Practical Hematologist

# Diagnosing and Managing Pediatric and Young Adult Patients Living with VWD

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## *Introduction*

Mary McGorray, MD, contributing author, had the pleasure of interviewing Dr. Sarah O'Brien, MD, MSc. Dr. O'Brien is a pediatric hematologist at Nationwide Children's Hospital and an Associate Professor of Pediatrics at The Ohio State University College of Medicine. She serves as the Director of Experimental Therapeutics for the Division of Pediatric Hematology/Oncology/BMT and leads a multi-disciplinary young women's hematology clinic at Nationwide Children's Hospital. Her clinical and research interests include the evaluation and diagnosis of bleeding disorders and the intersections between hematology and women's health.

*The following two-part newsletter addresses the clinical scenarios, diagnostic conundrums, and treatment challenges frontline clinicians encounter when considering the diagnosis of von Willebrand disease (VWD) in their patients. This newsletter will enhance the confidence of primary care providers, emergency room physicians, obstetricians/gynecologists, and advanced practitioners in diagnosing and managing pediatric and young adult patients living with VWD.*

*In our first of 2 newsletters, Dr. O'Brien clarifies the role of frontline physicians in the initial diagnosis, management, and subsequent follow-up of pediatric and young adult patients living with VWD.*

### *Dr. O'Brien, isn't the diagnosis of VWD too complicated for busy frontline doctors?*

In my opinion, yes and no. On the one side, I don't think any doctor is too busy to be able to recognize the signs and symptoms of VWD. That is what I always try to focus on when I'm speaking with non-specialists: What clues you might find during your visit. It is my hope that frontline doctors just have an *awareness* of bleeding disorders—and know what signs and symptoms to look for, and what initial tests could be ordered.

I agree that the nuances of laboratory testing for VWD can be complicated–as hematologists we are here to help. Once a patient is diagnosed with a bleeding disorder, then we can form a collaboration between the primary care provider, the hematologist, and, when caring for female patients, the gynecologist. We all work together regarding management.

### *What symptoms should pediatricians and adolescent medicine physicians look for in patients to consider the diagnosis?*

The three most common scenarios that we see are patients presenting with easy bruising, nose bleeds, or heavy menstrual bleeding. Those are the top three symptoms in this age group. Other possible

symptoms would be unusual bleeding after surgery, or sometimes we see oral cavity bleeding. We see that a lot with toddlers with what I call 'sippy-cup' incidents.

***Besides the more well-known symptoms of GI bleeding and post-operative bleeding, what symptoms should we be looking for in children?***

The above signs and symptoms are what we keep in mind when we are evaluating a patient. Pediatric patients with a family history of VWD require special consideration. If it is a young patient, they may not have had time to develop bleeding symptoms, or they may have not yet faced surgical challenges. We may **r**epeat testing in that patient or take a closer look at them.

***What signs and symptoms should we be 'in tune for' in the young woman with heavy menstrual bleeding?***

It's important that you *ask*. Those questions cannot be "Are your periods normal?" or, "Do you have any concerns about your periods?", because many young women, parents, and healthcare providers do not have a full understanding of what is a normal versus abnormal menses. You must ask detailed questions.

I think the four questions that I would keep in my 'tool belt' are:

- How many days is the period lasting?
  — More than seven days should be a flag.
- How often are they having to change their soaked menstrual product.
  — If that is less than two hours, that would be a flag for us.
- Do they have to get up at night to change a product?
- Are they passing large clots in their flow? We define large clots as those larger than the size of a grape.

***What algorithms would you recommend we follow to help guide us in choosing laboratory tests for diagnosing pediatric and adolescent patients?***

In terms of baseline testing, I think for a frontline provider, what makes sense to start with is a PT and a PTT because we *all* have access to those in our institutions. Then the basic tests that you want to send to evaluate for VWD include Factor VIII activity, von Willebrand antigen, and von Willebrand activity levels. That is most helpful for us as hematologists if all three of those have been sent, because we need all three to look at the whole picture.

***After we have completed the basic laboratory testing, and, their bleeding score is positive and they have a vWF:RCo assay less than 40 IU/dL, what now?***

So, if you have a patient who has an elevated bleeding score or bleeding symptoms, and they have an activity level of less than 40 IU/dL—that would be a patient I would initially have a strong suspicion for VWD. I think that patient definitely should be referred to a hematologist.

Our first step as hematologists will always be to repeat the VWF activity levels, and that's for a few reasons. One is, there are a lot of pre-analytic variables that go into VWD testing. When I'm talking with families and explaining why I need to repeat the test, I explain to them circumstances in which the blood draw might not be accurate**:**

- If the blood draw wasn't quite smooth.
- The tube could rattle on the truck in transport.
- The blood tube might have sat on the counter too long at the lab.

Other variables that affect VWF activity levels include illness, stress, recent exercise, your menstrual cycle, if you are on estrogen containing contraception, pregnancy, or whether you're anemic—these are all scenarios where you may see a false elevation in von Willebrand levels. It is always necessary to repeat them, to make sure you're getting consistently low values.

***Let's say the bleeding score is positive, how often would you repeat the von Willebrand serum levels?***

If I am suspicious that somebody has VWD, then I will repeat the labs. Then, if I'm getting lowish-normal levels, or I need a tie breaker—I'll repeat them again.

***Dr. O'Brien, when does a frontline clinician have enough diagnostic tests to say, "We should begin treatment"?***

I love this question because this is one of my big teaching points. We don't need to have a diagnosis to begin treatment for bleeding symptoms. As a provider, I always feel badly when I see a patient for heavy menstrual bleeding, who was referred by their PCP; first to gynecology, and then referred to me—the hematologist—and they're still having heavy menstrual bleeding months later while they've been waiting to get into all these specialist visits.

For example, for common symptoms like epistaxis I make sure that patients know how to clamp appropriately when they're having a nosebleed. That is something a lot of families don't understand. There are over-the-counter sprays that we can use to help with epistaxis. An ENT referral might be helpful and can be done at the same time.

For patients with heavy menstrual bleeding, they often may have iron deficiency or iron deficiency anemia, so the frontline provider can get them started on iron supplementation. They can also get them started on a medication for heavy menses. Oral contraceptives are usually the first line.

In pediatrics, sometimes providers aren't comfortable prescribing oral contraceptives (OCPs). I always recommend tranexamic acid (TA) as a simple medication with very few side effects, that can be started for women. Also, TA doesn't affect lab results. Antifibrinolytics are well tolerated and that is something that could easily be used while the patient and their family are waiting for their hematology appointment.

***In terms of that early workup that we discussed, should doctors be sending iron studies in addition to the studies you mentioned earlier?***

Yes. The frontline provider should send a ferritin level because that's the best way to evaluate iron stores. The ferritin level tells me where your iron is usually living. It is important for clinicians to understand what constitutes a low ferritin.

The World Health Organization defines iron deficiency as *a ferritin level of less than 15*. Many women are walking around with low iron, which results in the reference ranges at our hospitals becoming skewed. In my hospital, the reference range for ferritin goes all the way down to six! So, all those patients with a ferritin level between 6 and 14 are not being flagged in the system as abnormal, but they *all* have iron deficiency.

***Once we start treatment for von Willebrands disease, what is my first line of therapy?***

The two most common scenarios we would see would be epistaxis and heavy menstrual bleeding (HMB). Our first line treatment for a patient with VWD and epistaxis would be nasal desmopressin because it's something that you can administer quickly at the time of the nosebleed. For HMB, our first line therapy is going to be hormonal contraception because that is what works the best regardless of whether you have a bleeding disorder or not.

***What about TA in heavy menstrual bleeding?***

In my experience, either one can be used. I think that the hormonal contraception offers more benefits because it helps to regulate the patients' menstrual cycle and helps with dysmenorrhea and the mood changes that occur with menses— extra bonuses of OCPs.

In terms of reducing flow, TA does work as well, but it doesn't provide those other benefits. TA won't affect von Willebrand levels like estrogen does. TA is prescribed for five days, so if your patient has menses for 9 or 10 days in a row, then TA is a less preferable solution.

TA is a great starting medication and can allow for further discussions in a specialty office when you have more time for those longer discussions about OCPs.

***Are oral contraceptive pills your first choice?***

In my practice for young women, we use the words 'hormone medication'. I think that helps reduce barriers for a lot of our families because, I think that sometimes the term 'birth control pill' can raise alarms. We're emphasizing that these are medications and contraception is just one benefit of OCPs.

***Where can clinicians get guidance for dosing these medications? How do you dose desmopressin? TA?***

For nasal desmopressin, the important thing for frontline providers to know is the DDAVP we prescribe is different than the dosing for nasal DDAVP that is used for nocturnal enuresis. It is a much higher concentration of nasal spray. Sometimes we'll see an error because the wrong desmopressin is prescribed.

When we are using the correct dose of DDAVP, then the dosing is one spray of 150 micrograms if you're under 50 kilograms (kgs) and two sprays, one in each nostril, if you are 50 kgs or above. Nasal DDAVP causes our body to release the von Willebrand factor that's stored in our platelets. DDAVP also comes in IV formulation, which we will use for surgeries.

Antifibrinolytics, like TA also come in IV dosing, which we use when our patients have surgeries. In the outpatient setting the oral dose of TA is a 650-milligram pill. We prescribe 2 pills, 3 times a day, for the first five days of menses.

If our patient is having their wisdom teeth out, we'll do something before the surgery, and then have them use TA at that dosing for, perhaps, 72 hours after wisdom teeth extraction.

***What about dosing in factor replacement–plasma-derived von Willebrand Factors (pdVWFs)? Or recombinant von Willebrand Factor (rVWF)?***

When we dose factor, we always do that in a patient-specific manner. In general, the doses of factor are 50 units per kilogram. We will dose that anywhere between every 12 hours or every 48 hours, depending on what the patient's baseline levels are.

We also work with our pharmacists because those medications are so expensive. We try our best to not waste medication by only using part of a factor vial. If it would be safe to use the entire vial in our patient, then in rVWF, there's not anything different in terms of how much you dose. But one consideration is that the pdVWFs contain factor VIII, whereas the rVWF products do not contain factor VIII.

For example, if I have a patient living with obesity who has VWD and mildly low von Willebrand levels and elevated factor VIII levels—a common occurrence with obesity—then I might be more inclined to use rVWF factor for that patient. If I am using plasma derived VWF for that patient, I'm going to give the lowest dose possible so that I'm not making my patients' factor VIII levels too high.

## Summary

*We greatly appreciate Dr. Sarah O'Brien sharing her expertise and passion for improving the quality of life in pediatric and young adult patients living with VWD to guide frontline clinicians.*

*Please check in for Part II of this newsletter, when Dr. Sarah O'Brien answers more questions on the management and prophylactic treatment in young patients living with VWD.*

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