How to approach acute thrombosis and thrombocytopenia

Authors: Jeremy Schofield[A] and Cheng-Hock Toh[B]

ABSTRACT

Acute thrombosis and thrombocytopenia pose challenges to the clinician. Thrombocytopenia is naturally viewed as a risk factor for bleeding, and an association with acute thrombosis appears paradoxical. It presents typically as a medical emergency and requires treatment to be started before having confirmatory results. This review supports the attending clinician to recognise and manage conditions that are part of the thrombotic thrombocytopenic syndrome through four illustrative clinical cases. Common themes linking the underlying pathology and treatment are explored to highlight the continued relevance of this rare, but often devastating, presentation.

KEYWORDS: acute thrombosis and thrombocytopenia, thrombotic thrombocytopenic syndrome, thrombosis, thrombocytopenia

DOI: 10.7861/clinmed2023-0076

Introduction

The simultaneous presentation of acute thrombosis and thrombocytopenia is typically challenging to the attending clinician. Thrombocytopenia is naturally viewed as a risk factor for bleeding, especially when severe, and an association with acute thrombosis appears paradoxical. Additionally, acute thrombosis with acute thrombocytopenia is often a medical emergency requiring urgent treatment when results indicating its aetiology are often unclear.

The description of vaccine-induced immune thrombotic thrombocytopenia (VITT) following coronavirus disease 2019 (COVID-19) vaccination has highlighted the need to better recognise the spectrum of disorders associated with acute thrombosis and thrombocytopenia. Grouping these conditions as part of the thrombotic thrombocytopenic syndrome (TTS) might help in broadening understanding of, for example, their epidemiology and possible shared mechanisms; however, recognising their heterogeneity in requiring condition-specific management is also important because of the different biological triggering factors. This potential need for tailored management highlights the importance of getting the diagnosis right first time.

Authors: [A]academic clinical fellow, University of Liverpool, Liverpool, UK; [B]professor of haematology, University of Liverpool, Liverpool, UK, and consultant in haematology, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

This review aims to help the attending clinician make timely decisions in investigating and treating thrombosis and thrombocytopenia in the acute setting. Exemplar cases of TTS are described, although not all TTS conditions can be comprehensively reviewed here. TTS is defined by the Brighton Collaboration as the presence of thrombocytopenia ($<150 \times 10^9$/L) and confirmed macrovascular thrombosis.[1] Although sometimes considered interchangeably with VITT, TTS is distinct in not requiring the presence of anti-platelet factor 4 (PF4) antibodies.[2] Conditions that have been so classified include heparin-induced thrombocytopenia (HIT), VITT, cancer-associated thrombosis and thrombocytopenia (CATT), catastrophic antiphospholipid syndrome (CAPS) and disseminated intravascular coagulopathy (DIC).[3] Specifically for this article, the focus is on thrombotic events that can be radiologically confirmed (ie venous and arterial thromboembolism). Conversely, microvascular occlusive disorders that are distinct in causing microangiopathic haemolytic anaemia are not discussed here because they have a different pathogenesis. These conditions, such as thrombotic thrombocytopenic purpura (TTP), are managed differently and are well reviewed elsewhere.[4]

Thrombotic thrombocytopenic syndrome and exemplar clinical cases

The thrombotic and thrombocytopenic phenotype can be coincidental, such as in a patient whose thrombocytopenia is caused by chronic liver disease who develops thrombosis, or connected, as in VITT. Although coincidental TTS can carry an increased risk of thrombosis, such as immune thrombocytopenic purpura (ITP), they are not as strongly associated.[5] Four cases of related TTS that typically present acutely to the physician are discussed here and, although the individual conditions are thoroughly reviewed elsewhere, their collective presentation here is to better guide the attending clinician to differentiate and quickly orientate. DIC will not be discussed in detail because it characteristically results in microvascular as opposed to macrovascular occlusion.[6]

Case 1

Clinical

A 52-year-old woman presented to the emergency department with progressive breathlessness and lethargy. She was also experiencing chest pain, bilateral leg swelling and fevers. Three weeks previously, she had started taking lenvatinib for poorly differentiated thyroid cancer. Blood tests revealed a haemoglobin of 74 g/L (118–148 g/L), MCV 90 fL (80–100 fL) and platelets

32×10^9/L ($150–400 \times 10^9$/L). Her fibrinogen was 2.6 g/L (1.5–3.5 g/L), and the prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 10.4 s (9.0–12.7 s) and 28.8 s (20.5–33.4 s), respectively. Computed tomography (CT) pulmonary angiography confirmed a pulmonary embolism.

Aetiology

Cancer increases the risk of thrombosis and is the second most common cause of death in this patient cohort.[7] The aetiology of thrombosis and thrombocytopenia in a patient with cancer is multifactorial, which can be secondary to the disease, compression of local vascular structures or iatrogenic, such as central venous catheters (CVC) or chemotherapy. Thrombocytopenia might result from cancer invading the marrow, causing myelophthisis, or be iatrogenic from chemotherapy. Severe thrombocytopenia (platelets $<50 \times 10^9$/L) occurs in 11.2%, 10.6%, and 5.2% of those receiving gemcitabine, platinum and anthracycline-based regimes, respectively.[8] Post chemotherapy, platelets fall by day 7, reaching their nadir by day 14 and return to baseline by days 28–35.[8] Nutritional deficiencies, such as vitamin B12 and folate, should be considered.

There is a growing appreciation for the role of neutrophils in cancer-induced thrombosis. Cancer contributes to neutrophilia mainly through increased haematopoietic growth factors, such as granulocyte-colony stimulating factor (G-CSF).[9] Additionally, cancers can sensitise neutrophils to release neutrophil extracellular traps (NETs)[10] and patients with higher NET formation biomarkers have higher venous thromboembolism (VTE) rates.[11]

Diagnosis and management

It is recommended to treat cancer-associated thrombosis with a direct oral anticoagulant (DOAC) unless there are contraindications related to drug interactions or bleeding risk.[12] Given the potential increased bleeding risk of thrombocytopenia and use of DOACs in specific malignancies, low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) are recommended in this setting.[13]

Evidence suggests that therapeutic anticoagulation is generally safe when the platelet count is $>50 \times 10^9$/L.[14] When the platelet count is $<50 \times 10^9$/L, options include continuing therapeutic anticoagulation, provided there are no contraindications, with concurrent platelet transfusion to maintain a platelet count of $>50 \times 10^9$/L or dose-adjusted anticoagulation.[15] The International Society on Thrombosis and Haemostasis (ISTH) recommends using therapeutic anticoagulation with platelet transfusion where there is a higher risk of thrombus progression, whereas intermediate-dose anticoagulation can be given if there is a lower thrombus progression risk[13] (Table 1).

Inferior vena cava (IVC) filters are controversial in CATT; there is no proven mortality benefit and the risk of deep venous thrombosis (DVT) is increased twofold.[16] Therefore, IVC filters should only be considered in patients with an absolute contraindication to anticoagulation. Only retrievable IVC filters should be used with a planned retrieval date, and anticoagulation should be resumed at the earliest opportunity.

Case 2

Clinical

A 49-year-old man underwent surgical aortic valve replacement for severe aortic stenosis. He received cardiopulmonary bypass with UFH. He developed thrombocytopenia on day 8 (platelet count 22×10^9/L). Bilateral ultrasound doppler showed a proximal left lower limb DVT. A diagnosis of heparin-induced thrombocytopenia (HIT) was suspected and a 4Ts score showed high probability.

Aetiology

HIT is a prothrombotic state with high morbidity and mortality. Left untreated, thrombosis occurs in 50% of patients with HIT.[17] The incidence of HIT can be as high as 7% in specific patient groups receiving heparin.[18] Significant risk factors include surgical rather than medical patients, UFH as opposed to LMWH and treatment doses over prophylactic doses.[19,20]

Many patients have detectable anti-PF4/heparin antibodies (HIT antibodies) despite not developing clinical HIT. In a study of UFH use in cardiac surgery, 50% of patients developed HIT antibodies, but only 2% had clinical HIT.[21] Although the reason for this disparity is unknown, it highlights the need to avoid unrestricted HIT immunoassays as an initial screening test.

The pathogenesis originates from the heparin/PF4/IgG anti-PF4 antibody complex[22] and is unique in its absence of a primary IgM response.[23] Heparin complexes with PF4 and induces its conformational change. IgG antibodies are developed against, and bind to, this neoantigen, which activates platelets through the Fc gamma receptor IIA (FcγRIIa).[24]

Emerging evidence suggests that thrombocytopenia and thrombosis are separate entities. Thrombocytopenia results

Table 1. Treatment of acute cancer-associated thrombosis and thrombocytopenia

	High risk of progression: symptomatic segmental or more proximal PE, DVT, or a history of or recurrent/progressive thrombosis	**Low risk of progression: distal DVT, incidental subsegmental PE, catheter-related thrombosis, or other lower risk features**
Platelet count $>50 \times 10^9$/L	Treatment dose anticoagulation (LMWH)	Treatment dose anticoagulation (LMWH)
Platelet count $25–50 \times 10^9$/L	Therapeutic anticoagulation (LMWH or UFH) and platelet transfusions to maintain platelets $>40–50 \times 10^9$/L	Anticoagulate (LMWH or UFH) at 50% of therapeutic dose or prophylactic dose
Platelet count $<25 \times 10^9$/L	Therapeutic anticoagulation (LMWH or UFH) and platelet transfusions to maintain platelets $>40–50 \times 10^9$/L	Discontinue anticoagulation and review once platelet count $>25 \times 10^9$/L

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin.

Adapted from Brunson *et al.*[16]

from macrophage removal of immune complex-bound platelets, whereas thrombosis occurs through neutrophil activation to form NETs.[25] This might explain why heparin can occasionally induce transient thrombocytopenia without thrombosis.

Diagnosis and management

Given the urgency of starting treatment and the laboratory delay in obtaining immunoassay HIT results, treatment should be started based on the screening 4Ts HIT score.[26] Patients scoring 0–3 have a very low chance of positive clinical antibodies (0.8%), whereas scoring 4 or 5 or 6–8 equates to a positive clinical antibody risk of 11% and 34%, respectively.[26] Therefore, a 4Ts score of 0–3 can confidently exclude HIT without needing confirmatory tests, although a change in clinical circumstance should prompt reassessment.[27] Scoring 4–8 should be followed by a HIT immunoassay and treated as HIT until results are available. If the immunoassay is negative, heparin can be cautiously reintroduced as indicated[18] (Table 2).

Management involves stopping all heparin and changing to non-heparin anticoagulation. Non-heparin anticoagulants include argatroban, danaparoid, fondaparinux and DOACs.[18] In patients undergoing dialysis, argatroban or danaparoid should be considered.[28] In critically ill patients at risk of bleeding or who need urgent invasive procedures, argatroban might be preferred because of its shorter half-life. Although all DOACs might be suitable, a greater evidence base exists for rivaroxaban.[29] Given the risk of venous limb gangrene, vitamin K antagonists should be avoided until platelet recovery and, if currently being administered, should be reversed with vitamin K[30] (Box 1).

In patients with HIT without thrombosis, bilateral lower limb ultrasonography should be performed if this would change the duration of anticoagulation because of the significant risk of asymptomatic lower limb DVT.[18] This should be extended to include bilateral upper limb ultrasonography if a CVC is *in situ*.[31] Generally, platelet transfusions should be avoided because of the increased risk of arterial thrombus, unless there is bleeding or a need for high-risk procedures.[32]

Case 3

Clinical

A 53-year-old woman presented to the emergency department with a few days' history of worsening abdominal pain. She had a past medical history of systemic lupus erythematosus (SLE) with skin and joint manifestations, alongside laboratory evidence of a circulating lupus anticoagulant. On examination, her blood pressure was 193/96 mmHg; she had upper abdominal tenderness and bruises on her legs. Blood tests showed a haemoglobin of 100 g/L (118–148 g/L), platelets 8×10^9/L (150–400 $\times$ 10^9/L), PT 11.6 s (9.0–12.7 s), aPTT 42.8 s (20.5–33.4 s) and serum creatinine 158 µmol/L (67 µmol/L 4 weeks previously). A CT scan of abdomen demonstrated a splenic infarct secondary to thrombosis. Although initially thought to be concurrent ITP with acute thromboembolism, rapid deterioration in multi-system function led to a diagnosis of catastrophic antiphospholipid syndrome (CAPS).

Aetiology

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by clinical and laboratory criteria. It presents as either vascular thrombosis or pregnancy morbidity, with the requirement of either lupus anticoagulant or antiphospholipid (aPL) antibodies demonstrated on two occasions, at least 12 weeks apart.[33] A severe subtype of APS, known as CAPS, presents acutely with thrombotic storm and multiorgan dysfunction.[34] The incidence of CAPS among patients with APS is ~1% a year, with a mortality rate exceeding 50%.[35]

The pathogenesis of APS involves aPL antibodies binding to beta-2 glycoprotein 1. β_2GPI is postulated to have a role in haemostasis and complement regulation.[36] Infections are the primary trigger of aPL antibody generation. For example, it has been shown that S*treptococcus pyogenes* induces a

Table 2. 4Ts Score

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20×10^9/L	Platelet count fall 30–50% or platelet nadir 10–19×10^9/L	Platelet count fall <30% or platelet nadir <10×10^9/L
Timing of platelet count fall	Clear onset between day 5 and 10 or platelet fall ≤1 day (previous heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (eg missing platelet counts); onset after day 10; or fall ≤1 day (previous heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post-intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotising (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite
Scores	6–8: high risk of HIT; stop heparin and treat as HIT	4 or 5: intermediate risk of HIT; stop heparin and treat as HIT	0–3: low risk of HIT; consider alternative diagnosis

HIT = heparin-induced thrombocytopenia.

Adapted from Lo *et al*.[26]

Box 1. Management of heparin-induced thrombocytopenia

- Suspend all heparin. If on warfarin, reverse with vitamin K
- Start non-heparin anticoagulation; examples include
  - Argatroban
  - Danaparoid
  - Fondaparinux
  - Direct oral anticoagulants (consider argatroban or danaparoid in acutely unwell patients; they are given as an infusion, have a relatively short half-life and can be used in dialysis)
- Send for HIT immunoassay: if negative, consider restarting heparin and consider an alternative diagnosis
- Perform bilateral lower limb ultrasonography and upper limb ultrasonography, if central venous catheter is present
- Avoid platelet transfusions

Box 2. Diagnostic criteria for catastrophic antiphospholipid syndrome

Diagnostic criteria for catastrophic antiphospholipid syndrome (CAPS; adapted from Asherson *et al*[42]):

- Evidence of involvement of three organs, systems and/or tissues.
- Development of manifestations simultaneously or in less than 1 week.
- Laboratory confirmation of the presence of antiphospholipid (lupus anticoagulant and/or anticardiolipin and/or anti-β_2GPI antibodies) in titres >40 UI/l.
- Exclude other diagnosis.

Definite CAPS

- All four criteria.

Probable CAPS

- All four criteria, except for involvement of only two organs, systems and/or tissues
- All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart associable to the early death of a patient never tested for antiphospholipid before onset of CAPS
- 1, 2, and 4
- 1, 3, and 4, and development of a third event in >1 week but <1 month, despite anticoagulation treatment

conformational change in β_2GPI, resulting in the formation of anti-β_2GPI antibodies.[37] Anti-β_2GPI antibodies promote thrombosis by reducing activated protein C activity and activating complement.[38] aPL antibodies have been shown to cause NETosis, which contributes to thrombosis,[39] possibly through complement-dependent activation of neutrophils via C5aR1.[40]

The pathogenic model of CAPS is proposed to be a two-hit hypothesis. A study found that patients with CAPS had underlying mutations in the complement regulatory genes.[41] Whereas a complement-amplifying trigger might induce thrombosis in APS, the same trigger in predisposed individuals results in uncontrolled complement activation, leading to disseminated thrombosis in CAPS.[41]

Diagnosis and management

For a diagnosis of definite CAPS, all four diagnostic criteria are needed[42] (Box 2). This criterion has limited value in the acute setting when a patient is unlikely to fulfil the full diagnostic criteria before starting treatment. For example, histological diagnosis takes time and can carry an unacceptably high bleeding risk in the context of thrombocytopenia. For these reasons, it is recommended to treat empirically if there is a high index of suspicion.[43]

Treatment is based on anticoagulation and immune modulation. Anticoagulation (LMWH or UFH), glucocorticosteroids and either intravenous immunoglobulin (IVIG) or plasma exchange are recommended as first-line agents.[44] A precipitating factor was reported in 65% of events, with almost a half precipitated by infections, followed by malignancy, surgery and anticoagulation withdrawal.[45]

Case 4

Clinical

A 59-year-old man presented to the emergency department with a 8-day history of severe headache, associated with nausea and vomiting. He had no significant past medical history.
He had received his first ChAdOx-1 nCoV-19 vaccine 17 days previously. Initial CT imaging of his head was suspicious of a sinus venous thrombosis. This was subsequently confirmed with CT venography. Significant blood tests at presentation included: severe thrombocytopenia (platelets 41×10^9/L ($150–400\times10^9$/L)), mildly prolonged PT (14.7 s (9.0–12.7 s), aPTT 28.8 s (20.5–33.4 s)), mildly reduced fibrinogen (1.78 g/L) and a profoundly increased D-dimer of 97,635 ng/ml (<500 ng/ml). A presumptive diagnosis of VITT was made and confirmed with a PF4 enzyme-linked immunosorbent assay (ELISA), demonstrating a raised optical density (OD) of 2.75.

Aetiology

VITT is linked to the adenoviral Oxford-AstraZeneca and Johnson & Johnson COVID-19 vaccines. VITT incidence reduces with age, occurring in 1:50,000 in those <50 years and 1:100,000 in those >50 years. VITT occurs between days 5 and 30 post vaccine. It is primarily related to receiving the first dose, with a much lower incidence in second or subsequent doses.[46] There have been no confirmed case reports of VITT with the mRNA vaccines.[47]

VITT shares pathogenic similarities with HIT. VITT is associated with the development of IgG antibodies that bind to PF4 complexed platelets, causing platelet activation through FcγRIIa. Unlike HIT, this is independent of heparin and binds to a different location within the heparin-binding site.[48] Interestingly, heparin has been shown to inhibit formation of PF4/anti-PF4 immune complexes and promote their dissociation.[49] Together, the combination of PF4, anti-PF4 and activated platelets induces neutrophils to release NETs. The negatively charged DNA fibres within NETs bind the positively charged PF4, which acts as a reservoir for anti-PF4 antibodies to propagate the procoagulant response.[50]

Diagnosis and management

The diagnostic criteria of VITT have been set out by the UK Expert Haematology Panel.[51] Diagnostic criteria for VITT focus on five main criteria. A definite VITT fulfils all five criteria, whereas a probable VITT meets four criteria (with D-dimer >4,000 FEU) or if D-dimer is >2000 FEU and all other criteria are met (Box 3).

Box 3. Diagnostic criteria from the UK Expert Haematology Panel (adapted from Franchini *et al*[52])

- The onset of symptoms 5–30 days after vaccination against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (or ≤42 days in patients with isolated deep venous thrombosis or pulmonary embolism)
- Presence of thrombosis
- Thrombocytopenia (platelet count $<150 \times 10^9$/L)
- D-dimer level >4,000 FEU
- Positive anti- platelet factor 4 (PF4) antibodies on enzyme-linked immunosorbent assay (ELISA)

Treatment targets both the thrombosis and the VITT immune response.[52] Both venous and arterial thrombosis should be treated with anticoagulation and IVIG. Given its similarities with HIT, it has been hypothesised that heparin might worsen outcomes, although real-life data suggest that heparin exposure during VITT is not harmful.[46] Consideration should be given to using infusion-based treatment (argatroban or danaparoid) because of their relatively short half-life for urgent procedures or if bleeding occurs. At low platelet counts ($<30 \times 10^9$/L), the risk of bleeding increases. Guidance suggests considering argatroban at a therapeutic dose with platelet transfusion or using the reduced critical illness argatroban dose.[53] When using argatroban as anticoagulation treatment, switching to fondaparinux or a DOAC is suggested as soon as the bleeding risk has reduced. Where there is clinical deterioration despite first-line treatment, plasma exchange using fresh-frozen plasma should be considered, as well as high-dose steroids and rituximab[54] (Table 3).

Thrombotic thrombocytopenia syndrome and core approach

When encountering acute thrombosis with thrombocytopenia, the clinician must determine whether they are coincidental events, because the separate entities are not uncommon in clinical practice. The incidence of thrombosis increases with age and with increasing multi-morbidities.[55,56] Such patients might have other causes of thrombocytopenia, including from poly-pharmacy.[57] Equally, venous thromboembolism is not uncommon in pregnancy,[58] where there can be gestational thrombocytopenia.[59] It is essential to record a timeframe of events, whether this is duration of drug or vaccine exposure or historical platelet counts. The aetiology and management of a chronically falling platelet count in a patient with known cirrhosis will differ from an acute thrombocytopenia 7 days after heparin exposure. Whereas TTS as defined by the Brighton Collaboration requires platelets to be $<150 \times 10^9$/L, this will identify a significant proportion of coincidental TTS. A clinician should be particularly vigilant when the platelet count is $<100 \times 10^9$/L.

Fig 1 sets out these considerations and necessary investigations, which include confirming thrombocytopenia and excluding artefactual causes, such as platelet clumping. Supplementary tests can identify alternative causes of thrombocytopenia and should be required before starting treatment. Once TTS is suspected, confirmatory tests should be sent, and specific treatments started immediately in consultation with haematologists.

Discussion

Although these cases illustrate the different triggers for acute thrombotic thrombocytopenic problems, there are likely to be shared downstream mechanistic pathways. The observations suggest that there is more than just an overdrive in coagulation activation. First, thrombocytopenia is typically more severe than that following increased coagulation activation to generate thrombin, even when DIC is apparent. Second, thromboses often present in different vasculatures, (ie in both veins and arteries), thus suggesting a prominent role for platelet activation. Third, the immunologically driven cases are more rapidly catastrophic, with evidence of hypercytokinaemia to suggest coexisting systemic inflammation. In both HITT and VITT, there is added recruitment of signalling receptors, such as FcγRII, on platelets and leucocytes.[24,48] The additional contribution of neutrophils with increased NETosis might account for the rapid evolution and

Table 3. Management of vaccine-induced immune thrombotic thrombocytopenia

Acute treatment of VITT	
Anticoagulation:	Argatroban
	Danaparoid sodium
	Fondaparinux
	DOACs
	(where possible, avoid heparins; avoid using warfarin in patients with VITT until platelet count has returned to normal)
Immune modulation	IVIG dose 1 g/kg (consider second dose if inadequate response after 2 or 3 days)
Discuss need to transfer care	Consider need for on-site surgical specialities, such as neurosurgery
Fibrinogen	Keep fibrinogen >1.5 g/L; replace with either cryoprecipitate or fibrinogen concentrate
Platelets	Generally, avoid platelet transfusions
	Consider platelet transfusion if risk of bleeding is great, such as before to surgery or if 30×10^9/L to allow continued use of therapeutic dose argatroban

DOACs = direct oral anticoagulants; IVIG = intravenous immunoglobulin; VITT = vaccine-induced immune thrombotic thrombocytopenia.

Adapted from Cushman 2007.[55]

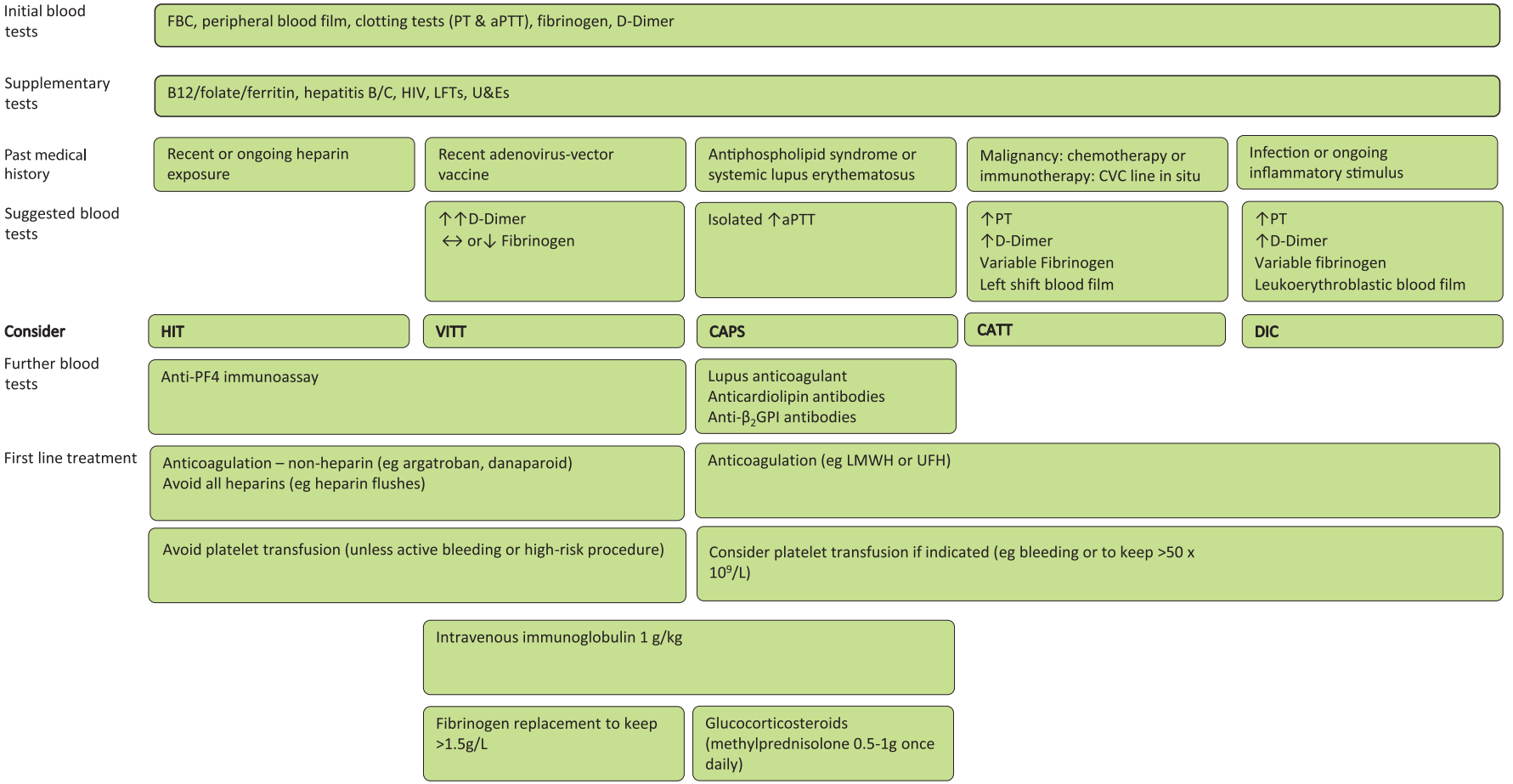

Fig 1. Initial diagnosis and management of thrombotic thrombocytopenia syndrome. aPTT = activated partial thromboplastin time; CAPS = catastrophic antiphospholipid syndrome; CATT = cancer-associated thrombosis and thrombocytopaenia; CVC = central venous catheter; DIC = disseminated intravascular coagulation; FBC = full blood count; HIT = heparin-induced thrombocytopaenia; HIV = human immunodeficiency virus; LFTs = liver function tests; PF4 = platelet factor 4; PT = prothrombin time; U&Es = urea and electrolytes; VITT = vaccine-induced immune thrombotic thrombocytopenia.

worsening thrombotic thrombocytopenic sequelae.[25,60] Of interest is the increasing recognition of NETs in the other causes of TTS (eg cancer and APS).[11,39] In SLE, anti-NETs antibodies have been described, which might interfere with dissolution and clearance of NETs.[61] Further research and understanding might pave the way for new treatments.

The common catastrophic pathway is likely to have some evolutionary reasoning in how host responses deal with biological alarm signals. For example, PF4 can electrostatically bind bacteria[62] and anti-PF4 antibodies could be a preserved antimicrobial immune response, which, in contemporary times, could also be unexpectedly triggered by heparin or adenoviral vector-based COVID-19 vaccines to cause an indiscriminate systemic immune response.[63] As demonstrated by VITT, clinicians need to be alert when presented with unexplained acute thrombosis and thrombocytopenia. Although there might be a move from adenoviral platforms in future vaccine development, the vector offers many advantages, which includes ease of manipulation and thermostability to allow for widespread distribution. Therefore, it is vital for further research into VITT to improve safety and build vaccine confidence.[50] Additionally, the recent case of VITT secondary to Gardasil 9 vaccination against the human papilloma virus, which comprises virus-like particles rather than adenoviral vectors, highlights the need for ongoing vigilance and awareness that VITT is not exclusive to the adenoviral vector-based COVID-19 vaccines.[64] Additionally, spontaneous HIT is becoming increasingly recognised from various triggers, including recently from post-total knee arthroplasty and post-bacterial infection.[65] Similar to VITT, there is a predilection toward unusual sites of thrombosis, including cerebral sinus thrombosis and arterial thrombosis. It is highly likely that further new triggers will emerge in time and, therefore, clinicians need to be vigilant and open-minded to diagnose and treat this life-threatening presentation. ■

Funding

This study is funded by the Liverpool University Hospitals NHS Foundation Trust (LUHFT) and the Department of Health and Social Care (DHSC), and is supported by the National Institute for Health Research (NIHR) (NIHR135073). The views expressed are those of the authors and not necessarily those of LUHFT, NIHR or the DHSC.

References

1 Chen R, Monash J. *Updated Brighton Collaboration case definition for Thrombosis with Thrombocytopenia Syndrome (TTS) 2021*. Decateur: Brighton Collaboration, 2021.
2 Makris M, Pavord S. Most cases of thrombosis and thrombocytopenia syndrome (TTS) post ChAdOx-1 nCov-19 are vaccine-induced immune thrombotic thrombocytopenia (VITT). *Lancet Reg Health Eur* 2021;12:100274.
3 Greinacher A, Langer F, Makris M *et al*. Vaccine-induced immune thrombotic thrombocytopenia (VITT): update on diagnosis and management considering different resources. *J Thromb Haemost* 2022;20:149–56.
4 Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood* 2017;129:2836–46.
5 Rodeghiero F. ITP and thrombosis: an intriguing association. *Blood Adv* 2017;1:2280.
6 Gando S, Levi M, Toh C-H. Disseminated intravascular coagulation. *Nat Rev Dis Primers* 2016;2:16037.
7 Cristinziano L, Modestino L, Antonelli A *et al*. Neutrophil extracellular traps in cancer. *Semin Cancer Biol* 2022;79:91–104.
8 Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park)* 2015;29:282–94.
9 Granger JM, Kontoyiannis DP. Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients. *Cancer* 2009;115:3919–23.
10 Demers M, Krause DS, Schatzberg D *et al*. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. *Proc Natl Acad Sci U S A* 2012;109:13076–81.
11 Mauracher LM, Posch F, Martinod K *et al*. Citrullinated histone H3, a biomarker of neutrophil extracellular trap formation, predicts the risk of venous thromboembolism in cancer patients. *J Thromb Haemost* 2018;16:508–18.
12 NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London: NICE, 2020.
13 Samuelson Bannow B, Lee A, Khorana A *et al*. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018;16:1246–9.
14 Khanal N, Bociek RG, Chen B *et al*. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. *Am J Hematol* 2016;91:E468–72.
15 Samuelson Bannow BR, Lee AY, Khorana AA *et al*. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: a systematic review. *Res Pract Thromb Haemost* 2018;2:664–9.
16 Brunson A, Ho G, White R, Wun T. Inferior vena cava filters in patients with cancer and venous thromboembolism (VTE) does not improve clinical outcomes: a population-based study. *Thromb Res* 2017;153:57–64.
17 Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med* 1996;101:502–7.
18 Cuker A, Arepally GM, Chong BH *et al*. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv* 2018;2:3360–92.
19 Smythe MA, Koerber JM, Mattson JC. The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. *Chest* 2007;131:1644–9.
20 Warkentin TE, Sheppard J-AI, Sigouin CS *et al*. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood* 2006;108:2937–41.
21 Warkentin TE, Sheppard JA, Horsewood P *et al*. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood* 2000;96:1703–8.
22 Arepally GM. Heparin-induced thrombocytopenia. *Blood* 2017;129:2864–72.
23 Greinacher A. Heparin-induced thrombocytopenia. *J Thromb Haemost* 2009;7:9–12.
24 Newman PM, Chong BH. Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4–heparin antibodies to platelets and the resultant platelet activation. *Blood* 2000;96:182–7.
25 Perdomo J, Leung HH, Ahmadi Z *et al*. Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia. *Nat Commun* 2019;10:1322.
26 Lo G, Juhl D, Warkentin T *et al*. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006;4:759–65.
27 Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood* 2012;120:4160–7.
28 Dutt T, Schulz M. Heparin-induced thrombocytopenia (HIT)-an overview: what does the nephrologist need to know and do? *Clin Kidney J* 2013;6:563–7.
29 Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood* 2017;130:1104–13.

30 Warkentin TE, Elavathil LJ, Hayward CP *et al*. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997;127:804–12.
31 Hong AP, Cook DJ, Sigouin CS, Warkentin TE. Central venous catheters and upper-extremity deep-vein thrombosis complicating immune heparin-induced thrombocytopenia. *Blood* 2003;101:3049–51.
32 Goel R, Ness PM, Takemoto CM *et al*. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. *Blood* 2015;125:1470–6.
33 Miyakis S, Lockshin MD, Atsumi T *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
34 Rodríguez-Pintó I, Moitinho M, Santacreu I *et al*. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. *Autoimmun Rev* 2016;15:1120–4.
35 Cervera R, Serrano R, Pons-Estel GJ *et al*. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015;74:1011–8.
36 McDonnell T, Wincup C, Buchholz I *et al*. The role of beta-2-glycoprotein I in health and disease associating structure with function: more than just APS. *Blood Rev* 2020;39:100610.
37 van Os GM, Meijers JC, Agar Ç *et al*. Induction of anti-β2-glycoprotein I autoantibodies in mice by protein H of *Streptococcus pyogenes*. *J Thromb Haemost* 2011;9:2447–56.
38 Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. *N Engl J Med* 2018;378(21):2010–21.
39 Yalavarthi S, Gould TJ, Rao AN *et al*. Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. *Arthritis Rheumatol* 2015;67:2990–3003.
40 Ritis K, Doumas M, Mastellos D *et al*. A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. *J Immunol* 2006;177:4794–802.
41 Chaturvedi S, Braunstein EM, Yuan X *et al*. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. *Blood* 2020;135:239–51.
42 Asherson RA, Espinosa G, Cervera R *et al*. Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment. *J Clin Rheumatol* 2002;8:157–65.
43 Legault K, Schunemann H, Hillis C *et al*. McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. *J Thromb Haemost* 2018;16:1656–64.
44 Tektonidou MG, Andreoli L, Limper M *et al*. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019;78:1296–304.
45 Cervera R, Rodríguez-Pintó I, Colafrancesco S *et al*. 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. *Autoimmunity Rev* 2014;13:699–707.
46 Pavord S, Scully M, Hunt BJ *et al*. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. *N Engl J Med* 2021;385:1680–9.
47 Klok FA, Pai M, Huisman MV *et al*. Vaccine-induced immune thrombotic thrombocytopenia. *Lancet Haematol* 2022;9:e73–80.
48 Huynh A, Kelton JG, Arnold DM *et al*. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopenia. *Nature* 2021;596:565–9.
49 Singh A, Toma F, Uzun G *et al*. The interaction between anti-PF4 antibodies and anticoagulants in vaccine-induced thrombotic thrombocytopenia. *Blood* 2022;139:3430–8.
50 Toh CH, Wang G, Parker AL. The aetiopathogenesis of vaccine-induced immune thrombotic thrombocytopenia. *Clin Med (Lond)* 2022;22:140–4.
51 Pavord S, Lester W, Makris M *et al*. *Guidance produced from the expert haematology panel (EHP) focussed on Covid-19 vaccine induced thrombosis and thrombocytopenia (VITT). Updated Guidance on Management*. London: British Society for Haematology, 2021.
52 Franchini M, Liumbruno GM, Pezzo M. COVID-19 Vaccine-associated immune thrombosis and thrombocytopenia (VITT): diagnostic and therapeutic recommendations for a new syndrome. *Eur J Haematol* 2021;107:173–80.
53 Accord Healthcare Limited. *Argatroban 1 mg/ml solution for infusion 2022*. www.medicines.org.uk/emc/product/10036/dhpcs#gref [Accessed 18 April 2023].
54 NICE. *COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT)*. London: NICE, 2022.
55 Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007;44:62–9.
56 Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost* 2010;8:2105–12.
57 George JN, Raskob GE, Shah SR *et al*. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998;129:886–90.
58 Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet* 1999;353:1258–65.
59 Reese JA, Peck JD, Deschamps DR *et al*. Platelet counts during pregnancy. *N Engl J Med* 2018;379:32–43.
60 Greinacher A, Selleng K, Palankar R *et al*. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *Blood* 2021;138:2256–68.
61 Zuo Y, Yalavarthi S, Gockman K *et al*. Anti-neutrophil extracellular trap antibodies and impaired neutrophil extracellular trap degradation in antiphospholipid syndrome. *Arthritis Rheumatol* 2020;72:2130–5.
62 Krauel K, Weber C, Brandt S *et al*. Platelet factor 4 binding to lipid A of Gram-negative bacteria exposes PF4/heparin-like epitopes. *Blood* 2012;120:3345–52.
63 Warkentin TE. Platelet-activating anti-PF4 disorders: an overview. *Semin Hematol* 2022;59:59–71.
64 Johansen S, Laegreid IJ, Ernstsen SL *et al*. Thrombosis and thrombocytopenia after HPV vaccination. *J Thromb Haemost* 2022;20:700–4.
65 Warkentin TE, Greinacher A. Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia. *Thromb Res* 2021;204:40–51.

Address for correspondence: Professor Cheng-Hock Toh, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Ronald Ross Building, 8 West Derby Street, Liverpool L69 7BE, UK.
Email: Toh@liverpool.ac.uk