

How to Recognize a Child with a Bleeding Disorder?

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Abstract

Children often exhibit bleeding symptoms as a result of their active lifestyle, or due to trauma or surgery. In growing children, mild bleeding symptoms are frequently observed. However, this does not necessarily indicate an underlying bleeding problem. As a paediatrician, it can be challenging to determine whether these symptoms are normal or indicative of an underlying bleeding disorder. This article provides a comprehensive overview of how to evaluate bleeding symptoms in children. It covers clinical presentations, diagnostic tools and laboratory assessments, and aims to help paediatricians identify children who may have a bleeding disorder and determine which patients require referral to a paediatric haematologist.

Physiology of haemostasis and coagulation

The process of blood clotting is initiated in response to injury to a blood vessel, with the objective of minimising blood loss (Figure 1). In the event of a wound, vasoconstriction will predominate, with platelets adhering to the exposed subendothelium due to von Willebrand factor (VWF). This process will result in the aggregation of additional platelets and the subsequent formation of a platelet clot. This phenomenon has been referred to as primary haemostasis. Subsequent to this, secondary haemostasis is initiated, which is characterised by a multifaceted interaction between coagulation factors and cofactors. This interaction occurs through the intrinsic and extrinsic coagulation cascade, resulting in the formation of fibrin. The fibrin formed will stabilise the platelet clot into a solid blood clot.

In order to prevent excessive clot growth, the inhibitors of the coagulation system are activated and regulate clot formation and fibrinolysis (1-3). The process of clot formation is dependent on the interplay between three fundamental components: the blood vessel wall, platelets, and clotting factors. Impaired blood clotting resulting in increased bleeding tendency may result from a disorder in any of these components (Table 1) (1-6).

Evaluation of a child with bleeding tendency

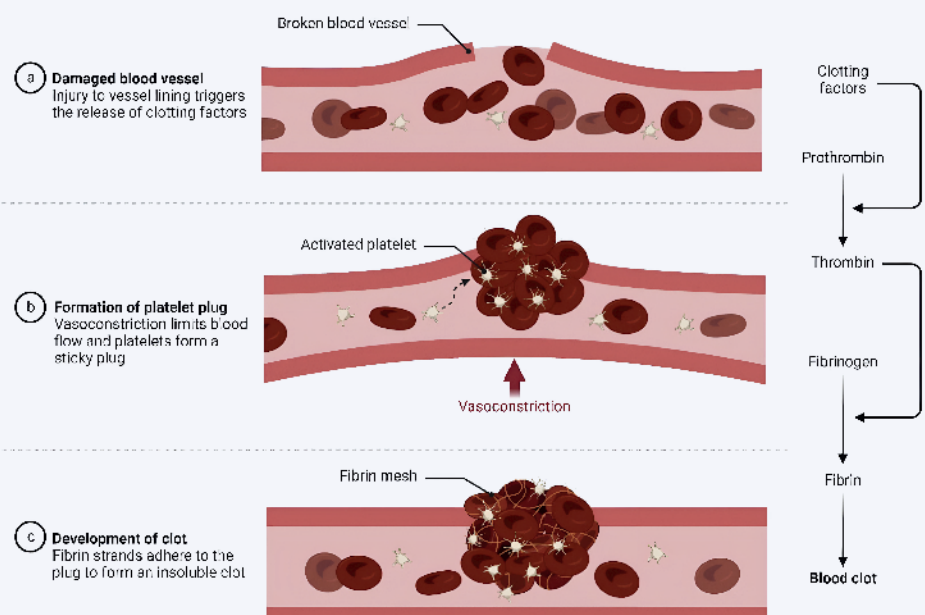
In children, typical manifestations of normal bleeding are occasional nosebleeds or small, superficial bruises (mainly on the lower extremities), often resulting from minor trauma. However,

pathological bleeding may manifest as spontaneous, recurrent, or excessive bleeding from minor injuries, mucocutaneous bleeding (e.g., frequent gum bleeding or nosebleeds, haematuria, excessive menstrual blood loss), or unexplained bruising in unusual locations (e.g., buttocks, back, thorax) (1-5,7-9).

A survey of 228 otherwise healthy children who had undergone a straightforward tonsillectomy and/or adenoidectomy revealed that a considerable number of them reported bruising easily (24%), bruising at least once a week (36%) and suffering from nosebleeds (39%). The questionnaires were compared with those of 31 patients with bleeding disorders (von Willebrand disease (VWD) and/or platelet function disorders). Respondents with a bleeding disorder more frequently displayed bruising on more than one body part

FIGURE 1: Blood clot formation in broken vessel. BioRender. (2019).

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(38.5%). Furthermore, a higher prevalence of larger bruises (29.6%) and haematomas (21.7%) was observed. These findings were in contrast to the control group without bleeding disorders, where such complications occurred in only 4.9%, 3.5% and 2.7% of cases, respectively(10).

History

A detailed medical history of the child is crucial. This comprises the presence of underlying diseases (e.g., liver, kidney, heart diseases) and the onset, frequency, and severity of bleeding episodes. For instance, the presence of intracranial haemorrhage, umbilical cord haemorrhage, bleeding following heel prick, or intramuscular vaccination in a neonate may be indicative of a bleeding pathology. The number of nosebleeds experienced by the child in the preceding 12 months should be ascertained, as should the duration of each episode and whether medical intervention was necessary, which could include cauterisation or transfusion. Furthermore, clinicians should inquire about bleeding following surgical or dental procedures, minor injuries and vaccinations. Adenoidectomy, tonsillectomy, as well as circumcision, are procedures that may reveal a blood clotting disorder due to the pronounced bleeding tendency during these procedures. For adolescent girls, a menstrual history is imperative, encompassing inquiries into the duration and volume of menstrual bleeding, the frequency of changing pads or tampons, and the presence of substantial blood clots (1-11).

The medical history should include information on the use of any medication that inhibits platelet aggregation (e.g., aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), some anti-epileptics and herbal medication) or inhibits coagulation (e.g., vitamin K antagonists or direct oral anticoagulants (DOACs)) (3,6,8).

An extensive family history of bleeding disorders should also be explored, both for female and male family members. In X-linked diseases, such as haemophilia, the presence of a bleeding tendency in brothers, (grand)fathers or uncles of the mother may serve as an indication of potential genetic susceptibility. In addition, consideration should always be given to the possibility of rare coagulation factor deficiencies in cases of consanguinity (1,5,7).

Physical Examination

A detailed physical examination should assess for signs of mucocutaneous bleeding, joint or muscle haemorrhages, and other abnormal bleeding patterns (1-11).

When inspecting the skin, particular attention should be paid to the presence of petechiae, as well as to the size and distribution of bruising. Haematomas measuring more than 5cm in diameter, or located in an atypical location, such as the trunk or back, may be indicative of underlying pathology. In addition to the skin, examination of the mucous membranes (e.g., the oral cavity and nasal mucosa) should be conducted to look for the presence of petechiae or bleeding foci. Redness, warmth, swelling, restricted movement or asymmetry in a joint or muscle may be signs of a hemarthrosis or muscle haemorrhage. As illustrated in Table 2, the clinical presentation may assist in differentiating between a platelet abnormality and a clotting factor defect.

Moreover, congenital thrombocytopenia and thrombocytopathy can be associated with a wide range of congenital abnormalities (e.g., cardiac, facial, parathyroid, renal, radius and thymus anomalies, psychomotor impairment, eczema, immunodeficiency, albinism,...). The presence of hyperlaxity of the joints and skin may be indicative of a connective tissue disorder.

Furthermore, an abnormal distribution of bruising (e.g., on the cheeks, ears, neck, upper arms, torso, genital region, or in the form of slap marks) or abnormal bleeding (including vaginal bleeding in prepubescent girls) should always be considered as possible indications of non-accidental trauma or child abuse (8,9).

TABLE 1: Bleeding disorders (non-exhaustive) based on the three components of coagulation (1-5, 9).

Platelet disorders	
Thrombocytopenia	Decreased production (e.g., congenital platelet deficiencies, bone marrow failure or infiltration, medication) Increased breakdown (e.g. immune thrombocytopenic purpura (ITP), haemolytic uremic syndrome) Pooling (splenomegaly) Dilution
Thrombopathies	Glanzmann thrombasthenia Bernard-Soulier syndrome Other platelet function defects Storage pool diseases Aspirin, anti-aggregants Chronic kidney insufficiency Cardiopulmonary bypass, etc.
Coagulation factor disorders	
Congenital procoagulant deficiencies	Haemophilia A (factor VIII) and B (factor IX) von Willebrand disease (VWD) rare coagulation factor deficiencies (factor II, V, VII, X, XI, XIII) a-, hypo- or dysfibrinogenemia
Acquired deficiencies	Vitamin K deficiency Liver disease Vitamin K antagonists (± overdose) Direct oral anticoagulants (± overdose) Diffuse intravascular coagulation Sepsis Inhibitors
Hyperfibrinolysis	α2-antiplasmin deficiency Plasminogen activator inhibitor-1 deficiency
Vascular	
Ehlers-Danlos syndrome (type IV), other connective tissue disorders	
Osteogenesis imperfecta	
Trauma	
Vitamin C deficiency	affecting collagen formation

Bleeding Assessment Tools

Standardized bleeding assessment tools have been developed to assist clinicians in a systematic evaluation of bleeding symptoms and the determination of the likelihood of an underlying bleeding disorder. The most widely used and validated bleeding assessment tools in paediatrics include the ISTH-BAT (International Society on Thrombosis and Haemostasis Bleeding Assessment Tool) and the Paediatric Bleeding Questionnaire (PBQ) (11-16).

The ISTH-BAT is a widely utilised instrument for both adults and children that assigns a numerical score based on the presence and severity of bleeding symptoms across multiple domains, namely epistaxis, cutaneous bruising, minor wounds, oral cavity, gastrointestinal tract bleeding, bleeding following surgery or dental procedures, haematuria, menorrhagia, post-partum haemorrhage, central nervous system bleeding, muscle haematomas, hemarthrosis and other bleedings. In children, a score of three or higher is considered abnormal and should prompt further evaluation by a paediatric haematologist. However, it is imperative to acknowledge the limitations of this instrument, as it may underestimate bleeding

in younger children who have not yet encountered the common haemostatic challenges that are typically experienced by older children and adults. Furthermore it may exhibit reduced sensitivity for acquired disorders such as immune thrombocytopenia (ITP) (13).

The PBQ is another tool that has been validated for the purpose of screening for VWD in children. The PBQ is a questionnaire that, beside the abovementioned domains, also assigns points for paediatric-specific symptoms, such as cephalohematoma, umbilical cord bleeding, post-venipuncture bleeding, post-circumcision bleeding and macroscopic haematuria. A score of two or more is considered as a 'positive' bleeding score. The PBQ has a high negative predictive value to exclude VWD in children (14-16).

These tools facilitate the standardisation of the evaluation of bleeding symptoms and can assist in determining which children require further laboratory testing or referral to a specialist. The sensitivity and specificity of these tests for predicting bleeding disorders in children are moderate to high depending of the pretest probability, and their interpretation should be informed by clinical judgment and in combination with laboratory findings (11-16) The American Academy of Paediatrics emphasises that while a detailed bleeding history is essential, family and patient history alone are insufficient to rule out bleeding disorders, and abnormal bleeding scores should prompt further evaluation (8).

Laboratory tests

The general strategy for laboratory elaboration of patients with a suspected bleeding disorder is outlined in Figure 2 and Table 3 (1-9,11).

Indications derived from the patient's or family history and physical examination may assist in the selection of preliminary screening tests for increased bleeding tendency. For instance, in a male patient with bleeding symptoms where haemophilia A is present in the family, a Factor VIII (FVIII) level will be determined as early as the first step.

It is also important to interpret laboratory results within the context of the clinical picture, as mild abnormalities may be observed in healthy children or may be influenced by factors such as medication, stress, infection, inflammation or blood type (where blood type O is associated with lower VWF levels). However, pre-analytical errors can also lead to incorrect test results. Examples include incorrectly or insufficiently filled tubes, inadequate mixing, a long period between collection and analysis, and excessive pinching. Furthermore, it should be noted that reference values of aPTT are higher and all coagulation factors (with the exception of FVIII and VWF) are lower in the initial six months following birth in both pre-term and full-term infants when compared with adult values. Consequently, it is strongly recommended that these children undergo re-evaluations at an older age to ascertain the presence of any abnormal values (7,17).

FIGURE 2: Algorithm for a practical approach of children with bleeding symptoms. aPTT: Activated partial thromboplastin time, PT: Prothrombin time, TT: Thrombin time, F: factor, VWF: von Willebrand Factor, FVIII: factor VIII, PFT: platelet function tests, FXIII: factor XIII, PAI-1: plasminogen activator inhibitor-1. Created in biorender.com

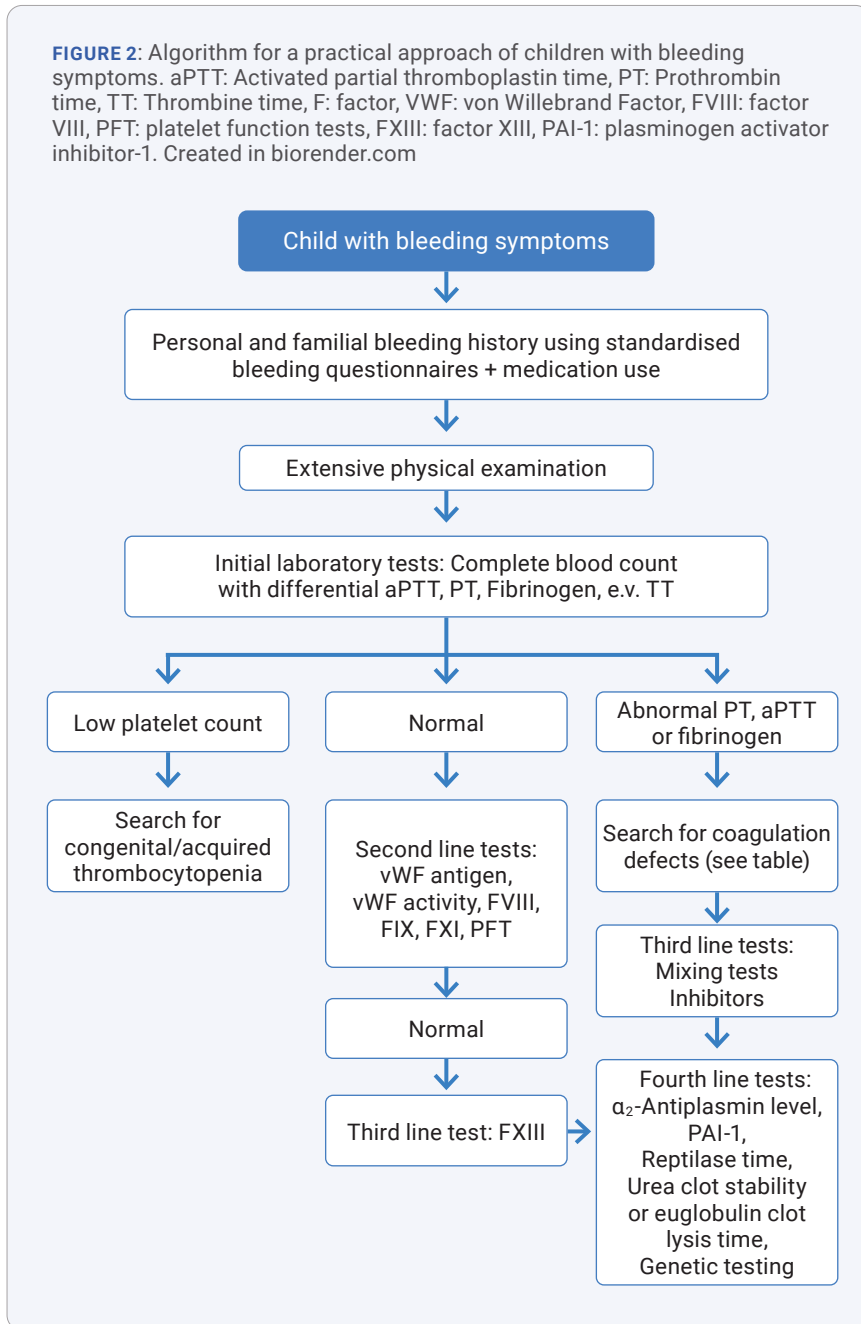


TABLE 2: Differences in presentation of bleeding symptoms in platelet disorders and coagulation factor deficiencies.

	Platelet disorder	Coagulation factor deficiency
Localisation bleeding	Skin Mucosa (epistaxis, gums, vaginal, gastro-intestinal tract)	Deep in soft tissues
Petechiae	Yes	No
Ecchymoses	Small, superficial	Large, deep
Haemarthrosis/muscle haemorrhage	Rare	Frequent
Bleeding after cut or scratch	Yes	No
Bleeding after surgery or trauma	Immediate or delayed (48h), mostly mild	Delayed (48h), mostly extensive

TABLE 3: Perinatal infection Risk (PIR) tool.

aPTT	PT	TT	Fibrinogen	Disorder
Normal	Normal	Normal	Normal	Normal profile, mild factor deficiency (incl. mild VWD), FXIII deficiency, Platelet function disorder, α 2-antiplasmin deficiency, PAI-1 deficiency, connective tissue disorder
↑	Normal	Normal	Normal	Deficiency of FVIII, VWF, FIX, FXI, FXII or lupus anticoagulant
Normal	↑	Normal	Normal	Deficiency of FVII, early liver failure or DIC, warfarin therapy, mild vitamin K deficiency
↑	↑	Normal	Normal	Deficiency of FII, FV, FX, vitamin K deficiency, supratherapeutic vitamin K antagonists, combination of factor deficiencies
↑	Normal or ↑	↑	Normal	Heparin (normal reptilase time)
Normal	Normal	↑	↓ (1-1.5g/L)	Hypofibrinogenemia, mild dysfibrinogenemia
↑	↑	↑	↓ (<1g/L)	Dysfibrinogenemia, afibrinogenemia, late DIC, liver failure

Of note, some patients may have a clinically significant bleeding phenotype but normal tests using the approach described here. However, they may have a bleeding disorder. In these patients genetic testing may help to get to the diagnosis (discussed in another paper of this special issue).

Referral to a paediatric haematologist

It is essential that children with suspected or confirmed bleeding disorders are referred to a paediatric haematologist. The urgency of referral depends on the severity of the symptoms. Immediate referral is indicated for children with life-threatening bleeding, such as intracranial, gastrointestinal or retroperitoneal, joint or muscle bleeding. It is also indicated for children with active bleeding and severe thrombocytopenia. A semi- or non-urgent referral should be considered for children with abnormal laboratory results, such as prolonged aPTT and/or PT on multiple occasions, low factor levels, persistent menorrhagia or a family history of bleeding disorders accompanied by suspicious symptoms. Even when child abuse is suspected, a comprehensive medical history, physical examination and laboratory tests are necessary, and a referral to a paediatric haematologist may be required (8,9).

Referral is also indicated for pre-surgical evaluation in all children with an unexplained history of bleeding, a positive bleeding

score, and/or abnormal laboratory results, in order to ensure appropriate perioperative management. Also, children with a bleeding phenotype of unknown origin should stay in follow-up in a paediatric haematology centre (7,8).

Summary

Easy bruising or bleeding symptoms are commonly observed in children, and it may be challenging for the paediatrician to distinguish between a normal situation, bleeding disorders or non-accidental traumatism and child abuse. The American Academy of Paediatrics stresses the importance of a meticulous evaluation of bleeding symptoms, a comprehensive medical history and physical examination, and a systematic initial laboratory workup. The initial diagnostic approach should be tailored based on clinical presentation and initial test results, with further specialised testing if necessary. Referral to a paediatric haematologist affiliated with a haemophilia centre is crucial for a definitive diagnosis and adequate management.

Statement

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