Mild bleeding disorders are a common reason for a referral to a hematologist and these conditions can be challenging to evaluate. Recent research has highlighted that some bleeding symptoms are quite common in the general population and that there is clinical variability in symptom expression among individuals with defined bleeding problems. Moreover, bleeding risks for many bleeding disorders are unknown. This article reviews symptoms and problems that can be considered suspicious of a mild form of bleeding disorder and the diagnostic investigations useful to evaluate these problems. A stepwise approach is presented for the diagnostic evaluation, to allow detection of common and rare coagulation and fibrinolytic defects, and adequate assessments of potential von Willebrand factor and platelet problems. Some common problems in the diagnosis and management of mild bleeding problems are reviewed, including the common failure to establish a diagnosis with testing. An approach is proposed for translation of knowledge to patients who are challenged by mild bleeding problems.

Causes of Mild Bleeding Disorders
Mild bleeding problems can be inherited or acquired. The inherited causes include partial deficiencies of coagulation factors and fibrinolytic proteins, and defects or deficiencies in von Willebrand factor and platelets and connective tissue problems (e.g., Ehler-Danlos syndrome). Abnormalities in von Willebrand factor are among the most common inherited causes, although platelet defects are also fairly common. Among the inherited coagulation protein deficiencies that cause mild bleeding problems, mild hemophilia, due to factor VIII or IX deficiency, is more common than mild factor XI deficiency, fibrinogen abnormalities (including dysfibrinogenemia) or other factor deficiencies. Although some heterozygote carriers of alpha2 plasmin inhibitor deficiency have mild bleeding problems, carriers of other fibrinolytic disorders, such as PAI-1 or factor XIII deficiency, are without symptoms.

Some patients referred for an evaluation of mild bleeding problems have an acquired condition that may not have been recognized as the cause of bleeding. The potential acquired causes to consider are diverse, ranging from autoimmune thrombocytopenia, acquired bone marrow disorders, hemorrhagic side effects of antiplatelet or anticoagulant drugs, acquired deficiencies (commonly of factor VIII or von Willebrand factor), thyroid disease, Cushing’s syndrome (including iatrogenic), liver and renal disease. Among patients referred for symptoms of a mild bleeding, the four most common diagnoses are platelet secretion defects, von Willebrand factor deficiency, platelet dense granule deficiency, and no diagnosis.

Clinical Manifestations of Mild Bleeding Disorders and the Bleeding History
The clinical manifestations of mild bleeding disorders vary and depend on the nature of the defect and its relative severity. In general, mild bleeding disorders are most troublesome at times of significant hemostatic challenges, although for women menorrhagia may be a major problem. While the medical history is essential to evaluating mild bleeding problems, its value for screening in a hematology referral setting has been questioned, as referred patients are quite likely to have a bleeding problem. The timing of abnormal bleeding after a challenge is often emphasized, to distinguish the delayed-onset bleeding problems more typical of deficient/defective coagulation or fibrinolytic proteins from immediate bleeding and bruising problems typical of defects in von Willebrand factor or platelets. However, this has not been formally assessed for mild bleeding problems. Some symptoms (e.g., nosebleeds, menorrhagia) are not specific to any one type of bleeding problem. Family history is important to the assessment of inherited bleeding problems and to identify others at risk for similar problems.

Few studies have evaluated the diagnostic utility of bleeding histories, which are influenced by the nature and severity of the bleeding defect, environmental factors (exposures to trauma) and the specific items queried. Our center developed a clinical history assessment tool (CHAT) for application to undiagnosed and diagnosed bleeding problems, using qualitative research methods and input from physicians and patients. An abbreviated version of
this tool was used to evaluate the features characteristic of
the Quebec Platelet Disorder and to gain insights into its
bleeding risks.\textsuperscript{13} A larger study of the CHAT is nearing
collection to evaluate information collected by this tool
prospectively in new patients referred to hematologists and
retrospectively in patients previously diagnosed with dif-
f erent bleeding disorders (including undiagnosed prob-
lems). Application of the abbreviated CHAT illustrated that
mild bleeding symptoms are quite common in the general
population (Table 1; topic reviewed in \textsuperscript{13}), although the
reasons are not well understood. The prevalence of some of
these symptoms limits their utility as diagnostic features.
Items generally accepted to be of value to bleeding histo-
ries include: the family history of bleeding; the type of
bleeding problem that triggered the referral; and whether
the problems are lifelong or recently acquired without a
history of bleeding when challenged earlier in life.\textsuperscript{12-14}
Questions about excessive bleeding, and its timing, with
surgery, dental extractions and trauma are important.\textsuperscript{12-14}
Although some patients can recall if bleeding problems
became evident fairly rapidly (or only after a delay) with
major procedures, for others, the timing is more readily
recalled for dental extractions and surgical procedures done
without general anesthesia. Medical notes from the sur-
geon or dentist, while they can be helpful, are rarely avail-
able. Information on whether the bleeding problems required
transfusions and/or other interventions is helpful.\textsuperscript{12-14} For
the history of surgical bleeding, it is helpful to inquire if large
bruises (hematomas) appeared around surgical incisions
(unpublished observations). A self-reported history of ex-
cessive bleeding after major trauma can be problematic to
evaluate as many individuals exposed to trauma claim to
have suffered excessive bleeding (Table 1).\textsuperscript{13}

For women, the bleeding history needs to include ques-
tions about bleeding with menstrual periods and abnormal
bleeding of childbirth, although both can reflect other prob-
lems (e.g., fibroids, uterine atony postpartum).\textsuperscript{12,13,15} Que-
ries about bruises and nosebleeds are often included in a
bleeding history.\textsuperscript{12-14} Like heavy menstrual periods, these
symptoms are more prevalent among individuals with bleed-
ing problems but are commonly reported by individuals
without recognized bleeding disorders (Table 1).\textsuperscript{4,13,16,17}
Questions about some types of bleeding (e.g., gum, urinary
tract) tend to be less useful, although there are exceptions.\textsuperscript{12,13}
Unlike severe bleeding problems, mild bleeding disorders
rarely necessitate changes in life-style. Unfortunately, the
magnitude of increased bleeding risk for many mild disor-
ders has not been determined, although it probably influ-
ences the bleeding history by affecting the frequency and
severity of bleeding with different challenges. Analogous
to mild thrombocytic disorders, mild bleeding disorders
may not be apparent until the individual is exposed to
significant challenges (e.g., major surgery), and the prob-
lem may not be manifest with all challenges.\textsuperscript{18} This may
explain why some individuals with documented biochemical
abnormalities (e.g., mild von Willebrand factor defi-
ciency) report minimal or no bleeding symptoms.\textsuperscript{18,19} Clin-
cal variability is also common, even within members of
families who share a defined defect,\textsuperscript{13,19} suggesting that
environmental and other genetic factors may ameliorate
bleeding risks. Although mild bleeding problems may not
become evident until exposure to significant hemostatic
challenges (such as surgery, dental extractions, major
trauma, menarche or childbirth),\textsuperscript{12,20,21} the negative predic-
tive value of surgical bleeding history (e.g., tonsillectomy
or other major surgery without abnormal bleeding) has not
been established for many disorders.\textsuperscript{12,13}

Gender has an influence on the manifestations of mild
bleeding disorders.\textsuperscript{4,15,16,20-23} Females are more commonly
referred for evaluation because of troublesome bleeding
with menses and/or childbirth.\textsuperscript{4,15,16,20,22,23} Prolonged and/or
heavy menstrual bleeding is quite prevalent in the general
population, but it is more common among referred indi-
viduals who are more likely to have a hemostatic de-
fect.\textsuperscript{4,13,15,16,20,22} Mild bleeding problems associated with
menorrhagia are quite diverse and include von Willebrand
disease and platelet disorders, mild factor deficiencies in
hemophilia carriers, more rare mild factor deficiencies, fi-
brinogen abnormalities and rare fibrinolytic defects.\textsuperscript{3,13}
Specific questions about menses (e.g., longer than 7 days,
limitations on lifestyle, rapid soaking of sanitary prod-
ucts, flooding accidents, menses prior to oral contracep-
tive use) are useful because many individuals are uncertain
about what amount or duration of menstrual flow is “nor-
mal.”\textsuperscript{13} Pictorial blood loss recordings are more accurate in
quantifying menstrual bleeding, and its response to therapy\textsuperscript{3}
but are not suitable for a single visit assessment. Profuse
and prolonged (\textgtr 10-14 days) menses may be reflected by

\textbf{Table 1. Prevalence of mild bleeding symptoms:}
symptoms reported by the unaffected relatives in a study
of the Quebec Platelet Disorder.

Adapted from McKay et al.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td></td>
</tr>
<tr>
<td>Abundant bruising or bleeding</td>
<td>26</td>
</tr>
<tr>
<td>Bruising without reason</td>
<td>34</td>
</tr>
<tr>
<td>Bruising disproportionate to trauma</td>
<td>12</td>
</tr>
<tr>
<td>Bruises that spread towards feet</td>
<td>\textless 1</td>
</tr>
<tr>
<td>and/or \textgtr an orange in size</td>
<td></td>
</tr>
<tr>
<td>Nosebleeds</td>
<td>24</td>
</tr>
<tr>
<td>Yes and with the following features:</td>
<td></td>
</tr>
<tr>
<td>Longer than 15 minutes</td>
<td>56</td>
</tr>
<tr>
<td>Requiring cautery</td>
<td>24</td>
</tr>
<tr>
<td>Dental extractions</td>
<td>74</td>
</tr>
<tr>
<td>Yes and with the following features:</td>
<td></td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>35</td>
</tr>
<tr>
<td>Bleeding \textgtr 24 hours afterwards</td>
<td>8</td>
</tr>
<tr>
<td>Bleeding problems with surgeries</td>
<td>9</td>
</tr>
<tr>
<td>Excessive bleeding after accidents</td>
<td>39</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Abundant menstrual bleeding</td>
<td>56</td>
</tr>
<tr>
<td>Menses longer than 7 days</td>
<td>7</td>
</tr>
</tbody>
</table>
Some bleeding history questions appear to have higher specificity, albeit lower sensitivity, for some types of bleeding disorders. For example, very large bruises and bruises that track downward suggest platelet or von Willebrand factor problems (and unpublished observations). In addition, bleeding that persists or becomes problematic 24 hours or longer after dental extractions raises the possibility of a bleeding disorder. Their value in determining a pretest likelihood for mild bleeding disorders is likely to be limited, particularly for hematology practices, where the process of referral means that the patient is already relatively likely to have a bleeding problem. While some strategies have been proposed for limiting investigations in preoperative patients, their value is unproven among patients referred to hematologists for investigation of suspected bleeding problems.

### Diagnostic Investigation of Mild Bleeding Problems

A broad range of investigations is often needed to evaluate mild bleeding problems. Many tests, particularly blood counts and less expensive coagulation screening tests for factor deficiencies, can be done simultaneously. Our center’s stepwise testing practices (outlined in Table 2) are derived from observations that some disorders can be detected by fairly simple strategies (e.g., dysfibrinogenemia) and that tests for platelet and von Willebrand factor defects, relative to factor deficiencies, are highly informative among individuals referred to a hematologist for mild bleeding symptoms. Laboratory investigations are coordinated with the first clinic visit assessment to permit simultaneous screening to detect many coagulation defects (with a PT, PTT, thrombin clotting time and fibrinogen level), platelet defects and von Willebrand factor abnormalities (Table 2). The subsequent diagnostic assessments are tailored to complete the diagnostic investigations indicated by results on initial evaluation and, if appropriate, to exclude rarer problems (Table 2). This strategy is modified when the referral information indicates that more restrictive testing may be appropriate (e.g., factor assays on the first visit for suspected hemophilia) or if some tests require referral to another center (Table 2). Blood counts are helpful in identifying mild bleeding associated with thrombocytopenia (including qualitative platelet function defects associated with bone marrow disorders) and acquired platelet dysfunction with very high platelet counts from myeloproliferative disorders.

While an isolated prolonged PTT in the diagnostic screen requires further testing to evaluate possible mild hemophilia or factor XI deficiency, false positive prolongations (due to lupus anticoagulants or mild factor XII deficiency) are common, particularly when reagents sensitive to lupus anticoagulants are used for screening. When the clinical suspicion of a mild factor deficiency is high, assays for factor VIII, IX or other relevant coagulation factors should be done. In rare cases, screening uncovers abnormalities in both the PT and PTT, suggesting mild deficiencies of factor II, X, or V or a combined deficiency of factor V and VIII. Because the PT and PTT are insensitive to mild quantitative or qualitative fibrinogen abnormalities, other tests (clottable fibrinogen, thrombin clotting time and reptilase time) are valuable for excluding these disorders (Table 2).

The diagnosis of deficiencies and defects in von Willebrand disease is likely to be limited, particularly for hematology practices, where the process of referral means that the patient is already relatively likely to have a bleeding problem. While some strategies have been proposed for limiting investigations in preoperative patients, their value is unproven among patients referred to hematologists for investigation of suspected bleeding problems.

#### Table 2. A staged approach to diagnostic testing for mild bleeding problems. If von Willebrand factor and platelet problems are not suspected, tests for these disorders can be omitted. If complete testing is not available, consider referral to a center that can complete the investigations.

**First assessment:**
- Complete blood count with blood film evaluation
- ABO blood group
- Ferritin
- PT, PTT
  - if abnormal, investigate for factor deficiencies
  - if hemophilia or other factor deficiencies strongly suspected, do factor VIII, IX, XI assays
- Thrombin clotting time and clottable fibrinogen
  - if abnormal, evaluate reptilase time and measure fibrinogen antigen
- Von Willebrand disease screen
  - factor VIII, von Willebrand factor antigen and ristocetin cofactor levels
  - multimers if screen is abnormal
- Platelet aggregation with the full panel of agonists
  - Our practice: testing done with the agonists ADP, collagen (two concentrations), arachidonic acid, thromboxane analogue, epinephrine and ristocetin
- Some centers may test platelet secretion with aggregation
- Evaluate for platelet dense granule deficiency
  - (first or subsequent assessment)
  - Consider tests for renal problems, liver or thyroid disease, if appropriate

**Subsequent assessments:**
- Confirm and further evaluate abnormalities identified on the first assessment
- Evaluate platelet secretion (or dense granules) if a platelet-type bleeding disorder is suspected but not diagnosed by initial tests, or if the aggregation abnormalities suggested a secretion or dense granule problem. Consider tests for rarer disorders (e.g., Scott's syndrome) if no abnormalities are found
- If the history suggests delayed bleeding problems, and no diagnosis was established, exclude mild deficiencies (factors VIII, IX, XI first) by factor assays and consider other tests (e.g., partial alpha2 plasmin inhibitor deficiency)
brand factor and platelets requires more complex investigations, and these tests may not be offered at many centers.\textsuperscript{1,2,5,28,29} Screening tests are of limited value among patients referred to a hematologist. Bleeding times are not sufficiently sensitive to screen for von Willebrand or platelet problems.\textsuperscript{30} Closure times, measured by the PFA-100\textsuperscript{TM}, have a higher sensitivity for von Willebrand factor deficiency but a poor sensitivity for common, mild platelet function defects.\textsuperscript{3,7,30} In addition, further diagnostic testing is required to investigate abnormal closure time results.\textsuperscript{5,7,28,30} Based on observations of high yields from combined diagnostic testing, we feel it is worthwhile to include simultaneous testing for von Willebrand factor and platelet disorders on the first diagnostic assessment of patients referred to hematologists with undiagnosed bleeding problems (Table 2). For individuals with bleeding and/or a family history of von Willebrand abnormalities, it is our preference to evaluate levels of von Willebrand factor antigen, ristocetin cofactor activity and factor VIII (with multimer assays if screen results are abnormal) and to perform collagen binding assays, if available.\textsuperscript{1,2,29,31} There is debate over the degree of von Willebrand factor deficiency that results in a clinically significant increased risk for bleeding,\textsuperscript{18} and there is considerable overlap between the reference range and levels among individuals with mild bleeding. Whether the lower von Willebrand factor levels in blood group O individuals constitute a measurable bleeding risk without other risk factors is uncertain.\textsuperscript{31} With uncertainties about the bleeding risks of borderline and mildly low von Willebrand factor levels, it may be safest to describe results by values rather than categorizing findings as indicating the presence or absence of disease.\textsuperscript{18} In individuals with an acquired bleeding history and definite von Willebrand factor deficiency, an acquired form of von Willebrand disease should be considered.\textsuperscript{32}

The laboratory diagnostic evaluation of suspected platelet disorders is challenging,\textsuperscript{5,6} and our practice is outlined in Table 2. Testing requires a review of the platelet count, mean platelet volume, blood film for abnormalities in leukocyte or platelet morphology, and assessment of platelet function and dense granules.\textsuperscript{5} Careful evaluation of the blood film can help establish rare diagnoses, such as gray platelet syndrome.\textsuperscript{5} Variability in the procedures used by clinical laboratories to evaluate platelet morphology and function compromises the detection of platelet disorders.\textsuperscript{28} Many laboratories offer aggregation studies without testing for dense granule deficiency and/or platelet secretion defects.\textsuperscript{28} The latter abnormalities are relatively common and they may not be detected by other assays.\textsuperscript{5,7,28,30} Tests for rare mild platelet disorders that are associated with procoagulant defects are rarely performed.\textsuperscript{5} Laboratory tests have a limited ability to distinguish some inherited platelet disorders associated with thrombocytopenia from chronic autoimmune thrombocytopenia (a diagnosis of exclusion).\textsuperscript{5} Thrombocytopenia due to suspected primary bone marrow disorders (with or without associated defects in platelet function) requires additional diagnostic tests.\textsuperscript{5}

Other useful laboratory evaluations for mild bleeding disorders include a ferritin level, which can provide a simple assessment of iron stores in individuals with menorrhagia or recent bleeding. Renal and liver function tests may provide the first clue that a mild bleeding problem reflects a secondary qualitative platelet defect and/or coagulopathy of liver disease. Renal function should also be assessed to evaluate for uremia if fibrinolytic inhibitor drug therapy is contemplated. Other testing can help exclude acquired bleeding due to an endocrine disorder, such as thyroid disease (which can cause von Willebrand factor abnormalities)\textsuperscript{34,35} or Cushing’s syndrome (which can be associated with platelet function abnormalities).\textsuperscript{36}

**Commonly Faced Problems in Management of Mild Bleeding Disorders**

It is difficult to outline an appropriate management algorithm that covers therapy for all mild bleeding disorders because this depends on the specific diagnosis and the bleeding problem that requires treatment (e.g., menorrhagia versus prevention of bleeding with surgery).\textsuperscript{1,5,8-10,15,20-22,32,37,38} There are trade-offs to consider between benefits and adverse effects of therapy, such as an increased risk of thrombosis (for example, with fibrinolytic inhibitor therapy or from withholding perioperative anticoagulant prophylaxis) and of hyponatremia and seizures with desmopressin.

Therapies may, however, offset adverse events, related to hemorrhage, and reduce the need for blood product support (with transfusion reaction/infectious risks). Potential risks/benefits of therapy need to be considered carefully, particularly when the efficacy of treatments or prophylaxis for mild bleeding problem are unknown and unverifiable (e.g., mild von Willebrand factor deficiency with only minimal bleeding symptoms) or if there are thrombotic risks (e.g., some dysfibrinogenemias).

Mild factor VIII deficiency, platelet function defects, von Willebrand factor deficiency, and some other mild bleeding problems (e.g., Ehler-Danlos syndrome) can be managed successfully with fairly simple maneuvers, such as desmopressin (DDAVP) prior to surgery.\textsuperscript{1,5,6,8,10,20,22,37,38,39} For many mild bleeding disorders, fibrinolytic inhibitor therapy with Amicar or tranexamic acid is used for dental and oral surgeries and it may reduce bleeding with other operative procedures.\textsuperscript{1,5,6,8,11,13,20,22,38} Fibrinolytic inhibitor therapy is also helpful for treating some rarer disorders.\textsuperscript{5,6,11,13,20,22,38} Mild factor IX deficiency and rare recessive coagulation disorders may need replacement therapies with major procedures.\textsuperscript{5,9} With drug therapy for mild platelet function problems, platelet transfusions are rarely needed.\textsuperscript{5,6} Other therapies, such as recombinant factor VIIa, are usually reserved for treating more severe disorders.\textsuperscript{5,9} Patients and their care providers need to be aware that the recommended dosage of desmopressin for treating bleeding problems is higher than the dosage recommended for other conditions, and patients should be warned about the potential ad-
verse effects of temporary fluid retention and hyponatremia.

For women with mild bleeding disorders, treatment may be needed to control menorrhagia or prevent abnormal bleeding with childbirth and epidural anaesthesia. The choices for menorrhagia management need to be tailored to patient preferences and include oral contraceptives, fibrinolytic inhibitors, intrauterine devices designed to reduce menorrhagia, DDAVP, endometrial ablation and hysterectomy. Initial therapy is often an oral contraceptive or a fibrinolytic inhibitor. Fibrinolytic inhibitors can be helpful for managing excessive menstrual bleeding with unsuccessful cycles in patients attempting to become pregnant. Side effects from DDAVP therapy for menorrhagia (related to fluid retention and hyponatremia with repeated dosing) often restrict use to second-line or adjunctive therapy. Patients may opt for surgical management if future pregnancies are not contemplated and medical therapy is not tolerated.

Drugs that inhibit platelet function (e.g., aspirin, clopidogrel) and anticoagulants can unmask or induce mild bleeding problems. Desmopressin improves in vitro hemostatic abnormalities induced by anti-platelet therapies but its effectiveness for treating serious bleeding from these drugs is not yet established. Bleeding from Cushing syndrome and thyroid disease require correction of the endocrine abnormality, whereas bleeding from uremia is often managed by correction of anemia.

Failure to establish a diagnosis or finding results of uncertain significance (e.g., borderline reduced von Willebrand factor levels) in a patient with mild mucocutaneous bleeding is a common problem in practice. A recent study reported undiagnosed problems in 54% of individuals with significant personal and family histories of mucocutaneous bleeding. Undiagnosed delayed bleeding problems appear to be less common (unpublished observations) and should be excluded by specific testing for factor deficiencies, fibrinogen abnormalities and fibrinolytic defects. When investigations are negative, consideration should be given to diagnoses that may have been overlooked or not evaluated. In addition, the patient’s history should be reviewed to determine whether the bleeding might be within “normal variability” or if it is more severe (e.g., repeated serious bleeding with surgical challenges) and, therefore, worthy of further investigation. When the major problem is menorrhagia, the same treatment options used to manage this symptom in individuals with a diagnosed bleeding disorder can be considered. However, failure to establish the diagnosis can be problematic for patients that need to undergo surgery or childbirth. Additional testing may uncover abnormalities that were missed (e.g., a platelet secretion defect, mild hemophilia or factor XI deficiency not detected by the PTT, dysfibrinogenemia or partial α2 plasmin inhibitor deficiency). Referral to another center may be necessary when diagnostic testing is not available for relatively common problems (e.g., platelet dense granule deficiency or platelet secretion defects).

Evidence is lacking on the best approach to managing undefined, mild bleeding problems, although some mild, “platelet-type bleeding disorders” respond to desmopressin and fibrinolytic inhibitor therapy. Fortunately, most referrals are not for acute bleeding, so there is often time to complete diagnostic testing and consider potential therapies.

Communicating knowledge to patients and other health care providers is an important aspect of the management of mild bleeding disorders. Patients vary in the extent of their knowledge about bleeding problems, test results and treatments. Moreover, they may not recall all of the information provided during assessment visits. Helpful strategies to consider include providing the patient with resource information and a summary note or card that outlines the diagnosis, results from diagnostic testing (even when no diagnosis was established), recommended treatments (with dosages and routes outlined) and precautions. These materials provide patients with a helpful reference that can be shared with other health care providers.

References