Thrombocytopenic emergencies

Thrombocytopenia is a commonly encountered haematological abnormality in the inpatient, most often mild with few clinical implications. The causes of thrombocytopenia are varied and can be classified by pathophysiological mechanisms (Stasi, 2012) as summarized in *Table 1*.

In most cases, thrombocytopenia is not a medical emergency and routine diagnostic assessment is appropriate. However, there are certain circumstances where thrombocytopenia may represent a life-threatening disorder. While many of these conditions are rare, early identification and treatment significantly reduce morbidity and mortality. This article focuses on three major thrombocytopenic emergencies:

1. Bleeding in the severely thrombocytopenic patient
2. Thrombotic microangiopathies
3. Heparin-induced thrombocytopenia.

Bleeding in the severely thrombocytopenic patient

Given the haemostatic function of platelets, bleeding complications are an obvious concern. There is no consensus on the definition of 'severe' thrombocytopenia, but in this article, it is considered to be a platelet count less than $50x10^9$/litre. Severely thrombocytopenic patients typically present with mucocutaneous bleeding (Provan et al, 2015), such as petechiae, gingival bleeding and epistaxis. Life-threatening spontaneous bleeding, including intracerebral haemorrhage, can occur with a platelet count less than $10x10^9$/litre.

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The management of patients will depend on the site and the severity of bleeding. Haemostatic support should always be combined with resuscitation and local measures to stop bleeding. Unless contraindicated, the administration of tranexamic acid, an antifibrinolytic agent, should also be considered. In guidelines produced by Estcourt et al (2017) for the British Society for Haematology, the recommended platelet transfusion thresholds are:

- Multiple trauma or intracranial haemorrhage – $100x10^9$/litre

Table 1. Causes of acquired thrombocytopenia

Pathophysiological mechanism	Examples	
Dilutional	Pregnancy	
	Fluid resuscitation	
	Massive transfusion	
Reduced marrow production	Vitamin B_{12} or folate deficiency	
	Liver failure – thrombopoietin deficiency	
	Drug and chemotherapy-induced myelosuppression	
	Aplastic anaemia	
	Myelodysplastic syndromes	
	Marrow infiltration	Acute leukaemia
		High grade lymphomas
		Solid organ malignancy
Immune-mediated destruction	Primary immune thrombocytopenia	
	Secondary immune thrombocytopenia	Viral, e.g. HIV, hepatitis C
		Autoimmune disease, e.g. systemic lupus erythematosus
		Drug-induced
		Lymphoproliferative disorders, e.g. chronic lymphocytic leukaemia
	Heparin-induced thrombocytopenia*	
Platelet consumption	Thrombotic microangiopathies	Thrombotic thrombocytopenic purpura
		Haemolytic uraemic syndrome
	Disseminated intravascular coagulation	
	Heparin-induced thrombocytopenia*	
Splenic sequestration	Splenomegaly	Portal hypertension, e.g. liver cirrhosis, portal vein thrombosis
		Lymphoproliferative disorders

**Thrombocytopenia in heparin-induced thrombocytopenia likely involves both immune-mediated and consumptive mechanisms.*

- Severe bleeding (e.g. upper gastrointestinal bleeding requiring red cell transfusion) – $50x10^9$/litre
- Non-severe bleeding – $30x10^9$/litre.

Unless otherwise specified by the on-call haematologist, patients requiring platelet transfusions should receive one adult dose (one unit or pool) of platelets followed by clinical and laboratory reassessment. It is important to stress that not all patients with non-severe bleeding and a platelet count below $30x10^9$/litre require transfusion. In many cases, bleeding will be self-limiting or may resolve with local haemostatic measures, such as nasal packing in epistaxis.

Certain groups of patients will require specialist intervention. For example, patients with immune thrombocytopenia often require additional measures to achieve a haemostatic platelet count, as transfused platelets will be targeted for destruction by the circulating autoantibodies. Treatment of severe bleeding in these patients usually involves combining platelet transfusions with immunosuppression in the form of corticosteroids, intravenous immunoglobulin or rituximab (Provan et al, 2010). Other groups of patients, such as those with disseminated intravascular coagulation, may also need blood components (fresh frozen plasma and cryoprecipitate) in addition to platelets.

Platelet transfusions are potentially harmful in some conditions. With the exception of life-threatening bleeding, platelet transfusions are contraindicated in patients with thrombotic thrombocytopenic purpura because of the risk of exacerbating the disease process (Scully et al, 2012). Similar concerns exist with regards to platelet transfusions in heparin-induced thrombocytopenia, leading to advice against prophylactic transfusions. However, Watson et al (2012) recommend that, if required, platelet transfusions can be safely used to treat bleeding in patients with heparin-induced thrombocytopenia.

It is important to keep in mind that while thrombocytopenia can lead to bleeding, massive haemorrhage in itself can also lead to thrombocytopenia. This is caused by haemodilution associated with fluid and red cell resuscitation as well as platelet consumption (Pham and Shaz, 2013). All acute hospitals should have major haemorrhage protocols, allowing for timely supply of red cells, platelets, fresh frozen plasma and cryoprecipitate, along with recommendations on transfusion thresholds (Hunt et al, 2015). In the event of major haemorrhage, which in practical terms should be considered bleeding with circulatory collapse, liaising with the haematology laboratory and the on-call haematologist is essential to ensure adequate haemostatic support.

Severely thrombocytopenic patients requiring emergency surgery should receive prophylactic platelet transfusions preoperatively to raise the platelet count to a haemostatic level. Estcourt et al (2017) define this as a platelet count above $50x10^9$/litre in major surgery and above $100x10^9$/litre in neurosurgery and ophthalmic surgery involving the posterior segment of the eye.

Thrombotic microangiopathies

Thrombotic microangiopathies are a heterogenous group of disorders characterized by microvascular thrombosis, leading to thrombocytopenia, microangiopathic haemolytic anaemia and end organ dysfunction. The two major thrombotic microangiopathies are thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome.

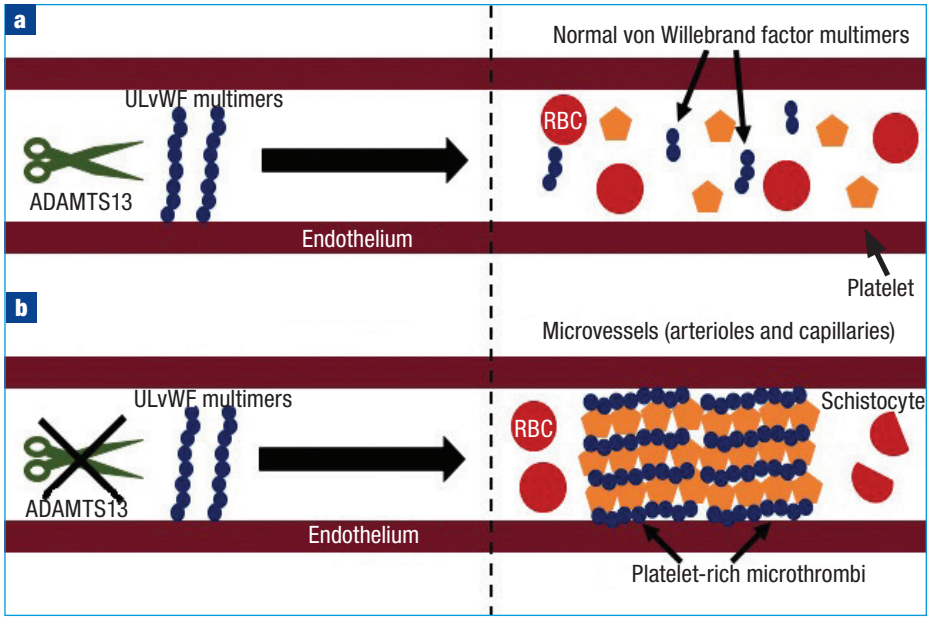
Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is the result of an acquired (autoimmune), or less commonly congenital, deficiency of ADAMTS13 – an enzym e responsible for cleavage of ultra-large von Willebrand factor multimers (Scully et al, 2008).

The pathophysiology of thrombotic thrombocytopenic purpura is summarized in *Figure 1*. Circulating ultra-large von Willebrand factor multimers spontaneously bind platelets in arterioles and capillaries to form platelet-rich microthrombi. Microvascular thrombosis leads to end organ dysfunction, especially neurological impairment. Circulating red cells are fragmented by the microthrombi leading to microangiopathic haemolytic anaemia (Scully et al, 2012). This results in the characteristic red cell fragments (schistocytes) seen on a blood film. The coagulation screen is usually normal, helping to differentiate thrombotic thrombocytopenic purpura from disseminated intravascular coagulation.

Thrombotic thrombocytopenic purpura should be considered in any patient with thrombocytopenia and microangiopathic haemolytic anaemia (Scully et al, 2012). Unlike patients with haemolytic uraemic syndrome, significant renal impairment is uncommon in patients with thrombotic thrombocytopenic purpura. Common features are neurological, ranging from headache to coma, and gastrointestinal, including ischaemic abdominal pain.

Figure 1. Pathophysiology of thrombotic thrombocytopenic purpura. a. In physiology, ADAMTS13 cleaves ultra-large von Willebrand factor (ULvWF) multimers, leading to normal blood flow through the microvasculature. b. In thrombotic thrombocytopenic purpura, uncleaved ULvWF multimers cause spontaneous platelet adhesion and aggregation producing platelet-rich microthrombi. Circulating red blood cells (RBC) are fragmented, causing microangiopathic haemolytic anaemia.



TOP TIPS

- Management of major bleeding in the thrombocytopenic patient should combine platelet transfusion with resuscitation and local haemostatic measures.
- Regardless of specialty, familiarity with your hospital's major haemorrhage protocol is essential and can significantly improve outcomes for patients presenting with major bleeding.
- Thrombotic thromobocytopenic purpura should be suspected in any patient presenting with thrombocytopenia and microangiopathic haemolytic anaemia.
- The 4 Ts is an accessible clinical prediction tool for heparin-induced thrombocytopenia, risk stratifying patients and informing further investigation and management.

Patients with thrombotic thrombocytopenic purpura can go from having vague symptoms, such as headache and lethargy, to being moribund in a matter of hours, so prompt recognition and management is essential. Untreated, it carries a mortality rate of 90% (Scully et al, 2012). All cases of suspected thrombotic thrombocytopenic purpura should be immediately discussed with the on-call haematologist, and if the index of suspicion is high, the patient should be transferred to a designated specialist centre.

The diagnosis is confirmed by an ADAMTS13 activity assay, and the mainstay of treatment in patients with acquired thrombotic thrombocytopenic purpura is plasma exchange to remove inhibitory autoantibodies and replace depleted ADAMTS13 protease. This is combined with immunosuppression, in the form of corticosteroids and rituximab, to treat the underlying autoimmune process (Scully et al, 2012). Even with the best treatment, mortality remains high at 15–20% (Scully et al, 2008), which highlights the importance of rapid recognition and initiation of plasma exchange and other measures.

Haemolytic uraemic syndrome

The other major thrombotic microangiopathy is haemolytic uraemic syndrome, which includes Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome and atypical haemolytic uraemic syndrome. Shiga toxin-producing *E. coli* haemolytic uraemic syndrome is most commonly caused by *E. coli* O157, with cattle serving as a frequent reservoir. Infection with Shiga toxin-producing *E. coli* causes a diarrhoeal illness (Keir et al, 2012). If the Shiga toxin enters the circulation, it can lead to renal microvascular thrombosis, producing the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. The condition primarily affects children, and treatment is supportive with management of fluid and electrolyte balance and, if required, renal replacement therapy (Keir et al, 2012).

Atypical haemolytic uraemic syndrome is a rare disorder caused by inherited, or less commonly acquired, defects in the regulation of the complement system (Legendre et al, 2013). This causes excessive activation of the complement system, leading to platelet activation and microvascular thrombosis. Acute kidney injury in the context of microangiopathic haemolytic anaemia and thrombocytopenia are the hallmarks of the condition (Scully and Goodship, 2014), differentiating it from thrombotic thrombocytopenic purpura in which renal impairment is not usually significant. An ADAMTS13 activity assay will be normal. Atypical haemolytic uraemic syndrome should be managed in a designated specialist centre. Treatment of this condition involves complement blockade with the terminal complement inhibitor eculizumab (Legendre et al, 2013). As this is primarily a renal disorder, its management is led by nephrologists rather than haematologists.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a potentially life-threatening complication of heparin administration. It is more commonly associated with the use of unfractionated heparin, but can occur with low molecular heparin as well. As the name suggests, the condition is characterized by thrombocytopenia, but the clinical presentation is predominantly characterized by arterial and venous thrombosis rather than bleeding (Watson et al, 2012).

The pathophysiology of the disease is complex and incompletely understood. In a variable proportion of patients (depending on factors including the patient population and the type of heparin), heparin administration results in the formation of antibodies, called heparin-induced thrombocytopenia antibodies, directed against heparin in complex with platelet factor 4, a chemokine released by activated platelets. Antibody binding results in further platelet activation, resulting in a self-perpetuating cycle of heparin-induced thrombocytopenia antibody binding, platelet activation and thrombin generation (Warkentin, 2003). The end result is arterial and venous thrombosis. Thrombotic complications include venous thromboembolism, stroke, myocardial infarction, limb gangrene and skin necrosis (Watson et al, 2012).

A clinical diagnosis of heparin-induced thrombocytopenia is difficult to make, but if it is suspected, urgent haematological advice is needed. Lo et al (2006) have produced a validated clinical prediction tool called the 4 Ts (*Table 2*) that risk stratifies patients based on clinical and laboratory criteria, before testing for heparin-induced thrombocytopenia antibodies.

The pre-test probability of heparin-induced thrombocytopenia is calculated as:

- 0–3 points – low probability
- 4–5 points – intermediate probability
- 6–8 points – high probability

Patients with a low pre-test probability of heparin-induced thrombocytopenia usually do not require any further assessment. Those with an intermediate or high probability should proceed to heparin-induced thrombocytopenia antibody testing to confirm or exclude the diagnosis, and may require empirical treatment pending the investigation results (Watson et al, 2012). This decision should be made by the on-call haematologist.

The treatment of suspected or confirmed heparin-induced thrombocytopenia consists of two main interventions. First, and most importantly, heparin should be discontinued immediately. Heparin-induced thrombocytopenia antibodies target platelet factor 4 when in complex with heparin, so elimination of heparin is key in stopping the disease process. Second, a non-heparin anticoagulant such as danaparoid or argatroban should be initiated, even in the absence of acute thrombosis, because of the high thrombotic risk (Watson et al, 2012).

In the acute management of heparin-induced thrombocytopenia, warfarin should

Table 2. 4 Ts – clinical prediction tool for heparin-induced thrombocytopenia

4 Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20x10^9/litre	Platelet count fall 30–50% or platelet nadir 10–19x10^9/litre	Platelet count fall <30% or platelet nadir <10x10^9/litre
Timing of platelet count fall	Clear onset between days 5–10 or fall within 24 hours if prior heparin exposure within last 30 days	Consistent with fall at days 5–10, but not clear (e.g. missing platelet counts) or onset after day 10 or fall within 24 hours if prior heparin exposure 30–100 days ago	Platelet count fall within 4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed), skin necrosis, acute systemic reaction post-intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

From Lo et al (2006)

not be used for anticoagulation, as it initially produces a prothrombotic state as a result of protein C depletion before effective anticoagulation is achieved (Warkentin, 2003). Further, patients who are on warfarin at the time of diagnosis of heparin-induced thrombocytopenia should have their warfarin stopped and reversed with vitamin K. As with thrombotic thrombocytopenic purpura, early recognition and treatment of heparin-induced thrombocytopenia significantly reduces associated morbidity and mortality.

Conclusions

Thrombocytopenic emergencies are relatively uncommon, making diagnostic assessment difficult. The incidence of thrombotic thrombocytopenic purpura in the UK is six per million per year (Scully et al, 2008), so it is not inconceivable that some doctors may never come across a patient with this condition. The on-call medical registrar is often the first person to assess these patients in accident and emergency or on the ward, so an awareness of these conditions can have significant implications for clinical outcomes. Bleeding is an obvious complication of severe thrombocytopenia, and management should include systemic haemostatic support with platelet transfusions in addition to resuscitation and local haemostatic measures.

Thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia are potentially fatal conditions if not recognized early and managed appropriately. Early involvement of the on-call haematologist is key. There are only a small number of true haematological emergencies, and a working knowledge of these conditions allows for timely management. **BJHM**

Conflict of interest: none.

Estcourt LJ, Birchall J, Allard S et al; British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. Br J Haematol. 2017 Feb;176(3):365–394. https://doi.org/10.1111/bjh.14423

Hunt BJ, Allard S, Keeling D, Norfolk D, Stanworth SJ, Pendry K; British Committee for Standards in Haematology. A practical guideline for the haematological management of major haemorrhage. Br J Haematol. 2015 Sep;170(6):788–803. https://doi.org/10.1111/bjh.13580

Keir LS, Marks SD, Kim JJ. Shigatoxin-associated hemolytic uremic syndrome: current molecular mechanisms and future therapies. Drug Des Devel Ther. 2012;6(6):195–208. https://doi.org/10.2147/DDDT.S25757

Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013 Jun 06;368(23):2169–2181. https://doi.org/10.1056/NEJMoa1208981

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):759–765. https://doi.org/10.1111/j.1538-7836.2006.01787.x

Pham HP, Shaz BH. Update on massive transfusion. Br J Anaesth. 2013 Dec;111(1) Suppl 1:i71–i82. https://doi.org/10.1093/bja/aet376

Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010 Jan 14;115(2):168–186. https://doi.org/10.1182/blood-2009-06-225565

Provan D, Baglin T, Dokal I, de Vos J. 2015. Oxford Handbook of Clinical Haematology. 4th edn. Oxford: Oxford University Press.

Scully M, Goodship T. How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome. Br J Haematol. 2014 Mar;164(6):759–766. https://doi.org/10.1111/bjh.12718

Scully M, Yarranton H, Liesner R et al. Regional UK TTP Registry: correlation with laboratory ADAMTS 13 analysis and clinical features. Br J Haematol. 2008 Sep;142(5):819–826. https://doi.org/10.1111/j.1365-2141.2008.07276.x

Scully M, Hunt BJ, Benjamin S et al; British Committee for Standards in Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012 Aug;158(3):323–335. https://doi.org/10.1111/j.1365-2141.2012.09167.x

Stasi R. How to approach thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2012;2012(1):191–197. https://doi.org/10.1182/asheducation-2012.1.191

Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol. 2003 May;121(4):535–555. https://doi.org/10.1046/j.1365-2141.2003.04334.x

Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol 2012 159(5):528–540. https://doi.org/10.1111/bjh.12059

KEY POINTS

- Thrombocytopenia is common and is usually mild and asymptomatic.
- Thrombocytopenic emergencies are rare but require timely recognition and management.
- Bleeding in the severely thrombocytopenic patient may require haemostatic support, with recommended platelet transfusion thresholds based on the site and severity of bleeding.
- Untreated thrombotic thrombocytopenic purpura is rapidly fatal, requiring a high index of suspicion and rapid initiation of plasma exchange.
- Heparin-induced thrombocytopenia is characterized by life-threatening thrombosis with the mainstay of treatment being discontinuation of heparin and administration of a non-heparin anticoagulant.
- In all cases of thrombocytopenic emergencies, early involvement of the on-call haematologist is key to ensuring appropriate management.