Diagnosis and Management of von Willebrand Disease: A community-wide effort to deliver evidenced-based clinical practice guidelines

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Von Willebrand disease (VWD) is the most common inherited bleeding disorder with as many as 1 in 1000 people affected by symptomatic bleeding, yet many patients go years without an accurate diagnosis while living with untreated bleeding.[1-3] A lack of awareness of the difference between normal and abnormal bleeding symptoms, coupled with the limited availability of specialized laboratory testing makes the diagnosis of VWD challenging.[4-7] The clinical complexity of VWD and the absence of extensive evidence to guide decision making means that there is considerable variability in the clinical management of the disorder.

It is precisely in the context of inadequate awareness, variability in clinical practice, and a paucity of high-quality evidence in the published literature that clinical practice guidelines are most needed. In 2015 the World Federation of Hemophilia (WFH) VWD and Rare Bleeding Disorders Committee presented a proposal to the WFH Medical Advisory Board for the development of VWD guidelines. Simultaneously, the National Hemophilia Foundation (NHF) issued a report from their Strategic Summit on VWD that called for “A well-qualified and authoritative organization, or a consortium of such organizations, [to] develop a new or updated evidence-based clinical practice guideline on VWD.” The American Society of Hematology (ASH) and the International Society on Thrombosis and Haemostasis (ISTH) reached the same conclusions and in 2017 the four organizations came together in an unprecedented international collaboration to develop guidelines on VWD [refs: VWD Diagnosis GLs, VWD Management GLs]

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Clinical practice guidelines are strongest when they are developed through a rigorous evidence-based process that involves experts in diagnosing, treating and living with a disorder.[8, 9] The methods team from the University of Kansas Outcomes and Implementation Research Unit and the McMaster GRADE centre, under the leadership of Professor Reem Mustafa, guided the Diagnosis and Management Panels through a systematic review and GRADEing of all available literature for each recommendation. The details are documented in the publications' supplementary materials.[refs: VWD Diagnosis GLs, VWD Management GLs] . While previous VWD guidelines lacked any patient involvement, people with VWD were fully integrated in developing these guidelines, representing approximately a quarter of each panels' membership. As full voting members, the voices of people living with VWD carried equal weight to those of clinicians and researchers in every phase of guideline development, from the GRADEing of the evidence gleaned from the systematic review to the detailed discussions of equity, cost-effectiveness, resource utilization, acceptability, feasibility, and patients' values and preferences, for each recommendation. The collaborating organizations contributed to trainings that prepared and empowered the patient panelists. the ASH ISTH NHF WFH Guidelines on the Diagnosis and Management of VWD published this month in *Blood Advances* set a new standard for patient involvement in the development of guidelines. In fact, involvement of the global VWD community bookended this guideline development process. At the very beginning, a trilingual stakeholder survey provided the foundation for the prioritization of clinical questions to be addressed. The overwhelming response to this survey (over 9,500 comments from over 600 participants, equal proportions of people with VWD and

healthcare professionals, from 71 countries) merited its own publication [10] and underscored the widespread unanimity on the crying need for VWD guidelines. Two years later over 100 individuals (approx. 15% patients and caregivers) from nearly 40 countries provided public comment on the draft guidelines. This appetite for tools to improve the diagnosis, management, and quality of life of people with VWD and the enthusiastic participation in initiatives to generate these tools, hopefully, bode well for the adoption and adaptation of the guidelines throughout the world.

The clinical manifestations of VWD may touch every aspect of an affected person's life. Thus, these guidelines are relevant to their interactions with all healthcare professionals, not just those specializing in the diagnosis and management of bleeding disorders. General practitioners, emergency physicians, dentists, internists, surgeons, gynecologists, obstetricians, anesthetists, and many more will do well to familiarize themselves with these guidelines.

The 11 diagnosis recommendations cover:

- The role of bleeding assessment tools (BAT) in the assessment of patients suspected of VWD
- Diagnostic laboratory cutoffs for type 1 and type 2 VWD
- The role of genetic testing vs. phenotypic assays for types 2B and 2N
- The reconsideration, rather than simple removal, of a type 1 VWD diagnosis, should VWF levels normalize over time

The eight management recommendations cover:

- Prophylaxis for severe and frequent bleeds

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- Desmopressin (DDAVP) trials to determine therapy
- Use of antithrombotic therapy (antiplatelet agents and anticoagulant therapy)
- Target VWF and factor VIII activity levels for major surgery
- Strategies to reduce bleeding during minor surgery or invasive procedures
- Management options for heavy menstrual bleeding
- Management of VWD in the context of neuraxial anesthesia during labour and delivery
- Management in the postpartum setting

A number of recommendations align with existing publications [11, 12] with the added value of a thorough evaluation of the evidence supporting them, while others provide important new guidance.

The Diagnosis Panel placed a high value on not missing the diagnosis of affected individuals in order to ensure access to care. This is reflected throughout the recommendations and exemplified in the cutoff recommended for the diagnosis of type 1, where a patient's bleeding symptoms were the primary consideration. Similarly, patient values, preferences, and access to care were important considerations when recommending a reconsideration, rather than a simple dismissal, of a type 1 VWD diagnosis in patients whose VWF levels normalize over time. The comprehensive but clear diagnostic algorithms provided in the figures of the Diagnosis Guidelines will assist professionals in tackling this complex decision tree.

The Management Guidelines also place a consistent emphasis on seeking optimal outcomes for individuals affected by abnormal bleeding. The recommendation of

prophylaxis for frequent and severe bleeds does not specify a VWD subtype, and the recommendations on the management of heavy menstrual bleeding point out that some women and girls may need prophylaxis to control bleeding. While VWD is inherited equally by men and women, women are disproportionately impacted by menstrual and postpartum hemorrhage. The particular need for guidance on issues specific to women's health was highlighted in the responses (of both men and women) to the stakeholder clinical question prioritization survey [10] and is reflected in the multiple recommendations devoted to heavy menstrual bleeding, neuraxial anesthesia, and postpartum management. Bleeding symptoms specific to women are also considered in the recommendations on the use of BATs in the Diagnosis Guidelines.

Like most clinical practice guidelines, these guidelines face the limitation that they simply cannot cover every topic for which guidance is needed. The prioritization process was valid and informed by many and varied perspectives, but some will invariably find that their most pressing concern did not make the cut. This is unavoidable and may even serve to spur other organizations to contribute similarly developed guidelines on some of these topics.

Globally, the biggest barrier to the implementation of many of the recommendations for both management and diagnosis of VWD will be the resources required. The Diagnosis Panel was cognizant of the lack of uniform availability of some of the assays that it recommends, and the expertise they require, while the Management Panel considered the resources required and limitations on access to many treatment options in their

deliberations. These restrictions are present in developed countries in regard to the availability and access to specialized diagnostic tests (and the facilities and expertise to perform them) and treatment options vary greatly within and between countries. In developing countries the challenges are much greater. While some of the recommendations can and should be adopted as aspirational targets and the focus of advocacy efforts with the weight of the ASH ISTH NHF WFH Guidelines behind them, others will be simply out of reach. The guideline authors recognize this reality and invite adaptations to local circumstances, based on the associated Evidence-to-Decision frameworks [13], the details of which are all available in the supplementary materials of the two publications.

As the community is aware, we lack published prospective studies conducted on large groups of patients with consistently defined outcome assessments and rigorous controls. That the GRADEing of the evidence to support the ASH ISTH NHF WFH Guidelines on the Diagnosis and Management of VWD recommendations was frequently assessed as offering low or even very low certainty is an honest indictment of the situation. It should not point to a weakness of the recommendations, however. The detailed summaries of the evidence in the publications and the Evidence-to-Decision framework tables allow those so inclined to conduct a similar analysis and reach their own conclusions. Assuredly, the recommendations presented in the publications are the results of careful deliberation and consideration and constitute the best advice available today. Importantly, the panels provided detailed lists of the most pressing areas of

further research for each recommendation. Hopefully, the coming years will see these lists frequently consulted and progressively diminished.

The publication of these guidelines is only the beginning of the quest to support patients, clinicians, and healthcare professionals in their shared decision making about VWD. In this next phase of dissemination, education, implementation, and advocacy the VWD community will be well served by the continued international collaboration between four important organizations (ASH, ISTH, NHF, and WFH), the integral involvement of people with VWD, and the genuine dedication of the healthcare professional panelists to the community. Educational resources that make this information accessible to people with VWD will be important in achieving the shared decision making recommended by the guidelines. Clinical webinars, multilingual short summaries, decision aids, patient-oriented materials, and more will feature in the work of all four organizations in the coming months and years. Advocacy efforts, such as the proposal to include subtypes of VWD in the International Classification of Disease, Tenth Revision, Clinical Modification, to facilitate patient care and research, are already underway and many more must follow. The bleeding disorders community must be creative and resourceful as educational and awareness raising campaigns must reach groups not always targeted by traditional outreach, in both the healthcare and public spheres.

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