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COMMENTARY

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TO THE EDITOR:

# von Willebrand disease: proposing definitions for future research

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## Introduction

von Willebrand disease (VWD) is a common bleeding disorder, which affects 1 in 100 individuals based on laboratory testing and at least 1 in 1000 individuals based on presence of abnormal bleeding symptoms.[1,2] VWD was first described almost 100 years ago, and since the initial report, major advances in both diagnostic testing and treatment options have improved outcomes for patients living with VWD; however, many patients still experience significant complications and barriers to treatment. An underlying problem is the lack of consistent unified definitions.

In recent work developing evidence-based guidelines for VWD,[3,4] it was noted that studies on VWD often used varying definitions. For example, studies of von Willebrand factor (VWF) concentrates did not have consistent definitions for major bleeding, studies on VWF prophylaxis did not use consistent definitions of what constituted a prophylaxis regimen, and studies on desmopressin did not use consistent definitions of desmopressin responsiveness. In addition, common bleeding conditions, such as heavy menstrual bleeding (HMB) and postpartum hemorrhage are variably defined. Such inconsistencies in describing study regimens and endpoints hinder the ability to compare study outcomes and to advance treatment of patients with VWD.

We propose definitions for future use in VWD research to facilitate comparison of treatment options. These definitions are based on the most common usage in the literature and endeavor to encompass the most common situations in VWD. The proposed definitions were derived from existing literature and discussed at the first in-person meetings of the guideline panels. Group members made amendments, and the consensus document was circulated to the group. All authors approved the final document.

## Desmopressin response

### Proposed definition

Desmopressin response requires an increase of at least >2 times the baseline VWF activity level and a sustained increase of both VWF and factor VIII (FVIII):C levels >0.50 IU/mL for at least 4 hours.

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Requests for data may be made by contacting the corresponding author, Veronica H. Flood, at vflood@mcw.edu.

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### Comment

Desmopressin is typically given either subcutaneously, IV, or intranasally. Response may be measured following any mode of administration, but in some instances (eg, children), intranasal administration may be suboptimal, and lack of measured response may be due to poor administration rather than true lack of response.

It is important to note that for some procedures, VWF activity levels of >0.50 IU/mL but <1.00 IU/mL may be insufficient. Neurosurgery or procedures with a very high bleeding risk may require levels of at least 1.00 IU/mL, and therefore, a patient may be "desmopressin responsive" but require VWF concentrate to achieve an adequate level for surgical hemostasis. Similarly, VWF concentrate may be required to maintain levels for a prolonged period due to tachyphylaxis.

Previous literature has used multiple definitions. Multiple sources used a similar definition with complete response when levels were at least 0.50 IU/mL.[5-8] Others used a definition of at least 3 times baseline increase and levels at least 0.30 IU/mL[9] or 0.40 IU/mL.[10] The authors feel it is most logical to use a specific cutoff that made physiologic sense; therefore, an increase of VWF into the normal range of >0.5 IU/mL is considered optimal. There is evidence that patients with VWF levels <0.50 IU/mL may experience bleeding[11]; therefore, a cutoff of 0.50 IU/mL is suggested. Prolonged increased VWF and FVIII levels are associated with risk of thrombosis[12,13]; therefore, the goal is to achieve optimal hemostasis while limiting the amount of time patients are exposed to excess VWF and FVIII.

Some patients may experience minor bleeding episodes that clinically respond to desmopressin (eg, nosebleeds) even when these proposed criteria for desmopressin responsiveness would not be met. This does not imply that desmopressin cannot be used in these situations, but rather the definition would allow documentation that a clinical response can be obtained and establish a standardized definition for future use in surgical or emergency situations or in clinical trials for people with VWD. Individual clinical response may also vary and should be taken into consideration in practice. Desmopressin has effects on coagulation beyond just elevation of VWF levels. There are also data suggesting desmopressin responsiveness may change with age, so repeat testing may be in order.[14,15]

## Prophylaxis

### Proposed definition

Prophylaxis in VWD is a period of at least 3 to 6 months of treatment consisting of VWF concentrate administered at least once weekly, or for women with HMB, use of VWF concentrate administered at least once per menstrual cycle.

### Comment

Most research studies of prophylaxis will likely require at least 6 months of therapy to establish efficacy and safety. However, in some situations, such as children with profound epistaxis during cold weather, a shorter duration may be appropriate; therefore, the definition includes the option of a shorter time period. Many patients on prophylaxis, however, will derive greater clinical benefit from prophylaxis for >6 months.[16]

There are currently several different VWF concentrates available, including plasma-derived formulations with both VWF and FVIII, as well as recombinant VWF (which does not contain FVIII). The use of specific products will likely depend on multiple factors and therefore is not specified here.

This definition is consistent with that used in previous studies of VWD prophylaxis[16-18] and includes an option for a shorter time frame in specific situations.

## Major bleeding in VWD

### Proposed definition

Major bleeding includes episodes requiring hospital admission, surgical intervention, blood transfusion, hemoglobin drop of ≥2 g/dL, bleeding involving critical areas (eg, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or recurrent bleeding affecting the ability to attend normal schooling, working, or social activity.

### Comment

This definition is consistent with previously published definitions by the International Society on Thrombosis and Haemostasis (ISTH) for major bleeding in both nonsurgical and surgical settings.[19,20] Recent definitions have been published regarding major bleeding for patients on anticoagulation therapy with more specific details in terms of cardiac bleeding.[21] Similar criteria to those proposed here have also been used in evaluation of bleeding for anticoagulation trials.[22]

In the VWD literature, the definition of major bleeding includes bleeding leading to hospital admission, treatment with VWF concentrate for at least 48 hours, or "life-threatening bleeding."[23] The definition proposed here does not include use of VWF concentrate because this should be started once any significant bleeding event is recognized. It is anticipated that these definitions would be used in studies of treatment of patients with an existing diagnosis of VWD. The ISTH bleeding assessment tool is commonly used to measure bleeding prior to diagnosis of VWD.[24] The proposed definition would be similar to a score of 4 on the ISTH bleeding assessment tool for blood transfusion or replacement therapy requirement.

## Major surgery

### Proposed definition

Major surgery includes surgical procedures involving cranial, spinal, and great body cavities, joints, impacted third molar extraction, or interventions where subject's life is imminently at risk. In patients with VWD, this category also includes tonsillectomy, dental extractions with use of mandibular block or multiple extractions, liver or kidney biopsy, gastrointestinal polypectomy, cervical cone biopsy, or extended procedures with high risk of bleeding.

### Comment

The definition has been addressed in several studies of VWF concentrate. Windyga and colleagues used a definition similar to that given above.[25] Gill and colleagues considered major surgery to be operations involving considerable hazard to life or limb and included multiple tooth extractions as major surgery.[26] Literature on treatment of anticoagulated patients undergoing surgery also provides a definition of major surgery, slightly broader in scope with inclusion of procedures lasting >45 minutes and greater detail

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**Table 1. Grading of hemostatic response for surgical procedures**

| Rating | Hemostatic assessment | Bleeding |
|---|---|---|
| Excellent | Hemostasis achieved was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject | No different than normal individuals |
| Good | Hemostasis achieved was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject | Slight oozing |
| Moderate | Hemostasis was clearly less than optimal for the type of procedure performed but was maintained without the need to change the treatment/regimen used | Moderate controllable bleeding |
| Poor | Patient experienced uncontrolled bleeding that was the result of inadequate therapeutic response to the treatment used | Uncontrolled bleeding |

on types of surgeries considered major, including laminectomy, prostate resection, polypectomy, variceal treatment, percutaneous endoscopic gastrostomy placement, and multiple tooth extractions.[27] Control of hemostasis is addressed in Table 1.[28,29]

## Heavy menstrual bleeding

### Proposed definition

Menstrual bleeding meeting any of the following criteria:

- Lasting ≥8 days
- Consistently soaks through 1 or more sanitary protections every 2 hours on multiple days
- Requires use of >1 sanitary protection item at a time
- Requires changing sanitary protection during the night
- Associated with repeat passing of blood clots
- Pictorial Blood Assessment Chart (PBAC) score >100

### Comment

In clinical practice, HMB is defined as excessive menstrual loss, which interferes with a woman's physical, social, emotional, and/or material quality of life.[30] In terms of blood loss, HMB is defined as a menstrual blood loss of >80 mL per period.[31] This objective assessment can only be obtained by laborious, expensive, and inconvenient measurements involving collection of used sanitary protections. Therefore, simple indirect methods, such as detailed menstrual history or the use of PBAC,[32] are used to provide a semiquantitative assessment of the blood loss and its severity as well as monitoring response to treatment. Although no consensus definition of HMB exists in the VWD literature, future research will benefit from consistency.

## Primary postpartum hemorrhage

### Proposed definition

Primary postpartum hemorrhage (PPH) includes blood loss ≥1000 mL within 24 hours of birth or any blood loss with the potential to produce hemodynamic instability. Of note, once blood loss exceeds 500 mL in a vaginal birth, early intervention with measures known to reduce PPH (eg, uterotonics, tranexamic acid) should be considered.

### Comment

Assessment of blood loss is essential to identify PPH and its severity. Visual estimation often provides an underestimate of actual blood loss especially with a blood loss of >1000 mL,[33] leading to a delay in diagnosis and timely activation of PPH protocols. Direct measurement of blood loss using graduated containers in combination with gravimetric weight measurement of blood on all drapes, incontinence pads, sanitary pads, and swabs, converting 1 g to 1 mL, provides a better estimation of blood loss with minimal resources.[34] No consensus definition of PPH exists in the VWD literature, but consistency is required for progress in future research.

## Secondary PPH

### Proposed definition

Secondary PPH includes blood loss that is heavier than normal lochial loss between 24 hours and 6 weeks postpartum and

- Necessitates medical review or intervention between 24 hours and 6 weeks postpartum, or
- Lasts beyond 6 weeks after childbirth

### Comment

Normal lochia is physiological vaginal bleeding postpartum. It is typically fresh red blood with mucus in the first 3 days after childbirth, tapering to dark red/brownish light loss by day 10 after delivery. It can last up to 6 weeks with brownish/yellowish watery discharge or spotting. The use of PBAC can be a useful to tool for assessment of lochia and its duration and should be used in women with bleeding disorders during the puerperium.[35]

## Conclusion

It is hoped that adoption of these definitions will improve the ability of researchers to achieve consistent endpoints in future VWD clinical trials, ultimately enabling improved treatments for affected patients.

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