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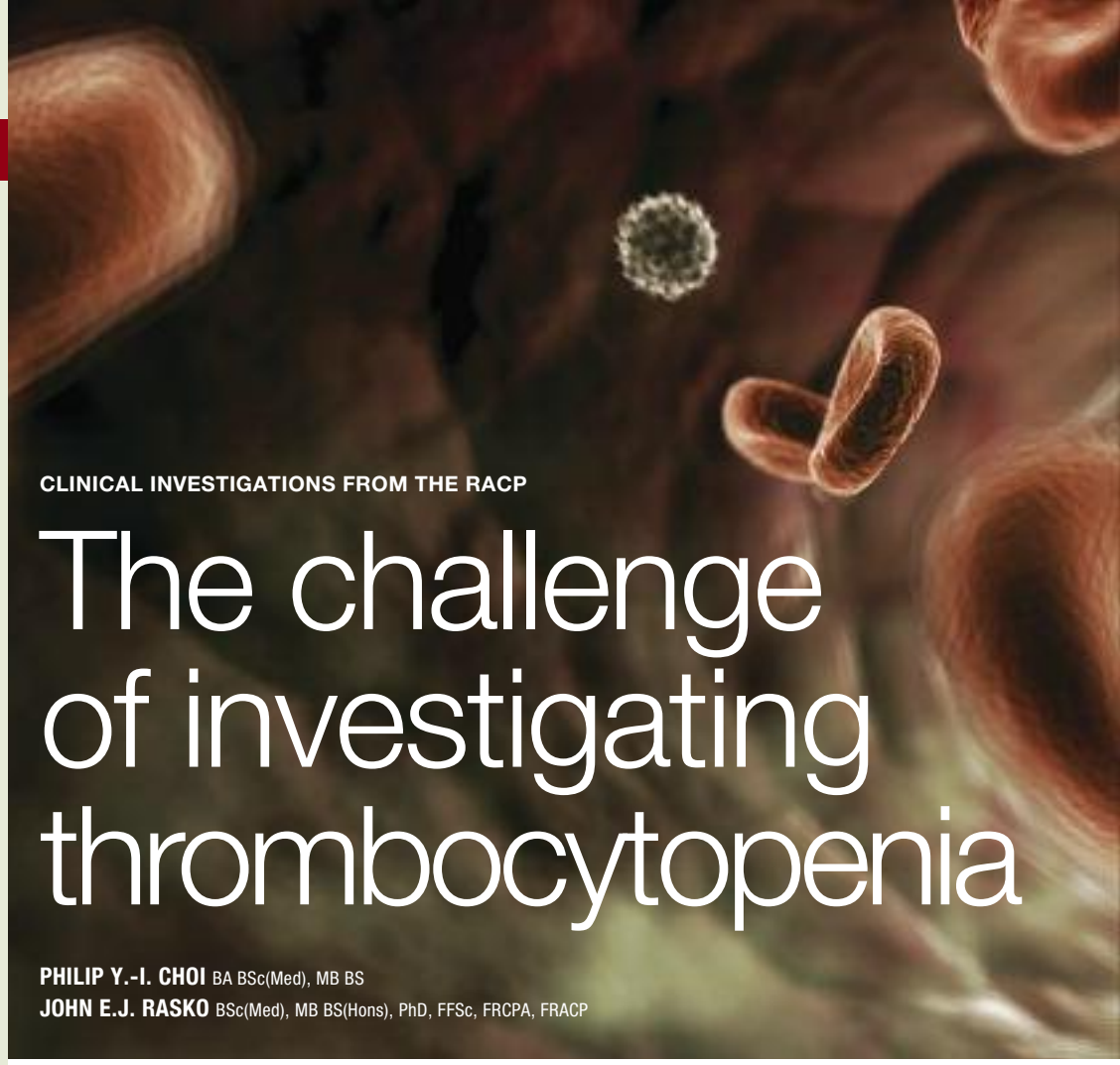


CLINICAL INVESTIGATIONS FROM THE RACP

The challenge of investigating thrombocytopenia

PHILIP Y.-I. CHOI BA BSc(Med), MB BS
JOHN E.J. RASKO BSc(Med), MB BS(Hons), PhD, FFSc, FRCPA, FRACP

Key points

- The diagnosis of thrombocytopenia needs to be confirmed by repeating the platelet count and excluding platelet clumps on blood film examination.
- Patients should be assessed for active bleeding and, if present, they should be referred to hospital immediately.
- Thrombocytopenia is commonly associated with a mucocutaneous bleeding pattern.
- Thrombocytopenia is due to reduced platelet production, increased platelet destruction or increased platelet sequestration.
- Immune thrombocytopenia is recognised as a disorder of both increased platelet destruction and inadequate platelet production.
- Prophylactic platelet transfusion is usually only needed when the platelet count is less than 10 x 10^9/L.
- Investigations should be directed by the clinical context because of the wide range of causes of thrombocytopenia.

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

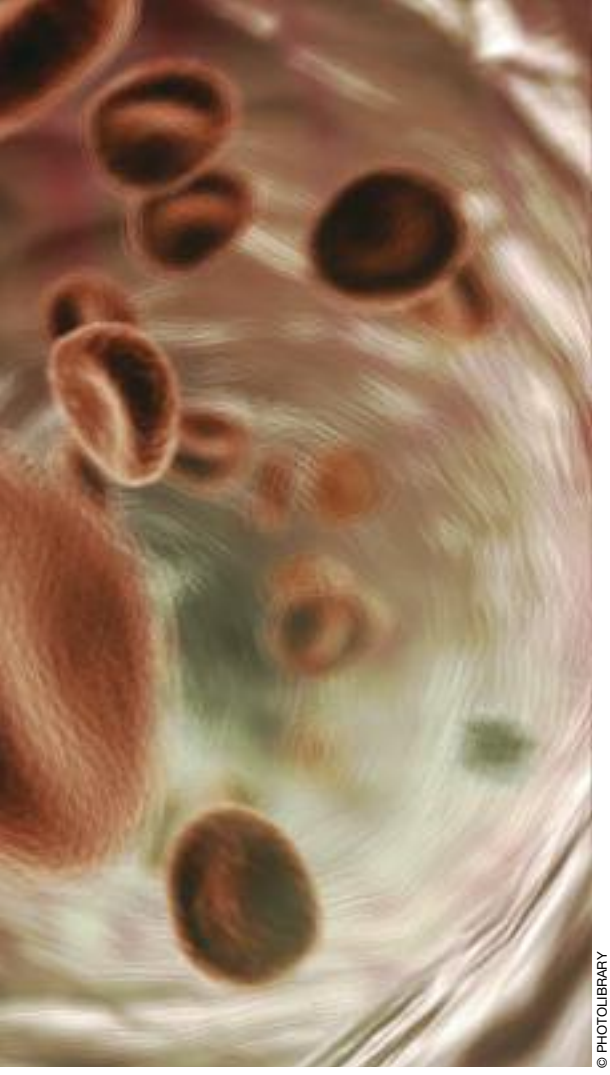
This is the first of two introductory articles on thrombocytopenia. In this first article, practical advice is provided to the GP faced with a patient who has a low platelet count. In the second article, clinical manifestations and treatment of patients with immune thrombocytopenia (ITP) are discussed as ITP is an important cause of thrombocytopenia requiring careful long-term management. The second article will also include a description of recent advances in the pathogenesis of ITP and emerging therapies.

IS IT REAL?

The first step in investigating a patient with thrombocytopenia is to confirm that it is genuine. Similar to many automated blood tests, the results are generally accurate but a repeat sample should always be collected and performed within a week, particularly if the platelet count is below 50 x 10^9/L. Repeat samples are important to confirm the presence of thrombocytopenia as well as to document any evidence of rapid deterioration requiring immediate referral of the patient to an acute care facility.

Dr Choi is an Advanced Trainee in haematology at the Institute of Haematology, Royal Prince Alfred Hospital, Sydney. Professor Rasko is a Haematopathologist at the Institute of Haematology, Royal Prince Alfred Hospital; Head of the Gene and Stem Cell Therapy Program, Centenary Institute and Sydney Medical School, University of Sydney; Head of the Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, Sydney, NSW.

SERIES EDITOR: Christopher S. Pokorny MB BS, FRACP, FRCP, FACG
Associate Professor Pokorny is conjoint Associate Professor of Medicine, University of New South Wales, and Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.



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Most automated analysers have an imprecision of at least 5 to 10% when counting platelets. This means that if the platelet count is reported as 50 x 10^9/L and the analysis is repeated on the same sample, a result between 45 and 55 x 10^9/L would be obtained. One should therefore be cautious about drawing any conclusions from small fluctuations in the platelet count because the true platelet count may not have changed at all.

Aside from analytical imprecision, there are many causes for spurious thrombocytopenia in the laboratory, as listed in the box on this page. The best strategies to overcome these potential errors include repeating the platelet count, asking for a formal blood film examination and correlating the result with clinical evidence of impaired haemostasis.

The clinical history of the patient should focus on symptoms of easy or excessive bruising with minimal trauma. In particular, muco - cutaneous bleeding is a common problem. Bleeding during routine brushing of teeth or blood found on the pillow in the morning might be early clues. One should also always enquire about the appearance of blood in bowel motions, menorrhagia or a recent history of recurrent epistaxis.

CAUSES OF SPURIOUS THROMBOCYTOPENIA

- Partial clotting of specimen
- Activation of platelets
- Ethylenediaminetetraacetic acid (EDTA)-induced *in vitro* phenomena (platelet agglutination, phagocytosis or satellitism around neutrophils)
- Other storage artefacts
- Giant platelets (too big for some analysers to recognise as platelets)

The clinical examination for thrombocytopenia should carefully document signs of petechiae (Figure 1) as well as larger areas of bruising. Inspection of the buccal mucosa is important but easily forgotten.

A thorough systems review should be performed when evaluating a patient with thrombocytopenia. Of the many causes of thrombocytopenia, common associations include portal hypertension from cirrhosis, pregnancy, infections, autoimmune diseases and drug use, including alcohol. The patient's choice of beverage is also important to consider as tonic water contains quinine, which is a common cause for drug-induced thrombocytopenia.

It is useful to correlate the severity of any bleeding with the degree of thrombocytopenia. Symptoms of severe bleeding with only mild thrombocytopenia should raise the suspicion of an alternative defect in haemostasis, such as a coagulation factor abnormality or platelet dysfunction.

INCIDENTAL VERSUS SYMPTOMATIC THROMBOCYTOPENIA

Often, a low platelet count will be detected incidentally when routine blood tests are performed in patients who do not have a prior history of easy bruising or bleeding. Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L.

Although most healthy adults will have a platelet count between 150 and 400 x 10^9/L, it is commonly believed that a level as low as 10 x 10^9/L is generally sufficient to protect

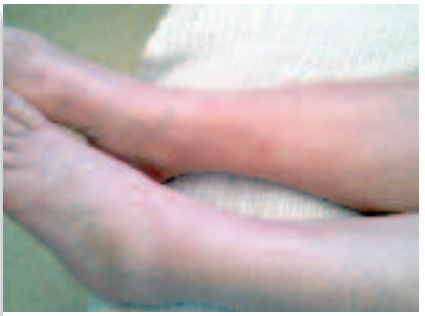


Figure 1. Petechiae on the lower legs.

against spontaneous intracerebral haemorrhage. A level of at least 50 x 10^9/L is adequate for normal vaginal delivery,[1] and any level above 80 x 10^9/L should be safe for most invasive procedures such as epidural anaesthesia. There are no randomised controlled trials to confirm the safety of this approach, so guidelines generally rely on retrospective case series[2] and expert opinion.[3]

Many patients who have a platelet count below normal remain asymptomatic. These patients still require a careful evaluation because the platelet count may fall over time, or it may fluctuate dramatically over several days.

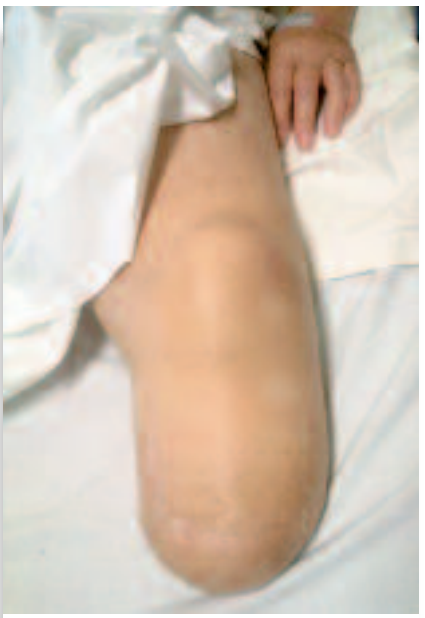


Figure 2. Left below-knee amputation following heparin-induced thrombotic thrombocytopenia syndrome (HIT).

In the special case of heparin-induced thrombotic thrombocytopenia (HIT; Figure 2), the platelet count may fall by 50% but still remain in the normal range of above 150 x 10^9/L. It is therefore important to recognise that the trend in platelet counts can be as important as the absolute value. For this reason, it is vital to monitor platelet counts weekly in patients who remain on any form of heparin, including low molecular weight heparins.

Catastrophic bleeding due to severe thrombocytopenia is often manageable if not preventable, particularly with early detection and careful monitoring. Access to blood product transfusion support may sometimes be necessary and patients who are geographically isolated from such services are best further investigated and managed closer to a larger centre. A 'group and screen' order to the blood bank may provide an additional level of safety in the event of catastrophic bleeding that demands immediate transfusion.

Thrombocytopenia can be graded in relation to the risks of bleeding, as described in Table 1. The threshold for treating thrombocytopenia in some disorders such as ITP is 30 x 10^9/L. The diagnosis of ITP requires a platelet count below 100 x 10^9/L. In the treatment of patients with ITP, a platelet count greater than 100 x 10^9/L is considered to represent 'complete response'.

WHEN SHOULD I REFER MY PATIENT TO HOSPITAL?

Immediate referral to hospital is required for any new patient with severe thrombocytopenia (platelet count below 50 x 10^9/L). We would also recommend immediate consultation at a haematology service for any new patient with moderate thrombocytopenia as, depending on the circumstances, it may also be appropriate to expedite review and management with an acute care admission. Patients with mild thrombocytopenia can usually be managed more conservatively unless it is associated with significant bleeding or bruising, in which case further investigation to exclude a concurrent coagulopathy should also be performed urgently.

Any patient with major bleeding, regardless of the platelet count, should be referred to a hospital emergency department. Furthermore, any patients at high risk from bleeding, for example, after neurosurgery, should be urgently reviewed in a fully equipped hospital.

HOW CAN THE RISK OF BLEEDING BE MINIMISED?

Patients with thrombocytopenia should avoid medications that can impair platelet function, such as aspirin, clopidogrel and

TABLE 1. BLEEDING RISK IN RELATION TO THROMBOCYTOPENIA*

Grade	Platelet count (x10^9/L)	Potential bleeding profile
0	>150	None
1	76–150	Petechial
2	51–75	Mild but clinically significant
3	25–50	Gross and may require transfusions
4	<25	Debilitating, retinal, cerebral or life-threatening

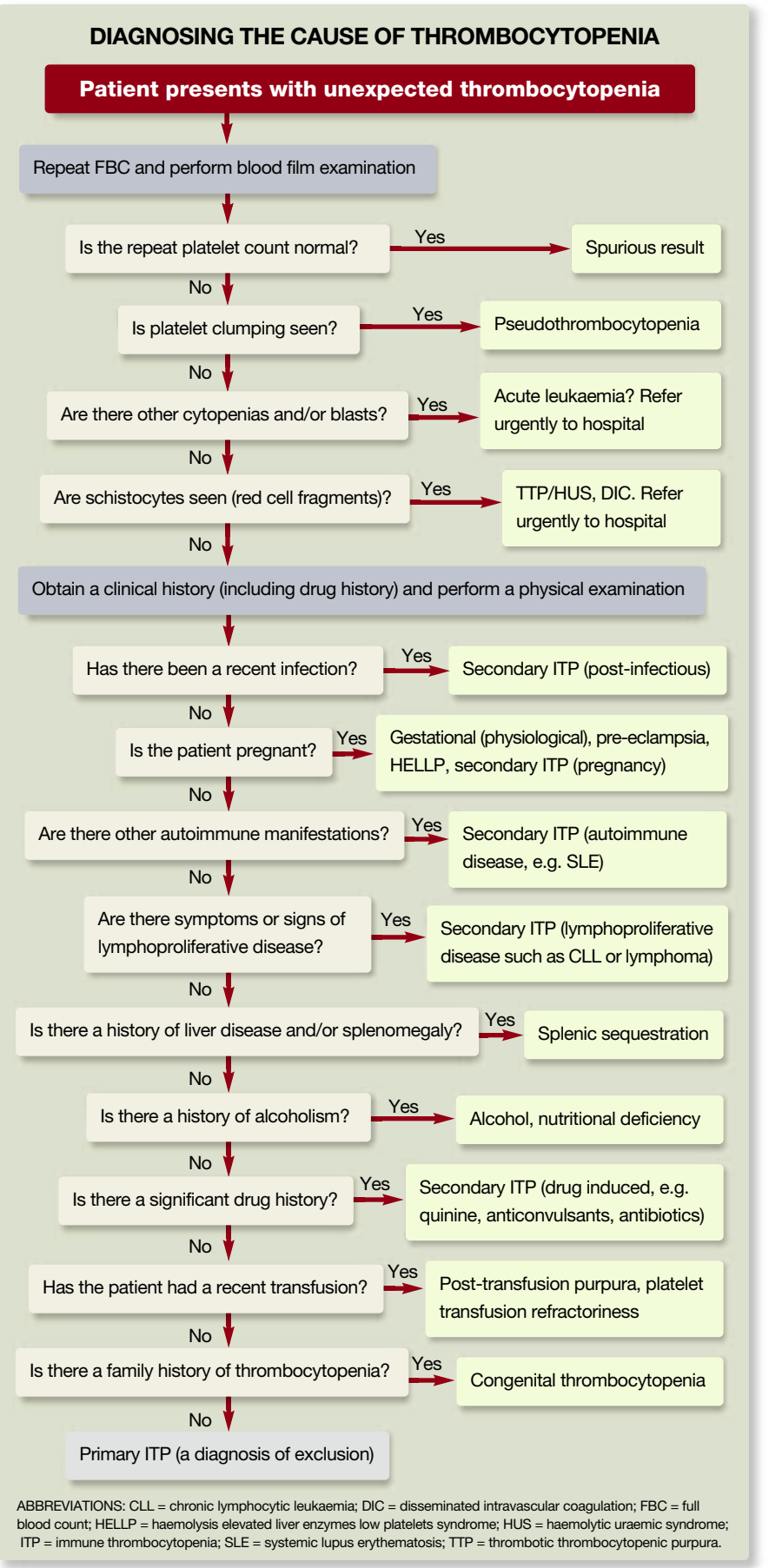
* Based on National Cancer Institute, USA, guidelines.

NSAIDs, many of which are available over-the-counter. It should also be noted that the duration of action of many anti-platelet agents might extend over many days. Unfortunately, some patients may also concurrently experience ischaemic heart disease and in these cases, careful consideration needs to be made to weigh the relative risks against the benefits of continuing antiplatelet therapy. An overall risk profile in the presence of unstable coronary artery disease and mild thrombocytopenia with no other risk factors for bleeding may favour the use of a single antiplatelet agent. Investigations into the cause of this mild thrombocytopenia should still proceed and be prioritised.

Other medications can impair coagulation, most obviously anticoagulants. Depending on the severity of the thrombocytopenia and the underlying indication for anticoagulation, these medications might also be suspended pending further investigation of the thrombocytopenia. Sometimes, anticoagulation itself may be the cause of thrombocytopenia (e.g. HIT) but this requires careful evaluation and generally inpatient management.

Antifibrinolytic agents that are 'procoagulant', such as tranexamic acid, may be helpful in patients with severe thrombocytopenia with mucosal bleeding or menorrhagia. These treatments are useful adjuncts to ameliorate the severity of minor bleeding, but do not treat the underlying cause of thrombocytopenia. They should be used with caution in patients with any history of thrombosis such as coronary artery disease, peripheral vascular disease or ischaemic stroke.

Other strategies to minimise bleeding include treating any underlying renal impairment, minimising the risk of bleeding by treating conditions such as peptic ulcer disease or haemorrhoids, and minimising risk of falls. The oral contraceptive pill may be helpful in controlling menses in some patients to minimise the duration of menorrhagia.



ABBREVIATIONS: CLL = chronic lymphocytic leukaemia; DIC = disseminated intravascular coagulation; FBC = full blood count; HELLP = haemolysis elevated liver enzymes low platelets syndrome; HUS = haemolytic uraemic syndrome; ITP = immune thrombocytopenia; SLE = systemic lupus erythematosis; TTP = thrombotic thrombocytopenic purpura.

TABLE 2. SPECIAL TESTS TO CONSIDER IN THROMBOCYTOPENIA

Clinical context	Suspected aetiology of thrombocytopenia	Suggested investigations
Heparin use (including low molecular weight heparin)	HIT	HIT screen (HPF4 antibodies by PaGIA, HIPA test, serotonin release assay) **Suspend heparin immediately upon suspicion and refer to a haematologist without delay**
Chronic liver disease	Portal hypertension	Ultrasound scan of the abdomen, liver function tests
Autoimmune disease (rash, arthritis, malaise and other unexplained inflammation)	Systemic lupus erythematosus	Measurement of CRP levels and ESR, dsDNA, ANA test, ENA test, measurement of C3 and C4 levels, antiphospholipid antibody test, rheumatoid factor tests, antiCCP antibody test
Pancytopenia	Bone marrow infiltration by malignancy	Blood film examination (leucoerythroblastosis, teardrop poikilocytes) bone marrow biopsy, serum electrophoresis
Sepsis	Disseminated intravascular coagulation	DIC screen (d-Dimer, thrombin time, fibrinogen level, APTT, prothrombin time)
Pregnancy	Pre-eclampsia, HELLP	Blood pressure, urinalysis (haematuria, proteinuria) liver function tests, haemolysis screen (lactate dehydrogenase, reticulocyte count, haptoglobins, bilirubin, direct antiglobulin test) **Urgent referral to an obstetrician is mandatory upon suspicion of pre-eclampsia**
Renal failure, neurological dysfunction, fevers, haemolysis, recent diarrhoeal illness (particularly in children)	Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome	Stool sample for *Escherichia coli*, verotoxin-producing *E. coli*, *Campylobacter* detection, blood film examination, DIC screen, haemolysis screen, ADAMTS13 antigen assay
No explanation for thrombocytopenia available – 'diagnosis of exclusion'	Immune thrombocytopenia	Antiphospholipid antibodies and lupus anticoagulant testing. In research settings and cases of diagnostic uncertainty: bone marrow biopsy, antiGP IIb/IIIa antibodies and antiGP Ib/IX antibodies (by MAIPA or immunobead), platelet-associated IgG (by flow cytometry)

ABBREVIATIONS: ANA test = antinuclear antibody test; AntiCCP = anticyclic citrullinated peptide antibody; AntiGP = antiglycoprotein; APTT = activated partial thromboplastin time; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ENA = extractable nuclear antigens test; DIC = disseminated intravascular coagulation; HIPA = heparin-induced platelet activation; HELLP = haemolysis elevated liver enzymes low platelets syndrome; HIT = heparin-induced thrombotic thrombocytopenia; HPF4 = heparin-platelet factor 4; Ig = immunoglobulin; MAIPA = monoclonal antibody-specific immobilisation of platelet antigens.

WHAT IS THE ROLE OF TRANSFUSION?

Platelet transfusions must be administered within a hospital service and are only indicated to prevent or treat thrombocytopenia-related bleeding. As discussed earlier, most patients with severe thrombocytopenia but a platelet count greater than 10×10^9/L are not at great risk of spontaneous haemorrhage and so do not require prophylactic platelet transfusion unless they are actively bleeding or at high risk of bleeding (for example, due to a planned elective procedure). Platelet transfusions are a limited resource, have risks including bacterial contamination and have a short shelf-life of only five days from blood donation. Therefore, platelet transfusions are reserved for only those cases in which there is a likely benefit.

Anaemia has been demonstrated to be an independent risk factor for bleeding in patients with acute myocardial infarction.[4] It is useful to correct concurrent anaemia prior to platelet transfusion. There is evidence that haemostatic function is improved when the haematocrit level is maintained above 35%[5] (or a haemoglobin level of about 120 g/L). The mechanism for this is thought to be multifactorial, including red cell scavenging of nitric oxide at the site of bleeding, as well as the effects of arachidonic acid and adenosine diphosphate that are present in red cells. Both of these effects stimulate platelet thromboxane production, thereby leading to local vasoconstriction and platelet aggregation.

WHAT INVESTIGATIONS SHOULD I ORGANISE?

The flowchart on page 31 provides an approach to the diagnosis of patients with thrombocytopenia. A list of special tests to consider in particular situations is

TABLE 3. DIFFERENT CAUSES AND FREQUENCIES OF THROMBOCYTOPENIA

Pathology	Cause	Incidence
Reduced platelet production		
Bone marrow disorders	Aplastic anaemia	0.2–0.4:100,000[6]
	Acute myeloid leukaemia	1.3:100,000 (under 65 years) 12.2:100,000 (over 65 years)[7]
	Myelodysplasia	0.5:100,000 (under 50 years) 12.6:100,000 (over all ages)[8]
	Vitamin B_{12} deficiency	12–14% prevalence in the elderly[9,10]
	Folate deficiency	8% prevalence (over 60 years)[11]
	Chronic alcoholism	Unknown
Congenital disorders of platelet production	Normal platelet size: Thrombocytopenia-absent-radii syndrome	0.42:100,000 live births[12]
	Congenital amegakaryocytic thrombocytopenia	Extremely rare (32 families worldwide)[13]
	Small platelet size: Wiskott-Aldrich syndrome	0.4:100,000 live male births[14]
	Large platelet size: Bernard Soulier syndrome	0.1:100,000[15]
	May-Hegglin anomaly	Extremely rare (65 families worldwide)[13]
	Grey platelet syndrome	Extremely rare (50 families worldwide)
Increased platelet destruction		
Immune disorders	Primary immune thrombocytopenia (acute and chronic)	3.2:100,000[16]
	Secondary: Drug-induced	1:100,000[17]
	Chronic lymphocytic leukaemia	2–6:100,000 (all ages) 12.8:100,000 (at age 65 years)[18] Immune thrombocytopenia in 1–5% of chronic lymphocytic leukaemia[19]
	Systemic lupus erythematosis	20–150:100,000[20] Thrombocytopenia in 1:3 of all systemic lupus erythematosis[21]
	Post-transfusion purpura	<1:700,000 transfusions[22]
	Neonatal alloimmune thrombocytopenia	1:800 to 1:1000 live births[23,24]
	Human immunodeficiency virus (HIV)	4–6:100,000[25]
Nonimmune disorders	Disseminated intravascular coagulation (DIC)	26–40% of DIC is due to infection 7–24% of DIC is due to malignancy 19–24% of DIC is due to surgery and trauma 8% of DIC is due to liver disease
	Thrombotic thrombocytopenic purpura	0.4–0.6:100,000[26]
	Haemolytic uraemic syndrome	0.19:100,000 (all ages) 1.4:100,000 (age less than 5 years)[27]
	Sepsis	57% of intensive care patients with sepsis
	Haemangiomas (Kasabach-Merritt)	0.3% of infants with haemangiomata[28]
	Type IIB von Willebrand disease	0.8–1.3% prevalence for all types of von Willebrand disease[29] of which type IIB is estimated to account for less than 5%[30]
	Pseudo von Willebrand disease	Extremely rare
Platelet sequestration		
Hypersplenism	Cirrhosis with portal hypertension	2–5% prevalence (autopsy studies)[31,32]

DRUGS CAUSING IMMUNE THROMBOCYTOPENIA

- Quinine, quinidine
- Abciximab, eptifibatide, tirofiban
- Gold salts
- Linezolid, rifampicin, sulfonamides, vancomycin
- Carbamezapine, phenytoin, valproic acid
- Cimetidine
- Paracetamol, diclofenac, naproxen
- Chlorothiazide
- Fludarabine, oxaliplatin

shown in Table 2. The various causes for thrombocytopenia and their frequencies are listed in Table 3.[12-39]

Congenital disorders of platelet production remain rare, but are increasingly recognised because of an improved understanding of the genetic basis for many of these conditions.[33] Novel strategies such as gene therapy are currently under investigation for diseases such as Wiskott-Aldrich syndrome and congenital amegakaryocytic thrombocytopenia.

CONSIDER COMMON CAUSES

Almost two-thirds of children with ITP present with a preceding febrile illness. Acute ITP of childhood is usually a transient, immune-mediated phenomenon considered to be secondary to autoantibody formation from postinfectious epitope spread. Of these children, 80% will remit within one year,[34] and the infectious agent is not commonly identified. Acute ITP can also occur following childhood vaccinations such as measles–mumps–rubella. Cytomegalovirus infection can cause severe congenital thrombocytopenia.

In adults, ITP may also be related to coexistent viral infections such as Epstein–Barr virus, cytomegalovirus, HIV and hepatitis C virus infections, as well as nonviral infections such as *Campylobacter, Helicobacter* and *Plasmodium* infections. A panel of tests to identify the infectious agent responsible can be helpful and be of therapeutic importance as outlined in Table 4.

Drug-induced thrombocytopenia is a frequently encountered dilemma. Some reference or experimental laboratories may provide specific testing for drugs implicated in causing thrombocytopenia. However, exploring the temporal relationship between the commencement of a medication and the onset of thrombocytopenia is the main clinical approach to its diagnosis. A list of common drugs implicated in thrombocytopenia is presented in the box on this page.

WHAT IS THE IMPORTANCE OF PLATELET RETICULOCYTES?

The proportion or absolute number of immature circulating platelets, known as platelet reticulocytes, can often be helpful in determining the cause of thrombocytopenia. Generally, conditions associated with increased 'peripheral' platelet destruction, such as immune-mediated causes, stimulate a compensatory response from the bone marrow and the proportion of immature platelets in the circulation is increased. Conversely, when the cause for the thrombocytopenia is due to inadequate 'central' bone marrow production, such as from infiltration by malignancy, then the proportion of immature platelets will be relatively low for a given platelet count. Automated full blood count analysers can often evaluate this variable although laboratories in Australia will not routinely report these values unless specifically requested.

TABLE 4. INFECTIONS IMPLICATED IN THROMBOCYTOPENIA

Infectious agents	Specific cause	Suggested investigations
Viral infections	Cytomegalovirus	Cytomegalovirus IgM, IgG serology
	Epstein–Barr virus	Epstein–Barr virus IgM, IgG serology
	Varicella zoster virus	Varicella zoster virus IgM, IgG serology
	Hepatitis C virus	Anti-hepatitis C virus antibodies
	HIV	Anti-HIV 1/2 antibodies
Bacterial infections	*Campylobacter jejuni*	Stool microscopy and culture
	Helicobacter pylori	*H. pylori* IgG serology, urease breath test, gastroscopy with biopsy
Parasitic infections	*Plasmodium falciparum, P. vivax, P. ovale*	Thick and thin films x 3, immunochromatography for malarial antigens

ABBREVIATION: Ig = immunoglobulin.

FUTURE DIRECTIONS

ITP is an important diagnosis to differentiate from other causes of thrombocytopenia. Although it has traditionally been considered a diagnosis of exclusion, it is now understood that ITP encompasses a multitude of pathological entities that lead to the production of platelet autoantibodies. These developments are reflected by the recent change in nomenclature for ITP, which was previously known as idiopathic thrombocytopenic purpura. ITP now encompasses a broader range of disease, and is subclassified as either primary (previously the true idiopathic cases) or secondary (to a growing list of known secondary causes).

Irrespective of the aetiology, autoantibodies in ITP lead to both increased peripheral destruction of platelets in the reticuloendothelial system, as well as to the depression of platelet production. This has been demonstrated by studies that show inappropriately low thrombopoietin levels in patients with ITP compared with patients with aplastic anaemia.[35]

Thrombopoietin is a hormone that is mostly produced in the liver and stimulates megakaryocyte proliferation and platelet formation. Synthetic thrombopoietin mimics are available for use in the treatment of ITP to stimulate platelet production.[36] In future, the measurement of plasma thrombopoietin levels may be more widely available as a diagnostic tool in the investigation of thrombocytopenia.[37]

WHEN SHOULD I REFER MY PATIENT TO A HAEMATOLOGIST?

Referral of a patient to a haematologist should be made when persistent or moderate-to-severe thrombocytopenia is unexplained by the clinical context. Often, a viral illness can be associated with mild thrombocytopenia that gradually improves, and with patients may not require referral. A patient with a history of liver failure or alcoholism may have thrombocytopenia due to portal hypertension. Generally, the urgency of referral should be dictated by the clinical situation: the presence of bleeding, the severity of thrombocytopenia, any accompanying cytopenias, or the presence of blasts on peripheral blood. If in any doubt, it is safest to refer patients to a haematologist early, as bleeding from severe thrombocytopenia can be life-threatening but often preventable with timely diagnosis and treatment.

Depending on the clinical context, the haematologist should be able to determine the need for further investigations, such as a bone marrow biopsy. Access to services such as platelet transfusions and to new treatment options for immune-mediated thrombocytopenia is best provided in the hospital context.

WHAT IS THE ROLE OF BONE MARROW BIOPSY?

Bone marrow biopsies provide detailed information about haemopoiesis. They enable the assessment of the morphology and provide the most decisive diagnostic test for abnormalities. However, these biopsies seldom reveal further information on the most common causes of thrombocytopenia, such as ITP and cirrhosis. Hence, the role of the bone marrow biopsy is primarily to exclude infiltrative causes of thrombocytopenia such as acute leukaemia.

Although bone marrow biopsies are simple procedures that can often by performed in less than 10 minutes, they can be associated with morbidity and they are generally an unpleasant procedure.[38] Sedation is often used when the clinical situation allows.

CONCLUSION

The investigation of thrombocytopenia is made difficult by the multitude of differential diagnoses to consider and the frequent need for urgency in arriving at this diagnosis. As the differential diagnoses are broad, the plethora of tests to organise can be expensive, time-consuming and confusing. ITP is always important to consider, but remains ultimately a diagnosis of exclusion.

Most differential diagnoses can be excluded expeditiously when guided by basic blood tests, such as the full blood count and blood film examination, as well as the clinical history. In those cases in which the diagnosis or management is difficult, timely advice should be sought from a haematologist. MT

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: Dr Choi: None.
Dr Rasko has received speaker fees from Amgen in the clinical development of thrombopoietin.

The challenge of investigating thrombocytopenia

PHILIP Y.-I. CHOI BA BSc(Med), MB BS **JOHN E.J. RASKO** BSc(Med), MB BS(Hons), PhD, FRCPA, FRACP

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