



# CLINICAL HEMOSTASIS REVIEW

*An Update on Advances and Issues in Hemostasis*

## Evaluation of Purpura in Children

*By Rebecca Jensen, MT(ASCP)*

### INTRODUCTION

Bruising can be the result of normal childhood activities. In some cases, however, bruising can be the initial presentation of a bleeding disorder. Bruising is rare in children under one year of age as is bleeding unless there is an underlying abnormality or the child is subject to non-accidental trauma.

Laboratory evaluation of neonates and children is difficult since venous access is limited and the blood collection may be difficult. The small blood volumes in children also necessitate performance of microcollection techniques in many cases.

Levels of the various blood proteins that participate in coagulation differ in the pediatric population due to the normal maturation of the hemostatic mechanism. It is therefore important to be aware of the age of the child in the evaluation of a potential congenital or acquired hemostatic disorder. Multiple normal ranges are required to discern a clotting disorder because coagulation factors do not follow a normal distribution during development. Furthermore, many of the coagulation proteins do not reach near-adult levels until six months of age and diagnosis of defi-

ciency states in younger individuals is not accurate.

### NORMAL DEVELOPMENT OF THE HEMOSTASIS SYSTEM

Decreased vitamin K levels due to the immaturity of liver in the neonate result in diminished amounts of functional clotting factors of factor II, VII, IX, and X in the healthy infant. Factors II, VII, and X are approximately 50% normal adult levels at birth while factor IX is approximately 30%. These vitamin K-dependent factors reach normal adult levels by two to three months of age and the prothrombin time (PT) generally falls within the adult normal range. See Table 1.

Contact factors develop slowly in the fetus and levels of factors XI, XII, prekallikrein, and high molecular weight kininogen are approximately 40% of adult levels at full term. By six months of age, the contact factors reach normal adult levels and the activated partial thromboplastin time (APTT) generally falls within the adult normal range. Additional blood clotting factors including factor V, factor VIII, and von Willebrand factor are at normal adult levels at birth.

The so called "naturally occurring

**Objective:** The reader will be able to define the purpuric lesions of ecchymoses and petechiae, and discuss the causes of purpura in children.

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anticoagulants" protein C, protein S, and antithrombin are decreased at birth compared to adult levels. Protein C levels rise slowly and are only at approximately 40% normal at six months of age. Adult levels are not achieved until the early teen years. Unlike protein C, protein S develops within the first three to ten months of life. Antithrombin levels reach adult values at approximately six months of age.

Platelet counts at birth are similar to adults with a range of 150,000 to 400,000 x 10<sup>9</sup>. Mean platelet volumes increase over the first few weeks of life and then remain within adult ranges throughout childhood. Remarkably, platelet function is similar to that of adult platelets within 48 hours of age.

### Definitions of Lesions

Purpura describes a dermal lesion of any size or configuration characterized by hemorrhage into the skin. Purpura can be the result of coagulation disorders, mechanical trauma, and systemic conditions that alter the vasculature or surrounding connective tissue. Purpuric lesions can be classified as petechial, or ecchymotic. Petechiae are nonblanching, macular pinpoint lesions less than 3mm in size with well-demarcated borders. Ecchymoses, differ from petechiae only in size and may be the result of a larger hemorrhagic lesion or a confluence of petechiae. Ecchymoses are purple to blue in hue, and fade to greenish-yellow as the extravasated cells deteriorate under the skin. Palpable purpura are raised purpuric lesions that represent a cutaneous manifestation of vasculitis. Purpuric lesions have been described for centuries and in fact acute idiopathic thrombocytopenic purpura was described by Welhof as early as the eighteenth century.

Several other alterations of normal skin tones can be distinguished from purpura upon physical exam. Hematomas are the result of bleeding between tissue planes and are generally greater than 1 cm in size. Erythema is a reddened skin condition due to increased cutaneous blood flow that occurs in association with fever, exercise, or emotional reactions. Telangiectasias are formed due to dilated capillaries commonly seen in the skin or mucous membranes. Unlike purpura, telangiectasias blanch with pressure.

### Clinical Manifestations

Clinical manifestations such as spontaneous bleeding, bleeding from multiple sites, bleeding accompanied by petechiae, multiple or large ecchymoses, or bleeding from unusual sites are highly suggestive of a hemorrhagic disorder and require immediate investigation and attention. Bruising is a common condition, especially in active children. However, bruises which are greater than two to three cm in diameter, more than two or three at once, raised, or away from the typical sites of injury should lead to an investigation of a bleeding disorder or possibly of physical abuse.

Spontaneous or deep tissue hemorrhage, or bleeding into joints or body cavities is most commonly associated with coagulation factor defects, primarily hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency).

The presence of non-palpable purpura generally implies a bleeding diathesis or abnormality of the microvasculature or its connective tissue support. Development of petechiae suggest a defect in primary hemostasis, while ecchymoses suggest an abnormality in fibrin clot formation. Palpable purpura is suggestive of an underlying vasculitis.

### PHYSICAL EXAM AND PATIENT HISTORY

The location, size, appearance (flat vs. raised, blanching vs. non-blanching) and number of purpuric lesions must be characterized. Simple bruising (purpura simplex) is usually characterized by ecchymoses less than 1cm in size. In purpura simplex, bruises tend to involve the extremities and development secondary to trauma. Ecchymosis or purpura larger than 2cm in size, involving the trunk, that develop in the absence of known trauma, suggests a possible hemostatic defect. It should be noted if multiple bruises are evident at various stages of resolution or if bruise configuration suggests the shape of a hand or instrument, as might be seen in lesions induced through nonaccidental trauma. In such instances, children may appear malnourished or neglected.

Bruising is frequent finding in children and does not necessarily herald a bleeding disorders. Up to 30% of children report bruises as often as once a week. Often bruising in children is the



result of trauma incurred during play or in the course of a toddler's attempts at walking. It is rare to observe bruising in children of less than one year of age. When present, a work up for a bleeding disorder should be entertained and consideration given to the possibility of nonaccidental trauma.

The general appearance of the child can provide important clues to the etiology of purpura. Children who appear sick or are febrile may have purpura secondary to sepsis or rickettsial infection (e.g. Rocky Mountain Spotted Fever). In addition, children who have thin skin and small, hyperextensible joints with easy bruisability may have a defect in connective tissue development such as Ehlers-Danlos syndrome. Sever vitamin C deficiency (scurvy) is rare in the pediatric population, and if seen occurs in children with abnormal diets due to psychiatric or developmental problems. Besides purpura, these children usually suffer perifollicular hyperkeratosis, bone pain, and inflammatory gingival disease.

Pediatricians are often important non-biased observers of bruising in infants and children. Suspicion of abuse should be an indication for screening tests to rule out the presence of bleeding disorders.

Along with the physical exam, a personal and family history can be paramount in detecting the presence of a bleeding disorder and distinguishing it from the nonpathologic bruising often seen in children. Table 2 suggests some questions which can be used during the investigation of a purpuric disorder in children.

## **DIFFERENTIAL DIAGNOSIS AND CAUSES OF PURPURA**

The presence of petechiae usually indicates vascular or platelet disorder, although some otherwise normal children develop petechiae (pressure purpura) on the face following vomiting or coughing episodes. Ecchymoses greater than 2 cm in diameter may indicate systemic hemorrhagic diathesis.

## **CLASSIFICATION OF PURPURA IN PEDIATRIC PATIENTS**

### **Palpable Purpura**

Palpable purpura are raised lesions that suggest underlying inflammation of the blood vessel wall. The most common forms of vasculitis in children are anaphylactoid purpura (Henoch

Schonlein Purpura [HSP]) and Kawasaki's disease. Purpuric papules and hemorrhagic bullae develop secondary to extravasation of red cells from the damaged vessels. In HSP, wheals and ecchymoses develop primarily over the extremities. Most children with HSP also complain of arthralgias and abdominal pain. Laboratory studies typically show evidence of renal impairment, with normal or elevated platelet count and normal PT and APTT. Kawasaki syndrome, also known as mucocutaneous lymph node syndrome is seen predominantly in children. It is an immune complex mediated vasculitis with multisystem involvement. Children typically present with fever, cervical lymphadenopathy, erythematous palms and soles, injection of the conjunctiva and rash.

### **Heritable Connective Tissue Disorders**

Individuals with hereditary defects in structural proteins such as collagen, frequently suffer easy bruising. This group of disorders includes Ehlers-Danlos Syndrome (EDS), osteogenesis imperfecta, and Marfan syndrome. In each of these disorders, hemostatic tests are usually normal. The easy bruisability is due to increased vascular fragility secondary to the structural protein deficit. EDS is a group of inherited disorders characterized by a defect in collagen production. Most varieties have in common thin skin, small hyperextensible joints, easy bruising and abnormal scarring. Diagnosis is based on physical findings, family history and in some cases evaluation of skin biopsy. Osteogenesis imperfecta is characterized by brittle bones and blue sclerae and in some patients easy bruising. Marfan syndrome is relatively common with an incidence of 1 in 10,000 and is characterized by tall stature with long extremities and cardiovascular manifestations such as dissecting aortic aneurysm.

### **Pigmented Purpuric Eruptions of Childhood**

Also known as capillaritis, pigmented purpura represent a group of benign dermatoses that present as pinpoint petechiae and purpura on a hyperpigmented base, usually on the legs. The etiology is unknown. The disorders may last months to years. The lesions are generally asymptomatic although

are sometimes associated with pruritis. Although diagnosis can be made by clinical appearance alone, skin biopsy is sometimes performed. Histologically, the pigmented purpura are characterized by dermal extravasation of erythrocytes and hemosiderin deposition. Two forms of pigmented purpura, specifically lichen aureus and Majocchi disease occur predominantly in children and young adults. Schamberg disease, another common form of pigmented purpura, may occur at any age. Typically there is no laboratory evidence of thrombocytopenia nor disorders of coagulation in patients with pigmented purpura.

### **Infectious Diseases**

Ecchymoses and dermal hemorrhage is frequently seen in patients with bacterial or viral sepsis and is a cutaneous manifestation of microvascular fibrin deposition. Acute meningococemia, disseminated gonococemia and Rocky Mountain Spotted Fever (RMSF) are typically associated with purpuric lesions. The rash in early RMSF consists of pink macules which blanch although over time, red cell extravasation occurs and the lesions become purpuric consisting of petechiae and ecchymoses. The lesions associated with disseminated gonococemia begin as petechiae and erythematous pustules but soon develop into purpuric pustules. In patients with meningococemia (even in the absence of DIC), petechiae and ecchymoses may be seen on the trunk and extremities.

Cutaneous lesions are commonly seen in patients in DIC and in almost 50% of patients, dermal lesions are the initial manifestation of this disorder. Recognition of these cutaneous lesions can lead to early diagnosis and initiation of appropriate therapy. The most common dermal lesion seen with DIC include petechiae, purpura, hemorrhagic bullae and purpura fulminans. The purpura associated with DIC may be palpable. Skin biopsy most often reveals microthrombi within dermal vasculature with red cell extravasation and in later biopsies, epidermal necroses.

Purpura fulminans is the sudden development of confluent ecchymotic skin lesions, especially involving the extremities, in association with DIC. Purpura fulminans is more common in children than in adults and in the major-

Hemostatic Parameter	Level at Birth	Children (age 6-10)	Adult Levels
Activated Partial Thromboplastin Time (sec)	42.9 (31.3-54.3)	same as adult	33.5 (26.6-40.3)
Prothrombin Time (sec)	13.0 (10.1-15.9)	same as adult	12.4 (10.8-13.9)
Thrombin Clotting Time (sec)	23.5 (19.0-28.3)	same as adult	25.0 (19.7-30.3)
Fibrinogen (g/L)	2.83 (1.67-3.99)	2.79 (1.57-3.73)	2.78 (1.56-4.00)
Factor II (U/ml)	0.48 (0.26-0.70)	0.88 (0.67-1.07)	1.08 (0.70-1.46)
Factor V (U/ml)	0.72 (0.34-1.08)	0.90 (0.63-1.16)	1.06 (0.62-1.50)
Factor VII (U/ml)	0.66 (0.28-1.04)	0.85 (0.52-1.20)	1.05 (0.67-1.43)
Factor VIII (U/ml)	1.00 (0.50-1.78)	0.95 (0.58-1.32)	0.99 (0.50-1.49)
Factor IX (U/ml)	0.53 (0.15-0.91)	0.75 (0.63-0.89)	1.09 (0.55-1.63)
Factor X (U/ml)	0.40 (0.12-0.68)	0.75 (0.55-1.01)	1.06 (0.70-1.52)
Factor XII (U/ml)	0.53 (0.13-0.93)	0.92 (0.60-1.40)	1.08 (0.52-1.64)
Factor XIIIa (U/ml)	0.79 (0.27-1.31)	1.09 (0.65-1.51)	1.05 (0.55-1.55)
Factor XIIIb (U/ml)	0.76 (0.30-1.22)	1.16 (0.77-1.54)	0.97 (0.57-1.37)
von Willebrand factor (U/ml)	1.53 (0.50-2.87)	0.95 (0.44-1.44)	0.92 (0.50-1.58)

**TABLE 1.** Reference Values for Coagulation Tests in the Healthy Full-term Infant, Child, and Adult.

let counts in women with ITP are not good predictors of low platelet counts in newborns, and in fact the majority of infants born to women with ITP in pregnancy have normal platelet counts at birth. Neonatal thrombocytopenia is typically self-limiting and platelet counts return to normal within three to four weeks. Other clinical conditions of the neonate that can be associated with thrombocytopenia include infections, respiratory distress syndrome, and congenital disorders such as Fanconi's aplastic anemia, May-Hegglin anomaly and Wiscott-Aldrich syndrome.

Acute Immune thrombocytopenic purpura (AITP) is a common disease in childhood and occurs most commonly in children from two

ity of cases is associated with severe deficiency of Protein C (PC) or Protein S (PS), which may be genetic or acquired. Children born with homozygous PC or PS deficiency may present with purpura fulminans the first week of life. The condition is fatal unless treatment is initiated. Acquired severe deficiencies of PC may occur in sepsis and in meningococcal or group B streptococcal infections. Antibodies to PS have been described in children with recent varicella infection causing severe PS deficiency and purpura fulminans. Childhood infection related purpura fulminans with DIC has a 50% mortality.

#### **Congenital and Acquired Factor Deficiencies**

Easy bruising is a commonly manifestation of congenital or severe acquired coagulation factor deficiencies, such as hemophilia A and hemophilia B. Vitamin K deficiency related to breastfeed-

ing, malabsorption or prolonged fasting is an important cause of acquired bleeding tendency which may be associated with easy bruising.

#### **Thrombocytopenia**

Thrombocytopenia, defined as platelet count less than  $150 \times 10^9$  can present at any age and may be associated with development of petechiae. Normal adult platelet counts of  $250,000/\text{mm}^3$  are reached by 18 weeks of gestation. The etiology of neonatal thrombocytopenia is diverse and includes increased destruction, decreased production, splenic pooling of platelets or a combination of these mechanisms.

Maternally-related causes of neonatal thrombocytopenia include immune thrombocytopenic purpura (ITP), idiopathic thrombocytopenia, Rh disease, maternal drug use, and preeclampsia. Of these disorders, maternal ITP is the most common. Maternal plate-

to six years of age and affects both sexes equally. Some adult cases are reported occasionally. In almost 85% of cases, the onset of AITP occurs one to three weeks after an acute viral illness. Sudden onset of petechiae, ecchymoses, and purpura are frequently the initial manifestations of AITP. Thrombocytopenia can be marked and platelet counts below  $20,000 \times 10^9$  are common. The duration of thrombocytopenia is three to six days but may recur.

Drug induced immune thrombocytopenia may affect children and neonates. Heparin-induced thrombocytopenia (HIT) has been reported in children as well as neonates. In those patients receiving heparin, platelet counts should be checked every two to three days. Although the incidence of HIT in pediatric patients is not known, a high degree of mortality and morbidity is associated with the finding.

1. Does the child have a bleeding history such as bleeding from the umbilical stump at birth or with circumcision?
2. Does the family have a history of bruising or bleeding disorders?
3. If and when purpura develop, do they occur in unusual locations such as the trunk?
4. Do the lesions only appear at pressure points or with events such as vomiting or coughing episodes, or around the elastic of clothing?
5. What is the ethnic origin of the child?
6. Has the child had major surgery without excessive bleeding?
7. Was the surgery prior to or following the current bleeding event?
8. Is the bleeding typically from a single site or multiple sites?
9. Does the child experience recurrent epistaxis? Have nosebleeds required emergency room treatment? Is the bleeding from both nares or unilateral?
10. If the child has experienced trauma, is the bleeding appropriate for the extent of trauma?
11. Is the bleeding prolonged, delayed, or recurrent?
12. What medications have been given that may have contributed to the bleeding?
13. Have there been recent dietary changes that may influence the bleeding?
14. Are other disease states present such as liver disease, renal disease, leukemia, or myeloproliferative disorders that may be associated with hemorrhage?

**TABLE 1.** These questions can be used when obtaining patient history to ascertain the likelihood of a bleeding disorder.

## CONCLUSION

The physician should be alert to causes of purpuric lesions in children including normal childhood activities that can result in bruising. Characterization of the lesions as well as complete patient and family history are paramount in the accurate diagnosis of pathologic bleeding in this population. Infectious and drug-related causes of purpura should be ruled out in children presenting with bruising.

**KEYWORDS:** *purpura, children, pediatric, primary hemostasis, platelets, bruising, ecchymoses, petechiae*

## REFERENCES

Andrew M, Schmidt B. *Hemorrhagic and thrombotic complications in children*. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, Third Edition. Philadelphia, PA: Lippincott Company. 1994;989-1022.

Banfield CC, Wilkinson JD. *Pigmented purpuric dermatitis*. *eMedicine Journal*. 2002;3(2):1.

Cahill MR, Lilleyman JS. *The rational use of platelet transfusions in children*. *Semin Thromb Hemost*. 1998;24(6):567.

Coulter Viewpoint. *Pediatric normal ranges*. Spring, 1995.

George JN. *How I treat patients with thrombotic thrombocytopenic purpura - hemolytic uremic syndrome*. *Blood*. 2000;96(4):1223.

Goodnight SH, Hathaway WE. *Bleeding associated with vascular disorders*. In: *Disorders of Hemostasis and Thrombosis: A Clinical Guide*, Second Edition. San Francisco, CA: McGraw-Hill. 2001;207-216.

Goodnight SH, Hathaway WE. *Evaluation of bleeding tendency in the outpatient child and adult*. In: *Disorders of Hemostasis and Thrombosis: A Clinical Guide*, Second Edition. San Francisco, CA: McGraw-Hill. 2001;52-60.

Jensen R. *Bleeding and clotting in the pediatric patient*. *Clinical Hemostasis Review*. 1999;13(8):1.

Jimenez JJ, Jy W, Mauro LM, Horstman LL, S Yeon. *Elevated endothelial microparticles in thrombotic thrombocytopenic purpura: Findings from brain and renal microvascular cell culture and patients with active disease*. *Br J Haematol*. 2001;112:81.

Kitchens CS. *Purpura and related hematovascular lesions*. In: Kitchens CS, Alving BM, Kessler CM, eds. *Consul-*

*tative Thrombosis*. Philadelphia, PA: WB Saunders Company. 2002;149-164.

Knöfler R, Weissbach G, Kuhlisch E. *Platelet function tests in childhood. Measuring aggregation and release reaction in whole blood*. *Semin Thromb Hemost*. 1998;24(6):513.

Kühne T, Imbach P. *Chronic immune thrombocytopenic purpura in childhood*. *Semin Thromb Hemost*. 1998;24(6):549.

Manco-Johnson M. *Current topics in neonatal and pediatric coagulation*. Source: unknown.

Michelson AD. *Platelet function in the newborn*. *Semin Thromb Hemost*. 1998;24(6):507.

Monagle PT, Andrew M. *Hemorrhagic and thromboembolic complications during infancy and childhood*. In: Colman RW, ed. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. Philadelphia, PA: Lippincott Williams and Wilkins. 2001;1053.

Parker F. *Skin diseases of general importance*. In: Goldman L, Bennett JC. *Textbook of Medicine*. Vol. 2/21<sup>st</sup> Edition. Philadelphia, PA: W.B. Saunders Company. 2000;2276-2298.

- Practical treatment guidelines: Warfarin therapy in children.* Available at <http://is.dal.ca/~mscully/warfchil.html/>. Accessed 2 February 1997.
- Pyeritz RE. *Ehlers-Danlos syndromes.* In: Goldman, L, Bennett JC. Textbook of Medicine. Vol. 1/21<sup>st</sup> Edition. Philadelphia, PA: W.B. Saunders Company. 2000:1119-1120.
- Rand ML, Carcao ML, Blanchette VS. *Use of the PFA-100® in the assessment of primary platelet-related hemostasis in a pediatric setting.* Semin Thromb Hemost. 1998;24(6):523.
- Robboy SJ, Mihm MC, Colman RW, Minna JD. *The skin in disseminated intravascular coagulation.* Br J Dermatol. 1973; 88:221.
- Sutor AH. *Acute immune thrombocytopenia in childhood. Are we treating the platelet count?* Semin Thromb Hemost. 1998;24(6):545.
- Taylor MRH, Holland CV, Spencer R, Jackson JF, O'Connors GI, O'Donnell JR. *Haematological reference ranges for schoolchildren.* Clin Lab Haem. 1997;19:1.
- Tristani-Firouzi P, Meadows KP, Vanderhooft S. *Pigmented purpuric eruptions of childhood: A series of cases and review of literature.* Pediatr Dermatol. 2001;18(4):299.
- Tsai HM. *Laboratory aspects of thrombotic thrombocytopenic purpura.* Hemostasis and Thrombosis Update. Temple University, Philadelphia, PA. 2001.
- Van Ommen CH, van Wijnen M, de Groot FG, van der Horst CM, Peters M. *Postvaricella purpura fulminans caused by acquired protein S deficiency resulting from antiprotein S antibodies: Search for the epitopes.* J Pediatr Hematol Oncol. 2002; 24(5):413.
- Walker I. *Classification of bleeding disorders.* In: Ginsberg J, Kearon C, Hirsh J (Eds). Critical Decisions in Thrombosis and Hemostasis. Ontario, Canada: B.C. Decker Inc.. 1998;330-337.
- Walker I. *Clinical assessment of excessive bleeding.* In: Ginsberg J, Kearon C, Hirsh J (Eds). Critical Decisions in Thrombosis and Hemostasis. Ontario, Canada: B.C. Decker Inc.. 1998;311-15.
- Walker I. *Investigation of abnormal bleeding.* In: Ginsberg J, Kearon C, Hirsh J (Eds). Critical Decisions in Thrombosis and Hemostasis. Ontario, Canada: B.C. Decker Inc.. 1998;316-321.
- Warkentin TE. *Diagnosis and treatment of disseminated intravascular coagulation.* In: Ginsberg J, Kearon C, Hirsh J (Eds). Critical Decisions in Thrombosis and Hemostasis. Ontario, Canada: B.C. Decker Inc.. 1998;322-329.
- Warner M, Kelton JG. *Approach to the patient with thrombocytopenia.* In: Ginsberg J, Kearon C, Hirsh J (Eds). Critical Decisions in Thrombosis and Hemostasis. Ontario, Canada: B.C. Decker Inc.. 1998;338-348.
- Weinstein M, Babyn P, Zlotkin S. *An orange a day keeps the doctor away: Scurvy in the year 2000.* Pediatrics. 2001; 108(3):E55.