Bleeders, bleeding rates, and bleeding score

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Summary. Bleeding symptoms are frequently reported even in otherwise healthy subjects, and differentiating a normal subject from a patient with a mild bleeding disorder (MBD) can be extremely challenging. The concept of bleeding rate, that is, the number of bleeding episodes occurring within a definite time, could be used as the unifying framework reconciling the bleeding risk observed in congenital and acquired coagulopathies into a single picture. For instance, primary prevention trials have shown that the incidence of non-major bleeding symptoms in normal subjects is around five per 100 person-years, and this figure is in accordance with the number of hemorrhagic symptoms reported by normal controls in observational studies on hemorrhagic disorders. The incidence of non-major bleeding in patients with MBDs (e.g. in patients with type 1 VWD carrying the C1130F mutation) is also strikingly similar with that of patients taking antiplatelet drugs, and the incidence in moderately severe bleeding disorders (e.g. type 2 VWD) parallels that of patients taking vitamin K antagonists. The severity of a bleeding disorder may therefore be explained by a bleeding rate model, which also explains several common clinical observations. Appreciation of the bleeding rate of congenital and acquired conditions and of its environmental/genetic modifiers into a single framework will possibly allow the development of better prediction tools in the coming years and represents a major scientific effort to be pursued.

Keywords: anticoagulants, diagnosis, epidemiology, hemorrhage, hemorrhagic disorders.

Introduction

There was a woman afflicted with haemorrhages for twelve years. She had suffered greatly at the hands of many doctors and had spent all that she had. Yet she was not helped but only grew worse. (Mark, 5:25–6)

Bleeding has always been an alarming clinical symptom in all human societies, and physicians have had varying degrees of success in diagnosing and treating bleeding patients [1,2]. Unlike other clinical manifestations, however, bleeding is likely to become even more common in the future, largely due to the ever-increasing use of antiplatelet or anticoagulant drugs in frail patients [3,4]. As an example, an increase in warfarin-associated intracerebral hemorrhage has been observed in recent years [5].

Because bleeding is part of the human experience, one of the most challenging tasks for a physician is to discriminate between ‘normal’ and ‘pathologic’ bleeding. There are at least two reasons why this distinction should be made. First, both patients and physicians may be willing to search for the cause of unexpected bleeding, for instance, postpartum major bleeding following an otherwise normal pregnancy: this is a diagnostic issue. Second, and most importantly, both patients and physicians are interested in the question ‘Am I (or is the patient) at risk of having another bleeding event?’ this latter being a prognostic issue. In fact, any diagnostic evaluation is ultimately aimed at improving prognosis, because both the patient and the physician (e.g. a surgeon) wish to reduce the bleeding risk, at least during invasive procedures.

In this article, we discuss the diagnostic and prognostic issues of patients with congenital bleeding disorders using an epidemiologic framework based on the concept of bleeding rate.

Definitions of bleeds: life-threatening, major, clinically relevant, minor, and trivial bleeding

Hemorrhages or bleeds may occur in every tissue and organ (see [6], Supplemental appendix, for a recent review of bleeding symptoms). Every bleeding symptom may, however, vary greatly in terms of magnitude: for instance, bleeds in the subcutaneous tissues may present as small pinpoint lesions (petechiae) or large bruises, and epistaxis...
may range from some blood-streaked mucus to a massive hemorrhage. Bleeding symptoms may also have different frequency patterns: epistaxis is very likely to recur, while postsurgical bleeding is most often an isolated symptom. Which clinical presentation should be considered as more severe or more suggestive of a blood disorder?

On the mild side of the clinical spectrum, trivial (or non-relevant) bleeding is very commonly encountered in clinical practise and can be indeed considered to be part of the normal human phenotype. Some examples are the loss of few drops of blood from the nose in a child or some blood-streaked sputum after teeth brushing. As a general guideline, trivial bleeding never interferes with daily activities or requires medical attention, and some practical advice has been suggested to identify it (Table 1).

Minor bleeding is a broad category encompassing a wide variety of symptoms that are, however, severe enough to interfere with the patients' everyday life, leading them to seek medical attention to relieve or prevent them. In this way, minor bleeding surface from the sea of normal human events become clinically relevant. As an example, a woman who misses a day of work because of heavy menses has a minor bleeding symptom.

Finally, major bleeding defines those episodes that may cause permanent damage to the patient or threaten his or her life. Following the seminal work by Landefeld and colleagues [7–11] and Graafsma et al. [12], a consensus on the minimal criteria needed to define major bleeding in patients receiving anticoagulant treatment has been reached [13,14]. Major bleeding is defined as ‘Fatal bleeding, or bleeding in a critical area (intracranial, intraspinal, intraocular, retro-peritoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or resulting in an haemoglobin fall ≥ 2 g dL⁻¹ or requiring transfusion ≥ 2 red blood cell (RBC) units’ [14]. In some recent clinical trials, major bleeding was further categorized as life-threatening when symptomatic intracranial, or associated with a decrease in the hemoglobin level ≥ 5 g dL⁻¹, or requiring transfusion of at least four RBC units of blood, use of inotropic agents or surgery, or when fatal [15]. Table 2 summarizes definitions of major and minor bleeding in recent methodological, consensus papers.

### Incidence of bleeding symptoms in healthy subjects

The incidence of major or minor bleeding symptoms in the general population is largely unknown, because no prospective studies specifically designed to address this question are available. However, some insights may be offered by placebo-controlled intervention trials. In the placebo arm of the Thrombosis Prevention Trial, which included 1272 men aged 45–69 years for a total observation time of 8071 person-years, four major bleeding episodes were observed, corresponding to a rate of about 0.05 cases per 100 person-years [16]. In the Women’s Health Study, the 19 942 subjects in the placebo arm (mean age 54.6 years) had an incidence of major bleeding (gastrointestinal bleeding requiring transfusion or hemorrhagic stroke) of 0.06 cases per 100 person-years [17].

Although these estimates may be biased by several factors (particularly by age, strongly influencing the incidence of major bleeding such as intracranial hemorrhage [18]), spontaneous major bleeding is very rare in the general population and almost always associated with predisposing factors such as gastrointestinal disease, anatomic lesions, or intracranial vascular malformations. Therefore, the occurrence of spontaneous major bleeding may be considered highly specific for the presence of a blood disease, particularly in the absence of anatomic lesions.

The incidence of non-major bleeding (i.e. trivial or minor bleeding) in the general population is obviously higher. In the Thrombosis Prevention Trial and in the Women’s Health Study, the incidence of non-major bleeding was 5.3 and 7.7 per 100 person-years, respectively.

### Table 1 Minimal criteria defining a non-trivial bleeding symptom (after Rodeghiero et al. [40])

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Epistaxis</td>
<td>Any nosebleed that causes interference or distress with daily or social activities</td>
</tr>
<tr>
<td>Cutaneous bleeding</td>
<td>Bruises are considered significant when five or more (≥ 1 cm) in exposed areas</td>
</tr>
<tr>
<td>Minor cutaneous wound</td>
<td>Any bleeding episode caused by superficial cuts (e.g. by shaving razor, knife, or scissors) or that requires frequent bandage changes</td>
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<tr>
<td>Oral cavity bleeding</td>
<td>Gum bleeding should be considered significant when it causes frankly bloody sputum and lasts for 10 min or longer on more than one occasion. Tooth eruption or spontaneous tooth loss bleeding should be considered significant when it requires assistance or supervision by a physician or lasts at least 10 min. Bleeding occurring after bites to lips, cheek, and tongue should be considered significant when it lasts at least 10 min or causes a swollen tongue or mouth</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>Any bleeding occurring after leaving the dentist’s office and requiring a new, unscheduled visit or prolonged bleeding at the dentist’s office causing a delay in the procedure or discharge</td>
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<tr>
<td>Surgical bleeding</td>
<td>Any bleeding judged by the surgeon to be abnormally prolonged that causes a delay in discharge or requires some supportive treatment</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Any bleeding that interferes with daily activities such as work, housework, exercise, or social activities during most menstrual periods</td>
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This means that a middle-aged subject has a 5–8% probability of having a minor or trivial bleeding episode every year or a ≈40% probability of having such an episode every 10 years based on the binomial distribution [19]. Even conservatively assuming that the bleeding risk is much lower in the first years of life and modeling an exponential increase in the bleeding risk with age (an assumption essentially made to account for sex-specific problems in women and trauma or surgical bleeding, presumably resulting in a higher bleeding risk in adults than in infants), the probability of having one or two minor hemorrhagic symptoms at age 30 may be as high as 33 and 6%, respectively (Fig. 1).

Based on these considerations, it is not surprising that a very high incidence of subjects reporting spontaneous minor bleeding symptoms has been observed by different studies. For instance, profuse menstrual bleeding has been reported to occur at least once during the fertile period in up to 44% of women; epistaxis in 5–36% of children; and at least one hemorrhagic symptom is reported by 40–50% of men and 50–60% of women [20–24]. Such figures were recently confirmed in a large investigation (n = 500) on the incidence of bleeding symptoms in normal subjects [25]. Using a well-characterized bleeding questionnaire and standardized data collection, the authors found that the most frequently reported hemorrhagic symptoms were menorrhagia (47% of women), epistaxis (25%), easy bruising (18%), and prolonged bleeding after tooth extraction (18%). Notably, women had more bleeding symptoms due to sex-specific problems (i.e. heavy menses, bleeding at delivery or during pregnancy).
These figures are in keeping with those expected on the basis of the incidence of non-major bleeding observed in the above-mentioned clinical trials, further supporting the idea that a retrospective assessment of the bleeding history from the patient may give valid (i.e. unbiased) information for epidemiological investigations on bleeding disorders [26].

What is a ‘bleeding phenotype’?

Based on its high specificity, a history of spontaneous major bleeding virtually ‘rules in’ a bleeding disorder, and an extensive laboratory workup is mandatory in these patients because of the suspicion of a ‘severe’ bleeding disorder, such as hemophilia or severe FVII deficiency. Patients presenting with these symptoms are relatively few, however, while clinicians are more often concerned with the diagnosis and management of patients who have a history of minor bleeding.

These patients reporting may be completely normal or may have a mild to moderate bleeding disorder (such as platelet secretion defects or von Willebrand disease), and they therefore lie somewhere in-between having some ‘risk factor’ for bleeding or having an autosomal dominant disorder with variable penetrance and expressivity [27,28].

From a theoretical point of view, a ‘bleeder’ is a patient with an increased bleeding rate, this latter probably being the best estimate of the bleeding severity in patients (at least for those without a history of major hemorrhage). The bleeding rate is simply the number of significant bleeding episodes that occurs within a defined time frame in the patient’s life (e.g. in the last 10 years or in the patient’ life span), that is

\[
\text{Bleeding rate} = \frac{\text{Number hemorrhages}}{\Delta t}
\]

For instance, based on the previously discussed bleeding incidence of five events per 100 person-years, healthy 40-year-old subjects would be expected to report about two hemorrhagic events (Fig. 2), for a bleeding rate equal to 2/40 years or one hemorrhagic event every 20 years. As mentioned before, this rate may be actually higher in females than in males because of sex-specific bleeding symptoms.

It would be extremely nice to have direct data on the actual incidence of bleeding in congenital bleeding disorders, but these are very sparse or unavailable. For the sake of comparison, we could therefore consider the bleeding rate in patients using drugs that actually mimic a bleeding disorder; for instance, aspirin-induced platelet dysfunction may be taken as a surrogate for a mild bleeding disorder (MBD). In the aspirin arm of the Thrombosis Prevention Trial, 532 non-major bleeding events were observed, for a bleeding incidence of 6.5 events per 100 person-years, which is in fact only marginally higher than the incidence observed in healthy subjects. Interestingly, our group recently reported a bleeding rate of 7.5 events per 100 person-years in patients having type 1 von Willebrand disease (VWD) carrying the von Willebrand factor (VWF) C1130F mutation, the prototype of a mild to moderate bleeding disorder [29].

Patients with a moderate bleeding disorder may be compared with those patients taking vitamin K antagonists (VKA), in whom clotting factors are maintained at approximately 20% of the normal activity. In the recent RELY trial [15], patients taking VKA had a rate of non-major bleeding of 16.3 events per 100 patient-years, a figure that is lower than that observed in a recent prospective study on two severe subtypes of VWD, types 2A and 2M VWD, in which patients had rates of non-major bleeding of 107 and 40 per 100 person-years, respectively [30].
Using the figures obtained from these two models (as epitomes of mild and moderately severe bleeding disorders), we may estimate the number of expected bleeding episodes occurring during the lifetime of a patient as we previously did for normal subjects (Fig. 2).

In patients with a moderately severe bleeding disorder, at least two non-major bleeding episodes are expected in middle-aged patients. In fact, the presence of at least two hemorrhagic symptoms was required for the diagnosis of von Willebrand disease (VWD) in a consensus-based statement [31]. Furthermore, in the International Multicenter Study (IMS), having more than two bleeding symptoms showed a 99.5% specificity for the diagnosis of VWD in obligatory carriers [32].

On the contrary, in patients with an MBD, the expected number of bleeding episodes is very close to that observed in healthy subjects, making it very difficult to suspect an MBD from the patient’s bleeding history before age 40 and requiring the use of an appropriate laboratory panel to exclude an MBD in young patients. Indeed, in the IMS, the sensitivity of clinical criteria alone was 50%; in another prospective study, the sensitivity of clinical criteria for the diagnosis of MBD was 41% [33].

Finally, a more severe bleeding disorder may be suspected when a patient reports hemorrhagic symptoms at a young age. This is quite apparent from Fig. 2, showing that the number of hemorrhagic symptoms is higher in the young only when a more severe disorder (e.g. VKA treatment) is present. This is well confirmed by the clinical observations that in patients with FVII deficiency, a young age of presentation correlates with hemophilia-like symptoms in subsequent years [34,35] and that the age of first joint bleed correlates with hemophilia severity [36].

Bleeding assessment tools

The closeness of the bleeding patterns in normal subjects and in MBD patients indicates the need for stringent standardization and validation of the clinical tools used to collect the bleeding history, and this has been recognized ever since the first provisional criteria were proposed for the diagnosis of VWD [31] and further reinforced by the seminal IMS on obligatory VWD carriers that first made use of the Vicenza bleeding score. Subsequent multicenter studies on VWD promoted both the use of similar tools to collect the bleeding history and a common way of summarizing the severity of bleeding symptoms allowing genotype-phenotype correlations [32,37–39]. Such tools are also known as bleeding assessment tools (BATs) and include a questionnaire to investigate the bleeding history and an interpretation grid to score for the most severe presentation of each bleeding symptom. In the grid, bleeding events (e.g. epistaxis, or menorrhagia) are scored from 0 (if absent) up to 4 (major bleeding, requiring transfusion or surgery) [40]. The sum of the severity of each reported symptom in a given patient is known as the individual bleeding score [41–44].

The clinical relevance of the bleeding score has been evaluated in different cohorts of patients, and all studies demonstrated high specificity (> 95%) with sensitivity ranging from 40% to 100% [32,33,39,45–47]. Notably, although basically the same questionnaires were used in these studies, different interpretation grids were applied without increasing the discriminating ability [48]. These figures confirm that, especially for MBD, even a highly standardized data collection and interpretation tool cannot improve the sensitivity of clinical diagnosis, as previously discussed. In fact, in the IMS, the sensitivity of the bleeding score was only marginally higher than that reached by considering as abnormal those subjects reporting more than two bleeding symptoms [32], a finding recently confirmed also in a pediatric population [45].

The similar sensitivity of criteria based on the bleeding score or the number of bleeding symptoms is not surprising, because both are related to the bleeding rate, particularly in healthy subjects and in patients with MBD. In these patients, the bleeding rate is rather low and bleeding events are usually non-major, each one reaching a score around 1–2 using the Vicenza grading score. Hence, if in a healthy, middle-aged subject we expect up to two non-major bleeding events, then the upper limit for a normal bleeding score should be expected to be below 3–4; this limit should be possibly higher in women than in men because of the sex-specific bleeding symptoms. In fact, both these predictions are confirmed by the observed scores in subjects with a mean age of 49 years, with women having higher bleeding scores [32].

If the bleeding rate is constant or even slightly increasing with age, the number of bleeding symptoms and the related bleeding score would be expected to be lower at a younger age. At present, however, there are no data on the distribution of the bleeding score at different ages and whether different cutoffs of the bleeding score would improve the sensitivity in young patients or the specificity in older patients. For instance, based on Fig. 2, a bleeding score above two could be considered abnormal in at age 30, but normal at age 60.

This picture may change as the severity of a bleeding disorder increases. In this setting, the bleeding rate is much higher and we also expect symptoms to recur in the same patient. Because the bleeding score in such instances only records the more severe presentation of symptoms (e.g. need for RBC transfusion after menorrhagia), it is insensitive to the increased bleeding rate expected in severe bleeding disorders. For instance, a hemophiliac having six hemarthroses per year would get the same bleeding score as one who experienced just one hemarthrosis throughout his entire life. Therefore, while the currently used bleeding score is certainly promising tool for the diagnosis of MBD, its clinical utility for the diagnosis
and prognosis of severe bleeding disorders still needs to be assessed.

The ISTH has recently proposed a new consensus-based BAT [40]. This tool, developed from the original IMS (Vicenza) questionnaire to ensure compatibility with previous investigations, aims at standardizing the various interpretation grids (and the resulting bleeding scores) and at collecting more detailed data on the bleeding rate of spontaneous, non-trivial bleeding. It is therefore hoped that in the next year, more precise estimators of the bleeding rates will be available for patients with congenital bleeding disorders. The ISTH BAT is also coupled with an electronic repository, set up and kept by the Rockefeller University Center for Clinical and Translational Science, designed to collect and possibly merge information on bleeding symptoms and rates in different patient populations [49]. Details on both the ISTH BAT and repository are available online [50], and the use of these tools should be strongly encouraged.

To date, perhaps the greatest clinical utility of bleeding scores lies in their high negative predictive value, and therefore on the exclusion of subjects in which further testing may be unnecessary. A normal activated partial thromboplastin time and a normal bleeding score almost completely excluded the presence of a bleeding disorder in a prospective study on patients referred for hemostatic evaluation [33]. Laboratory evaluation should, however, always be considered in those very young patients in whom the bleeding history may be completely negative due to lack of hemostatic challenges.

Could we predict bleeding?

One of the most urgent clinical needs is to predict the patient’s bleeding risk, particularly in situations in which antihemorrhagic treatments could be administered. For instance, should a patient with borderline reduction in VWF (e.g. 30 IU dL\(^{-1}\)) be treated with desmopressin before tonsillectomy? At present, we do not have data that could offer guidance in such situations, and treatment is still based on expert opinion [51]. Spontaneous bleeding could never be reliably predicted, which is also evident from the generally low performance of bleeding prediction rules applied to patients taking VKA [52–56].

However, at least for patients with VWD, there is weak evidence that a history of bleeding correlates with a higher risk of future bleeding. In the European MCMDM-VWD1 Study, the bleeding score computed only from the history of spontaneous mucocutaneous symptoms (epistaxis, cutaneous bleeding, bleeding from minor wounds) was superior to VWF measurement for the prediction of surgical bleeding (c-statistics = 0.78) [39]. Hence, the presence of a bleeding history in patients with VWD may suggest the need for more aggressive prophylaxis before invasive procedures. Furthermore, in a cohort study in 46 patients with type 2A and 61 with type 2M VWD, the bleeding score measured at time of patient enrollment predicted a higher bleeding incidence in the 2-year follow-up period, with patients having a bleeding score above 9 showing a nearly 6-fold higher risk of bleeding than those with a bleeding score in the normal range (below 3) [30]. Similar results were also observed in a large, prospective investigation performed in 814 patients with predominantly type 1 and type 2 VWD in Italy [57]. In this study, a bleeding score > 10, a bleeding time > 20 min, and VWF/RCo levels below 10 IU dL\(^{-1}\) were all associated with increased bleeding risk, but the bleeding score trumped the other determinants of severity at multivariate analysis, remaining the strongest predictor of bleeding with a 5.5-fold high bleeding risk; patients with VWF/RCo > 30 IU dL\(^{-1}\) and FVIII:C > 40 IU dL\(^{-1}\) always had bleeding scores < 5 at presentation.

Therefore, while the prediction of bleeding and the tailoring of the best therapeutic strategy in individual patients are still unsatisfactory, it seems reasonable that the bleeding history be considered a critical step in the clinical evaluation of patients, and for this reason, it seems reasonable to include it in the diagnostic and management strategies of patients with bleeding disorders [51,58].

Conclusions and future developments

A correct appreciation of the importance of bleeding manifestations and of the incidence of bleeding in the individual patient is probably one of the most important skills that physicians should achieve in any hemostasis curriculum [59]. It is quite clear that the presence of significant bleeding should be clearly distinguished from trivial bleeding, as failure to do so could result in misdiagnosis of an otherwise healthy subject. On the other hand, we have shown that the bleeding history and the bleeding score are tightly related to the individual bleeding rate, which defines the severity of a bleeding disorder.

Despite the extraordinary advances in the clinical investigation of bleeding symptoms that we have witnessed in the last decade, several areas need to be covered to further improve the validity and usefulness of a quantitative approach for the diagnosis and management of bleeding disorders.

First, the validity of bleeding scores has been investigated only in patients with MBD, but has never been proven in patients having a severe bleeding disorder. For the latter group, appropriately designed prognostic studies are needed in the future and the development of prognostic indices is an open field for investigation. Second, the use of electronic databases, and possibly of widely available, web-based instruments, should be encouraged and supported. Bleeding questionnaires obtained from patients with bleeding disorders may contain a huge amount of information and are especially precious,
because such information from rare patients can usually be obtained just once in their lifetime. For these reasons, the formation and availability of large databases on bleeding disorders, either congenital or acquired, will provide a unified framework for clinicians and researchers alike.

Disclosure of Conflicts of Interests

The authors state that they have no conflict of interest.

References


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