Investigation of the child with easy bruising

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The presentation of a child with easy bruising can be alarming for both parents and practitioners alike. Bruising is a common feature of active toddlers and children. The clinical presentation, pattern of bruising, associated features (for example, bleeding and petechiae), past history and family bleeding history help to distinguish the child with normal bruising from one with abnormal bruising.

Normal haemostasis

Normal coagulation requires the co-ordinated regulation of platelet, plasma and tissue functions to result in the formation of a localised and stable clot. Tissue damage with the exposure of subendothelial tissue provides a surface for the adhesion, aggregation and activation of platelets. Tissue and platelet factors stimulate the activation of the coagulation cascade, resulting in the deposition of a loose fibrin meshwork that is converted into a stable clot by fibrin cross-linking. Haemostasis is balanced by antithrombotic, thrombolytic and fibrinolytic mechanisms to maintain clot localisation and prevent extension.

Isolated abnormalities in platelets, clotting factors and the fibrin cross-linking or degradation pathway lead to characteristic patterns of bleeding. The hallmark of platelet dysfunction is the combination of petechiae, bruising and mucosal bleeding. Clotting factor deficiency is associated with deep tissue bleeding, whereas problems with either fibrin cross-linking activity or excessive fibrinolysis result in recurrent bleeding after apparently normal clot formation.

History and presenting features

In the active toddler or child, bruising results from impact between a hard surface and areas of the body where bony prominences lie close to the surface. Bruising is often seen on the forehead or along the shins of normal healthy toddlers and around the elbows of older children.

Features that warrant closer scrutiny include bruising:

- in atypical locations, such as the face, trunk, abdomen, buttocks or thighs
- that is out of proportion to minor trauma, especially when it involves the mouth,

IN SUMMARY

- **Causes of easy bruising in childhood include platelet disorders (e.g. idiopathic thrombocytopenic purpura) and deficiency of haemostatic factors (e.g. von Willebrand's disease and the haemophilias).**
- **Other causes that do not primarily involve haemostasis, such as nonaccidental injury, malignancy and meningococcal infection, must not be overlooked in the child with easy bruising.**
- **A detailed history, including a family history, a physical examination and an understanding of the haemostatic process, provide the basis for clinical diagnosis.**
- **Simple tests, including full blood count, blood film and coagulation screen, are usually the most appropriate initial investigations to confirm diagnosis and guide management.**

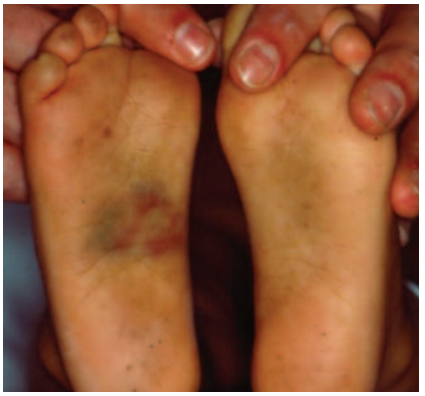


Figure 1. Bruising in a child subjected to physical abuse. Features that strongly suggest the diagnosis of child physical abuse include the unusual location and the straight lower edge of the bruise.

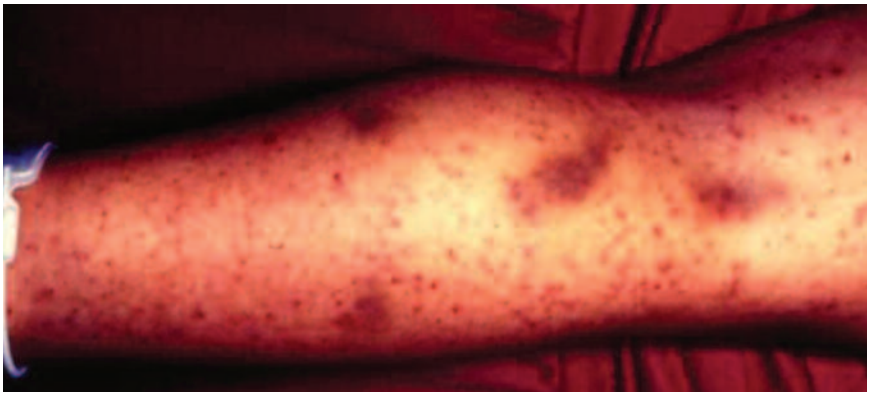


Figure 2. Fulminant purpuric rash in a child. Severe infections, such as meningococcal disease, can be accompanied by a purpuric rash consisting of bruises and petechiae. The rash is due to local infection and inflammation of small blood vessels, resulting in bleeding into the skin and subcutaneous tissue. Meningococci can often be identified and cultured from smears of the purpuric rash.

muscles or joints
- that is associated with mucosal bleeding and petechiae
- in the unwell child.

A presentation that raises consideration of child abuse includes:
- bruising inconsistent with the child's developmental capabilities – for example, bruising in the premobile child
- bruising associated with unexplained injuries
- patterned bruises, suggesting blows by a particular object – for example, a looped cord, belt, hand or shoe (Figure 1).

The onset and progression of the bruising may provide important diagnostic clues. For example:
- the sudden appearance of bruising and petechiae in the otherwise well toddler after a recent viral illness suggests acute idiopathic thrombocytopenic purpura (ITP)
- the toddler presenting with recurrent muscle or joint bleeding following minor trauma may have von Willebrand's disease (vWD) or haemophilia
- the pale child with a progressive illness consisting of bruising, petechiae, bony tenderness and fever may have acute leukaemia
- the unwell child with a brief illness characterised by fever, bruising, petechiae and altered level of consciousness may have meningococcal disease (Figure 2).

The child's previous health may provide relevant contributory information on reasons for decreased clotting factor production, excessive platelet consumption or abnormal platelet function. Examples of such include recent viral illnesses; diet and vitamin K prophylaxis in the neonatal period; exposure to medications (intentional or otherwise), particularly NSAIDs, antibiotics and anticoagulants; and pre-existing medical conditions such as liver disease or renal impairment. A recent gastrointestinal illness associated with bloody diarrhoea may indicate possible haemolytic uraemic syndrome.

A personal history of excessive bleeding is important, but many children will not have experienced events that unmask a bleeding tendency. It is important to ask about the patient's bleeding or bruising following separation of the umbilical cord, immunisations, minor surgery (for example, circumcision) and dental work, minor trauma especially to the mouth, and joint swelling.

A family history of excessive bleeding should be sought, covering as many members of the family as possible and focusing on:
- excessive bleeding after minor trauma
- prolonged bleeding with minor dental or surgical procedures
- prolonged and recurrent nose bleeds from both nostrils (not controlled by pressure within 15 minutes)
- menstrual periods lasting longer than seven days, especially in the presence of clots, flooding and the use of multiple pads.

However, it must be borne in mind that a negative family history does not exclude the possibility of a significant bleeding disorder.

Physical examination

An assessment should be made on whether the child is sick or well and the location and pattern of bruising. Other features that should be sought include:
- fever (>38.5°C)
- hypertension
- petechiae
- mucosal, gastrointestinal or genitourinary bleeding
- enlarged lymph nodes

- enlarged liver or spleen
- swollen, hot or tender joints (particularly knee or ankle)
- bony tenderness or irritability
- decreased level of consciousness
- neck stiffness.

Occasionally, the presence of unusual features may lead to the diagnosis of a rare condition that can present with excessive bruising. For example, Fanconi anaemia may present with thrombocytopenia, but it is also associated with café au lait spots, hyperpigmentation, short stature, thumb or arm defects (particularly involving the radius) and renal or genitourinary abnormalities.

Approach to investigation

The approach to investigation should be guided by the clinical condition of the child. In the case of the unwell child with features suggestive of bacterial sepsis, early administration of broad spectrum antibiotics (ideally after taking a blood culture) and transfer to hospital should be prioritised. Relevant further investigations can be performed as the child's condition stabilises.

In most instances emergency treatment will not be needed. Simple initial investigations, including a full blood count, examination of the blood film and coagulation screening, combined with the clinical presentation, will confirm the clinical diagnosis and guide the need for further investigation (Table).

Important information that may be yielded from the full blood count includes the identification of thrombocytopenia, anaemia, leucocytosis or leucopenia. The blood film will confirm the platelet count and provide additional information such as the presence of reactive lymphocytes, left shift, toxic granulation or circulating leukaemic blasts.

Most laboratories include a prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (APTT) in coagulation screening (see the box on this page for an explanation of these). Generally, the bleeding time is not helpful due to problems with reliability and standardisation in children under the age of 2 years; however, it may provide useful information in older children. The platelet function analyser (PFA 100) has been developed as a laboratory assay of primary haemostasis to replace the bleeding time. It measures the time taken for a platelet plug to form in the presence of activators of platelet function. This is prolonged in vWD and in the presence of platelet function disorders; however, the results may be unreliable in the setting of significant thrombocytopenia.

Causes of easy bruising

Acute idiopathic thrombocytopenic purpura (ITP)

Presentation

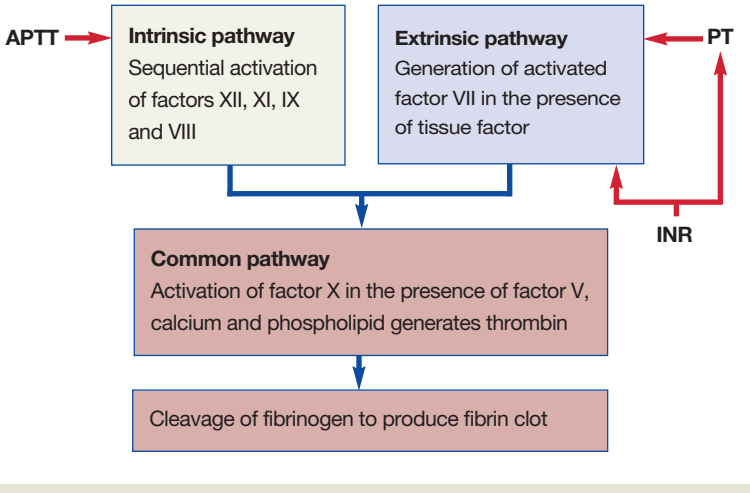
Acute ITP is due to immune-mediated peripheral platelet destruction. The onset is heralded by the sudden appearance of bruising, petechiae and, sometimes, mucosal bleeding in an otherwise well child. There may be a history of a recent viral infection. Acute ITP can follow exposure to medications, including penicillin. The physical examination is usually normal, and the presence of significant adenopathy or hepatosplenomegaly suggests a different diagnosis.

Site of action of screening tests in the coagulation cascade

The activated partial thromboplastin time (APTT) and prothrombin time (PT) measure the intrinsic and extrinsic pathways of the coagulation cascade, respectively. The international normalised ratio (INR) is a standardised measure of the PT and extrinsic pathway, allowing comparison of results measured in different laboratories.

An isolated prolonged APTT suggests a deficiency in, or an inhibition of, one of the coagulation factors in the intrinsic pathway (factor XII, XI, IX or VIII). This may occur with haemophilia (due to factor VIII or factor IX deficiency) or, sometimes, in von Willebrand's disease, in which there can be low levels of both von Willebrand's factor and factor VIII.

Conversely, an isolated prolongation of the PT suggests a deficiency of factor VII, which can be the result of liver disease, vitamin K deficiency or anticoagulant medications, such as warfarin. The levels of factor VII are likely to be reduced in these situations due to its shorter half-life compared with those of other clotting factors.



Acute ITP usually occurs in childhood, with a peak incidence between the ages of 1 and 4 years. ITP in children over the age of 10 years may be the initial manifestation of an underlying congenital or acquired disorder, such as Fanconi anaemia or systemic lupus erythematosus. Some rare congenital disorders such as the Wiskott Aldrich syndrome, X-linked thrombocytopenia or Bernard Soulier syndrome should be considered when ITP occurs in an infant under the age of 1 year.

Acute ITP is usually self-limiting, with the platelet count recovering in most patients within six months of diagnosis. Roughly 10 to 15% of patients follow a chronic course, with a persisting low platelet count for more than six months from diagnosis.

Investigation

Bone marrow examination does not need to be performed in all cases. However, it must be performed when there are features suggesting malignancy, such as significant adenopathy or hepatosplenomegaly on examination, or the presence of anaemia or neutropenia on full blood count. Bone marrow examination has been recommended before starting corticosteroid treatment or when there has been no response to treatment.

Management

There is a paucity of evidence based guidelines and clinical trials to guide the management of acute ITP. The risk of serious bleeding, such as intracranial haemorrhage, is low at about 0.5%.

Treatment of acute ITP has not been standardised and some practitioners elect to observe with careful monitoring, whereas others treat to maintain the platelet count at a 'safe' level (usually >20 x 10^9/L). However, treatment is indicated for children with bleeding from the gastrointestinal or genitourinary tracts, excessive mucosal bleeding, or any evidence of a CNS bleed. These children should be referred to a specialist paediatrician or a paediatric haematology centre. Treatment options, which include oral corticosteroids or intravenous gamma globulin (Intragam P, Intraglobin F, Sandoglobulin), should be individualised and discussed fully with the family. Agents that impair platelet function, such as aspirin and NSAIDs, should be avoided, and these children should not receive intramuscular injections until platelet recovery occurs.

von Willebrand's disease

Presentation

von Willebrand's disease is the most common inherited bleeding disorder, with an incidence of 1 to 2% in the general population. It is associated with easy bruising, mucosal or gum bleeding and prolonged bleeding following minor trauma or surgery, especially dental or ENT surgery. The disease is due to either a deficiency of, or a defect in, the von Willebrand Factor (vWF). vWF is a large, multimeric carrier protein for factor VIII and enhances haemostasis by binding to both damaged tissue and platelets, thus stimulating the coagulation pathway.

Investigation

A personal and family history of bleeding are important in diagnosing vWD since the diagnosis of mild disease can be difficult to demonstrate, even on repeated laboratory testing. The vWF protein is an acute phase reactant and thus its levels can be increased by physiological stress, resulting in normal functional assays of vWF activity.

Results that suggest vWD are a normal PT and INR in the presence of a slightly prolonged APTT. The APTT may be prolonged because vWF is a carrier protein for factor VIII and, therefore, the plasma levels of factor VIII can be decreased in proportion to the low vWF. The bleeding time may also be prolonged. Platelet aggregation in the presence of ristocetin is reduced but is normal in the presence of other activators of platelet function.

There are three types of vWD:

- type 1, in which there is a reduced amount of vWF
- type 2, a qualitative defect in vWF
- type 3, a total absence of vWF.

Type 1 vWD is the most common, accounting for 70 to 80% of cases. Results that confirm the diagnosis of type 1 vWD are reduced vWF levels (but with a normal pattern of vWF multimers) and decreased vWF activity measured by reduced aggregation of platelets in the presence of ristocetin cofactor.

Management

Type 1 vWD can be treated with desmopressin (Minirin, Octostim), administered as an intravenous injection or nasal spray, which stimulates the release of vWF from endothelial cells, thereby increasing serum levels of both vWF and factor VIII. However, treatment should be considered only when there are problems with prolonged bleeding (for example, recurrent epistaxis or menorrhagia) or excessive bruising, or as prophylaxis for surgical procedures. Response to desmopressin should be documented. Bleeding in patients unresponsive to desmopressin can be managed with factor replacement since vWF is found also in plasma-derived factor VIII concentrates.

Haemophilia A and B

Presentation

Haemophilia A is due to factor VIII deficiency and haemophilia B to factor IX deficiency. Haemophilia A is more common, accounting for about 85% of cases. However, the haemophilias are clinically indistinguishable since factors VIII and IX form a complex that is central to the further activation of the coagulation cascade after tissue damage.

Most children with severe haemophilia present by the end of the first year of life. Some children with severe haemophilia tolerate minor surgery in early infancy without major incident whereas others

continued

Table. The child with easy bruising: clinical and laboratory features

Feature	ITP	vWD	Haemophilia	Leukaemia	Sepsis
Onset	Acute (days)	May be present from birth	May be present from birth	Progressive over weeks	Progressive over hours or days
Presenting features	Petechiae, bruising and mucosal bleeding	Mucosal bleeding, bleeding after minor trauma and surgery	Bruising, deep muscle or joint bleeds with minimal trauma	Petechiae, bruising, mucosal bleeding, bone pain, irritability, fever and infection	Petechiae, purpura, irritability, fever, neck stiffness and decreased consciousness
Family history of bleeding	No	Yes, but may be subtle and unrecognised	Yes, but negative in about 30% of cases	No	No
Inheritance	Sporadic	Autosomal dominant Type 1 vWD	X-linked recessive	Sporadic	Sporadic
Examination	Normal	Normal	Normal apart from muscle and joint haematomas	Hepatosplenomegaly, lymphadenopathy, bone pain and infection	Fever, meningism, purpura, decreased level of consciousness
Haemoglobin	Normal	Normal	Normal, but may be reduced after large muscle bleed	Reduced	Normal
White cell count	Normal	Normal	Normal	Reduced, normal or increased	Reduced, normal or increased
Platelet count	Reduced (usually $<20 \times 10^9$/L)	Normal	Normal	Reduced	Normal
Blood film	Reduced or absent platelets and reactive lymphocytes (sometimes)	Normal	Normal	Pancytopenia and abnormal cells (e.g. leukaemic blasts)	Evidence of severe infection (e.g. left shift and toxic granulation)
PT/INR	Normal	Normal	Normal	May be prolonged	May be prolonged
APTT	Normal	Normal, but may be prolonged	Prolonged	May be prolonged	May be prolonged
Further investigations	Not indicated unless atypical features or prolonged course	PFA 100, studies of vWF antigen, activity and multimer analysis. Factor VIII level may be low	Mixing studies, coagulation factor assay and gene mutation detection	Bone marrow aspirate	Blood culture, lumbar puncture, fibrinogen and D-dimers

Abbreviations: APTT = activated partial thromboplastin time, INR = international normalised ratio, ITP = idiopathic thrombocytopenic purpura, PFA 100 = platelet function analyser, PT = prothrombin time, vWD = von Willebrand's disease, vWF = von Willebrand factor.

Child abuse	Liver disease
May have previous unexplained injuries	Chronic
Multiple bruises and other injuries of varying ages	Bruising, haematemesis and melaena
No	No
Not applicable	Sporadic
Bruising, other injuries and bone pain due to other injuries	Splenomegaly, jaundice
Normal	Normal, may be reduced after large bleed
Normal	Normal
Normal	May be reduced with splenomegaly and portal hypertension
Normal	Normal
Normal	Prolonged
Normal	Normal
Skeletal survey, bone scan and fundoscopy	Repeat coagulation studies after giving vitamin K, liver function tests, hepatitis serology, investigation for structural, metabolic and immunological causes of liver disease

may bleed profusely. Haemophilia is associated with deep tissue bleeding, particularly into the joints of the lower limbs, but it may present also with haematomas after intramuscular injection. Moderate and mild haemophilia may become clinically apparent only after trauma or minor surgery such as dental procedures.

Investigation

The genes for both factor VIII and IX lie on the X chromosome, explaining the sex-linked recessive inheritance. The family bleeding history may not be informative since up to 30% of newly diagnosed cases result from a spontaneous mutation that is found in the patient and sometimes in the mother's egg cells (germline mosaicism) but that is not present in other family members.

Laboratory investigation shows a prolonged APTT with a normal PT. Normalisation of APTT by mixing the patient's plasma with normal plasma strongly suggests factor deficiency, which can be confirmed by assaying individual coagulation factor levels. Factor levels define the severity of the disease and the likelihood of recurrent bleeds. Severe haemophilia is associated with factor levels less than 2% of normal, moderate haemophilia with levels 2 to 10% and mild haemophilia with levels greater than 10%.

Genetic counselling and gene mutation detection are appropriate and can be used to counsel the family regarding future pregnancies and facilitate prenatal diagnosis where appropriate.

Management

All children with haemophilia should be managed in conjunction with a paediatric haemophilia centre. In the past, major morbidities associated with severe haemophilia have included:

- a destructive arthropathy due to either poorly managed acute joint bleeds or recurrent joint bleeds (Figure 3)
- the transmission of blood-borne viral infection.

These problems have been ameliorated by prophylactic factor transfusion, the production of recombinant clotting factors and enhanced procedures to inactivate viral contaminants of pooled plasma products.

Recombinant factor VIII (Kogenate FS, ReFacto) and factor IX (BeneFIX) are commercially available and are replacing factor concentrates. The recombinant products have reduced the risk of transmitting blood-borne viruses. They are used in patients who have not been previously transfused or have not been infected by a blood borne virus.

Prophylactic factor transfusion reduces the incidence of developing joint complications and is given either two (for factor IX) or three (for factor VIII) times

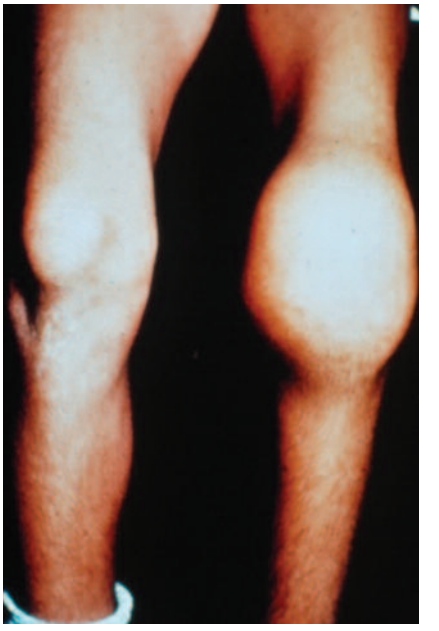


Figure 3. Target joint in a boy with severe haemophilia. Recurrent joint bleeds have led to a destructive arthropathy associated with wasting of the muscles around the knee joint. This complication can be avoided with the combination of prophylactic factor transfusion and judicious management of acute joint bleeds.

weekly. Joint bleeds, which can still occur despite prophylaxis, must be treated early and aggressively to prevent joint damage.

Life threatening situations, such as CNS bleeds, retroperitoneal bleeds, bleeds into large muscle groups or the neck, must be managed urgently with the aim of attaining and maintaining factor levels at 100% of normal.

Other causes of significant bruising

There are several other possibilities that must be considered in the appropriate clinical context, including sepsis, malignancy, liver disease and child abuse (Table). Appropriate investigation and management of these conditions are beyond the scope of this article and are best performed in conjunction with appropriate specialist advice.

When there is a reasonable suspicion that child abuse has occurred, the case must be reported to the appropriate statutory authority. The safety of the child and other children in the family needs to be ensured. These issues and the need for further investigation can be discussed with the child protection team at the closest paediatric centre.

Other more rare haematological causes of easy bruising with normal screening tests include:

- platelet function disorders (Glanzmann's thrombasthenia or Bernard Soulier syndrome)
- collagen and blood vessel disorders (such as Ehlers Danlos syndrome or Henoch Schönlein purpura)
- defects in the generation of the fibrin clot (e.g. hypofibrinogenaemia)
- premature destruction of the cross-linked fibrin clot.

In these rare situations specific laboratory testing can be undertaken in consultation with a paediatric haematologist.

Conclusion

The clinical condition of the child presenting with easy bruising should guide investigations. In most cases, simple tests, such as full blood count, blood film and coagulation screening, are the most appropriate investigations to confirm diagnosis and guide management. MT

Further reading

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