Yes	Cardiology Consultant decision Will usually require a single agent	Yes	Lifelong
Septal defect device occlusions: ASD or VSD	Yes	Aspirin 5 mg/kg once daily (max. 75 mg OD)	Yes	6 months
Electrophysiological studies (EPS) + Radiofrequency ablation (RFA)	Yes	Aspirin 5mg/kg once daily (max. 75 mg OD)	Yes	6 weeks
Dilated cardiomyopathy	Yes	Heparin 10–20 units/kg/hr Discuss with the cardiology team	Once feeding Aspirin 5mg/kg/day, (max. 75 mg OD)	Cardiology team to decide
Intra-cardiac thrombi	Yes	Heparin (UH or LMWH) Aim for therapeutic anti-Xa	Discuss with Haematology	Surgery-related intracardiac thrombi should be discussed with the cardiac surgical team
Aortic coarctation stent	No			

Pacemaker insertion	No			

Procedures undertaken in cardiac patients post cardiac surgery

For the following procedures to be performed in PICU or on the cardiology wards a clotting screen should have been sent within the last 6 hours and the results checked and documented on the results sheet or in the patient notes.

Any abnormalities should be discussed with the cardiac surgeons and consideration should be given to correcting coagulation abnormalities with blood products. The procedures should be delayed until the parameters are within the agreed ranges. This will require repeat testing after any attempts at correction, unless otherwise decided by the surgical team, which will depend on the clinical situation.

In describing the following procedures, Heparin is assumed to be a continuous infusion of unfractionated heparin.

a. <u>Insertion of thoracic drains (surgical method)</u>

- If patient on warfarin, delay procedure until INR less than 2. Discuss omitting or reducing the Warfarin with Haematology and cardiac surgery if INR>2.
- If patient on any dose of heparin - stop heparin infusion for 3 hours before insertion
- After procedure, ensure there is no procedure-related bleeding, then recommence Warfarin as prescribed by haematology, or recommence heparin.

For percutaneous (Seldinger) drains, INR levels and time of heparin stoppage should be discussed with the surgical team.

b. <u>Insertion of peritoneal dialysis (PD) catheters</u>

- If patient on warfarin, delay until INR less than 2 Discuss omitting or reducing the Warfarin with haematology and Cardiac Surgery if INR>2.
- If on any dose of heparin - stop the heparin infusion for 3 hours before insertion
- After procedure ensure there is no procedure-related bleeding, then recommence Warfarin as prescribed by haematology, or recommence heparin as per table below

c. <u>Removal of thoracic drains / PD catheters</u>

- If patient on warfarin, the INR must be less than 4. Discuss omitting or reducing the Warfarin dose with Haematology and Cardiac Surgery if INR>4.
- If patient on therapeutic doses of heparin – stop the heparin infusion for 1 hour before removal
- No need to stop prophylactic heparin (10 units/kg/hour) infusion
- After procedure, ensure there is no procedure related bleeding then recommence Warfarin as prescribed by haematology or recommence heparin.

d. Removal of direct (transthoracic) atrial lines i.e. LA, RA, PA

For more detail refer to "removal of direct atrial lines in the post-operative cardiac patient "guideline.

Ensure that:

- Platelet count above 100 x 10^9/L.
- If patient on Heparin infusion, prophylactic or therapeutic, stop infusion for 1 hour.

  If patient on warfarin, delay until INR less than 2. Discuss omitting or reducing Warfarin with Haematology and Cardiac Surgery if >2.
- Ensure there is one unit of cross-matched blood available in the PICU or ward fridge.

  Two hours after line removal an echocardiogram should be performed, and, if there is no procedure-related bleeding, Warfarin or heparin can be recommenced.

e. Removal of pacing wires

For more detail refer to "Removal of external pacing wires in the post-operative cardiac patient " guideline

- If patient on warfarin, delay until INR less than 2. If >2 discuss omitting or reducing the Warfarin dose with haematology and Cardiac Surgery.
- If on Heparin, prophylactic or therapeutic, stop infusion for 1 hour prior to procedure.
- Two hours after removal an echocardiogram should be performed, and, if there is no procedure-related bleeding, Warfarin or heparin can be recommenced.

f. Chest exploration/closure

- Ensure clotting is checked and discussed
- If patient on warfarin discuss with the surgical team
- If patient on therapeutic doses of heparin – stop for 3 hours
- No need to stop prophylactic heparin infusion (10units/kg/hour)
- Ensure there is one unit of cross matched blood available in the PICU fridge
- After procedure, ensure there is no procedure-related bleeding, and then recommence Warfarin or heparin.

Notes on above procedures

Note 1: Transition to long-term anticoagulation:-

1) Aspirin
   i) Aspirin is commenced once absorbing feeds
   ii) Heparin is stopped after the 2nd dose of Aspirin
2) Warfarin and LMWH: send referral to anticoagulation service and commence as per dosing recommendations on page 2 & 3.

Note 2: For standard Fontan patients, who are extubated early, the LA line has to be removed the next morning before the ICU ward round.

Preparation includes:

- At the admission and ICU handover and at the evening round it has to be mentioned that heparin should not be started until the LA line has been removed and post removal bleeding has been excluded by echocardiography.
- Send FBC and coagulation screen so that the results are available by 07:00. Check results before the line is removed
- A unit of blood for the patient has to be available in the PICU fridge at 07:00
- Organise for an echocardiogram post line removal and monitor drains for bleeding

If the atrial line needs to stay longer or the patient is not discharged to the ward the next day after surgery, then discuss the anticoagulation regime with the surgical team.

Note 3: Send a referral form should be sent to the anticoagulation service; these can be sourced from ward 12 or coagulation laboratory, or see appendices. The anticoagulation nurse can be contacted via switch board.

Note 4: According to *Reference 1,* the indicated INR range applies to bi-leaflet mechanical or Medtronic Hall aortic valve prostheses in patients with no risk factors. For other types of aortic prostheses or in patients with risk factors discuss with the surgical team as the INR range indicated is 2.5-3.5. Patients with risk factors include: atrial fibrillation or loss of atrial kick, severe systemic ventricular dysfunction, previous thromboembolism, any hyper-coagulable state.

Note 5: According to *Reference 1,* the indicated INR range applies to any type of mitral prosthesis and to any type of patients.

Note 6: According to *Reference 1,* the indication excludes patients with risk factors. Patients with risk factors include: atrial fibrillation or loss of atrial kick, severe systemic ventricular dysfunction, previous thromboembolism, any hyper-coagulable state. For such cases discuss with the surgical team as Warfarin may be indicated (INR range 2-3).

Section 5. Warfarin

Use of Warfarin for inpatients and outpatients .

Warfarin is an effective, oral anticoagulant which works though interference with the carboxylation of vitamin K dependent clotting factors. Therapeutic monitoring of warfarin is carried out using the INR (Internationalised Normalised Ratio): a commonly used therapeutic range is 2-3, with higher ranges used in specific circumstances, e.g. mechanical mitral valve replacement. It is difficult to warfarinise infants, and warfarin should not be used in children who have not been fully weaned. The effects of warfarin will be affected by a number of drugs (see appendix), by the clinical status of the patient, by abnormal liver function and by the vitamin K status of the patient. All these factors should be considered when prescribing warfarin and any questions about anticoagulation discussed the Anticoagulation nurse Practitioner.

INRs can fluctuate quickly in children on warfarin compared with adults and can lead to problems with achieving consistent therapeutic ranges. Discuss problems of over or under-coagulation with the Anticoagulation nurse Practitioner.

1. INITIATING WARFARIN THERAPY.

Since the half-lives of the vitamin K dependent coagulation factors vary from 6 to 72 hours and the half-life of Warfarin is 2.5 days, changes made in the dosage will not be fully reflected by the INR until day 3 or 4.

When starting a patient on warfarin anticoagulation:

- Obtain a baseline blood count, coagulation screen and LFTs. All children with a thrombotic event requiring warfarinisation should be discussed with a consultant haematologist prior to starting anticoagulation.

- Warfarin is often introduced in addition to heparin. In the treatment of an acute venous thrombotic event, heparin should be continued for a minimum of 5 days. It is usual practice to start warfarin alongside heparin due to the lowering effect of warfarin on plasma levels of protein C. When the INR has been >2.0 for 2 consecutive days the heparin may be discontinued

- Prescribe Warfarin on the in-patient drug chart.

2. WARFARIN LOADING DOSE REGIME.

a) Protocol for Oral Anticoagulation Therapy To Maintain an INR Between 2 and 3.

I **Day 1**: If the baseline INR is 1.0 to 1.3: **Dose 0.2 mg/kg**

Halve loading dose if liver function tests abnormal

If INR >1.3, discuss dosage with haematologist

If weight > 45 Kg, give 9 mg warfarin.

II **Days 2-4***: If the INR is:

INR	Action
1.1-1.3	Repeat initial loading dose
1.4-1.9	50% of initial loading dose
2.0-3.0	50% of initial loading dose
3.1-3.5	25% of loading dose
>3.5	Withhold until INR < 3.5 then restart at 50% decreased dose.

III **Maintenance oral anticoagulation dose guidelines:**

INR	Action
1.1-1.4	Increase by 20% of dose
1.5-1.9	Increase by 10% of dose
2.0-3.0	No change
3.1-5.0	Reduce dose or withhold (discuss with haematology consultant)
>5.0	Withhold until INR < 3.5, then restart at 20% of reduced dose

*Note that Fontan patients and children with right heart disease commonly increase their INR very quickly following the introduction of warfarin, and the above dosing regimen may need to be modified.

Post loading doses are always undertaken by the Anticoagulation team.

3. Management of warfarin anticoagulation for In-Patients.

- INRs are checked using either whole blood and a CoaguChek coagulometer or citrated blood taken from a vein.
- For Ward 12 patients INRs are measured by trained nurses using the CoaguChek XS Plus near patient testing device, or by a venous sample sent to the Coagulation Laboratory.
- For all other wards INRs are measured on venous blood samples sent to the Coagulation Laboratory, or alternatively by contacting the Anticoagulation nurse specialist who may be able to check with a CoaguCheck machine.
- All wards are informed of the doses to be given and next test date for the INR on ICE.

Prior to discharge, all patients must receive a Warfarin talk, a patient information booklet (Living with your child's Warfarin treatment, Living with Warfarin, all about your treatment) and a drug interaction sheet (see appendix). For Ward 12 patients, trained and assessed nurses will give the talk, and for all other wards contact the Anticoagulation Nurse Practitioner.

If the child is being discharged to another hospital it is the responsibility of the referring team to make the follow-up arrangements.

The child/family must have:-

- A contact name and number for the follow up appointment
- Name of department where appointment is
- An appointment date and time before being discharged.
- The coagulation laboratory will fax the patient's anticoagulation records if a fax number is made available prior to discharge.

When Warfarin patients are admitted to Birmingham Children's hospital, the Coagulation Laboratory should be informed and a new anticoagulation referral form must be submitted.

4. Management of warfarin anticoagulation for Outpatients.

For those patients being monitored at Birmingham Children's Hospital an appointment should be made through the Anticoagulation Nurse Practitioner. Clinics are held on Monday and Friday 09.00 – 11.30 hrs. in the Waterfall House, Outpatient 2, and first floor.

Letters are not routinely sent from this clinic to GPs so it is vital that discharge letters are sent promptly, as the GP is responsible for supplying the prescription for Warfarin once the patient is discharged.

5. REVERSAL OF WARFARIN IN CHILDREN.

There are a number of situations where the anticoagulant effect of warfarin needs reversal. The INR may fluctuate due to changes in medication, diet, clinical status or compliance and overanti-coagulation may result. A child on warfarin may develop bleeding even with a therapeutic INR. Warfarin reversal may be necessary prior to surgery or another clinical intervention.

The urgency of reversal is dependent on the clinical situation and the prolongation of the INR. All over anti-coagulated/bleeding patients on warfarin should be discussed with a haematologist, as should those warfarinised patients requiring a surgical intervention.

The following protocol should be used for warfarin reversal:

INR	TARGET 2-3	TARGET 4-5
4-5	Dose reduction	Dose reduction
5-6	Dose omission	Dose reduction
6-7	Dose omission	Dose omission
7-8	Dose omission	Dose omission
>8	Dose omission+ Vitamin K	Dose omission+ Vitamin K

The dose of vitamin K is **30 micrograms per kg**, given orally or IV. Repeat INR 4 hours after vitamin K administration. Repeat doses may be required.

Vitamin K will reverse the effects of warfarin for a few days and care should therefore be used when considering its use in artificial valve patients or other high risk patients. It may be better to consider the use of Beriplex (Prothrombin complex concentrate) if a rapid, temporary reversal of warfarin is required, such as prior to surgery (see below).

Emergency Reversal Of Warfarin

- Fresh Frozen Plasma/Octaplas is relatively **ineffective** in the urgent, temporary reversal of Warfarin.
- **Prothrombin Complex Concentrate (Beriplex) is the treatment of choice and should always be prescribed after discussion with a Haematologist.**
- Beriplex is stored in the Haemophilia Unit, first floor, Waterfall house (open 9am-5pm, Mon-Fri) or satellite fridge in Blood Bank. Recommended dose: 15-50 units/kg depending on the INR and clinical situation.
- **Always discuss possible use with haematologist.**

Section 6. The Anticoagulation Service at BCH.

The aim of this service is to offer standardised and clinically effective anticoagulation management to inpatients and outpatients on anticoagulant therapy.

1. Referral of patients.

- An Anticoagulation Request Form (see Appendix) must be completed when referring the patient to the anticoagulation service for monitoring of anticoagulation.
- The request form can be obtained from the Coagulation Laboratory, ext. 9869. **All** sections of the form **must** be filled in.
- Once completed, the form must be returned to the Coagulation Laboratory.
- Completed forms are only accepted between Mondays to Fridays 9am to 330 pm.
- Please phone the coagulation lab on 9869/9870 to advise them if you have sent a referral.
- If a referral form is late in arriving, please commence doses as per recommendations in this guideline/ wait for following day/ speak to the on call Haematology Consultant on call.
- **Patients will not be dosed until the completed request form is received.**

2. Key Personnel

Consultant Haematologist — Dr J Motwani ext. 9843 or BCH switchboard.
Dr Jonathan Lancashire ext. 9846 or BCH switchboard

Anticoagulation Nurse Practitioner — Rebecca Gibson ext. - 8868

- Coagulation Laboratory — ext.- 9869/9870
- Haematology Specialist Registrars — bleep through switchboard.

3. Management of warfarin anticoagulation for Outpatients.

For those patients being monitored at Birmingham Children's Hospital an appointment should be made through the Anticoagulation Nurse Practitioner. Clinics are held on Monday and Friday 09.00 – 11.30 hrs. In Outpatient 2, first floor, Waterfall house.

Letters are not routinely sent from this clinic to GPs so it is vital that for inpatients being discharged, discharge letters are sent promptly as the GP is responsible for supplying the prescription for Warfarin once the patient is discharged.

About 80% of patients on long term warfarin will be monitored at home using a CoaguCheck coagulometer. The INR result is phoned by the parent/carer to the anticoagulation nurse if in-hours Monday to Friday, or to the haematology laboratory out of hours. Dosing will be undertaken either by the anticoagulation nurse or haematology consultant/registrar.

Section 7. Thrombolysis

Principles

- The use of systemic or catheter-directed tPA for life, limb or organ-threatening thrombosis must be restricted to patients who have been subject to a multidisciplinary discussion involving: the admitting speciality, the relevant intensive care unit, general surgery and plastic surgery (where appropriate), interventional radiology and haematology.
- Discussions must be at a consultant level.
- Where a decision is made to use systemic or catheter-directed tPA, there must be explicit agreement that appropriate clinical and haematological monitoring of the patient is carried out.
- Failure to institute rigorous clinical and haematological monitoring may lead to life-threatening haemorrhage irrespective of the outcome for the thrombotic episode.
- Medical and nursing staff using this drug must be familiar with its mode of action and the rationale for close monitoring.
- Consent will be taken before giving systemic or catheter directed tPA

Rationale

It is occasionally necessary to consider the use of systemic or locally directed recombinant tissue plasminogen activator (tPA, Alteplase) to treat children with life or limb-threatening venous or arterial occlusion. Although clinical trials are underway which might clarify best practice in the use of thrombolysis in children, evidence is currently largely anecdotal and potential benefit should be weighed carefully against the undoubtedly greater risk of bleeding than with anticoagulation alone.

Alteplase can be administered systemically or via a catheter sited by interventional radiology (IR) adjacent to/within the thrombus. Attempts can be made to remove thrombus mechanically via the use of a mechanical thrombectomy device, with or without the use of thrombolytics.

Alteplase converts plasminogen to plasmin which breaks fibrin down to its degradation products (FDPs). Alteplase will bring about lysis of both a pathological thrombus and any other haemostatic plug (e.g. a small cerebral vessel injury, recent surgical anastomosis) and hence can bring about successful lysis of a thrombus but can also cause catastrophic bleeding at an unrelated site.

Alteplase activates circulating plasminogen as well as that bound to fibrin and hence causes systemic fibrinolysis with a drop in fibrinogen levels which can lead to a hyperfibrinolytic process, ultimately resulting in disseminated intravascular coagulation (DIC).

Indications for systemic tPA

Include but are not restricted to, the following:

- Spontaneous or catheter-related arterial or venous thrombosis which is compromising the blood supply to or from the affected limb or other organ
- Superior vena cava obstruction
- Atrial thrombus
- Massive pulmonary embolus with cardiovascular instability
- Bilateral renal vein thrombosis
- Extensive IVC occlusion without renal vein thrombosis
- Small bowel ischaemia
- Extensive thrombus likely to result in long-term morbidity

Standard anticoagulation should always be started immediately whilst thrombolysis is being discussed.

Relative Contraindications to systemic tPA

The following situations will increase the risk of bleeding in a patient having systemic or catheter-directed tPA and must be brought to the attention of the teams involved in planning thrombolysis.

- Bleeding within the previous few weeks
- Surgery within 7-10 days
- CNS surgery, trauma or haemorrhage (> grade 2) within 30 days
- CNS tumour
- Thrombocytopenia or coagulopathy that cannot be corrected
- Lumbar puncture within the last 7 days
- Pregnancy
- CPR within the previous 7 days
- Severe liver disease
- Significant prematurity

Thrombolysis regimen.

Prior to starting a tPA infusion, always:

- Check FBC; U&E and LFT; coagulation screen including PT, APTT,TT and fibrinogen
- Ensure current Group & Save
- In neonates, give 10-20 ml/kg of FFP as they have a relative deficiency of plasminogen
- Correct any coagulopathy after discussion with haematology.
  Ensure platelet count is >100 and fibrinogen >1 g/l
- Stop warfarin/ NSAIDS and other antiplatelet agents if relevant
- Reverse warfarin if INR is prolonged
- Place a sign over the patient's bed stating that they are having an alteplase infusion.
  - Invasive procedures such as catheterisation, intubation and cannula insertion should be postponed if possible and carried out with extreme care if unavoidable
  - Lumbar puncture absolutely contraindicated
  - IM injections, arterial blood gases (stabs) and NSAIDs contraindicated
  - Caution with some manual physiotherapy techniques may be necessary
- TEDS stockings if appropriate for age.

Depending on whether the alteplase is being administered systemically or via a locally sited catheter, the dosing regimen varies. Catheter directed thrombolysis may be more efficacious and it allows a smaller dose to be administered, but evidence to suggest it is safer is conflicting.

i. Systemic thrombolysis

The use of a relatively high dose of tPA as a systemic infusion requires informed discussion between the multidisciplinary team and the child's parents/carers. Discussion should centre around efficacy of treatment in the particular clinical situation, and the actual (rather than perceived) risk of haemorrhage. The dosing regimen used is variable; concurrent use of low dose heparin followed by full anticoagulation is recommended; reversal of tPA requires plasma infusion.

Starting dose of tPA = 0.1-0.6 mg/kg/hour for up to 6 hours (maximum total dose 90 mg)

- The starting dose will take into account the bleeding risk of the child. 0.2mg/kg/h is often used as starting dose.
- 10 units/kg/h of unfractionated heparin (UF) may be administered concurrently with the alteplase, after discussion with haematology.
- Check FBC, coagulation screen after 3 hours and at end of tPA infusion and correct platelet count and fibrinogen as necessary to maintain platelet count > 100 $x10^9$/l and fibrinogen > 1g/l.
- **Once alteplase infusion has been stopped, increase UF heparin dose to a therapeutic level and aim to keep the antiXa level between 0.35 - 0.7 units/ml**
- Repeat doses can be administered. The decision to continue should be made following repeat imaging and consultant level discussion about efficacy and the haematological parameters. The dose may be increased if no improvement in thrombosis has been seen on repeat imaging.
- 10-20 ml/kg of FFP should be administered prior to continuing.

ii. Catheter - directed thrombolysis (CDT)

Catheter-directed thrombolysis involves administration of a thrombolytic agent (tPA) directly into the thrombus via one or more specialised intra-vascular catheters. The catheter is wedged within the clot so that the thrombolytic is infused directly into the clot itself through multiple side holes. The catheter is placed as part of a procedure in IR, usually after formal venography with or without attempted thrombectomy and usually under general anaesthesia.

CDT aims to generate faster thrombolysis while using lower doses of thrombolytic, theoretically decreasing complications associated with systemic administration. The technique may be less effective in chronic clot as it may not be possible to lodge the catheter deep within the thrombus. During CDT, patients are managed in an intensive care setting and clotting parameters are closely monitored to assess the patient's fibrinolytic state (see above). Angiography/venography in IR is performed every 4–12 hours depending on the clinical situation, allowing decisions to be made regarding thrombolytic dose, catheter position and continuation of treatment.

Beware false reassurance that thrombolytic agents stay localised; a proportion of the thrombolytic does migrate systemically.

Starting dose of catheter-directed PA infusion is 0.01-0.1mg/kg/h for up to 24 hours.

- 10 units/kg/h of UF heparin may be administered concurrently with the tPA, after discussion with haematology.
- Repeat FBC and coagulation screen at least 6 hourly throughout infusion or if clinically indicated. Maintain platelet count > 100 x10^9/l and fibrinogen > 1g/l.
- Repeat doses can be administered after discussion as above

Once the tPA infusion has been stopped, increase UF heparin dose to a therapeutic level and aim to keep the anti-Xa level between 0.35 – 0.7 units/ml.

Monitoring of efficacy

The frequency and modality of monitoring the limb or other affected area to assess response should be determined by the team involved at the time thrombolysis is initiated as this will vary depending on the vessels involved and the ability to repeat imaging at this site.

tPA-related haemorrhage

In case of life-threatening bleeding while on thrombolysis, stop infusion and discuss with haematology consultant immediately. Consider Cryoprecipitate (10-15 mls/kg), Octaplas (10-15mls/kg), tranexamic acid, fibrinogen concentrate along with red cell and/or platelet transfusion as necessary.

Section 8. Management of arterial line associated reduced limb perfusion

1. Introduction

- Accurate, continuous monitoring of blood pressure using an arterial line catheter is often required in PICU.
- Arterial occlusion related to vascular access in children is uncommon.
- Clinically significant embolic or thrombotic events related to arterial catheter occurred in only 0.85% of children with arterial catheter [(1)]. However, silent but complete occlusion of radial arteries was noted in 63% of neonates after decannulation [(2)].
- Arterial lines may cause arterial compromise due to physical obstruction, clot, intimal flap or spasm.
- The consequences of reduced arterial flow may be life or limb threatening or lead to growth disturbance or cold intolerance.
- Evidence for management of reduced perfusion related to arterial catheters is largely from case series rather than RCTs. This section represents a synthesis of published algorithms and is a consensus document between clinicians in relevant departments at BCH, including PICU, Haematology, Plastic Surgery, Radiology and Pharmacy. It will be reviewed by the Clinical lead for PICU, the Anaesthetic Clinical Lead and the BCH Thrombosis Group at least every three years.

2. Purpose

The purpose of this document is to guide medical and nursing staff in PICU or theatres in the management of arterial line associated limb ischemia.

3. Content

3.1 Principles of arterial line care

- Full clinical evaluation and recording of arterial status of limb prior to line insertion
- Meticulous clinical observation of arterial line sites (PICU arterial line care bundle)
- Early recognition of arterial line malfunction
- Early recognition of reduced limb perfusion associated with arterial line
- Multi-disciplinary approach
- Re-establishment of limb perfusion
- Clear communication to the child's parents

3.2 Risk factors for arterial thrombosis

- Small size vessels (neonates)
- Large size arterial lines (greater than 22G)
- Multiple arterial stabs/cannulations
- Sepsis
- Hypotension
- Inotrope requirement
- Hyper viscosity
- Site of line insertion. Analysis of BCH PICU data showed that perfusion related incidents per 1000-patient-line-days was 6.9 for brachial, 6.1 for femoral & 6.1 for axillary lines against only 1 per 1000 line days for radial line. Hence radial arterial line insertion is recommended.

3.3 Features of disordered limb perfusion due to arterial thrombus

- Pale distal limb
- Cold distal limb
- Weak or absent distal pulses
- Evidence of neurosensory deficit (in conscious older children)
- Loss of pulse oximetry trace
- Arterial trace dampened or non-existent
- Absent hand held Doppler pulses
- Mottling of skin
- Necrotic areas on skin

- Pain on moving limb
- Tense muscle compartments on palpation. When undertaking intramuscular pressure measurement by needle manometry, readings > 20mmHg are abnormally high and > 40 mmHg mandate immediate fasciotomy.
-

4. Management of arterial line associated reduced limb perfusion

The management algorithm shown in **appendix 4** emphasises a multi-disciplinary approach involving the patient's own overseeing clinician, the plastic surgical team and/or vascular surgery team and radiologist for the initial stages of management [3] Treatments utilised in progression are heparinisation, thrombolysis and surgery.

4.1 Diagnosis, referral process and monitoring (also see appendix 4):

- Any concerns about perfusion distal to arterial line should immediately be escalated to medical staff or ANP and to team leaders or PICU nursing co-ordinator

- PICU clinician should review, examine and diagnose or rule-out arterial line related ischaemia within 15 minutes of concern being raised.

- If arterial line related ischaemia is diagnosed, the arterial line should be removed immediately in the majority of cases. Always discuss with PICU consultant prior to removing line from patients on ECMO)

- If the perfusion of limb does not improve or deteriorates despite 15 minutes after arterial line removal, immediate heparinisation (discuss with PICU consultant) and plastic surgery referral should be made. The patient should be reviewed by plastic surgery team within 30 minutes of the referral.

- It is usually the duty of medical/ANP staff to refer to on-call plastic surgery registrar by telephone in the first instance. The referring clinician should be clear about their concern about **'threatened limb'**.

- All cases of arterial line related ischaemia must be discussed with a Plastic surgery consultant. This is usually done by the on-call plastic surgery registrar after their initial review.

- The bedside nurse should document pulse, colour and capillary refill distal to arterial line insertion site (where possible) every 30 minutes on the PICU observation chart till perfusion is acceptable to the clinical team. The type and frequency of observations will then depend on the response of the limb and will vary from half hourly upwards. Any deterioration in the limb perfusion will require an immediate escalation to the plastic surgery team. The documentation should be done on the chart by inserting an 'arterial line monitoring' sticker at the lower end of continuous IV infusion part of the chart. The arterial line sticker (**appendix D**) can be printed off from the label printer.

- Documentation of limb temperature, pulse oximetry and hand-held Doppler signal monitoring may also be required. Need for these must be determined on a case-by-case basis in discussion with plastic surgery.

- Number of observations done on affected limb must be balanced against need for minimal handling of the affected limb. Minimal handling assists recovery of perfusion in case of vessel spasm.

- Attempts should be made to keep the child centrally and peripherally normothermic.

- Plastic surgeons/PICU clinicians should consider if formal Doppler/duplex ultrasound examination is required and if so when.

4.2 Heparinisation

- It is recommended that children with arterial thrombosis start a heparin infusion to achieve targeted anti-XA levels of 0.35-0.7 units/ml **(see Section 1).**

- The infusion will continue for 3 hours in the first instance and further duration will be guided by the plastic surgical team.

- Conversion to low molecular weight heparin to complete a maximum of 2 weeks of treatment may be considered. Refer to Anticoagulation nurse practioner/ team for further advice.

- Relative contra-indications to heparin include active bleeding, intraventricular haemorrhage and heparin induced thrombocytopenia. Discuss with PICU consultant, parent specialty team and haematologist when in doubt.

4.3 Thrombolytic therapy (Consultant team decision only)

- Administration of thrombolytic therapy is advised for children with limb-threatening or organ-threatening arterial thrombosis who fail to respond to the initial 3 hours of unfractionated heparin therapy and who have no known contraindications to thrombolysis treatment.

- At Birmingham Children's Hospital, the decision to use thrombolysis should be made only by the multi-disciplinary consultant team involved.

- The Haematology consultant on-call should be made aware of decision to use thrombolysis as soon as possible for guidance on dose, duration and monitoring of therapy.

- Tissue plasminogen activator (Alteplase) is a protein involved in breakdown of blood clots. As an enzyme it catalyses the conversion of plasminogen to plasmin, the major enzyme responsible to clot breakdown. It is the most appropriate drug to use because of its high fibrin affinity, preferential activation of plasminogen bound to fibrin, lack of antigenicity and short half-life (4 minutes in plasma and 45 minute thrombolytic effect).

- **Consideration of thrombolysis, Thrombolytic regimens and contraindications to thrombolysis, are described in Section 7 of these Guidelines.**

4.4. Surgery

As the site of arterial damage is known, exposure of the vessel in ischaemic limbs will reveal the damaged artery and any intra-arterial thrombosis. This thrombus can be removed by arteriotomy and a venous patch may be necessary to reconstruct the vessel. Direct injection of low-dose alteplase may also be done intra-operatively. The early involvement of the plastic surgical team allows these multi-disciplinary treatment decisions to be made.

4.5. Interventional Radiology

Catheter-directed thrombolysis involves administration of alteplase directly into the thrombus via one or more specialised intra-vascular catheters. The catheter is wedged within the clot so that the thrombolytic is infused directly into the clot itself through multiple side holes. The catheter may be placed surgically or as part of a procedure in IR, usually after formal angiography and usually under general anaesthesia. This technique aims to generate faster thrombolysis while using lower doses of thrombolytic, theoretically decreasing complications associated with systemic administration.
Angiography is performed every 4–12 hours depending on the clinical situation, allowing decisions to be made regarding thrombolytic dose, catheter position and continuation of treatment. Beware false reassurance that thrombolytic agents stay localised; a proportion of the thrombolytic does migrate systemically.

Note: Access to catheter-directed thrombolysis may not be always accessible 24x7.
However, interventional radiology consultant on-call (cross-cover rota with BCH and UHB) should be accessible via switchboard.

Venous Thromboembolism Prophylaxis in Burns

Background

Patients with burn injuries are at an increased risk of venous thromboembolism (VTE). They are at higher risk of venous thromboembolism (VTE) as they display all three components of Virchow's triad: endothelial injury, hyper-coagulopathy and stasis. In patients with burn injury, direct injury to the endothelium, activation of thrombotic and fibrinolytic pathways, ventilatory support, multiple surgeries, sepsis, multiple central line insertions and immobilisation all contribute to the increased risk of VTE. (1–4) Harrington *et al* found that increasing total body surface area (TBSA) burned significantly increases the risk of VTE. (5). Although the true incidence of VTE in burn patients has not been adequately quantified, symptomatic VTE occurs in 0.2-7% of this population. VTE prophylaxis has proven clinical effectiveness and affords a reduction in the morbidity associated with such events, but the benefits and risk of complications need to be balanced in order to provide the best quality of care. Standard dosing of low molecular weight heparin (LMWH) may be insufficient to achieve target anti-factor Xa levels in acute burn patients as it correlates with weight and burn area (%TBSA).(6) A higher initial LMWH dose and routine monitoring of anti-factor Xa levels are therefore recommended.(7)

Methodology

The "Burn risk score assessment for VTE" and "Management for VTE prophylaxis" has been developed in 2014 by the Burns Team (Federica D'Asta and Yvonne Wilson) and Haematology Team (Mike William) reviewing and combining the available burn specific literature and the BCH "Adolescent risk assessment for VTE" ADOLESCENT*. The following version has been reviewed and approved by Miss E Chipp and Mr D Wilson

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BURNS RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

A risk assessment should be conducted on admission to the hospital for all burn patients. It is recommended that all patients should be daily re-assessed during their inpatient stay as risk may change. Thrombosis risk and bleeding risk should be considered together for each individual patient.

Document daily this risk assessment record in the patient's medical notes and tick box on theatre checklist. Form needs to be reviewed by surgical team either pre-op on ward or in theatre at WHO checklist time.

THROMBOSIS RISK			
Patient related	**Tick**	**Admission related**	**Tick**
Adolescent/Postpubertal		Central venous line in situ	
Active cancer or cancer treatment		Likely to have significantly reduced mobility for 3 days or more	
Use of oestrogen-containing contraceptive therapy		Major trauma (or lower limbs in cast)	
Pregnancy or < 6 weeks post partum		Burns with extensive involvement of both lower extremities	
Obesity (BMI >30 , take wt [in kg]/ height [$m^{2]}$)		Duration of surgery predicted > 90 mins or multiple operations	
Known thrombophilia disorder that makes blood clotting more likely		Burns or skin loss >20%	
Personal history VTE		PICU admission	
First degree relative with a history of VTE under the age of 40 years		Inhalation injury	
One or more significant medical co-morbidities (e.g. nephrotic syndrome, sickle cell disease, inflammatory bowel disease, congenital heart disease)			
TOTAL	____	**TOTAL**	____

BLEEDING RISK			
Patient related	**Tick**	**Admission related**	**Tick**
Active bleeding		Procedure with high bleeding risk	
Acquired bleeding disorders (such as acute liver failure)		Lumbar puncture / epidural / spinal anaesthesia expected within the next 12 hours	
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR > 2)		Lumbar puncture / epidural / spinal anaesthesia within the previous 4 hours	
Acute stroke			
Thrombocytopenia (platelets < 75 x 10^9 / L) Heparin allergy or HIT			
Uncontrolled systolic hypertension			

Inherited bleeding disorders (such as haemophilia and von Willebrand's disease)			
TOTAL	___	**TOTAL**	___

BURNS MANAGEMENT GUIDELINES FOR VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS

In all patients, ALWAYS:
Consider general measures to reduce the risk of VTE:

- Maintain adequate hydration
- Mobilise early after surgery
- Upper extremity site for Central Venous Lines is preferred
- Remove Central Venous Lines as soon as possible

After considering bleeding risks:

2 ticks on thrombosis risk	TEDs and intermittent pneumatic compression stockings in theatre and on the ward, if size appropriate and applicable. If not, consider pharmacological Thromboprophylaxis with LMWH
3 ticks on thrombosis risk	Thromboprophylaxis with LMWH
If risks of bleeding are present, discuss with haematology consultant. If an increased risk of bleeding is documented on the risk assessment- Thromboprophylaxis with LMWH is contraindicated	

If pharmacological **prophylaxis** is considered, subcutaneous Enoxaparin should be administered at prophylactic dose

Prophylactic dose Enoxaparin	child<2mo: 0.75 mg//kg/dose q12h child>2mo: 0.5 mg/kg/dose q12h
After 3rd dose (preferably morning dose) check Anti-Xa LMWH levels (4-6 hours post injection)	

For prophylaxis target: Anti Xa level: **0.1-0.5 IU/mL**
For therapeutic target: Anti Xa level: **0.5-1 IU/mL**

If enoxaparin started, fill the referral form to Coagulation Laboratory, Haematology Department. Subsequent doses of enoxaparin and details of next Anti Xa testing will be suggested by Anticoagulation team.
Remember: possible complications of LMWH are bleeding and Heparin Induced Thrombocytopenia (HIT).

Notes
Patients undergoing surgical procedures
- **Timing of morning dose can be adjusted on day of surgery to allow administration under general anaesthesia**

Patients with significant oedema
- **Unfractionated Heparin iv infusion should be considered** - **AntiXa levels or aPPT level should be monitored**

Anti-Xa Assay (chromogenic) on the IL ACL TOP 500 Coagulometer

Purpose of the examination

Monitoring of patient anticoagulation is imperative in management of their treatment. The utilisation of the chromogenic Anti Xa assay is employed in the quantitative determination of LMW/ UF heparin from the patient's plasma.

Principle and method of the procedure used for the examination

Heparin is a sulphated glycosaminoglycan's and accelerates up to 2000-fold the inhibitory effect of anti-thrombin on coagulation proteases. It is available therapeutically in two forms: unfractionated and low molecular weight. Heparin (UF or LMW) in the test sample binds with anti-thrombin forming a heparin-AT complex.

This complex inhibits factor Xa, which has been added in excess in the assay.
Residual Xa activity is measured by its action on a specific chromogenic substrate, and is sensitive and highly specific for Xa.

The resulting release of the chromogen paranitroaniline is measured at 405nm, and the reaction is inversely proportional to the concentration of heparin in the plasma.

In a one stage anti-Xa assay (as with the IL assay), there is no exogenous addition of anti-thrombin, therefore the assay result is dependent on the anti-thrombin level of the test sample at levels of anti-thrombin outside the range 35-130%. (Relevant in infants)

The presence of dextran sulphate in the buffer reduces the influence of PF4, which binds to heparin.

Clinical Utility

This Assay can be used for the measurement of both UFH and LMWH in patient's plasma

Analytical performance characteristics

This IL assay can measure both UFH and LMWH (all types) using a single calibration line and use of the

appropriate standards.

Reference to QI-198 for current practice and on-site testing.

Environmental and safety controls

C.O.S.H.H.

Refer to SOP 1253b for general information. In addition avoid contact of substrates and reagents with skin and eyes.

Wear suitable protective clothing. Dispose of in suitable sharps type bin, do not empty into drains or sinks.

	Liquid Anti-Xa	UF Heparin Controls	LMWH Heparin Controls
Hazard class	None	None	None
Risk phrases	None	None	None
Safety phrases	none	None	None

Patient preparation

Not applicable

Interferences and cross reactions

Severe lipaemia can significantly affect this assay. If samples are severely lipaemic and analysis is necessary, a modified analysis can be performed. Perform 1 in 2 dilution with normal pooled plasma and multiply result by the dilution factor. Any questions or queries regarding dilution of sample should be discussed with section lead or senior.

The comment "Sample severely lipaemic, suggest interpret results with caution. Dilution correction made to enable sample processing. Any queries suggest discuss with consultant haematologist." Must be added to the report to reflect this modification to process (reference to QI-167). Samples collected for monitoring purpose should be collected 4 hours after initial dose or after the dose has been adjusted. If concerned refer/ contact the Consultant Haematologist

Type of sample/additive

- 1.3mL whole blood taken into 3.2% buffered sodium citrate (NO HEPES added). See SOP1248 'Specimen collection', by venous or arterial blood collection.

- It is possible to measure an Anti Xa level on a sample obtained by capillary collection (see SOP 1248 (INR)). This has been validated in QI-56. There is an increased possibility of sample activation and poor quality samples being obtained using this technique; however it can be useful when venous access is difficult. Ideally samples should still be taken venous or arterially and this should be the recommendation, however if access is particularly difficult or there are exceptional circumstances, capillary bottles for collection can be supplied from the laboratory to the user on a named patient basis. Ensure that a capillary citrate bottle (0.5ml; blue top) is provided.

Equipment Required

Testing is performed using the ACL TOP 500 analyser. Manufactured and supported by Werfern. 'Top 1' is the analyser which analysis for the Anti Xa can be performed.

Reagents Required

Anti Xa assay:	Heparin controls (D1)
	Chromogenic substrate (R3/R4)
	Factor Xa reagent (R3/R4)
	Clean B diluted (R4)

Anti-Xa reagents:

	Manufacturer	Order Code	Pack Size
Factor Xa reagent	IL	0020302610	5 x 2.5ml
Chromogenic substrate	IL	0020302620	5 x 3ml

Heparin reagents are stored in the bottom of coagulation fridge 2 and do not require any reconstitution. Mix by inversion x 6 before use, stable for up to one month after opening dependent on QC value obtained.

Quality control and calibration of Anti-Xa assay:

	Manufacturer	Order Code	Contents	Pack Size
Heparin calibrators	IL	0020300600	Calibrator 1 Calibrator 2 Calibrator 3	2 x 1ml 2 x 1ml 2 x 1mL
LMWH low control	IL	0020300220	Combined LMWH high and low controls	5 x 1ml
LMWH high control	IL	0020300210	Combined LMWH high and low controls	5 x 1ml
UFH low control	IL	0020300320	Combined UFH high and low controls.	5 x 1ml
UFH high control	IL	0020300310	Combined UFH high and low controls.	5 x 1ml

All quality control and heparin calibration material are stored in the bottom of reagent fridge 2. Reconstitute all with 1ml of distilled water for 30 minutes, mix by inversion x 6 before use.
Controls are stable for 48 hours after reconstitution when stores at 2-8°c
Anti- Xa reagents are stable for 1 month after vial opened. Ensure that all reagents and QC material are within date prior to testing.

Calibration procedures and metrological traceability

Tri-level heparin calibrators (0, 0.8 and 2.0U/ml) are provided. All three are needed to make the chromogenic assay curve. Reconstitute calibrators and place in sample cups labelling appropriately. Place calibrators into racks where patient samples would normally go. Identify the calibrators on the TOP by selecting sample type as calibrator and then selecting the suitable sample ID: hep 1, 2 or 3. **New** a**ssay curves should be ran using fresh chromogenic substrate and liquid heparin reagents**.

To run calibration curve:
Calibration, Status list
Double click on required curve

Then **Test feasibility**

If feasibility is ok, then click on the **running man.**

Calibration curves are performed at least every 3 months as part of planned maintenance schedule. All new curves should be followed by both IQCs.

The assay standards are traceable to the WHO international standards for UF (WHO 07/328) and LMW (WHO 01/608) heparin. Refer doc 1259

Pre acceptance/ Pre use testing

Pre acceptance testing is performed by visual inspection of the reagent upon receipt. Ensure there is no damage to packaging, and record on document 1253c3.
Pre Use testing is performed. Refer to SOP 1253p and 1253c1. Complete documents 1250c3 and 1253c1. Record on QC/QM log (doc 1002) when in use. Any concerns discuss with section lead/ senior BMS.

Pre-analytical Requirements

- Ascertain patient history. Ensure which heparin they are on, and perform correct QC.
- Centrifuge sample using the Rotofix (10Min 3000 rpm) or Pico centrifuge (2 minutes at 13000 rpm)
- Remove cap prior to loading onto analyser.
- Visual inspection of the sample to ensure there is no apparent lipaemia, icterus, haemolysis or clot in sample.

Procedural steps

Ensure that the IQC is acceptable and that all appropriate reagents are on board the analyser.
Place sample on board, ensure that the barcode has been correctly identified. – If the patient has been correctly booked in the correct assay should already be selected. If however it has not been pre-selected, double click in test box and select heparin assay screen tab.
Select the Anti Xa test by left clicking on the request.

Click running man.

NB: Testing can only be performed on TOP 1. It is only necessary to have diluted clean B on board as well as the anti-Xa reagents and appropriate controls to be able to run the assay, no additional reagents required.

Results

The result is automatically generated with a printout from the analyser in IU/mL

Measurement of uncertainty

Refer doc 1038a2

Quality control procedures

I.Q.C.

Place liquid heparin reagents in rack R4 and the controls in rack D1.

Enter QC, results list. Double click anywhere on screen.

Run relevant heparin control (either UFH or LMWH) by ticking controls on list and clicking running man.

N.B.

If testing a patient on **UFH** reconstitute both low and high **UFH** controls.

If testing patient on **LMWH** reconstitute both low and high **LMWH** controls.

Confirm QC result is within acceptable range (1253c4) before running patient sample. Seek section lead/ senior advice if QC unacceptable, a new calibration curve may be required. Calibration curves are performed at least every 3 months as part of planned maintenance schedule. The Anti Xa, LMWH controls should also be performed at least once a month, again as part of the planned maintenance schedule. All QC and calibration events are recorded on board the analyser in the maintenance area. Any problems with QC or calibration should be recorded on the QC/QM log and escalated to section lead if appropriate.

EQA

We participate in UK NEQAS EQA scheme.

Biological reference intervals

UFH = 0.35-0.70

LMWH = 0.50-1.10

(Reference range quoted from T2000; reference Trust Heparin guideline H&O/12/1020)

Laboratory clinical interpretation

For guidelines see SOP 1212 anticoagulant therapy in ACL TOP SOP/ NEQAS folder located on the coag shelf in A20.

Out of range results – Action required

If results are out of therapeutic range the requesting clinician **must** be informed by telephone. If additional advice required suggest they discuss with consultant Haematologist. This comment should be added to the T2000 report.

Potential sources of variation

Poor venepuncture or additional pre-analytical variables may contribute to erroneous results. All abnormal results must be actioned as described above and repeat samples requesting as necessary. Any concerns should be raised to the requesting clinician and advised to discuss with the clinical haematology team.

Result reporting – T2000

Should be validated using Modulab (see SOP 1280b) for release to T2000 and reported in the 'XA' set on telepath.

Transfer the provided result in the anti-Xa box to either unfractionated or LMWH fields for reporting in 'result entry'. Release results to the coagulation authorisation queue (Cntrl+R). Confirm result is correct and authorise result (Cntrl+A).

References

- QI-140, QI-56; QI-167; QI-198
- Trust Heparin guideline H&O/12/1020
- WHO 07/328
- WHO 01/608
- SCH haematology SOPs as reference in text.

Section 9. THROMBOPROPHYLAXIS

Venous thrombosis is relatively uncommon in children compared with adults. The incidence of paediatric thrombosis however is increasing, and there are multiple factors which contribute to this increase, including acquired risk factors such as the use of central lines, immobility, sepsis, malignancy and also congenital risk factors such as protein C deficiency, Factor V Leiden etc (congenital thrombophilia).

Although venous thrombosis may occur all through childhood, there are 2 peak age groups at risk for VTE, these being neonates and adolescents/teenagers; the incidence of VTE then increases significantly throughout adult life.
The term **Thromboprophylaxis** describes the use of various measures to reduce the risk of thrombosis. These measures may be simple, such as early mobilization of post-surgery patients, avoidance of dehydration, or may involve the use of mechanical interventions such as compression stockings or the use of pharmacological Thromboprophylaxis, usually with heparin.

When considering which patients should be offered Thromboprophylaxis, the perceived risk of thrombosis should be assessed, as should the risk of intervention, particularly if heparin is being considered. All adults admitted to hospital undergo a thrombosis risk assessment as mandated by the Department of Health, with at risk individuals given Thromboprophylaxis. Although such risk assessment is not as yet mandatory in the paediatric age group, it would seem logical to consider risk assessment for particular patient groups such as teenage surgical patients, PICU patients, children with prolonged immobility etc. A paediatric VTE risk assessment score chart has been introduced at BCH (and other paediatric hospitals) and has been piloted for adolescent and post pubertal surgical patients. A similar assessment sheet is in use for burns patients (see appendix).

The VTE risk assessment chart is shown below. It should serve as a basis for the consideration of Thromboprophylaxis in all patients considered being at an increased risk of VTE throughout the hospital. Thromboprophylaxis does not entail giving heparin to all patients and it would be anticipated that only a minority will require pharmaceutical Thromboprophylaxis, the remainder being managed by excluding risk factors where possible or short term mechanical Thromboprophylaxis.

RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE) FOR ADOLESCENTS AGE 13-18 YEARS	
Date of admission	PLEASE AFFIX PATIENT LABEL HERE
Risk assessed by	
Designation	
Signature	
Date	

Review the patient related factors shown on the assessment sheet for thrombosis risk, ticking each and any box that applies. Clinicians may consider further risks apply in addition to those listed.

Bleeding Risk

Patient Related	Tick	Admission Related	Tick
Acquired bleeding disorders (such as acute liver failure)		Neurosurgery, spinal surgery or eye surgery, Cardiac.	
Untreated inherited bleeding disorders (such as haemophilia and Von Willebrand Disease)		Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours	
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)		Lumbar puncture/epidural/spinal anaesthesia within the previous 24 hours	
Thrombocytopenia		Active bleeding	
Uncontrolled systolic hypertension (>230/120 mmHg)			

Thrombosis Risk

Patient Related	Tick	Admission Related	Tick
Central venous catheter		Significantly reduced mobility for 3 days or more	
Active cancer or cancer treatment		Severe trauma with ISS (Injury Severity Score) >9	
Dehydration		Spinal cord injury with paralysis	
Known Thrombophilia		Total anaesthetic + surgical time >90 minutes	
Obesity (BMI>30kg/m2)		Acute severe sepsis	
One or more significant medical comorbidities (e.g. congenital or low output heart disease, sickle cell disease, metabolic or inflammatory conditions)		Surgery involving pelvis or lower limb with a total anaesthetic + surgical time >60 minutes	
Parental/family history of VTE age <40 years		Critical care admission intubated and ventilated	
Use of oestrogen-containing contraceptive therapy		Severe burns	
Pregnancy or <6 weeks post-partum (NICE Guideline, 2018)			

If an increased risk of bleeding is documented on the risk assessment – thromboprophylaxis with LMWH is relatively contraindicated

Prescribe the appropriate intervention if required and complete all the prescription chart documentation

Outcome *(tick any that apply)*

No Thromboprophylaxis	
Mechanical Thromboprophylaxis	
Low Molecular Weight Heparin (LMWH)	
Risk Assessment Score:	

Completed by:

Date:

Local Guidelines can be found on Hospital Intranet or NICE Guidelines at:
http://www.nice.org.uk/Guidance/CG/Published and http://www.nice.org.uk/guidnace/CG92 This

document has been adapted from the Department of Health template (Gateway reference no. 10278) Revision 1 – Oct 2011.

Birmingham Children's Hospital

Haematology Department

REQUEST FOR WARFARIN DOSING

ALL SECTIONS MUST BE COMPLETED

Name		**Registration No.**
DOB	**Ward**	**Consultant**
Address **Tel No.**		**GP Name** **GP Address** **GP Tel No.**

Patient's weight (Kg) | **Blood Group (If Known)**
Reason for Anticoagulation:
Concurrent drugs:
Commencement of anticoagulant therapy: **Doses given so far (Inc. dates):**
Target INR : **Duration of anticoagulant therapy required:**

Clinician's Name: **Bleep Number:**	**Date:**

Appendix 2

Birmingham Children's Hospital

Haematology Department

REQUEST FOR ENOXAPARIN DOSING

ALL SECTIONS MUST BE COMPLETED

Name		**Registration No.**
DOB	**Ward**	**Consultant**
Address **Tel No.**		**GP Name** **GP Address** **GP Tel No.**
Patient's weight (Kg)		**Blood Group (If Known)**
Reason for Anticoagulation:		
Concurrent drugs: **Renal function : normal/abnormal (please delete)**		
Commencement of anticoagulant therapy: **Doses given so far (inc. dates):**		
Target anti-Xa level :		
Duration of anticoagulant therapy required:		
Clinician's Name: **Date:** **Bleep Number:**		

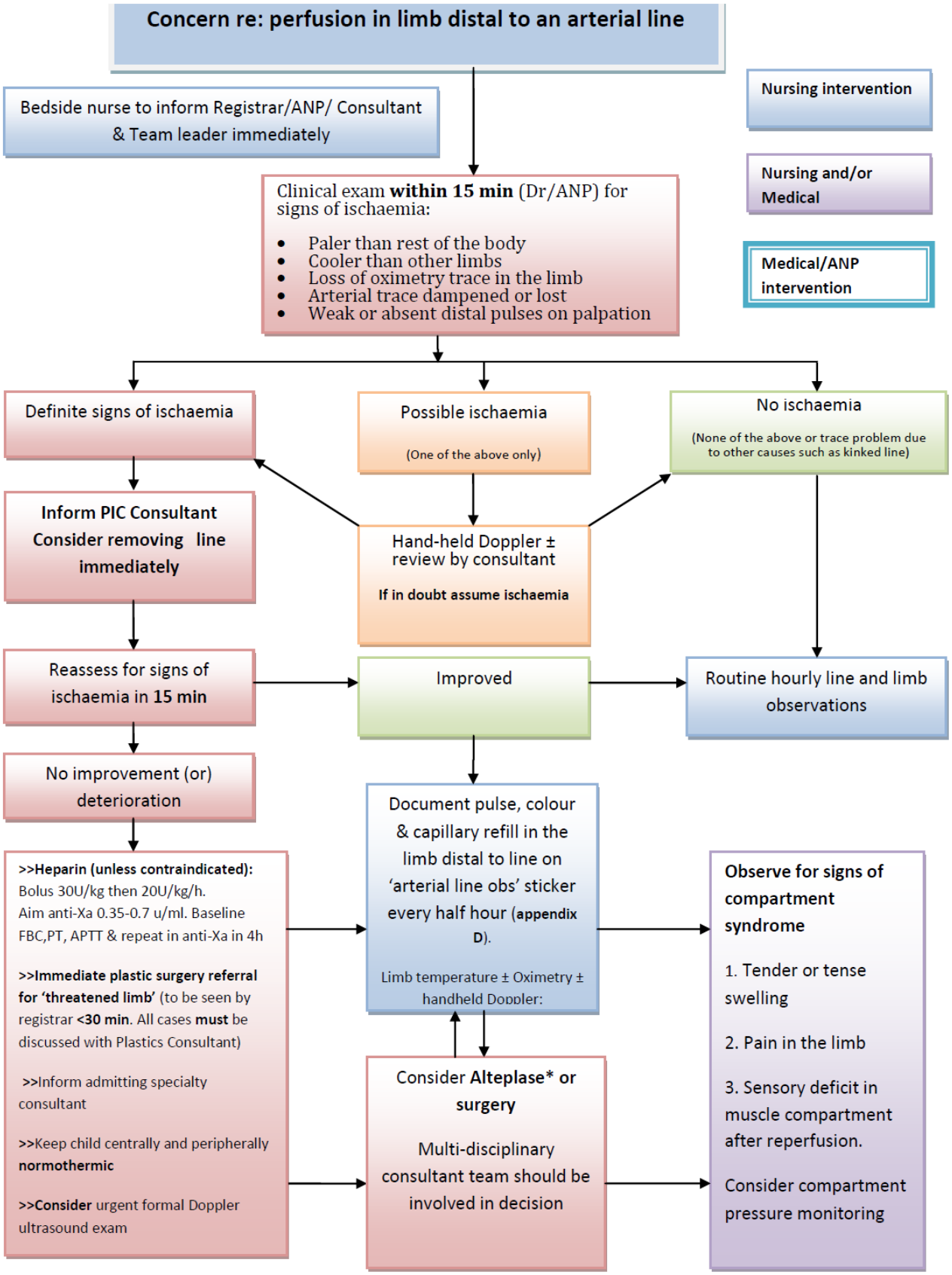
Drug Interactions with Oral Anticoagulants

In Children.

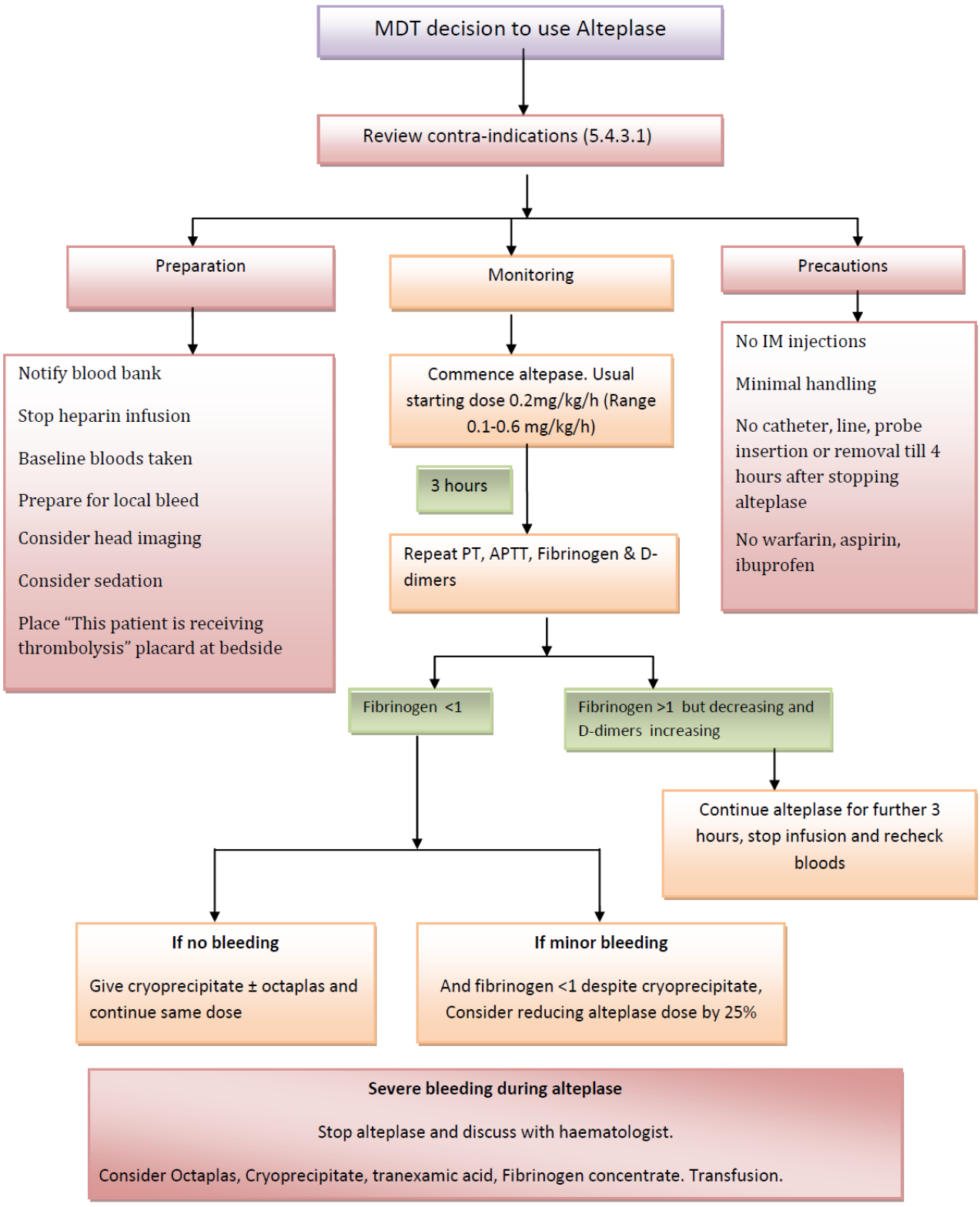
This is not a complete list of drugs that interact with Warfarin. If in doubt, please contact the Anticoagulant Nurse Practitioner (0121 333 8868) or BCH Pharmacy. Always inform the Anticoagulant Nurse of any changes in medication.

Drugs that inhibit the action of oral anticoagulants, INR falls.	**Drugs which potentiate the action of oral anticoagulants, INR increases.**
• **Antibacterials-** Rifampicin. • **Antidepressants-** Tricyclics. • **Antiepileptics-** Carbamazepine, Phenytoin, Primidone. • **Antifungals-** Griseofulin. • **Antivirals-** Amprenavir, Atazanavir, Nevirapine,Ritonavir. • Barbiturates. • **Cytotoxics-** Azathioprine, Mercaptopurine, Mitotane. • **Lipid-** regulating drugs- Colestyramine. • **Oestrogens and Progesterone-** contraceptive pill. • **Ulcer Healing drugs-** Sucralfate. • **Vitamins-** Vitamin K. **Non Prescribed medication.** **'**Over the counter' remedies/medicines may affect the INR, it is important to inform the Anticoagulant Nurse if you start taking any. Examples of these are: • **Co- enzyme Q-10** –reduces the effect of Warfarin • **Garlic –**increases the effect of Warfarin • **Gingko Biloba –**increases the effect of Warfarin • **Ginseng –** reduces the effect of Warfarin • **Green Tea-** reduces the effect of Warfarin • **Omega 3-** increases the effect of Warfarin • **St John's Wort -** reduces the effect of Warfarin	• Alcohol • Allopurinol • **Anabolic Steroids and Corticosteroids.** • **Analgesics-** Aspirin, Diclofenac (avoid intravenous), Mefenamic Acid, Piroxicam, Tramadol. Prolonged regular use of Paracetamol, • **Anti-arrhythmics-** Amiodarone, Propafenone. • **Antibacterials-** Cephalosporins,Chloramphenicol, Ciprofloxacin, Clarithromycin, Erythromycin, Levofloxacin, Metronidazole, Nalidixic Acid, Norfloxacin, Ofloxacin, Penicillins, Sulphonamides, Tetracyclines, Tigecycline,Trimethoprim • **Antidepressants-** Mirtazapine, Selective serotonin re-uptake inhibitors (SSRIs), Tricyclics, Venlafaxine. • **Antidiabetics-** Sulphonylureas. • **Antiepileptics-** Phenytoin, Valporate. • **Antifungals-** Floconazole, Itraconazole, Ketoconazole, Voriconazole. • **Antimalarials-** Proguanil. • **Antiplatelets-** Aspirin, Dipyridamole (increased risk of bleeding due to antiplatelet effect). • **Antivirals-** Amprenavir, Atazanavir, Nevirapine, Ritonair, Saquinavir. • **Anxiolytics-** Chloral, Triclofos. • **Cytotoxics-** Etoposide, Fluorouracil, Ifosfamide, Sorafenib. • **Hormone antagonists-** Danazol. • **Lipid- regulating drugs- Colestyramine**, Simvastin. • Testosterone. • **Thyroid Hormones-** Thyroxine. • **Ulcer Healing drugs-** Cimetidine, Esomeprazole, Omeprazole. • **Vaccines-** possibly by Influenza vaccine.

APPENDIX 3 : **ARTERIAL LINE ASSOCIATED ISCHAEMIA: MANAGEMENT SUMMARY**



APPENDIX 4: **MANAGEMENT OF PATIENT ON ALTEPLASE : SUMMARY**



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   The online version of this article, along with updated information and services can be found at http://chestjournal.chestpubs.org/content/141/2_suppl/e737S.full.html

   Supplementary material related to this article is available at

   http://chestjournal.chestpubs.org/contents/suppl/2012/02/03/141.2_suppl. e737S.DC1.html

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   8.**Thrombolysis in Children. Williams MD.. British Journal of Haematology, 148 : 26-36, 2010.**

   9) Venous thromboembolism occurring during adolescence. Biss T et al. Archives of Disease in Childhood 2016; 101, 427-432.

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PROTAMINE Injection for Anti-Coagulation Reversal

Presentation

- Protamine 10mg in 1ml (5ml ampoule)

Prescribing

Reversing *unfractionated heparin*:

1.) Calculate the number of units of heparin given in last 3 hours. Note time last heparin dose given from current time to work out the dose of protamine per 100 units of heparin

Time from last **heparin** dose	Dose protamine for each 100 units of heparin (max 50mg protamine)
Less than 30 minutes	1mg protamine per 100 units
30-60 minutes	0.75mg protamine per 100 units
61-120 minutes	0.5mg protamine per 100 units
Over 120 minutes	0.25mg protamine per 100 units

Reversing *low molecular weight heparin (enoxaparin)*:

1.) Calculate the amount of enoxaparin given in last 24 hours.

Time from last **enoxaparin** dose	Dose protamine for each 1mg of enoxaparin (max 50mg protamine)
Less than 8 hours	1mg protamine per 1mg enoxaparin
8 hours or over	0.5mg protamine per 1mg enoxaparin

Maximum dose protamine 50mg regardless of heparin or enoxaparin given

Storage

Store at room temperature

Preparation/ Dilution

Can be given undiluted. If dilution needed to ease administration, use sodium chloride 0.9%.

Route of Administration

Central Preferred (only give peripherally if central access not available)

Rate of Administration

Slow IV injection over 10 minutes.

Stability

Use immediately - assign expiry of 1 hour on IV additive label.

Flushes

Sodium chloride 0.9%.

Common Compatibilities at Terminal Y-site

IV maintenance fluids containing sodium chloride or glucose, with or without potassium chloride.

PROTAMINE Injection for Anti-Coagulation Reversal

Monitoring/ Other comments

Anaphylaxis has been reported with protamine administration- there is a greater risk of this in patients who have hypersensitivity reactions to fish or shellfish.
Hypotension, bradycardia and flushing are signs that the injection is being given too quickly- if this occurs give the injection over 20-30 minutes.
Heparin has a shorter half-life therefore less protamine is required as time from last heparin dose increases.

Extravasation Risk

Extreme of pH	Hyperosmolar	Vasoactive	Vesicant
Yes- 2.5-3.5	No- 290	No	No

Calculation example

4 kg patient has mistakenly received 100units/kg/hour for last 4 hours. Heparin infusion was stopped 40 minutes previous when pump checked. Protamine is required.

Amount of heparin in last 3 hours = 4 x 100 units x 2.3 hours = 920 units
30-60 minutes lapsed since heparin last given therefore 0.75mg of protamine per 100 units heparin needed = 9.2 x 0.75mg = 7mg protamine

Prescribe on once only section of drug chart as protamine 7mg IV.

To prepare:
Draw 0.7ml protamine 10mg in 1ml solution into syringe and make up to 3ml. Label as per trust policy and give over at least 10 minutes.

Argatroban Standard operating procedure

Indication

- Argatroban is a direct thrombin inhibitor delivered as an infusion that is used as anticoagulation in patients with heparin induced thrombocytopenia.
- It has hepatic metabolism so is beneficial for patients with heparin induced thrombocytopenia with renal impairment
- Argatroban should only be prescribed after discussion with consultant haematologist
- Full anticoagulation should be considered for all patients diagnosed with heparin induced thrombocytopenia whether any thrombosis is present or not.

Drug

Argatroban (exembol) is supplied as a concentrate. One 2.5 ml vial supplies 250mg Argatroban (250mg/2.5ml). This should be diluted to 1mg/ml concentration. It is suggested dilute one vial (2.5ml) in 250ml 0.9% sodium chloride or 5% glucose. When using the regime for critically ill patients 50mg (0.5ml) should be diluted to total volume 50ml in 0.9% sodium chloride or 5% glucose. The multidose vial can be pierced multiple times and stored at 25ºC for up to 28 days.

Dose

- Intravenous unfractionated heparin or subcutaneous low molecular weight heparin should be stopped prior to starting Argatroban
- A baseline APTT should be taken before Argatroban infusion is commenced
- Standard dose 2 micrograms/kg/minute
- Reduced dose of 0.5 micrograms/kg/minute in those who are critically ill, post cardiac surgery or have moderate liver impairment (Child-Pugh Class B)

Initial intravenous infusion rates are detailed in table below:

	STANDARD 2 microgram/kg/min	CRITICALLY ILL/HEPATIC IMPAIRMENT 0.5 microgram/kg/min
Body weight (kg)	Rate (ml/hr)	Rate (ml/hr)
50-59	6	1.5
60-69	7	1.8
70-79	8	2.1
80-89	10	2.4
90-99	11	2.7
100-109	12	3.0
110-119	13	3.3
120-129	14	3.6
130-139	16	3.9
140-149	17	4.2

Monitoring

- Check baseline APTT
- Check APTT after initiation/changes at the following frequencies
  - STANDARD – after 2 hours
  - CRITICALLY ILL/HEPATIC IMPAIRMENT – after 4 hours
- Target APTT ratio 1.5-3.0
- Once APTT within target on two occasions monitor daily

Dose modification

If APTT less than 1.5 infusion rate should be increased:

-STANDARD – increase by 0.5 microgram/kg/min

-CRITICALLY ILL/HEPATIC IMPAIRMENT – increase by 0.1 microgram/kg/min

Maximum rate is 10 microgram/kg/minute. Infusion rate changes shown below:

Body weight	STANDARD Rate increase (ml/hour)	CRITICALLY ILL/ HEPATIC IMPAIRMENT Rate increase (ml/hour)	MAXIMUM RATE (ml/hour)
50-59	1.5	0.3	30
60-69	1.8	0.35	36
70-79	2.1	0.4	42
80-89	2.4	0.5	48
90-99	2.7	0.55	54
100-109	3.0	0.6	60
110-119	3.3	0.65	66
120-129	3.6	0.7	72
130-139	3.9	0.8	78
140-149	4.2	0.85	84

If APTT is above 3.0 then stop infusion until APTT 1.5-3.0 and restart infusion at half previous rate.

Over anti-coagulation

If excess bleeding, stop infusion, check APTT. No antidote is available but Argatroban has short half-life and APTT should normalise within 2-4 hours.

Warfarin

Warfarin can be started once platelets in normal range. Dose should be expected maintenance dose. As Argatroban can also prolong the INR both warfarin and Argatroban should be given for at least 5 days and Argatroban stopped when INR is above 4 for two days. If INR is above 5, stop Argatroban for 4 hours and check the APTT.

Use to stop clotting of circuit during dialysis

If using Argatroban to cover haemodialysis, a bolus dose of 250 microgram/kg should be given, followed by infusion of 2 microgram/kg/min. Stop infusion one hour before end of dialysis.

References

- Mitsubishi Pharma Europe. *Summary of Product Characteristics: Exembol 100mg/ml concentrate for solution for infusion.* http://www.medicines.org.uk/emc/medicine/26622 Accessed 5/6/2015
- Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin induced thrombocytopenia: second edition. British Journal of haematology 2012; 159(5): 528-540