Intensive Care Unit
Standard Operating Procedure

Thromboprophylaxis in Intensive Care

Intensive Care BELFAST

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Contents

1. Key Points

- **All** patients admitted to the Intensive Care (ICU) are considered at **high risk for venous thromboembolism** (VTE) and must have both a VTE, as well as bleeding, risk assessment completed on admission.
- Deep vein thrombosis (DVT) is extremely common in ICU patients. This is important to prevent as it can lead to a Pulmonary Embolus (PE), a potentially fatal complication and a major cause of in-hospital death.
- **Contra-indications to pharmacological thromboprophylaxis must be assessed on admission**, particularly those with active bleeding, intracranial bleeding, thrombocytopenia (platelets <75 x 10^9) or those with a planned surgical procedure in the next 6 hours. If contra-indicated, two forms of mechanical prophylaxis should be administered.
- **Pharmacological prophylaxis** is **SUPERIOR** to mechanical methods for preventing DVT. Combining these methods together has been shown to reduce the incidence of DVT [1].
- Patients admitted to ICU who do not have increased bleeding risk or contra-indications should receive pharmacological VTE prophylaxis in the form of Low Molecular Weight Heparin (LMWH) [2].
- VTE / bleeding risk should be assessed **DAILY** for every patient in ICU. Daily **TED removal** and **assessment of skin** integrity should form part of this assessment.
- VTE prophylaxis reduces but does NOT eliminate the risk of VTE entirely.
- The standard for ICU is **pharmacological prophylaxis with LMWH PLUS mechanical prophylaxis** with either Thromboembolic Deterrent Stockings (TEDs) or Sequential Compression Devices (SCDs) unless LMWH is contra-indicated.

  Recommendation:

  Enoxaparin **PLUS either** **(1) Thromboembolic Deterrent Stockings (TEDs)** OR

  (2) Sequential Compression Devices (SCDs)

- Dosing, prescribed at **22:00** once at night:

▪ Standard:	Enoxaparin 40mg
▪ Low body weight (< 40kg):	Enoxaparin 20mg
▪ Obesity (weight >100kg):	Enoxaparin 0.5mg/kg
▪ Renal impairment (eGFR <30):	Enoxaparin 20mg
▪ CRRT	Enoxaparin 20mg *(<80kg)* / 40mg *(>80kg)*

- **Trauma patients are at high risk of VTE.** The use of VTE prophylaxis is recommended in trauma patients, however a thorough **assessment of bleeding risk** must be incorporated into the decision making.
- **VTE prophylaxis in TBI is challenging.** An assessment and decision on the administration of pharmacological DVT prophylaxis should be performed **daily.**
- There is a **virtual haematology ward round** on MS **TEAMS Monday – Friday at 3pm** for haematology advice. Our haematology team are happy to be called at any time if there is any doubt regarding thromboprophylaxis or anticoagulation.

2. Background

Critically unwell patients are at high risk for VTE, therefore any patient admitted to intensive care unit should be deemed to be high risk. Several studies have demonstrated this. One prospective study found the incidence of DVT over the course of ICU admission was 9.6% [3].

Despite the administration of standard VTE prophylaxis, the incidence of DVT in ICU patients remains high [4]. One study found the incidence of DVT in high-risk ICU patients receiving VTE prophylaxis was 12% [5].

NICE recommend that all patients admitted to ICU should have VTE prophylaxis with LMWH unless contraindicated. All ICU patients should have a **daily risk assessment** for VTE, and bleeding risk performed.

3. VTE Risk Assessment

Major Risk Factors

- Critical illness (all ICU patients)
- Surgery and trauma
  - *major abdominal, pelvic, hip/knee replacements*
- Traumatic Brain Injury
- Sepsis
- Thrombophilia
  - *factor V Leiden mutation, antiphospholipid antibody syndrome, deficiency of antithrombin III, protein C or protein S, prothrombin gene mutation, hyperhomocysteinemia, high concentrations of factor VIII or XI, increased lipoprotein (a)*
- Obstetrics
  - *late pregnancy, Caesarean section, puerperium.*
- Prolonged immobility
- Age > 60 years
- Previous VTE
- Active cancer
- Lower limb paralysis / fractures

Minor Risk Factors

- Cardiovascular
  - *congenital heart disease, congestive heart failure*
- Oestrogens
  - *oral contraceptive pill, hormone replacement therapy (HRT)*
- Chronic Disease
  - *Chronic obstructive pulmonary disease (COPD) neurological disability, Inflammatory Bowel Disease (IBD), myeloproliferative disorder*
- Obesity

ICU Specific Risk Factors

- Acute Kidney Injury / Renal Replacement Therapies
- Platelet transfusion
- Central venous catheter (CVC) insertion
- Vasopressor use

4. Mechanical Thromboprophylaxis

Mechanical thromboprophylaxis can help to prevent DVT, however it is **not as effective as pharmacological thromboprophylaxis.** It should therefore be used in **combination** with pharmacological methods or when pharmacological methods are contra-indicated.

There are two main types of mechanical thromboprophylaxis:

1. **Thromboembolic Deterrent Stockings (TEDS)**

   - TEDs are tight stockings that are placed on patient's lower limbs. They are believed to prevent thrombosis by stimulating lower limb venous flow.

   - There is limited evidence for efficacy of TEDs, but systemic reviews have found they are better at reducing risk of DVT when compared to no thromboprophylaxis.

2. **Sequential Compression Devices (SCDs) or Intermittent pneumatic compression (IPC)**

   - SCDS are inflatable sleeves wrapped around the calves which inflate and compress at intervals to increase venous return. They prevent DVT by enhancing blood flow in the deep veins, thus preventing venous stasis. They also reduce plasminogen activator inhibitor-1 (PAI-1), thereby increasing fibrinolytic activity.

   - The evidence is slightly better for SCDs with several studies demonstrating their effectiveness in preventing DVT for immobilised patients. The UK multicentre trial 'CLOTS 3' assessed 2800 immobile patients who had suffered a stroke and compared treatment with SCDs to no SCDs. They found at 30 days a significant reduction in the rate of DVT in femoral and popliteal veins for the SCD group [6]. They reported skin injuries were reported in 3% in the SCD group compared with 1% in the group without. Another study compared SCDs with enoxaparin against enoxaparin only in critically unwell patients admitted to ICUs in Saudi Arabia, Canada, Australia, and India. They found no effect on the incidence of proximal DVTs using adjuvant SCDs, but also found no difference in number of patients with skin injuries [7].

Summary for Mechanical Thromboprophylaxis

Indications

- Use in combination with pharmacological thromboprophylaxis

  OR

- **2 methods** of mechanical thromboprophylaxis in patients with high bleeding risk in when pharmacological methods are contraindicated.

Contraindications:

- Leg ischaemia due to peripheral vascular disease
- Symptomatic peripheral vascular disease or clinical concern
- Bilateral leg trauma
- Skin, muscle, or bone grafting to lower limbs
- Major lower limb surgery
- Acute stroke (the use of TEDs is contraindicated as per NICE guidance [8])

Complications

- Skin breakdown* *(especially in frail patients).*

* Attention must be paid to the correct fitting of SCDs to avoid skin breakdown.

5. Pharmacological Thromboprophylaxis

Pharmacological prophylaxis is **superior** to mechanical prophylaxis. This has been demonstrated in many studies. A systemic review and meta-analysis of trials studying VTE in critically unwell patients found that any type of heparin thromboprophylaxis decreases DVT and PE in both medical and surgical critically ill patients [9].

ALL patients admitted to ICU are considered at high risk for DVT.

5.1 Prescription

- Pharmacological VTE prophylaxis should be prescribed for **ALL patients on admission**, unless contra-indicated due to risk of bleeding (see below).
- **Enoxaparin**, a low molecular weight heparin (LMWH), is used as pharmacological thromboprophylaxis within the Belfast HSCT.
- Prescribe for **22:00** once daily

NB: Enoxaparin is porcine derived so contraindicated for those individuals who would decline e.g. for religious reasons. Fondaparinux 2.5mg SC daily is an alternative.

5.2 Dosing

Normal renal function

- Standard:	**Enoxaparin 40mg**
- Low body weight (< 40kg):	Enoxaparin 20m
- Obesity (actual body *weight > 100kg*):	Enoxaparin 0.5mg/kg

Renal dysfunction

- Impaired renal function (*eGFR < 30*):	Enoxaparin 20mg
- On CRRT:	
weight < 80kg	Enoxaparin 20mg
weight > 80kg	Enoxaparin 40mg

Dosing should be reviewed **daily** with consideration to changing renal function and urine output.

5.3 Duration

- VTE prophylaxis should be continued until the patient is **fully ambulatory** or **discharged** from hospital.

5.4 Monitoring

Anti-factor Xa levels

- **NOT recommended** when prescribing LMWH as **thromboprophylaxis** [10].
- An Anti-factor Xa level should ONLY be sent for patients receiving therapeutic LMWH.
- An Anti-factor Xa level should be taken following at least 3 doses to allow levels to stabilise
- Anti-factor Xa level should be sent **4 hours after** the last dose of LMWH is administered (i.e. send at 0200 when a prophylactic dose was given at 22:00).
- The therapeutic range for twice daily Enoxaparin is **typically 0.5-1.0 iu/ml.**

Renal dysfunction

- The American Society of Haematology (ASH) 2018 guidance suggests **against** using anti-factor Xa monitoring to guide LMWH dose adjustments due to low certainty in evidence.

- The ASH recommend using **dose adjusted** for renal function or switching to alternative anticoagulant with lower renal clearance (e.g unfractionated heparin) [10].

Obesity

- The ASH 2018 guidance suggest **against** using anti-factor Xa monitoring but to consider LMWH dosing based on **actual body weight** (ABW) [10]

- No maximal body weight for dosing has been set.

5.5 Contraindications to pharmacological thromboprophylaxis

Active or suspected active bleeding *(e.g., gastrointestinal, intracranial haemorrhage, trauma etc)*

Bleeding risk

- Thrombocytopenia* *(NICE guidance states a platelet count* ***< 75 x 10^9/L*** *however this is not specific to a critical care population. Given the higher risk in this population a lower threshold of* ***< 50 x 10^9 /L*** *may be more appropriate)*
- Severe coagulopathy
- Untreated inherited or acquired bleeding disorders *(e.g., traumatic coagulopathy, decompensated liver failure etc)*

**It may be acceptable to administer LMWH where platelet counts are less than 75 x 10^9/L. This must be directed by senior members of the medical team / following haematology advice.*

Full anticoagulation

- Heparin infusion with a therapeutic APTT
- On warfarin in whom the INR is therapeutic

Neurosurgical

- Patients admitted immediately post-neurosurgery with an External Ventricular Drain (EVD) or intracranial pressure (ICP) monitor in situ.
- Traumatic Brain Injury *(requires* ***discussion*** *with neurosurgical team – see section below)*
- Post spinal surgery *(requires* ***discussion*** *with spinal surgical team)*

Heparin Induced Thrombocytopenic (HIT) – *see section below*

Neuraxial procedure / Intervention

- Lumbar puncture/epidural/spinal expected **within the next 12 hours**
- Lumbar puncture/epidural/spinal anaesthesia within **previous 4 hours**
- Spinal epidural placement or removal *

**Placing or Removing epidural should be done 12 hours prior to next dose of LMWH. Once epidural removed, hold next dose of LMWH until > 4 hours post removal.*

6. Specific Patient Cohorts

6.1 Trauma

Trauma patients are at high risk of VTE. Depending on the severity of the injuries, these patients can have coagulation abnormalities, prolonged immobility, major surgery and are often critically unwell, all leading to increased VTE risk.

Traumatic injury has been shown to cause decreased level of functional protein C and abnormal antithrombin levels, leading to a prothrombotic state. Estimates of incidence vary amongst studies. A systemic review reported a 12% overall incidence of VTE in trauma patients not receiving prophylaxis and 7% for those receiving mechanical prophylaxis only [11]. Thromboprophylaxis has been shown to reduce the risk of DVT in trauma patients with LMWH being more effective than mechanical methods alone [11].

The use of VTE prophylaxis is recommended in trauma patients, however a thorough **assessment of bleeding risk** must be incorporated into the decision making.

The approach to VTE prophylaxis in trauma patients is difficult, ill-defined and depends greatly on severity of injuries, planned surgical procedures and risk of bleeding. However, given that this population is at high risk for VTE, severely injured patients should receive early VTE prophylaxis.

Risk factors for VTE in trauma patients:

- Spinal cord injury
- Head trauma
- Lower extremity fracture
- Pelvis fracture
- Surgical intervention
- Increased age
- Femoral vein line insertion
- Surgical repair venous injuries
- Prolonged immobilisation / hospital stay
- High injury severity score

Recommendations in Trauma:

- Low bleeding risk: **Combined prophylaxis** with LMWH PLUS mechanical prophylaxis *(unless contra-indicated*)*
- High bleeding risk: **LWMH is contra-indicated**. Mechanical prophylaxis should be used alone being better than no prophylaxis.

*Care must be taken with mechanical prophylaxis in trauma patients. Mechanical prophylaxis is contra-indicated if lower extremity fractures or ischaemia is present.

6.2 Traumatic Brain Injury

VTE prophylaxis in TBI is challenging. Pharmacological thromboprophylaxis carries the risk of worsening even minor intracranial bleeds which may be devastating. The Brain Trauma Foundation Guidelines for DVT prophylaxis in severe TBI advise a level 3 recommendation *(i.e. insufficient evidence for level 1 or 2)* of combined pharmacological with mechanical prophylaxis [12].

Given the risk for expansion of intracranial haemorrhage, it is recommended to commence mechanical prophylaxis *(TEDs or SCDs)* in the first instance and discuss with neurosurgery (+/- consider interval CT imaging) to guide a decision on the timing of pharmacological prophylaxis commencement.

There is limited evidence to recommend the optimal timing for pharmacological prophylaxis. One systemic review from 2020 found that early pharmacological prophylaxis within 72 hours in patients who had stable repeat CT scans was associated with reduced VTE incidence and no worsening of intracranial haemorrhage [13].

Given a lack of evidence, pharmacological prophylaxis should be commenced on a **case-by-case basis**, under advice from a **senior neurosurgeon** and only once the **benefit of DVT prophylaxis outweighs the risk** of further intracranial haemorrhage.

An assessment and decision on the administration of pharmacological DVT prophylaxis should be performed daily. The outcome must be documented clearly in the electronic patient record.

Recommendations in TBI

- Commence mechanical prophylaxis (SCDs / TEDs)
- A **daily risk assessment** should be carried out. A decision to commence or withhold pharmacological prophylaxis must be documented.
- LMWH prophylaxis should ONLY be commenced in these patients under the advice from a senior neurosurgeon. A brain injury should be deemed stable, and the benefit of pharmacological prophylaxis is considered to outweigh the risk.

7. Heparin Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) is a potentially fatal pro-thrombotic complication of heparin use that occurs in 5% of patients. It is caused by an autoantibody (HIT antibody) which is directed against platelet factor 4 (PF4) complexed with heparin. This causes platelet activation and leads to an extremely **high risk for thrombosis**. Although rare, it has a **high mortality** rate. The risk of HIT is lower with LMWH than with unfractionated heparin (UFH). Cohorts that carry the greatest risk of HIT include cardiac, renal and trauma patients.

Clinical features include

- **Thrombocytopenia** *(90% patients)*
- **Thrombosis** *(50% patients)*
- **Anaphylaxis-like reaction**

7.1 Diagnosis

The diagnosis of HIT involves the following:

1. **Clinical scoring system** (4Ts score)
2. **Laboratory testing** (HIT antibody ELISA +/- functional assay).

**The laboratory will NOT process this if a HIT score is not provided. If score 4 or more it will process between the hours of 9 am and 4pm.*

4 Ts Scoring System

This is a clinical scoring system used to determine the **probability** of a patient having HIT [14, 15]. A score of 0 - 3 points give a low probability of HIT (<1%), 4 - 5 points intermediate probability (10%) and 6 - 8 points a high probability.

Clinical Feature			Points
1. Thrombocytopenia			
- Plt count drop > 50%	**AND**	Plt nadir > 20,000	**2**
- Plt count drop 30-50%	*OR*	Plt nadir 10,000 -19,000	**1**
- Plt count drop < 30%	*OR*	Plt nadir < 10,000	**0**
2. Timing of onset of Platelet count drop after heparin exposure (days)			
- Clear onset 5-10 days OR 1 day if exposure within past 5 to 30 day			**2**
- Probably 5 to 10 days OR > 10 days OR < 1 day if exposure within past 31 to 100 days			**1**
- < 4 days without exposure within past 100 days			**0**
3. Thrombosis / other sequelae			
- Confirmed new thrombosis OR skin necrosis, anaphylactoid reaction, adrenal haemorrhage.			**2**
- Suspected, progressive or recurrent thrombosis, skin erythema			**1**
- None			**0**
4. Alternative Cause for thrombocytopenia			
- None			**2**
- Possible (sepsis)			**1**
- Probable (DIC, medications, within 72 hours of surgery)			**0**

Laboratory testing (HIT antibody test)

1. Immunoassay (ELISA) – this is reported in optical density (OD units).

OD < 0.6	= Low probability
OD 0.6 – 1.99	= Indeterminate results -> request functional HIT assay
OD >2 or > 1.5 PLUS high 4Ts score	= **HIT confirmed**

2. Functional assay – this is reported as negative or positive.

7.2 Management

If 4Ts score is **low probability**:

- DO NOT order a HIT antibody testing
- Continue heparin (unless already discontinued due to thrombocytopenia) and evaluate for other causes of thrombocytopenia

If 4Ts score is **intermediate or high probability**

- STOP HEPARIN
- Discuss anticoagulation with haematology (options include Fondaparinux or Argatroban).
- Request a HIT antibody test

Treatment goals:

1. **Stop platelet activation** as soon as possible

   - If intermediate/ high probability of HIT, immediately stop heparin.
   - Heparin should be stopped. Patients can be re-challenged with heparin over 90 days; however this should be discussed with haematology.

2. **Anticoagulate with non-heparin anticoagulant**

   - Options include Argatroban, Bivalirudin, Danaparoid or Fondaparinux.
   - The 2018 American Society of Haematology guidelines suggest the use of fondaparinux for suspected or confirmed HIT [15].
   - DOACs can be used, however the evidence is not well established.

Recommendations for suspected HIT

1. If there is a clinical suspicion (i.e. thrombocytopenia, thrombosis) = Calculate the **4Ts score**
2. If HIT suspected based on the 4Ts score (intermediate / high probability with score >4) = **STOP HEPARIN** and discuss further testing and management with haematology. Contact the coagulation team through the **haemophilia centre ext. 40444.**
3. Testing for HIT antibody includes ELISA and functional assay. This should ONLY be done when there is a high clinical suspicion of HIT (4Ts score > 4).
4. The choice of anti-coagulation treatment should be discussed with haematology.

8. When to discuss VTE thromboprophylaxis with haematology?

There is a virtual haematology ward round on **TEAMS Monday – Friday at 3pm** for haematology advice.

Our haematology team are happy to be called at any time if there is any doubt regarding thromboprophylaxis or anticoagulation. However, the following should warrant discussion with haematology:

- Severe coagulopathy
- Suspected or confirmed Disseminated Intravascular Coagulation (DIC)
- Severe thrombocytopenia
- Inherited Thrombophilia Disorder
- Suspected HIT (4Ts score is intermediate or high probability)
- Confirmed HIT (HIT antibody test positive)

8.1 Links

Link to BHSCT VTE guidelines:
https://bhsct.sharepoint.com/sites/Policies/PolicyLibrary/Forms/AllItems.aspx?id=%2Fsites%2FPolicies%2FPolicyLibrary%2FVenous thromboembolism in over 16s - Reducing the risk of Hospital acquired deep vein thrombosis or pulmonary embolism%2Epdf&parent=%2Fsites%2FPolicies%2FPolicyLibrary

Link to MS Teams Haematology ward round:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_ODNhNjBmYmItMjUwMi00NTBkLTg2ZWUtZTY2NDk1MTEzMjJh%40thread.v2/0?context=%7b%22Tid%22%3a%229c9a30de-d8d7-4aa4-9600-4be7625ff6c5%22%2c%22Oid%22%3a%22b9e42a26-9897-4365-84e7-55e41b111441%22%7d

9. Abbreviations

VTE	**Venous thromboembolism**
DVT	**Deep Vein Thrombosis**
PE	**Pulmonary Embolus**
LMWH	**Low Molecular Weight Heparin**
UFH	**Unfractionated Heparin**
TEDs	**Thromboembolic Deterrent Stockings**
SCDs	**Sequential Compression Devices**
CRRT	**Continuous Renal Replacement Therapy**
HIT	**Heparin Induced Thrombocytopenia**

10. References

1. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD005258. doi: 10.1002/14651858.CD005258.pub2. PMID: 18843686.
2. https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-admitted-to-critical-care
3. Cook D, Crowther M, Meade M, Rabbat C, Griffith L, Schiff D, Geerts W, Guyatt G. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med. 2005 Jul;33(7):1565-71. doi: 10.1097/01.ccm.0000171207.95319.b2. PMID: 16003063.
4. Khouli H, Shapiro J, Pham VP, Arfaei A, Esan O, Jean R, Homel P. Efficacy of deep venous thrombosis prophylaxis in the medical intensive care unit. J Intensive Care Med. 2006 Nov-Dec;21(6):352-8. doi: 10.1177/0885066606292880. PMID: 17095499.
5. Paul E. Marik MD, Lynn Andrews RVT, Baltej Maini MD. The incidence of deep venous thrombosis in ICU patients. Chest, Vol 111, Issue 3. March1997. 661-664. https://doi.org/10.1378/chest.111.3.661
6. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. The Lancet, Volume 382, Issue 9891, 516 – 524
7. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. https://www.nejm.org/doi/full/10.1056/NEJMoa1816150
8. https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-acute-coronary-syndromes-or-acute-stroke-or-for-acutely-ill-patients
9. Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013 Sep;41(9):2088-98. doi: 10.1097/CCM.0b013e31828cf104. PMID: 23782973.
10. Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, Shehab N, Mock J, Myers T, Dentali F, Crowther MA, Agarwal A, Bhatt M, Khatib R, Riva JJ, Zhang Y, Guyatt G. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 Nov 27;2(22):3257-3291. doi: 10.1182/bloodadvances.2018024893. PMID: 30482765; PMCID: PMC6258922.
11. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. Cochrane Database Syst Rev. 2013 Mar 28;(3):CD008303. doi: 10.1002/14651858.CD008303.pub2. PMID: 23543562.
12. https://braintrauma.org/guidelines/guidelines-for-the-management-of-severe-tbi-4th-ed#/:guideline/10-deep-vein-thrombosis-prophylaxis
13. Spano PJ 2nd, Shaikh S, Boneva D, Hai S, McKenney M, Elkbuli A. Anticoagulant chemoprophylaxis in patients with traumatic brain injuries: A systematic review. J Trauma Acute Care Surg. 2020 Mar;88(3):454-460. doi: 10.1097/TA.0000000000002580. PMID: 31923051.
14. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006 Apr;4(4):759-65. doi: 10.1111/j.1538-7836.2006.01787. x. PMID: 16634744.
15. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, Linkins LA, Rodner SB, Selleng S, Warkentin TE, Wex A, Mustafa RA, Morgan RL, Santesso N. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018 Nov 27;2(22):3360-3392. doi: 10.1182/bloodadvances.2018024489. PMID: 30482768; PMCID: PMC6258919.