Bleeding Disorders in Congenital Syndromes

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Children with congenital syndromes with multiple anomalies need a multidisciplinary approach to their care, along with continued surveillance for rare manifestations such as a bleeding diathesis, which may not be evident at diagnosis. This accompanying bleeding diathesis due to thrombocytopenia or other coagulation defects may be a part of the syndrome that is not routinely addressed. Consequently, this may go unrecognized in these children until they face hemostatic challenges, which is not uncommon (given the number of corrective surgeries performed for the congenital defects) in this population leading to unanticipated surgical bleeding. Counseling for these families should include discussions regarding potential spontaneous or trauma-related bleeding associated with these syndromes that can evolve over time. This review aims to highlight congenital syndromes where hemostatic defects have been reported, aid the treating primary care physician (PCP) to adequately workup these patients as part of surveillance or before scheduled procedures and recommends guidelines for appropriate and timely referral to the hematologist.

Achieving hemostasis is a complex process starting with endothelial injury that results in platelet plug formation, which is then strengthened by deposition of fibrin formed by the proteolytic coagulation cascade. Platelets initially attach to subendothelial collagen and von Willebrand factor (vWF) via glycoproteins VI and 1bα (GPVI, GPIbα). This leads to activation of platelets releasing Thromboxane A2 (TxA2) and conforming the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on the platelet surface into its high affinity state, which now binds to fibrinogen and vWF. This further leads to release of platelet granule contents (fibrinogen, Factor V, platelet factor 4, Calcium, ADP, ATP, serotonin, vWF) leading to an extremely procoagulant surface and

abstract

Pediatricians provide a medical home for children with congenital syndromes who often need complex multidisciplinary care. There are some syndromes associated with thrombocytopenia, inherited platelet disorders, factor deficiencies, connective tissue disorders, and vascular abnormalities, which pose a real risk of bleeding in affected children associated with trauma or surgeries. The risk of bleeding is not often an obvious feature of the syndrome and not well documented in the literature. This makes it especially hard for pediatricians who may care for a handful of children with these rare congenital syndromes in their lifetime. This review provides an overview of the etiology of bleeding in the different congenital syndromes along with a concise review of the hematologic and nonhematologic clinical manifestations. It also highlights the need and timing of diagnostic evaluation to uncover the bleeding risk in these syndromes emphasizing a primary care approach.


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platelet aggregation. The stage is now set for the cascade of serine proteases (factors V, VII, VIII, IX, X, XI, XII, XIII) activated by the release of tissue factor, which culminate in the cleaving of thrombin to form an insoluble fibrin mesh leading to a stable clot at the site of injury. With the many players involved in coagulation, it can be seen how the clinical bleeding phenotype can be modified by gene–gene interactions by improving or worsening the integrity of clot formation directly or indirectly. Therefore, this review will focus on congenital syndromes associated with quantitative (thrombocytopenia) and qualitative platelet function defects (ie, defects in platelet generation or defects at 1 or more levels of platelet activation) and coagulation factor deficiencies. It will also highlight congenital syndromes where bleeding can result from defects in the underlying connective tissue or anatomic malformations that increase predisposition to bleeding. It will further discuss basic evaluation of these patients on the basis of a high index of suspicion and highlight what phenotypes need specialist referral for both health maintenance and prevention of surgical bleeding and discuss general treatment principles. Table 1 and Supplemental Tables 5 and 6 summarize the key features of the congenital syndromes discussed in this review.

### COMMON CONGENITAL SYNDROMES ASSOCIATED WITH A BLEEDING DIATHESIS

#### Chromosomal Syndromes

A fault in chromosome distribution during cell division leads to aneuploidy, which can be associated with thrombocytopenia but is rarely severe. Hohlfeld et al in a study of 5194 fetal blood samples (17 to 41 weeks) reported 4.7% samples (247 samples) with thrombocytopenia (platelet counts <150 000/μL), out of which 17% (43 samples) were due to chromosomal anomalies. The prevalence was 54% in Trisomy 13, 86% in Trisomy 18, 31% in Turner syndrome, and 6% in Trisomy 21–Down syndrome (DS). However, Hord et al reported mild to moderate thrombocytopenia (platelet counts 40 000–100 000/μL) in 28% of neonates with DS. The exact mechanism is not known, but is thought to be due to decreased platelet production, from chronic fetal hypoxia, which also leads to intrauterine growth retardation. DS (Trisomy 21) is also associated with other hematologic findings, such as polycythemia, neutropenia, abnormal circulating blasts, erythroblastosis, and giant platelets. Approximately 10% of neonates with DS have transient myeloproliferative disorder, which can present with isolated thrombocytopenia or thrombocytosis, leukocytosis, or persistent peripheral blood blasts. These abnormal blood cells will self-resolve in most infants by 3 months after birth; however, 20% can have more progressive disease. Both transient myeloproliferative disorder and myeloid leukemia associated with DS (ML-DS), which presents at 1 to 4 years of age, have somatic mutations in the megakaryocyte erythroid transcription factor GATA-1. ML-DS has a preceding myelodysplastic phase with patients presenting with progressive anemia and thrombocytopenia, which then develops into leukemia. DS-associated acute lymphoblastic leukemia develops after age 4 years, presenting with cytopenias, and often lower platelet counts than ML-DS patients. Therefore, all DS patients should have a complete blood cell count at birth and if found to have any hematologic abnormalities should be referred to hematology. Other trisomies such as Trisomy 13 and Trisomy 18 have very distinct clinical patterns (Table 1), and the diagnosis is usually made soon after birth. Although survival beyond infancy is rare, life expectancy is improving. Recognizing thrombocytopenia is important because these conditions have associated cardiac, respiratory, and craniofacial anomalies that may need corrective or palliative surgeries. Surgical planning in these patients needs a multidisciplinary team with screening blood work to identify thrombocytopenia, which if present will need platelet transfusions pre- and postoperatively depending upon the complexity of the surgery guided by the hematologist.

Turner syndrome (45, X) can be associated with transient thrombocytopenia (31% of patients) in the newborn period. Due to the single functional X chromosome, girls can inherit X-linked conditions like hemophilia, but this has only very rarely been described. Therefore, prolonged bleeding events warrants referral to a hematologist for workup. Gastro-enteral bleeding can occur in Turner syndrome due to associated inflammatory bowel disease or often unrecognized intestinal telangiectasias (incidence of 7%). DiGeorge syndrome (22q11.2 del) is the most common micro deletion syndrome with associated mild macrothrombocytopenia in 30% of patients resulting from deletion of the contiguous GP1BB gene in the deleted Chromosome 22q11 locus, which codes for the subunit of the platelet adhesion receptor. Immune dysfunction is common in these patients and it is estimated that immune thrombocytopenic purpura is 200 times more common in these patients as compared with the general population. These platelet abnormalities need to be identified early on and specifically before corrective cardiac surgeries. Close collaboration with a hematologist before these surgeries will help avert bleeding complications.

Noonan syndrome is a relatively common autosomal dominant
multisystem disorder with a prevalence of 1 in 1000 to 2500 individuals. Patients with Noonan syndrome with germ-line mutations in PTPN11 need to be monitored for the development of myeloproliferative disorder or juvenile myelomonocytic leukemia. Prevalence of bleeding disorders in Noonan syndrome has been well described (ranging between 50% and 89%) if positive bleeding history or abnormal hemostatic laboratory values are considered, whereas it ranges between 10% and 42% if both history and laboratory values are considered. Thrombocytopenia is not reported as commonly; however, platelet function defects are frequent with a prevalence of 27%. Up to 37% of these patients can have factor XI deficiency while von Willebrand disease and mixed factor deficiencies are also reported. Due to the complex phenotype, a significant proportion of these patients need surgical procedures. A reasonable screening process can begin with obtaining a platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and Factor XI levels at a minimum even in the absence of bleeding symptoms and if there is a significant bleeding history to include platelet function testing and testing for other components of the clotting cascade in consultation with the hematologist.

Connective Tissue Disorders

Easy bruising and bleeding are prominent manifestations of heritable collagen disorders with Ehlers-Danlos syndrome

### TABLE 1 Features of Congenital Syndromes Associated With Thrombocytopenia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence</th>
<th>Clinical Features</th>
<th>Incidence of Thrombocytopenia</th>
<th>When to Refer to Hematology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>1 in 660</td>
<td>Cognitive impairment, hearing issues, thyroid issues, heart defects, gastroenteral atresias, cataracts</td>
<td>7–26%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All patients with any hematologic abnormalities</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1 in 5000</td>
<td>Cleft lip and palate, polydactyly, rocker bottom feet, cutis aplasia, omphalocele, VSD, PDA, neural tube defects</td>
<td>54%&lt;sup&gt;a&lt;/sup&gt; (All patients had platelet counts &gt;100,000/μL)</td>
<td>Platelet count &lt;150,000/μL</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1 in 5000</td>
<td>Dolichocephaly, micrognathia, overriding fingers, cardiac septal defects, horse shoe kidney, psychomotor retardation, feeding issues</td>
<td>86%&lt;sup&gt;a&lt;/sup&gt; (20% with platelet counts 50,000–100,000/μL)</td>
<td>Platelet count &lt;150,000/μL</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>1 in 2500</td>
<td>Coarctation of aorta, aortic stenosis, short stature, ovarian failure, horseshoe kidney, cubitus valgus, low posterior hairline, webbed neck</td>
<td>31%&lt;sup&gt;a&lt;/sup&gt; (18% with platelet counts 50,000–100,000/μL)</td>
<td>Platelet count &lt;100,000/μL or between 100,000 and 150,000/μL and needs surgery</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>1 in 4000</td>
<td>Typical facies, thymic abnormalities, hypocalcemia, velopharyngeal insufficiency, conotruncal cardiac defects, tetralogy of Fallot, truncus arteriosus, aortic arch anomalies</td>
<td>30%&lt;sup&gt;b&lt;/sup&gt; (Usually mild macrothrombocytopenia)</td>
<td>Platelet count &lt;150,000/μL and/or rapidly falling platelet counts in the context of viral illness should be referred to rule out ITP</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>1 in 1000–2500</td>
<td>Facial dysmorphism, cardiac anomalies, short stature, bony and genital anomalies.</td>
<td>6.2%&lt;sup&gt;b&lt;/sup&gt; (27% have platelet function defects)</td>
<td>Any patient with thrombocytopenia and all patients before surgery to evaluate platelet function and other components of clotting cascade.</td>
</tr>
<tr>
<td>Wiskott–Aldrich syndrome</td>
<td>1 in 4 million</td>
<td>Microthrombocytopenia, eczema, immune defects</td>
<td>Microthrombocytopenia is universal feature (platelet counts 5000–50,000/μL)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Refer all patients. Also refer to Immunology.</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td>1 in 10,000</td>
<td>Growth retardation, synphrys, limb abnormalities and cognitive impairment</td>
<td>35% (15/43 patients) with platelet counts &lt;100,000/&lt;sup&gt;d&lt;/sup&gt; (16% had ITP with majority progressing to chronic ITP; 11% had transient thrombocytopenia)</td>
<td>Check platelet count at diagnosis and every 5 years if asymptomatic. Platelet count &lt;100,000 or rapidly falling platelet count refer to hematologist to rule out ITP</td>
</tr>
<tr>
<td>Jacobsen syndrome</td>
<td>1 in 100,000</td>
<td>Dymorphogenesis of hands and feet, frequent cardiac defects and cognitive impairment</td>
<td>Macrothrombocytopenia (88.5%) with varying degrees of platelet function defects (platelets with giant α granules, storage pool defects and delayed maturation of megakaryocytes)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Any patient with thrombocytopenia and all patients before surgery to evaluate platelet function.</td>
</tr>
</tbody>
</table>

PDA, patent ductus arteriosus; VSD, ventricular septal defect.

<sup>a</sup> Prevalence data from fetal samples (Hohlfeld et al).
(EDS) being the most prevalent. Although collagen proteins are an integral part of capillary scaffolding, they also contribute to platelet activation, adhesion, and aggregation. EDS is a clinically and genetically heterogeneous group of conditions with varying degrees of skin hyperextensibility, joint hypermobility, delayed wound healing, and atrophic skin scarring. There are 5 subtypes with a combined prevalence rate of 1 in 5000 individuals. Type IV EDS (vascular type) carries the gravest prognosis affecting medium and large sized vessels. It can initially present as easy bruising and gum bleeding, but depending on the vessels affected can have bleeding from every possible site of the body, including fatal intraabdominal bleeding. The other subtypes of EDS manifest with soft, fragile hyperextensible skin along with joint dislocations and bony abnormalities. The diagnosis is often challenging in children, especially when there is no family history and can lead to extensive hemostasis-related bleeding workups, which are often normal. In the office setting, clinicians can use the Beighton scoring system (Fig 1) for evaluation of joint hypermobility and refer patients with high scores to the geneticist for further evaluation and confirmatory genetic testing. Capillary fragility is common among all subtypes with variable degrees of platelet function defects and coagulation factor deficiencies (factors VIII, IX, XI, XII, and XIII) being reported. Desmopressin has been shown to reduce bleeding risk and postoperative bleeding in pediatric patients with EDS, suggesting that a weakened platelet collagen interaction underlies the bleeding tendency in EDS. Therefore, individuals with suspected or confirmed diagnosis of EDS with any bleeding symptoms or planned surgical procedures should be referred to a hematologist.

**Abnormalities in Vasculature**

Hereditary hemorrhagic telangiectasia (HHT) or Osler–Weber–Rendu syndrome is a common autosomal inherited disorder with altered defects in vascular integrity with an incidence of 1 in 5000 individuals. The underlying genes ENG, ACVRL1, SMAD4 encode proteins leading to elevated expression of vascular endothelial growth factor. This leads to characteristic clinical manifestations of dilated and tortuous postcapillary venules (telangiectasias) without intervening capillaries, which have a higher propensity to bleed due to inherently elevated perfusion pressures. In HHT, telangiectasias can develop in the nasal mucosa within the first decade and worsen with age, presenting with severe and recurrent nosebleeds. While evaluating significant and prolonged epistaxis in a pediatric patient, the PCP should inquire about bleeding from other sites, presence of anemia and gastro-enteral bleeding, and strokes related to arterio venous malformations among close family members. It

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**FIGURE 1**

The Beighton Scoring system for joint hypermobility. Degree of mobility assessed by passive maneuvers in 5 joints. Total score: 0–9. Hypermobility score: ≥5. (Figure reproduced with permission from Arthritis Research UK; http://www.arthritisresearchuk.org)
might be difficult to make a diagnosis in childhood as characteristic telangiectasias are often not present until later or present as benign-looking mucocutaneous red spots that go unnoticed by providers. 

Otorhinolaryngologists should be consulted early on in a child with prolonged recurrent nose bleeds to look for these telangiectasias without which the diagnosis may be missed until a later encounter with a life-threatening bleeding episode.

**RARE CONGENITAL SYNDROMES ASSOCIATED WITH A BLEEDING DIATHESIS**

**Inherited Platelet Disorders**

Many of the inherited thrombocytopenias are clinically mild and may go unrecognized unless faced with hemostatic stressors such as menses, surgery, trauma, or childbirth. A thorough bleeding history is a crucial component in the evaluation of these patients, including obtaining previous blood counts if available. Particularly, time should be devoted to eliciting the family history with special attention to hemostatic stressors such as menorrhagia, bleeding after teeth extractions, blood transfusions after surgery, or unexplained anemia. Platelet counts should be determined in family members with bleeding symptoms. The pattern of bruising and bleeding disproportionate to trauma should raise suspicion for nonaccidental trauma even in patients in whom congenital platelet disorders are suspected. The use of standardized bleeding assessment tools is very useful in this setting. The Pediatric Bleeding Questionnaire identified high bleeding scores (>96% of patients) in a cohort of 23 patients with known inherited platelet disorders.

**Diagnostic criteria**

Supplemental Table 5 outlines the various features of inherited thrombocytopenic syndromes. The underlying molecular defect can be restricted to platelets alone or in some cases can involve other cells thereby resulting in multisystem dysfunction. Evaluation of the patient and the family for presence of immune deficiency, hearing loss, albinism, and renal findings will point to an underlying syndromic cause of thrombocytopenia. This is further complicated by the fact that all components of the syndrome may not be present in affected individuals and therefore a high index of suspicion is key to their diagnoses. While working up these patients, it is important to collect fresh blood samples with citrate as the anticoagulant to eliminate the phenomenon of pseudothrombocytopenia. Automated platelet counters are not accurate in the presence of macro or micro thrombocytopenia and manual inspection of peripheral smears under Giemsa or Wright stain provide important information regarding platelet number, size, and granularity. After recognition of these syndromes, further diagnostic evaluation of platelet disorders needs careful preparation (a nontraumatic blood draw to preserve component proteins of the coagulation cascade), specimen handling, and interpretation and should be carried out in conjunction with an experienced hematologist who can accurately interpret the clinical and laboratory findings. Although light transmission aggregometry and its modification lumiaggregometry are used for initial screening for platelet function defects, there are limitations of standardization and reproducibility. However, it can help identify platelet adhesion or aggregation defects, platelet granule release defects on the basis of which further confirmatory testing can be carried out.

Wiskott–Aldrich syndrome is a rare autosomal recessive disorder due to defects in the WASP gene (Xp 11.22) with an incidence of 4 per million live births. The clinical features classically include the triad of microthrombocytopenia (platelet counts 5000–50,000/µL) presenting as bruising and purpura in the neonatal period, eczema that develops around infancy and immune defects with recurrent sinopulmonary infections in midchildhood. A high index of suspicion should prompt referral to a hematologist who may recommend splenectomy to ameliorate bleeding symptoms associated with thrombocytopenia or bone marrow transplantation, which is usually curative (Table 1 and Supplemental Table 6).

**Bone Marrow Failure Syndromes**

Thrombocytopenia in inherited bone marrow failure syndromes (IBMFS) presents as a component of progressive marrow failure, which is the hallmark of these syndromes. Thrombocytopenia may present in the neonatal period in congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radii (TAR) manifesting as petechial bleeding and rarely leading to catastrophic intracranial...
hemorrhage. Unlike other IBMFS, the thrombocytopenia in TAR improves after infancy and may rise to levels safe to perform surgery, suggesting that nonlife-threatening procedures could be delayed until after infancy. Fanconi anemia presents with thrombocytopenia as the first hematologic manifestation during midchildhood, whereas in Shwachman–Diamond syndrome it appears later, having been preceded by neutropenia for variable amounts of time. Supplemental Table 6 outlines the various IBMFS that have thrombocytopenia as part of the syndrome. The pathognomonic physical features can aid in recognizing the underlying IBMFS, but it is important to realize that half of these patients may not be recognized until adulthood.

Chromosomal Disorders

Cornelia De Lange syndrome (heterozygous mutation of NIPBL gene) is an autosomal dominant rare inherited disorder that can have transient thrombocytopenia at birth. More recently a higher incidence of chronic immune thrombocytopenia (ITP) in these patients has also been described (see Table 1). Self-injurious behavior is often a component of the syndrome that compounded with thrombocytopenia can lead to an increased risk of intracranial bleeding. It has been proposed to get platelet counts for these patients at diagnosis, with any unusual bleeding symptoms and at 5 yearly intervals if asymptomatic and refer to hematology for severe bleeding symptoms.

Jacobson syndrome (11q syndrome) is perhaps the most well described congenital syndrome with thrombocytopenia that poses significant morbidity to affected children. The clinical phenotype is variable with macrothrombocytopenia a frequent (88.5% of patients) feature of the syndrome and a number of other platelet abnormalities described, including platelet function defects (Table 1). It is important to recognize that abnormal platelet function usually persists despite resolution of thrombocytopenia in some patients. Therefore, formal platelet function testing with a plan for platelet transfusions are indicated before major procedures despite normal platelet counts.

Other Congenital Disorders

Storage disorders such as Gaucher disease and Niemann–Pick disease present with splenomegaly either due to direct splenic infiltration or portal hypertension. While caring for these patients, it is important to keep in mind that platelets can pool and sequester inside the abnormally enlarged spleen, which can lead to acute life-threatening thrombocytopenia. Von Gierke disease (glycogen storage disease 1) has been shown to have associated platelet function defects. Once these disorders are diagnosed, it would be important to obtain a baseline platelet count and refer to a hematologist for bleeding symptoms or before a surgical procedure for a comprehensive evaluation of the bleeding phenotype and recommendations for surgery.

GENERAL GUIDELINES FOR HEALTH MAINTENANCE AND MANAGEMENT OF BLEEDING SYMPTOMS

Newborn Period

Thrombocytopenia is encountered fairly commonly (up to 25% of admitted newborns) in the NICUs with rates increasing with prematurity. The challenge lies in identifying which of these can stem from an underlying inherited disorder. Fetal platelets are found in circulation by ~5 weeks of gestation and start reaching adult values by 22 weeks. The diagnostic approach should be based on the gestational age, onset of thrombocytopenia (<72 hours indicating likely placental, perinatal factors; >72 hours indicating postnatally acquired infections), and the clinical status of the newborn (sick versus well appearing). Karyotype testing should be done in all obviously dysmorphic infants with thrombocytopenia. Inherited causes of thrombocytopenia are in general rare and rarely present in the newborn period. If a clear family history is present, the hematologist should be consulted to guide appropriate timing of confirmatory testing and help manage thrombocytopenia in the neonatal period. This should include a comprehensive delivery plan with contraindication for instrumental delivery, vacuum, or use of fetal scalp monitoring. Early onset thrombocytopenia <72 hours, presence of macrothrombocytes in the smear, limb abnormalities, and platelet counts usually >50 000/μL are good clues pointing to an underlying inherited defect. In the setting of a well appearing infant with isolated thrombocytopenia and absence of any other features, it is reasonable to treat for immune-mediated causes of thrombocytopenia (neonatal alloimmune thrombocytopenia) until platelet antigen incompatibility can be demonstrated between mother and infant serologically. Most allo or auto antibodies against neonatal platelets clear from the circulation over time with platelet counts normalizing within 1 to 2 weeks in most infants. Persistence of thrombocytopenia beyond 8 to 12 weeks after birth should warrant a hematology consult especially in the absence of any immunologic factors or genetic syndromes.

Infancy and Beyond

The reader is referred to health supervision guidelines for various genetic syndromes, which are a useful resource for physicians.
involved in the care of these children.43–46 Periodic hematologic screening has been recommended in Noonan syndrome, DS, Turner syndrome, and Jacobsen syndrome as outlined in previous sections.

The comprehensive care of children and adolescents with syndromes mentioned in this review should include careful attention to oral hygiene to prevent gum bleeding, hormonal control of menstrual bleeding, and avoidance of medications such as aspirin and nonsteroidal anti-inflammatory analgesics. Dental procedures should ensure good local hemostasis with fibrillar collagen products along

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Management of Common Bleeding Symptoms With Identified Platelet/Coagulation Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td><strong>Associated With Platelet Defect</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Place patient in sitting position with neck forward. Firmly compress tip of nose for 20 min.</td>
</tr>
<tr>
<td></td>
<td>Daily saline nasal lubrication and humidification of room air.</td>
</tr>
<tr>
<td>Do not: Stick toilet paper, cotton balls in nose as can dislodge clot Do not: squeeze bony part of nose as no blood vessels here</td>
<td>Desmopressin$^b$ intranasal spray 150 μg/dose: 2 sprays for adult, and 1 spray for &lt;50 kg child</td>
</tr>
<tr>
<td>Oral mucosal bleeding (spontaneous)</td>
<td>Ensure good dental hygiene and periodic dental cleanings</td>
</tr>
<tr>
<td></td>
<td>Compression with gelatin sponge</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Hormonal regulation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising/minor lacerations</td>
<td>Protective cushions/pads as indicated. Rarely if compromising may need specific treatment</td>
</tr>
<tr>
<td>Life-threatening bleeding (CNS, GI bleeding)</td>
<td>Avoid contact sports, wear helmets/protective devices as indicated in conditions with severe deficiencies.</td>
</tr>
<tr>
<td></td>
<td>Immediate evaluation to rule out intracerebral bleeding. Treat first, image once stabilized.</td>
</tr>
</tbody>
</table>

CNS, central nervous system; GI, gastrointestinal; IV, intravenously; TID, 3 times per day.
$^a$ Catalina Healthcare, Mendon, NY.
$^b$ Also useful in connective tissue disorders.
$^c$ Concomitant use of estrogen and tranexamic acid carries a black box warning due to increased risk of thrombosis and if used should be separated by 4 hours.
$^d$ Bayer Healthcare Pharmaceuticals, Whippany, NJ.
with other indicated systemic hemostatic therapy because of abundance of fibrinolysis in the mouth. Children with a high risk of bleeding should avoid contact sports, heavy exercise, or isometric exercise and wear protective pads to avoid deep hematomas and bruising. Nonweight bearing exercises such as aqua therapy should be encouraged to promote a healthy lifestyle. Some of these children can have restrictive diets and vitamin K and vitamin C may need to be supplemented, the deficiencies of which can aggravate the underlying bleeding disorder. Common bleeding symptoms and their management are addressed in Table 3.

Antifibrinolytic agents (ε amino caproic acid and tranexamic acid) inhibit plasmin activity, thereby strengthening clot formation and can be used for prevention of minor trauma-induced or minor surgical bleeding especially involving mucosal surfaces that are rich in fibrinolytic enzymes in areas such as the mouth, nose, uterus, and gastrointestinal tract. Desmopressin (1-deamino-8-D arginine vasopressin) increases platelet aggregation by increasing plasma levels of vWF and factor VIII, thus improving platelet adhesion and function. It has been shown to be useful in various platelet secretion and granule defects, EDS and Noonan syndromes, where it can improve platelet function and promote hemostasis. Both 1-deamino-8-D arginine vasopressin and/or antifibrinolytic agents can be used as monotherapy or adjuvant therapies to more definitive treatment. Hemostasis therapy should be tailored on the basis of the underlying hemostatic defect, severity of bleeding symptoms, or hemostatic challenge of planned surgery and results of the bleeding evaluation. Although platelet transfusion seems straightforward, the development of alloantibodies may cause platelet refractoriness and therefore should be reserved for serious bleeding symptoms. In some cases, judicious and tailored use of fresh-frozen plasma (FFP), cryoprecipitate, and rVIIa may be indicated. The use of rVIIa is approved in Glanzmann’s thrombasthenia where it improves platelet aggregation and fibrin and thrombin generation. Point of care devices, such as thromboelastogram, which can quantify global hemostasis and monitor response to therapeutic agents, are increasingly being explored in clinical settings such as trauma and surgery, which can provide improved bleed management and patient outcomes. Further studies are needed to evaluate the impact of thromboelastogram to improve patient outcomes in bleeding disorders.

GUIDELINES FOR MANAGEMENT BEFORE SURGICAL PROCEDURES

Patients suspected to have a congenital syndrome with a bleeding diathesis (symptomatic or asymptomatic) must have a sequential evaluation at least 2 to 4 weeks before a scheduled surgical procedure as proposed in Fig 2. Bleeding assessment tools are useful to get a standardized bleeding history and calculate bleeding scores.
<table>
<thead>
<tr>
<th>Symptom/Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>No or trivial (&lt;5 per year)</td>
<td>&gt;5 per year or &gt;10 min duration</td>
<td>Consultation only</td>
<td>Packing, cautery, or antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>No or trivial (&lt;5 per year)</td>
<td>&gt;1 cm and on trauma</td>
<td>Consultation only</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>No or trivial (&lt;5 per year)</td>
<td>&gt;5 per year or &gt;5 min duration</td>
<td>Consultation only or steri-strips</td>
<td>Surgical hemostasis or antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Reported at least once</td>
<td>Consultation only</td>
<td>Surgical hemostasis or antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
<td>—</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>None done or no bleeding in at least 2 extractions</td>
<td>Reported, no consultation</td>
<td>Resuturing, repacking, or antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>No bleeding in at least 2 surgeries</td>
<td>Reported, no consultation</td>
<td>Consultation only</td>
<td>Surgical hemostasis, antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Reported or consultation only</td>
<td>Consultation only</td>
<td>Antifibrinolics or contraceptive pill use</td>
<td>D&amp;C or iron therapy</td>
<td>—</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Never</td>
<td>Posttrauma, no therapy</td>
<td>Spontaneous or traumatic, requiring replacement therapy or desmopressin</td>
<td>Spontaneous or traumatic, requiring replacement therapy or desmopressin</td>
<td>—</td>
</tr>
<tr>
<td>Postpartum</td>
<td>No bleeding in at least 2 deliveries</td>
<td>Reported or consultation only</td>
<td>Consultation only</td>
<td>D&amp;C or iron therapy</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
</tr>
<tr>
<td>Muscle hematoma</td>
<td>Never</td>
<td>Never</td>
<td>—</td>
<td>D&amp;C or iron therapy or antifibrinolics</td>
<td>—</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Never</td>
<td>Never</td>
<td>—</td>
<td>D&amp;C or iron therapy or antifibrinolics</td>
<td>—</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>No bleeding</td>
<td>Consultation only</td>
<td>Surgical hemostasis, antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>No reported</td>
<td>Consultation only</td>
<td>Surgical hemostasis, antifibrinolics</td>
<td>Blood transfusion, replacement therapy, or desmopressin</td>
<td>—</td>
</tr>
</tbody>
</table>

TABLE 4: The Components and Scoring of the Pediatric Bleeding Questionnaire

which can help recognize individual bleeding risk. The components of the Pediatric Bleeding Questionnaire are presented in Table 4 for review. A thorough head to toe physical examination to identify and uncover bleeding risk should focus on hyperextensibility, telangiectasias, palpable bruises, splenomegaly, ecchymoses, and petechiae. All medications and alternative therapies (including herbal preparations) should be carefully reviewed, and any medications known to affect hemostasis should be discontinued or substituted. A basic workup should include a complete blood count, PT, and aPTT with mixing studies (when PT/aPTT are prolonged), which helps distinguish a clotting factor deficiency from nonspecific coagulation inhibitors. In syndromes with known qualitative platelet defects, platelet function analysis (PFA-100), which has replaced the bleeding time, should be included as part of the initial workup if available. Further testing should be guided by a pediatric hematologist who can then order confirmatory testing. Knowledge of the underlying platelet abnormality can guide further platelet function testing because the use of specific platelet agonists can limit the amount of blood drawn in pediatric patients. A multidisciplinary team involving the surgeon, hematologist, and anesthesiologist should tailor a treatment plan before surgery for these patients with the judicious use of platelets and other blood components to avoid alloimmunization especially because patients with clinical syndromes may require more than 1 corrective procedure. The risk of bleeding due to any underlying thrombocytopenia in part depends upon the nature of the surgery, critical need for maintaining postoperative hemostasis and promoting healing, and individualized target platelet count depending upon the type of surgery. Regional anesthesia and epidural catheters may be contraindicated depending on the level of thrombocytopenia and other hemostatic defects.

**CONCLUSIONS**

Abnormalities in hemostasis leading to clinical bleeding are an often unidentified component of many congenital syndromes. These abnormalities are important for the PCP to recognize and anticipate, thereby prompting timely referral to the hematologist to adequately manage these patients to prevent catastrophic bleeding.

**ABBREVIATIONS**

aPTT: activated partial thromboplastin time  
DS: Down syndrome  
EDS: Ehlers-Danlos syndrome  
FFP: fresh-frozen plasma  
HHT: hereditary hemorrhagic telangiectasia  
IBMFS: inherited bone marrow failure syndromes  
ITP: immune thrombocytopenia  
ML-DS: myeloid leukemia associated with Down syndrome  
PCP: primary care physician  
PT: prothrombin time  
TAR: thrombocytopenia associated with Down syndrome  
vWF: von Willebrand factor

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