Complete Summary

GUIDELINE TITLE

The diagnosis, evaluation, and management of von Willebrand disease.

BIBLIOGRAPHIC SOURCE(S)

National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI). The diagnosis, evaluation, and management of von Willebrand disease. Bethesda (MD): U.S. Department of Health and Human Services; 2007 Dec. 112 p. [398 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 04, 2007, Desmopressin Acetate (DDAVP, DDVP, Minirin, & Stimate): New information has been added to the existing boxed warning in Desmopressin's prescribing information about potential increased risk for severe hyponatremia and seizures.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

von Willebrand disease (VWD)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Internal Medicine
Medical Genetics
Obstetrics and Gynecology
Pediatrics
Surgery

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To present clinical recommendations for diagnosis, treatment, and management of von Willebrand disease (VWD)

TARGET POPULATION

Patients with suspected or confirmed von Willebrand disease

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis and Evaluation

1. History and physical examination
2. Laboratory testing
    - Complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (PTT), and thrombin time or fibrinogen level
    - Tests for von Willebrand disease

        - von Willebrand factor ristocetin cofactor activity (VWF:RCo)
        - von Willebrand factor antigen (VWF:Ag)
        - Factor VIII (FVIII) activity
    - Additional tests as needed (ratio of VWF activity to antigen, VWF multimer study, ristocetin-induced platelet aggregation, VWF collagen binding activity, FVIII binding assay, gene sequencing, VWF antibodies, platelet-binding studies)

Management/Treatment

1. General management
    - Immunization against hepatitis A and B
    - Genetic counseling
    - Counseling regarding avoiding platelet-inhibiting drugs (e.g., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs])
    - Restriction of fluids to maintenance levels
2. Treatment of bleeding and prophylaxis for surgery
    - Intravenous or nasal desmopressin (1-desamino-8-D-arginine vasopressin) (DDAVP)
    - VWF concentrate (pre-operative and with pharmacokinetic monitoring for major surgery)
    - Antifibrinolytics
    - Topical agents (fibrin sealant, bovine thrombin)
    - Clinical monitoring for major bleeding
3. Management of menorrhagia and hemorrhagic ovarian cysts
    - Combined oral contraceptives
    - Levonorgestrel intrauterine device
    - DDAVP, antifibronolytics, or VWF concentrate for women who desire pregnancy
4. Management of pregnancy and childbirth
    - Evaluation by hematologist and high-risk obstetrician
    - Prophylaxis with DDAVP or VWF
    - Monitoring of VWF:RCo and FVIII levels
5. Management of acquired von Willebrand syndrome
    - Trial of DDAVP or VWF with drug level monitoring
    - High-dose immune globulin intravenous (IGIV)

MAJOR OUTCOMES CONSIDERED

- Frequency and duration of bleeding in patients with von Willebrand disease (VWD)
- Specificity and sensitivity of laboratory tests
- Specificity and sensitivity of screening examination
- Adverse effects of drug therapy
- Blood levels of therapeutic/prophylactic drugs
- Duration of treatment
- Incidence of miscarriage and bleeding during pregnancy
- Incidence of postpartum hemorrhage

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Three section outlines, approved by the Expert Panel chair, were used as the basis for compiling relevant search terms, using the Medical Subject Headings (MeSH terms) of the MEDLINE database. If appropriate terms were not available in MeSH, then relevant non-MeSH keywords were used. In addition to the search terms, inclusion and exclusion criteria were defined based on feedback from the Panel about specific limits to include in the search strategies, specifically:

- Date restriction: 1990–2004
- Language: English
- Study/publication types: randomized-controlled trial; meta-analysis; controlled clinical trial; epidemiologic studies; prospective studies; multicenter study; clinical trial; evaluation studies; practice guideline; review, academic; review, multicase; technical report; validation studies; review of reported cases; case reports; journal article (to exclude letters, editorials, news, etc.)

The search strategies were constructed and executed in the MEDLINE database as well as in the Cochrane Database of Systematic Reviews to compile a set of citations and abstracts for each section. Initial searches on specific keyword combinations and date and language limits were further refined by using the publication type limits to produce results that more closely matched the section outlines. Once the section results were compiled, the results were put in priority order by study type as follows:

1. Randomized-controlled trial
2. Meta-analysis (quantitative summary combining results of independent studies)
3. Controlled clinical trial
4. Multicenter study
5. Clinical trial (includes all types and phases of clinical trials)
6. Evaluation studies
7. Practice guideline (for specific health care guidelines)
8. Epidemiological
9. Prospective studies
10. Review, academic (comprehensive, critical, or analytical review)
11. Review, multicase (review with epidemiological applications)
12. Technical report
13. Validation studies
14. Review of reported cases (review of known cases of a disease)
15. Case reports

Upon examination of the yield of the initial literature search, it was determined that important areas in the section outlines were not addressed by the citations,

possibly due to the date exclusions. In addition, Panel members identified pertinent references from their own searches and databases, including landmark references predating the 1990 date restriction, and 2005 and 2006 references (to October 2006). Therefore, as a followup, additional database searching was done using the same search strategies from the initial round, but covering dates prior to 1990 and during 2005 and 2006 to double check for key studies appearing in the literature outside the limits of the original range of dates. Also, refined searches in the 1990–2006 date range were conducted to analyze the references used by Panel members that had not appeared in the original search results. These revised searches helped round out the database search to provide the most comprehensive approach possible. As a result, the references used in the guidelines included those retrieved from the two literature searches combined with the references suggested by the Panel members. These references inform the guidelines and clinical recommendations, based on the best available evidence in combination with the Panel's expertise and consensus.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence*

Ia Evidence obtained from meta-analysis of randomized controlled trials

Ib Evidence obtained from at least one randomized controlled trial

IIa Evidence obtained from at least one well-designed controlled study without randomization

Ib Evidence obtained from at least one other type of well-designed quasi-experimental study

III Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlational studies, and case studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

* Source: Acute pain management: operative or medical procedures and trauma. (Clinical practice guideline.) Publication No. AHCPR 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, February 1992.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

During the spring of 2004, the National Heart, Lung, and Blood Institute (NHLBI) began planning for the development of clinical practice guidelines for von Willebrand disease (VWD) in response to the Fiscal Year 2004 appropriations conference committee report (House Report 108-401) recommendation. In that report, the conferees urged NHLBI to develop a set of treatment guidelines for VWD and to work with medical associations and experts in the field when developing such guidelines.

In consultation with the American Society of Hematology (ASH), the Institute convened an Expert Panel on VWD, chaired by Dr. William Nichols of the Mayo Clinic, Rochester, MN. The Expert Panel members were selected to provide expertise in basic sciences, clinical and laboratory diagnosis, evidence-based medicine, and the clinical management of VWD, including specialists in hematology as well as in family medicine, obstetrics and gynecology, pediatrics, internal medicine, and laboratory sciences. The Expert Panel comprised one basic scientist and nine physicians—including one family physician, one obstetrician and gynecologist, and seven hematologists with expertise in VWD (two were pediatric hematologists). Ad hoc members of the Panel represented the Division of Blood Diseases and Resources of the NHLBI. The Panel was coordinated by the Division for the Application of Research Discoveries (DARD), formerly the Office of Prevention, Education, and Control of the NHLBI. Panel members disclosed, verbally and in writing, any financial conflicts.

Charge to the Panel

Dr. Barbara Alving, then Acting Director of the NHLBI, gave the charge to the Expert Panel to examine the current science in the area of VWD and to come to consensus regarding clinical recommendations for diagnosis, treatment, and management of this common inherited bleeding disorder. The Panel was also charged to base each recommendation on the current science and to indicate the strength of the relevant literature for each recommendation.

Panel Assignments

After the Expert Panel finalized a basic outline for the guidelines, members were assigned to the three sections: (1) Introduction and Background, (2) Diagnosis and Evaluation, and (3) Management of VWD. Three members were assigned lead responsibility for a particular section. The section groups were responsible for

developing detailed outlines for the sections, reviewing the pertinent literature, writing the sections, and drafting recommendations with the supporting evidence for the full Panel to review.

Clinical Recommendations—Grading and Levels of Evidence

Recommendations made in this document are based on the levels of evidence described in the "Rating Scheme for the Evidence" field, with a priority grading system of A, B, or C. Grade A is reserved for recommendations based on evidence levels Ia and Ib. Grade B is given for recommendations having evidence levels of IIa, IIb, and III; and Grade C is for recommendations based on evidence level IV. None of the recommendations merited a Grade of A. Evidence tables are provided at the end of the original guideline document for those recommendations that are graded as B and have two or more references.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendations made in this document are categorized using the scheme below (see the "Rating Scheme for the Strength of the Evidence" field for the definitions of the Levels of Evidence).

Grade of Recommendation*

Grade	Evidence	Recommendation Level
A	Ia, Ib	Required-at least one randomized-controlled trial as part of the body of literature of overall good quality and consistency
B	IIa, IIb, III	Required-availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Required-evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

*Source: Laffan M, Brown SA, Collins PW, Cumming AM, Hill FG, Keeling D, Peake IR, Pasi KJ. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. Haemophilia. 2004 May;10(3):199-217.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The National Heart, Lung, and Blood Institute (NHLBI) sought outside review of the guidelines through a two-fold process. The following Government agencies and professional organizations were invited to review the draft document and submit comments: Centers for Disease Control and Prevention, Food and Drug Administration, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Physicians, American Society of Hematology, American Society of Pediatric Hematology/Oncology, College of American Pathologists, Hemophilia & Thrombosis Research Society, National Hemophilia Foundation Medical and Scientific Advisory Committee, and the North American Specialized Coagulation Laboratory Association. In addition, the guidelines were posted on the NHLBI Web site for public review and comment during a 30-day period ending September 22, 2006. Comments from the external review were compiled and given to the full Panel for review and consensus. Revisions to the document were then made as appropriate. The final draft, after Panel approval, was sent through review within the National Institutes of Health (NIH) and finally approved for publication by the NHLBI Director.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the levels of evidence (Ia-IV) and grades of recommendations (A–C) can be found at the end of the "Major Recommendations" field.

Diagnosis and Evaluation

The following recommendations include specific clinical history, physical findings, laboratory assays, and diagnostic criteria that this Panel suggests will allow the most definitive diagnosis of von Willebrand disease (VWD).

- Tests such as the bleeding time, platelet function analyzer (PFA-100®), or other automated functional platelet assays have been used but there are conflicting data with regard to sensitivity and specificity for VWD. Therefore, the Panel believes current evidence does not support their routine use as screening tests for VWD.
- The Panel believes that platelet-based assays should be used for the ristocetin cofactor method.
- The Panel emphasizes the importance of the timing of the phlebotomy for assays, with the patient at his/her optimal baseline as far as possible. (For example, VWF levels may be elevated above baseline during the second and third trimesters of pregnancy or during estrogen replacement, during acute inflammation such as the perioperative period, during infections, and during acute stress.) The careful handling and processing of the sample is also critical, particularly if the sample will be sent out for testing at a distant location.

I. **Evaluation of Bleeding Symptoms and Bleeding Risk by History and Physical Examination**

Summarized in Figure 3 and Box 1 in the original guideline document.

A. Ask the following broad questions:

1. Have you or a blood relative ever needed medical attention for a bleeding problem, or have you been told you had a bleeding problem? **(Grade B, level IIb)** (Sramek et al., 1995)

   If the answer is "Yes" to either of the broad questions above, ask the additional probes:

   a. Have you needed medical attention for bleeding? After surgery? After dental work? With trauma?
   b. Have you ever had bruises so large they had lumps? **(Grade B, level IIb)** (Sramek et al., 1995)

2. Do you have or have you ever had:
   a. Liver or kidney disease?
   b. A blood or bone marrow disorder?
   c. A high or low platelet count?

   If the answer is "Yes" to any of these questions, obtain relevant details. **(Grade C level IV)**

3. Are you currently taking, or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], clopidogrel)?

   If the answer is "Yes", obtain relevant details. **(Grade C, level IV)**

B. If answers to questions I.A.1 are positive, ask if the patient or any blood relatives have had:

1. A bleeding disorder, such as von Willebrand disease or hemophilia?
2. Prolonged bleeding, heavy, or recurrent from:
   a. Trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
   b. Surgical procedures, such as tonsillectomy?
3. Bruising with minimal or no apparent trauma, especially if you could feel a lump?
4. Spontaneous nosebleeds that required more than 10 minutes to stop or needed medical attention?
5. Dental extractions leading to heavy, prolonged, or recurrent bleeding?
6. Blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
7. Anemia requiring treatment or received a blood transfusion?
8. For women, heavy menses, characterized by the presence of clots greater than an inch in size and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

If answers to above questions I.B.1–8 are positive, obtain relevant specific information. **(Grade B, level IIb)** (Sramek et al., 1995; Drews et al., 2002)

C. Perform a physical examination to include evaluation for:
   1. Evidence for a bleeding disorder, including size, location, and distribution of ecchymoses (e.g., truncal), hematomas, petechiae, and other evidence of recent bleeding and/or anemia. **(Grade C, level IV)**
   2. Evidence that suggests other causes or risks of increased bleeding, such as jaundice or spider angiomata (liver disease), splenomegaly, arthropathy, joint and skin laxity (e.g., Ehlers-Danlos Syndrome), telangiectasia (e.g., hereditary hemorrhagic telangiectasia), or evidence of anatomic lesions on gynecologic examination. **(Grade C, level IV)**

Laboratory testing should be guided by the history and physical findings (see section I.) and the initial laboratory evaluation (see II.A., below). For example, findings of liver disease may lead to a different or additional laboratory evaluation rather than an evaluation for VWD (see II.B., below).

II. Evaluation by Laboratory Testing

A. Initial laboratory evaluation for the etiology of a bleeding disorder should include:
   1. A complete blood count ([CBC] including platelet count), prothrombin time (PT), activated partial thromboplastin time (PTT), and optionally either thrombin time or fibrinogen level.
   2. If laboratory abnormalities besides the PTT are present (the platelet count may also be decreased in type 2B VWD), in conjunction with the history and physical examination findings, consider bleeding disorders other than VWD or additional underlying diseases.
   3. If the mucocutaneous bleeding history is strong, consider performing initial VWD assays at the first visit (See II.B., below).
   4. If there are no abnormalities on initial blood testing, or if there is an isolated prolonged PTT that corrects on the 1:1 mixing study, the following three tests for VWD should be performed (II.B., below), unless another cause for bleeding has been identified and VWD is not likely (see Figure 4 in the original guideline document). For further laboratory evaluation, physicians may consider referral to a hemostasis center because of the special sample handling and testing requirements (see Table 10 in the original guideline document). **(Grade C, level IV)**

B. Initial tests for diagnosing or excluding VWD include the following three tests:
   1. von Willebrand factor ristocetin cofactor activity (VWF:RCo)
   2. von Willebrand factor antigen (VWF:Ag)
   3. Factor VIII activity

(Grade B, level III) (Rodeghiero, Castaman & Dini, 1987; Gill et al., 1987; Favaloro et al., "Laboratory diagnosis," 2004; Favaloro et al., "Assessment," 2000)

C. If any one of the above test results is abnormally low, a discussion with or a referral to a hemostasis expert is appropriate. In addition to repeating the initial three tests (in most cases), the specialist may recommend appropriate studies from the following:
   1. The first set of additional tests may include:
      a. Evaluation of the ratio of VWF activity (VWF:RCo and/or von Willebrand factor collagen-binding activity [VWF:CB]) to VWF antigen (only in laboratories that have defined reference ranges for the ratio[s]) **(Grade B, level III)** (Hillery et al., 1998; Mancuso et al., 1996; Nitu-Whalley et al., "Identification," 2000; Dean et al.,2000; Favaloro et al., "Laboratory diagnosis," 2004; Federici et al., "Ristocetin cofactor," 2000)
      b. VWF multimer study **(Grade B, level III)** (Studt et al., 2001)
      c. Ristocetin-induced platelet aggregation **(Grade B, level III)** (Ruggeri et al., 1980)
      d. VWF collagen binding activity (VWF:CB) **(Grade B, level IIb)** (Favaloro et al., "Laboratory diagnosis," 2004; Favaloro, 2000; Favaloro et al., "Discrimination," 2000)
   2. Studies in selected patients, especially those who have discordantly low FVIII activity compared to VWF levels and who are suspected of having type 2N VWD, should include a FVIII binding assay (VWF:FVIIIB) **(Grade B, level IIb)** (Mazurier & Meyer, 1996; Schneppenheim et al., 1996; Rodgers et al., 2002)
   3. Additional studies in selected persons may include:
      a. Gene sequencing **(Grade C, level IV)**
      b. Assays for antibodies to VWF **(Grade C, level IV)**
      c. Platelet-binding studies **(Grade B, level III)** (Scott & Montgomery, 1991)

III. Making the Diagnosis

A. *Clinical criteria*. These criteria include personal and/or family history and/or physical evidence of mucocutaneous bleeding. Until further validation of scoring systems and criteria for assessing bleeding history and the probability of VWD, especially type 1 VWD, the Expert Panel suggests that an increasing number of positive responses to the questions about bleeding (see Figure 3 and Box 1 in the original guideline document) and abnormal findings on physical examination increase the likelihood that an individual has a bleeding disorder, including possible VWD.

AND

B. *Laboratory criteria*. The values in the following table represent prototypical cases without additional VWF (or other disease)

abnormalities in the patient. In practice, exceptions occur, and repeat testing and clinical experience are important and may be necessary for interpretation of laboratory results.

1. Although published evidence is limited, for defining the ratio of VWF:RCo/VWF:Ag to use for distinguishing type 1 VWD versus type 2 VWD variants (A, B, or M), the Expert Panel recommends a ratio of <0.5–0.7 until more laboratories clearly define a reference range using large numbers of normal subjects and persons who have type 1 VWD and type 2 VWD variants. **(Grade C, level IV)** (Hillery et al., 1998; Mancuso et al., 1996; Nitu-Whalley et al., "Identification," 2000; Dean et al.,2000; Favaloro et al., "von Willebrand disease," 2004; Federici et al., "Ristocetin cofactor," 2000)
2. The panel currently recommends that 30 IU/dL be used as the "cut-off" level for supporting the definite diagnosis of VWD for the following reasons:
    - There is a high frequency of blood type O in the United States, and it is associated with "low" VWF levels (Gill et al., 1987)
    - Bleeding symptoms are reported by a significant proportion of normal individuals (Silwer, 1973; Sramek et al., 1995; Drews et al., 2002; Mauser Bunschoten et al., 1988)
    - No abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels **(Grade C, level IV)** (Casana et al., 2001; Castaman et al, 1999; Miller et al., 1979)

This recommendation does not preclude the diagnosis of VWD in individuals with VWF:RCo of 30–50 IU/dL if there is supporting clinical and/or family evidence for VWD. This recommendation also does not preclude the use of agents to increase VWF levels in those who have VWF:RCo of 30–50 IU/dL and may be at risk for bleeding.

Condition	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	Ratio of VWF:RCo/VWF:Ag
Type 1	<30*	<30*	v or Normal	>0.5–0.7
Type 2A	<30*	<30–200*+	v or Normal	<0.5–0.7
Type 2B	<30*	<30–200*+	v or Normal	Usually <0.5–0.7
Type 2M	<30*	<30–200*+	v or Normal	<0.5–0.7
Type 2N	30–200	30–200	vv	>0.5–0.7
Type 3	<3	<3	vvv (<10 IU/dL)	Not applicable
"Low VWF"	30–50	30–50	Normal	>0.5–0.7
Normal	50–200	50–200	Normal	>0.5–0.7

v refers to a decrease in the test result compared to the laboratory reference range.

*<30 IU/dL is designated as the level for a definitive diagnosis of VWD; there are some patients with type 1 or type 2 VWD who have levels of VWF:RCo and/or VWF:Ag of 30–50 IU/dL.

+The VWF:Ag in the majority of individuals with type 2A, 2B, or 2M VWD is <50 IU/dL.

Management Recommendations

IV. **Testing Prior to Treatment**

A. Before treatment, all persons suspected of having VWD should have a laboratory-confirmed diagnosis of type and severity of VWD. This recommendation does not preclude treatment that may be indicated for urgent or emergency situations, despite the absence of confirmatory laboratory data. **(Grade C, level IV)** (Lak, Peyvandi, & Mannucci, 2000; Federici, 2004; Silwer, 1973; Sramek et al., 1995; Drews et al., 2002; Mauser Bunschoten et al., 1988; Woods et al., 2001; Ziv & Ragni, 2004)

B. Persons who do not have a definite diagnosis of VWD but who have VWF:RCo levels of 30–50 IU/dL and have a bleeding phenotype may merit treatment or prophylaxis of bleeding in certain clinical situations. **(Grade B, level III)** (Nitu-Whalley et al., "Type 1," 2000)

C. Persons with >10 IU/dL VWF:RCo and >20 IU/dL FVIII activity levels should undergo a trial of desmopressin: 1-desamino-8-D-argnine vasopressin (DDAVP) while in a nonbleeding state. Persons with levels below these thresholds are less likely to demonstrate clinical or laboratory responses to DDAVP, but a DDAVP trial should still be considered in these individuals. **(Grade B, level IIa)** (Mannucci et al 1985; de la Fuente et al., 1985; Federici et al., 2004; Mannucci et al., 1981; Rodeghiero et al., 1989)

V. **General Management**

A. Treatment of persons who have VWD is aimed at cessation of bleeding or prophylaxis for surgical procedures. **(Grade C, level IV)** (Sadler et al., 2000; Federici, Castaman, & Mannucci, 2002; Pasi et al., 2004)

B. Continued bleeding, despite adequately replaced VWF:RCo and FVIII activity levels, requires evaluation of the person for other bleeding etiologies, including anatomic. **(Grade C, level IV)**

C. Long-term prophylaxis is currently under investigation in an international cooperative study, and the long-term risks and benefits should be considered carefully. **(Grade C, level IV)** (Berntorp & Petrini, 2005; Sumner & Williams, 2004)

D. Individuals who are more than 2 years of age, who have VWD and have not already been vaccinated, should be immunized against hepatitis A and B. **(Grade C, level IV)** (National Hemophilia Foundation [NHF], 2001)

E. Persons who have VWD should have the opportunity to talk to a knowledgeable genetic counselor. **(Grade C, level IV)** (Kadir, 1999)

F. At diagnosis, persons who have VWD should be counseled to avoid aspirin, other NSAIDs, and other platelet-inhibiting drugs. **(Grade C, level IV)** (Barbui, Rodeghiero, & Dini, 1977; Rosentein & Zacharski, 1979; Stuart et al., 1979)

G. Restriction of fluids to maintenance levels should be considered in persons receiving DDAVP (especially for young children and in surgical settings) to avoid the occurrence of hyponatremia and seizures. **(Grade C, level IV)** (Bertholini & Butler, 2000; Das, Carcao, & Hitzler, 2005; Smith et al., 1989)

VI. **Treatment of Minor Bleeding and Prophylaxis for Minor Surgery**

A. Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with intravenous or nasal DDAVP, if appropriate, based on trial testing. **(Grade B, level IIa)** (Castaman et al., 1995; Castaman & Rodeghiero, 1996; de la Fuenta et al., 1985; Revel-Vilk et al., 2003; Mariana et al., 1984)

B. If elevation of VWF is necessary and response to DDAVP is inadequate, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units. **(Grade C, level IV)** (Nitu-Whalley et al., 2001; Lillicrap et al., 2002)

C. For prophylaxis for minor surgery, initial treatment should be expected to achieve VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL. **(Grade B, level III)** (de la Fuenta et al., 1985; Revel-Vilk et al., 2003; Federici et al., "Optimising local therapy," 2000; Nitu-Whalley et al., 2001)

D. For minor surgery, VWF:RCo and FVIII activity levels of at least 30 IU/dL and preferably >50 IU/dL should be maintained for 1–5 days. **(Grade B, level III)** (Jimenez-Yuste et al., 2002; Kreuz et al., 1994; Nitu-Whalley et al., 2001; Thompson et al., 2004)

E. For persons who have VWD, management of minor bleeding (e.g., epistaxis, simple dental extraction, or menorrhagia) with DDAVP and proper fluid restriction can be performed without laboratory monitoring unless Stimate® or DDAVP is used more than three times within 72 hours. **(Grade C, level IV)** (Lethagen, Frick, & Sterner, 1998; Amesse et al., 2005)

F. For persons who have mild to moderate VWD, antifibrinolytics combined with DDAVP are generally effective for oral surgery. VWF concentrate should be available for persons who cannot receive DDAVP or who bleed excessively despite this combined therapy. **(Grade B, level IIb)** (Castaman et al., 1995; de la Fuenta et al., 1985; Rodeghiero et al., 1988; Federici et al., "Optimising local therapy," 2000; Mariana et al., 1984; Nitu-Whalley et al., 2001; Saulnier et al.,1994)

G. Topical agents, such as fibrin sealant or bovine thrombin, may be useful adjuncts for oral surgery in persons who have VWD. Careful attention to hemostasis of an extraction socket and to suturing of sockets is also important in oral surgery in persons who have VWD. **(Grade C, level IV)** (Federici et al., "Optimising local therapy," 2000; Rakocz et al., 1993)

VII. Treatment of Major Bleeding and Prophylaxis for Major Surgery

A. All treatment plans should be based on objective laboratory determination of response of VWF:RCo and FVIII activity levels to DDAVP or to VWF concentrate infusion. **(Grade B, level IIb)**. (Federici, 2004; Rodeghiero et al., 1989; Allen et al., 1999; Derkay, Werner, & Plotnick, 1996; Kreuz et al., 1994; Manno et al., 1998; Nitu-Whalley et al., 2001; Shah, Lalwani, & Koerper, 1998; Dobrkovska, Krzensk, & Chediak, 1998; Hanna et al., 1994; Lillicrap et al., 2002; Lubetsky et al., 1999; Michiels et al., 2004; Thompson et al., 2004; Scharrer, Vigh, & Aygoren-Pursun, 1994; Gill et al., 2003)

B. Whenever possible, all major surgeries and bleeding events should be treated in hospitals with a 24-hour/day laboratory capability and with clinical monitoring by a team including a hematologist and a surgeon skilled in the management of bleeding disorders. **(Grade C, level IV)**

C. For severe bleeding (e.g., intracranial, retroperitoneal) or for prophylaxis of major surgery, initial target VWF:RCo and FVIII activity levels should be at least 100 IU/dL. Subsequent dosing should maintain VWF:RCo and FVIII levels above a trough of 50 IU/dL for at least 7–10 days. **(Grade B, level III)** (Kreuz et al., 1994; Nitu-Whalley et al., 2001; Dobrkovska, Krzensk, & Chediak 1998; Hanna et al., 1994; Lillicrap et al., 2002; Lubetsky et al., 1999; Michiels et al., 2004; Thompson et al., 2004; Scharrer, Vigh, & Aygoren-Pursun, 1994; Gill et al., 2003)

D. To decrease risk of perioperative thrombosis, VWF:RCo levels should not exceed 200 IU/dL, and FVIII activity should not exceed 250 IU/dL. **(Grade C, level IV)** (Makris et al., 2002; Mannucci, 2002; Mannucci et al., 2002)

E. For major surgical procedures in selected patients with type 3 VWD or acquired von Willebrand syndrome (AVWS) who are at risk for poor VWF recovery because of inhibitors, a pre-operative trial infusion of VWF concentrate with pharmacokinetic laboratory monitoring should be considered. **(Grade C, level IV)**

VIII. Management of Menorrhagia and Hemorrhagic Ovarian Cysts in Women Who Have VWD

A. Women who have menorrhagia or abnormal vaginal bleeding should have a full gynecological evaluation before therapy. **(Grade C, level IV)** (Chuong & Brenner, 1996)

B. In the adolescent or adult woman who does not desire pregnancy, but may desire future childbearing, the first choice of therapy for menorrhagia should be combined oral contraceptives. **(Grade B, level III)** (Foster, 1995)

C. In the adolescent or adult woman who does not desire pregnancy, but may desire future childbearing, the first choice of therapy to prevent hemorrhagic ovarian cysts should be combined oral contraceptives. **(Grade C, level IV)** (Bottini et al., 1991; Ghosh et al., 1998; Jarvis & Olsen, 2002)

D. If a woman would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy for menorrhagia should be the levonorgestrel intrauterine system. **(Grade B, level IIb)** (Kingman et al., 2004)

E. For the woman who desires pregnancy, DDAVP, antifibrinolytics, or VWF concentrate may be tried to control menorrhagia. **(Grade C, level IV)** (Foster, 1995)

F. Dilation and curettage is not usually effective to manage excessive uterine bleeding in women who have VWD. **(Grade C level IV)** (Greer et al., 1991; Kadir et al., 1999)

IX. Management of Pregnancy and Childbirth in Women Who Have VWD

A. Women planning for pregnancy should have, before conception, an evaluation with a hematologist and a high-risk obstetrician, both of whom are skilled in the management of VWD. **(Grade C, level IV)** (Kadir, 1999)

B. Women who have type 1, type 2, or type 3 VWD, with FVIII or VWF:RCo levels <50 IU/dL or a history of severe bleeding:

1. Should be referred to a center that has high-risk obstetrics capabilities and with expertise in hemostasis for prenatal care, delivery, termination of pregnancy, or management of miscarriage. **(Grade C, level IV)**
2. Should receive prophylaxis with DDAVP or VWF concentrate before invasive procedures. **(Grade C, level IV)** (Kadir, 1999; Kouides 2001)
3. Should achieve VWF:RCo and FVIII levels of at least 50 IU/dL before delivery and maintain that level for at least 3–5 days afterward. **(Grade C, level IV)** (Pasi et al., 2004; Mannucci, 2004; Greer et al., 1991; Kadir et al., 1998; Kouides, 2001)

C. If VWF:RCo and FVIII levels can be monitored and maintained above 50 IU/dL during labor and delivery, and no other coagulation defects are present, then regional anesthesia may be considered. **(Grade C, level IV)** (Kadir et al., 1998)

D. Because coagulation factors return to prepregnancy levels within 14–21 days after delivery, health care providers should be in close contact with women during the postpartum period. **(Grade C, level IV)** (Kouides, 2001)

X. **Acquired von Willebrand Syndrome**

A. Individuals who have AVWS and who require surgery should be considered for a pharmacokinetic trial of therapy with DDAVP and/or VWF concentrate, with monitoring of VWF:RCo and FVIII levels, to evaluate for possible accelerated clearance of VWF. **(Grade C, level IV)** (Federici et al., "Acquired von Willebrand syndrome," 2000; Kumar, Pruthi, & Nichols, 2003)

B. For persons who have AVWS and who bleed excessively despite therapy with DDAVP and VWF concentrate, treatment with high-dose immune globulin intravenous (IGIV) should be considered, especially in immunoglobulin G (IgG) isotype monoclonal gammopathy of uncertain significance (MGUS) (See page 47 in the original guideline document for a discussion of this non-U.S. Food and Drug Administration [FDA]-approved use). **(Grade B, level IIa)** (Federici et al., "Acquired von Willebrand syndrome," 2000; Federici et al., 1998; Arkel, Lynch, & Kamiyama, 1994; Macik et al., 1988; van Genderen, et al., 1995)

Definitions:

Grade of Recommendation*

Grade	Evidence	Recommendation Level
A	Ia, Ib	Required-at least one randomized-controlled trial as part of the body of literature of overall good quality and consistency
B	IIa, IIb, III	Required-availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Required-evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good

Grade	Evidence	Recommendation Level
		quality

*Source: Laffan M, Brown SA, Collins PW, Cumming AM, Hill FG, Keeling D, Peake IR, Pasi KJ. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. Haemophilia. 2004 May;10(3):199-217.

Level of Evidence*

Ia Evidence obtained from meta-analysis of randomized controlled trials

Ib Evidence obtained from at least one randomized controlled trial

IIa Evidence obtained from at least one well-designed controlled study without randomization

Ib Evidence obtained from at least one other type of well-designed quasi-experimental study

III Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlational studies, and case studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

* Source: Acute pain management: operative or medical procedures and trauma. (Clinical practice guideline.) Publication No. AHCPR 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, February 1992.

CLINICAL ALGORITHM(S)

Clinical algorithms are provided in the original guideline document for the following:

- Initial evaluation for van Willebrand disease (VWD) or other bleeding disorders
- Laboratory assessment for VWD or other bleeding disorders

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of patients with von Willebrand disease (VWD)

POTENTIAL HARMS

- Minor side effects of desmopressin (1-desamino-8-D-arginine vasopressin) (DDAVP) are common and include facial flushing, transient hypertension or hypotension, headache, or gastrointestinal upset, but these effects rarely limit clinical use. Water retention after a dose of DDAVP, with an increase in urinary osmolality, is universal; however, decreased serum sodium in otherwise healthy adults is variable and is related to multiple doses. In the case of repeated dosing, all patients should be instructed to limit fluid intake to maintenance levels for 24 hours. Prophylactic use of DDAVP complicates the management of fluids and electrolytes for surgery or during childbirth. Seizures have been associated with hyponatremia after DDAVP administration, primarily in young children. Most pediatric hematologists do not use DDAVP in children under the age of 2 years.
- Myocardial infarction after treatment with DDAVP has been reported, although rarely, in patients who have mild hemophilia A. DDAVP should be avoided in patients who are at very high risk for cardiovascular or cerebrovascular disease, especially the elderly, as underlying inhibition of plasminogen activation with DDAVP-related vasoconstriction contributes additional prothrombotic effects in these patients. Because of reported complications in other patient populations, DDAVP should be used with caution for brain, ocular, and coronary artery surgeries, and von Willebrand factor (VWF) concentrate replacement generally is used in these settings. DDAVP does not appear to increase myometrial contractility significantly; consequently, pregnancy is not an absolute contraindication but use of DDAVP is rarely indicated.
- Adverse reactions to Alphanate SD/HT®, a lyophilized concentrate of von Willebrand factor (VWF) and Factor VIII (FVIII), are rare but include allergic and anaphylactic symptoms, urticaria, chest tightness, rash, pruritus, and edema. If these reactions occur, the infusion should be stopped, and appropriate treatment should be given as required. The product should be used with caution in patients who have known risk factors for thrombosis, as there have been a few reports of venous thromboembolism associated with high levels of FVIII. Risk factors include old age, previous thrombosis, obesity, surgery, immobility, hormone replacement therapy (HRT), and use of antifibrinolytic therapy.
- The antifibrinolytic drugs aminocaproic acid and tranexamic acid can both cause nausea and vomiting; less frequent but serious side effects include thrombotic complications. Both drugs are excreted renally, and dose adjustment or avoidance is advisable when significant renal insufficiency is present.
- The topical use of plasma-derived bovine or human proteins imparts a theoretical risk of disease transmission and of potential allergic and other immune reactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

Disseminated intravascular coagulation (DIC) and/or bleeding from the renal parenchyma or upper urinary tract are relative contraindications to antifibrinolytic agents. Renovascular thrombi have followed use of fibrinolytic agents in patients with DIC and have caused renal failure. Patients have also experienced urinary tract obstruction with upper urinary tract bleeding related to large clots in the renal pelvis or lower urinary tract. Changes in color vision during therapy with tranexamic acid require cessation of the drug and ophthalmologic examination.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The von Willebrand disease (VWD) guidelines from the U.S. Expert Panel are based on review of published evidence as well as expert opinion. Users of these guidelines should be aware that individual professional judgment is not abrogated by recommendations in these guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI). The diagnosis, evaluation, and management of von Willebrand disease. Bethesda (MD): U.S. Department of Health and Human Services; 2007 Dec. 112 p. [398 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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2007 Dec

GUIDELINE DEVELOPER(S)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

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GUIDELINE COMMITTEE

National Heart, Lung, and Blood Institute (NHLBI) von Willebrand Disease Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Expert Panel Members: William L. Nichols, Jr., MD (*Chair*) (Mayo Clinic, Rochester, MN); Mae B. Hultin, MD (Stony Brook University, Stony Brook, NY); Andra H. James, MD (Duke University Medical Center, Durham, NC); Marilyn J. Manco-Johnson, MD (The University of Colorado at Denver and Health Sciences Center, Aurora, CO, and The Children's Hospital of Denver, CO); Robert R. Montgomery, MD (BloodCenter of Wisconsin and Medical College of Wisconsin, Milwaukee, WI); Thomas L. Ortel, MD, PhD (Duke University Medical Center, Durham, NC); Margaret E. Rick, MD (National Institutes of Health, Bethesda, MD); J. Evan Sadler, MD, PhD (Washington University, St. Louis, MO); Mark Weinstein, PhD (U.S. Food and Drug Administration, Rockville, MD); Barbara P. Yawn, MD, MSc (Olmsted Medical Center and University of Minnesota, Rochester, MN)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The participants who disclosed potential conflicts were:

Dr. Andra H. James (medical advisory panel for ZLB Behring and Bayer; NHF, MASAC)

Dr. Marilyn Manco-Johnson (ZLB Behring Humate-P® Study Steering Committee and Grant Recipient, Wyeth Speaker, Bayer Advisor and Research Grant Recipient, Baxter Advisory Committee and Protein C Study Group, Novo Nordisk Advisory Committee)

Dr. Robert Montgomery (Aventis Foundation Grant; GTI, Inc., VWFpp Assay; ZLB Behring and Bayer Advisory Group; NHF, MASAC)

Dr. William Nichols (Mayo Special Coagulation Laboratory serves as "central lab" for Humate-P® Study by ZLB Behring).

All members submitted financial disclosure forms.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the National Heart, Lung, and Blood Institute (NHLBI) Web site.

Print copies: Available from the NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com.

AVAILABILITY OF COMPANION DOCUMENTS

None provided

PATIENT RESOURCES

The following is available:

- Facts about Von Willebrand disease. 2006.

Electronic copies: Available at the National Heart, Lung, and Blood Institute (NHLBI) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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