Mild bleeding disorders:
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Here we outline different types of MBDs, paying particular focus to bleeding associated with low von Willebrand factor levels and mild platelet defects. We give practical, evidence based advice on the investigation and management of patients with a suspected or known MBD, considering the scenarios of an acute bleed, stable outpatient, peri-surgical management and thrombosis.

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Title: Mild Bleeding Disorders: What Should Every Clinician Know?

Author Details

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HKH and PLRN conceived and wrote the manuscript. KF and GCL critically appraised the manuscript.

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Conflict of Interest Statement

The authors declare no conflicts of interests.
Abstract

Patients with mild bleeding disorders (MBDs) are under-recognised and frequently present to general physicians. The underlying reasons for bleeding are multifactorial. There is little in the way of evidence to guide diagnostic and management decision making in patients with MBDs.

Here we outline different types of MBDs, paying particular focus to bleeding associated with low von Willebrand factor levels and mild platelet defects. We give practical, evidence based advice on the investigation and management of patients with a suspected or known MBD, considering the scenarios of an acute bleed, stable outpatient, peri-surgical management and thrombosis.

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Keywords

Bleeding; Coagulation; Haemostasis; von Willebrand’s Factor; Platelets; Mild Bleeding Disorders

Key Points
The majority of mild bleeding disorders (MBDs) are acquired.

Clinical history is the most important part of an assessment of a patient with a known or suspected MBD.

An individual patient’s bleeding phenotype for any given MBD is variable due to the complex interplay of genetic and environmental factors.

Laboratory testing is not always diagnostic or informative in a patient with an MBD.

Close liaison with a haematologist is recommended in managing patients with MBDs.

Introduction

Patients with severe bleeding disorders are usually diagnosed early in life, especially when there is a family history of excessive bleeding in which case diagnosis can be made in the neonatal period or in some cases antenatally. Patients with severe bleeding disorders are managed by specialist centres (referred to as haemophilia centres, although they manage a variety of bleeding conditions) with clear management plans in place in the event of bleeding episodes presenting to non-specialist centres. It is far more likely, however, for a general physician to come across a patient with symptoms of mild bleeding. In this review, we propose to define what is meant by mild bleeding and outline the underlying causes, how these patients typically present, how they should be investigated and managed by general physicians and if and when specialist referral is appropriate. Severe bleeding disorders are well characterised and will not be discussed further here other than to use them for comparison.
Typically, patients with mild bleeding disorders (MBDs) present to clinicians in adulthood after haemostatic challenges, such as dental surgery or traumatic injury, which result in a bleeding episode(s) considered to be unusually severe. Women often present earlier than men because menstruation and childbirth provide significant haemostatic challenges. It is common for patients to have had numerous episodes of disproportionate or excessive bleeding prior to an inherited bleeding disorder being considered as a possible cause.

Major bleeding has been previously defined as; symptomatic bleeding into a critical area such as the brain or spinal cord; bleeding which causes a reduction in Haemoglobin of ≥ 20 g/l or requires transfusion of ≥ 2 units of packed red cells; or bleeding causing death\textsuperscript{1}. For a bleeding disorder to be classified as severe, it has to result in spontaneous major bleeding such as haematomas, haemarthroses, CNS, GI and umbilical cord bleeding\textsuperscript{2}. An MBD by contrast, is often difficult to tease apart from bleeding symptoms experienced by normal individuals. Various studies have attempted to define what are normal rates of bleeding in healthy people\textsuperscript{3}. The frequency of spontaneous or provoked bleeding symptoms in the general population varies between 3 – 26% depending on study and type of bleeding, with one study reporting 73% of those questioned having had one bleeding symptom and 43% two symptoms\textsuperscript{4}. The bleeding patterns of those diagnosed as having an MBD can be very similar to this\textsuperscript{5}, hence a standardised method of assessing bleeding has been developed by the International Society on Thrombosis and Haemostasis (ISTH) called the Bleeding Assessment Tool (ISTH BAT). It was specifically designed to capture mild recurrent bleeding that may have been missed by previously used scoring systems. It comprises assessment of 14 bleeding symptoms with each being graded as 0-4 based on the worst bleeding event of that type ever experienced by the patient. Results are considered abnormal if ≥4 for men,
≥6 for women and ≥3 for children. It has been validated for von Willebrand’s Disease (vWD) and platelet defects in adults and children but not for haemophilia or rarer bleeding disorders such as fibrinogen deficiency or factor XIII deficiency. We will further discuss its use and limitations in MBDs below.

Once patients have been diagnosed with a bleeding disorder, the UK Haemophilia Centre Doctors’ Organisation (UKHCDO) and NHS England guidance dictates that patients should be registered with a Comprehensive Care Centre (CCC) with care provided by consultants, specialist nurses and specialist physiotherapists trained in the treatment of patients with haemophilia and other bleeding disorders. The CCC will then link in with a more local Haemophilia Centre (HC) and coordinate the patient’s care between them to include 24 hours a day, 7 days a week care, including protocols for out-of-hours care and emergency management as well as routine outpatient review. This guidance applies to MBDs as well as severe bleeding disorders.

**Different Types of Bleeding Disorder**

Causes of bleeding disorders can be broadly split into those that affect the coagulation cascade, those that affect platelet number or function and those that cause problems with the vasculature. The causes of MBDs can be classified in the same way but, with some exceptions which will be discussed later, this is not always clinically useful as treatment is often generic and is based on the clinical bleeding phenotype rather than the underlying diagnosis. It is probably more helpful to view the disorders illustrated below as risk factors for bleeding rather than causes. This is in much the same way that smoking status, cancer or...
recent trauma are considered risk factors for thromboembolic disease rather than the underlying cause.

Acquired mild bleeding disorders are much more common than their hereditary counterparts and thus the former will be the focus for this review. A table summarising the different underlying pathologies associated with MBD is included for reference (Table 1).

**Disorders of the coagulation cascade**

Vitamin K antagonists (VKAs) and Direct Oral Anticoagulants (DOACs) induce bleeding through reduction of vitamin K dependent clotting factors II, VII, IX and X or inhibition of Factors X / II respectively\(^\text{11}\). There are existing extensive reviews of management of patients taking these drugs and therefore they will not be covered in detail.

Dietary deficiency of Vitamin K is common, particularly in long term hospital inpatients. It results from poor intake of vitamin K rich foods, such as spinach, from changes in gastrointestinal bacteria due to antibiotics, or due to fat malabsorption. The most common clinical sequelae are mild prolongation of the Prothrombin Time (PT), or an increased sensitivity to warfarin, but it only rarely results in excessive bleeding\(^\text{12}\).

Inherited coagulation factor deficiencies generally cause a severe bleeding disorder or are very rare. The commonest inherited bleeding disorder is vWD with quoted rates as high as 1.3% in the general population. There are several subtypes of vWD which are classified based on measurements of von Willebrand Factor (vWF) level, activity and interactions with platelets. The bleeding phenotype varies based on the subtype\(^\text{13}\). It is important, however,
to distinguish between vWD and a disorder called “Bleeding with low vWF as a risk factor”. The reportedly high rates of vWD are probably an over estimate. They are based on an Italian study\textsuperscript{14} where 1200 children and their relatives were questioned to see if they had bleeding symptoms. All 47 people found to have low vWF levels were then followed up for 13 years and only one person had a clinically significant bleeding event in that time, implying that people incidentally found to have low vWF levels should not be labelled as having VWD because they are unlikely to have a bleeding event. There is not always a direct inverse relationship between bleeding score and laboratory parameters used to assess VWD (Lester W, unpublished data, personal communication), although some papers have shown a correlation in large patient populations\textsuperscript{15}. These findings reiterate that clinical and family history is of paramount importance in assessment and in deciding which patients should have laboratory investigations. Although historically levels of VWF <0.5 iU/ml are considered to be the cut off for normal, recent guidelines suggest that a cut off level of 0.3 iU/ml should be used to diagnose vWD. Patients with bleeding and vWF levels of 0.3-0.5 iU/ml should be labelled as having a “bleeding disorder with low vWF as a risk factor” rather than vWD. It is noteworthy that a diagnosis of vWD carries with it many implications such as not being allowed a career in the armed forces.

Factor XI deficiency is noteworthy because it is one of the more common inherited bleeding disorders and has very heterogenous bleeding. There is very poor correlation between the factor level and the bleeding phenotype\textsuperscript{16} and this presents some treatment challenges.

Factor XII deficiency does not cause any bleeding, but does cause prolongation of the activated partial thromboplastin time (APTT). Its diagnosis commonly results from routine
clotting screens being performed prior to invasive procedures. The finding of a prolonged APTT invariably causes delays to these procedures but no other clinical sequelae. It is included here as an example of why clotting screens should only be performed on patients who have a history of excessive bleeding or a positive ISTH BAT.

Other disorders of the coagulation cascade which can cause mild bleeding include liver disease. This causes bleeding because of loss of production of the procoagulant clotting factors and clotting screens such as the PT and APTT can be used as a proxy measurement of their loss. Unfortunately the clotting times measured by these tests do not correlate well with bleeding because they do not take into account the presence or absence of the anticoagulant proteins, also produced by the liver, such as protein C, protein S and antithrombin, or platelet abnormalities. There is still much discussion in the literature as to the best method to use to measure the bleeding risk in patients with liver disease.\textsuperscript{17}

**Disorders of platelet number / function**

There are numerous rare inherited disorders of platelet function with eponymous names that are well known. Those that cause MBD are far less well known and include problems with the platelet cytoskeleton such as the MYH9 related disorders or with secretion of platelet granules such as with Wiskott Aldrich and Hermansky Pudlak syndromes. As well as bleeding, these conditions are associated with other systemic features such as deafness, nephropathy and early cataracts (MYH9); eczema and immunodeficiency (Wiskott Aldrich); or oculocutaneous albinism, colitis and pulmonary fibrosis (Hermansky Pudlak).\textsuperscript{18}

Abnormalities in the platelet ADP receptor P2Y12 also cause MBD. An acquired deficiency of P2Y12 signalling occurs with the antiplatelet drugs clopidogrel, prasugrel and ticagrelor
which cause major bleeding at rates of between 3 and 12% in different studies\textsuperscript{19}. Of note clopidogrel and prasugrel (as well as aspirin) are irreversible platelet inhibitors and thus their effects on bleeding last for the lifetime of the platelet (i.e. 7-10 days after clearance of the drug). Eptifibatide, tirofiban and abciximab are used for the treatment of acute myocardial infarction. They inhibit the platelet fibrinogen receptor GPIIb / IIIa which normally functions to strengthen clots by allowing fibrinogen cross-linking to occur between platelets. They are all associated with bleeding\textsuperscript{20-22} and, in addition, abciximab can cause a temporary immune mediated thrombocytopenia.

Renal failure’s association with haemostatic problems is multifactorial with the most significant effects being through impaired platelet granule secretion\textsuperscript{23} and problems with platelet interaction with the vessel wall through low levels of platelet receptors GPIb and GPIIb/IIIa (VWF and fibrinogen receptors respectively). As well as causing coagulation factor deficiencies, liver disease also causes reduction in platelet number (previously thought to be merely due to sequestration in the enlarged spleen but now known to be due to multiple mechanisms) and also in platelet function through activation of inhibitory pathways within platelets\textsuperscript{24}.

Immune Thrombocytopenia (ITP) is a heterogenous disorder with a very variable bleeding (and sometimes pro-thrombotic\textsuperscript{25}) phenotype, which is not well correlated with the absolute platelet count. There are extensive guidelines on diagnosis and management of patients with ITP\textsuperscript{26}. It will not be covered any further here.

\textbf{Disorders of the vasculature}
Problems with the vasculature impair haemostasis and cause MBD through increased vessel fragility and weakness resulting from defects in the supportive tissue of blood vessels (Ehlers Danlos Syndrome, Scurvy and Marfan’s syndrome) or defects in the blood vessels themselves (Hereditary Haemorrhagic Telangiectasia (HHT)).

**Practical advice on the investigation and management of a patient presenting with mild bleeding**

In managing patients with an MBD, we will discuss several scenarios that the general physician is most likely to encounter. Broadly, this will be divided into patients with a suspected diagnosis and those with a known MBD. A key point is the difficulty in making specific recommendations; MBDs by their nature have a variable bleeding phenotype, often with an unknown risk, and the range of scenarios is substantial. In most cases, a balanced discussion of bleeding risk both from the patient’s underlying condition and as a result of any medical or surgical procedure between the patient, haematologist and relevant specialty is essential. For elective procedures this discussion should occur well in advance of the planned date to allow a treatment plan to be documented and circulated amongst the various teams involved.

**The patient with a suspected MBD**

In this scenario, there are several aspects that should be considered. In the emergency situation the critical point to stress is that life and limb saving procedures should continue regardless of the bleeding phenotype. Most MBDs are amenable to relatively conservative measures for control, and on these occasions proceeding as for a patient with no bleeding disorder would be a potential option. The area where bleeding risk should be seriously
considered is where uncontrolled bleeding can have a catastrophic effect – the classic scenario being a neurosurgical procedure.

It is important to try and establish how significant a bleeding history the patient has. In a significant proportion of patients, this can be established through close enquiry about haemostatic challenges\(^3\). Whilst the ISTH BAT is useful as a research tool, it is cumbersome for routine use. It is useful to ask whether the patient has had previous surgery. If so, did they require added measures, blood product transfusion or a return to theatre because of bleeding? Common procedures that can suggest a bleeding disorder include dental extraction and tonsillectomy. In addition, a family history can be suggestive, and this should be sought specifically if a patient mentions a bleeding tendency. In women, menorrhagia since menarche is suggestive\(^3\). A potential pitfall is asking about post-partum haemorrhage (PPH) as pregnancy itself causes the patient to become prothrombotic, MBDs may very well be masked close to delivery. However, repeated PPH without an obvious obstetric cause can be suggestive. A summary of useful questions and investigations that can be used in order to identify a patient with a potential MBD is given in Table 2.

As a minimum, these patients should have a full blood count and blood film, a PT, APTT, Fibrinogen level (usually Clauss fibrinogen), and renal and liver function requested. These tests have a short turnaround time, are more useful in the context of a patient with a high pre-test probability of a bleeding tendency, and can identify a subset of acquired and congenital bleeding disorders. Beyond this, liaison with a haematologist is recommended to consider further testing, for example for vWF antigen and activity.
Acute management of bleeding

As with any patient with bleeding, it is important not to forget general supportive measures. Resuscitation should proceed as per standard care with a view to control haemorrhage using appropriate techniques, be this with direct pressure, endoscopy, interventional radiology or open surgery. Often, in a suspected MBD, tranexamic acid (TxA) can be used empirically as an intravenous bolus (discussed in greater detail below). Liaison with a clinical haematologist can facilitate laboratory testing, and if bleeding is not responding to standard measures, some of the empirical options mentioned below may be considered.

Emergency invasive procedures

As with a significant bleed, if a patient requires limb or life saving surgery this should not be delayed for a full work up of an MBD. The key point is to weigh up the risk of the procedure against the risk of bleeding, and this can often lead to discussion with multiple specialties. Consideration of alternative strategies, or possibly deferring a procedure will depend on the individual situation. For example, in a patient with a possible subarachnoid haemorrhage and a suspected MBD, earlier recourse to CT angiography with digital subtraction imaging may be considered before a lumbar puncture to examine for xanthochromia.

Elective procedures

In general, with an elective procedure, we would recommend an initial discussion with a haematologist followed by a referral for comprehensive assessment. Although the timescale to investigate and register a patient for an MBD will depend on the individual centre, most units will be able to perform a clinical risk assessment depending on the type of surgery and the urgency in an appropriate timeframe.
Thrombosis

The management of arterial and venous thrombosis in patients with an MBD is a complex area with no standardised guidance. Due to the multiple factors that determine a person’s tendency to bleed or develop thrombosis, collecting enough data for individual MBDs presents a challenge. If a patient with an MBD develops thrombosis, we would advocate a review of the bleeding history, and a careful discussion involving the patient, haematologists and the relevant specialty managing the thrombosis. In general, a trial of standard care would be considered, with patient education regarding the risks and signs of bleeding. However, in circumstances where the bleeding is significantly worsened by antiplatelet or anticoagulant treatment, a review for exacerbating factors would be necessary, with consideration for either a trial of an alternative agent or a dose reduction.

The patient with a known MBD

In this scenario, as with the unknown patient, it is important to stress that the management of life and limb threatening emergencies should not be delayed. The patient will usually be known to a CCC, and may carry a card with their diagnosis. Patients with a known MBD can vary significantly with regards to their knowledge of their disorder. By definition, an MBD suggests that it is less likely to affect the patient day to day and so some patients may not ascribe significance to the diagnosis.

If a patient is registered with a CCC, liaison with the specialist team is advised at the earliest opportunity. In these circumstances the department will have a record of the severity of the bleeding disorder and a suggested protocol for management. The haematologist is likely to
suggest a course of action depending on the individual scenario. Potential options can include:

**Trial of procedure**

If the MBD is considered significantly mild, and the surgery is relatively low risk for bleeding, the procedure can go ahead with minimal intervention. This is often used with superficial, soft tissue procedures, i.e. where bleeding is likely to be simple to control. In some circumstances, a trial of procedure can be advised with adjunctive treatment on standby. As a comparison, there are various guideline recommendations as to which procedures can proceed as normal in patients receiving antiplatelet and anticoagulant therapy\(^\text{31}\). Ultimately, the operator is best placed to assess bleeding risk of the procedure, and should document this discussion with the patient and haematologist.

**Tranexamic acid**

TxA is a synthetic lysine analogue that inhibits fibrinolysis through competitive binding of plasminogen. It is on the World Health Organisation’s list of essential medicines\(^\text{32}\), and has been licenced for menorrhagia, epistaxis and dental extraction in haemophilia, and more recently in any massive trauma and PPH\(^\text{33,34}\). It can be administered intravenously or orally prior to a procedure, and is usually continued for several days afterwards. Although there is a theoretical risk of thrombosis, this has not been borne out in large clinical trials\(^\text{33,34}\). The main contraindications to consider are haematuria (where there is a risk of clot retention) and disseminated intravascular coagulation.

**Desmopressin**
This synthetic derivative of antidiuretic hormone has been licenced for use in mild to moderate haemophilia and vWD. The mechanism of action is through the release of stored vWF and factor VIII from the subendothelium, with a peak action 90-120 minutes after subcutaneous or intranasal administration\textsuperscript{35}. Although doses can be repeated at 12 hourly intervals, tachyphylaxis can occur due to acute reduction in subendothelial vWF stores. The medication is contraindicated in unstable angina and heart failure, and the patient and physicians should be made aware of the risk of fluid overload. Desmopressin should also be used with caution in elderly patients, because of the rarely reported increased risk of precipitating cardiac ischaemia\textsuperscript{36}.

**Platelet transfusion**

This is rarely used in the context of an MBD. Use of meticulous haemostasis, TxA and desmopressin are often sufficient for most contexts. In the patient with a platelet disorder and a high-risk procedure, transfusion of a single unit of platelets may be considered as a way of temporarily overcoming the defect\textsuperscript{37}. In this scenario, the platelet transfusion should be given immediately pre-procedure.

**Plasma and plasma derived products**

The use of fresh frozen plasma in MBDs is very limited, and generally avoided due to lack of efficacy and associated risks. The same is true for cryoprecipitate, and prothrombin complex concentrate. Indications for the use of these products are beyond the scope of this review, though are well established\textsuperscript{38}.

**Conclusions**
Patients with an MBD represent a unique clinical challenge, and can present to any specialty. Whilst the mechanism for a significant number of MBDs can be identified, the phenotype remains variable due to the interplay of genetic and environmental factors. In addition, testing for individual MBDs requires expertise to perform and interpret. For these reasons, the clinical history remains of utmost importance in the general management of these patients. The nature of these conditions means that liaison with a specialist centre, multidisciplinary assessment and a careful judgement of the balance of risk in each individual circumstance is required to safely manage these patients.

References


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Dietary Vitamin K Deficiency  
Liver Disease |
| | Hereditary | Mild haemophilia A+B  
Some types of vWD  
Bleeding with low VWF as a risk factor  
Factor XI deficiency |
| Disorders of platelet number / function | Acquired | Drugs: Aspirin, P2Y12 inhibitors,  
GPIIb/IIIa inhibitors  
Renal and Liver Disease  
ITP |
| | Hereditary | MYH9 related disorders  
Wiskott-Aldrich syndrome  
Hermansky Pudlak syndrome |
| Disorders of the vasculature | Acquired | Vitamin C deficiency |
| | Hereditary | Ehlers Danlos syndrome  
HHT and other vascular malformations  
Marfan’s syndrome |
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