

Patterns of von Willebrand Disease Screening in Girls and Adolescents With Heavy Menstrual Bleeding

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OBJECTIVE: To estimate the frequency of von Willebrand disease screening and factors that affect screening frequency in a national sample of girls and adolescents with heavy menstrual bleeding.

METHODS: In this retrospective cohort study, we used a national claims database for privately and publicly insured patients between 2011 and 2013 for girls aged 10–17 years. Diagnostic criteria of heavy menstrual bleeding were the presence of one inpatient or two outpatient International Classification of Diseases, 9th Revision codes for heavy menstrual bleeding. We defined severe heavy menstrual bleeding as heavy menstrual bleeding plus an inpatient stay for menstrual bleeding, iron deficiency anemia, or blood transfusion. To assess whether patient- or facility-level characteristics affected screening, we performed logistic regression analysis including patient age, health care provider type seen at first visit for menorrhagia, patient residence in a metropolitan statistical area (proxy for urban vs rural inhabitation), and approximate travel time to the nearest hemophilia treatment center.

RESULTS: We identified 23,888 postpubertal girls and adolescents with heavy menstrual bleeding (986 with

severe heavy menstrual bleeding). Von Willebrand disease screening was performed in 8% of females with heavy menstrual bleeding and 16% with severe heavy menstrual bleeding. Younger age at diagnosis, commercial insurance, and living within a metropolitan statistical area were associated with higher screening rates. Patients who underwent testing for iron deficiency anemia had the highest likelihood of undergoing screening (odds ratio 7.08, 95% CI 6.32–7.93). Among patients living in a metropolitan statistical area, those 60 minutes or more from a hemophilia treatment center were less likely to undergo screening.

CONCLUSION: Despite recommendations by the American College of Obstetricians and Gynecologists for more than 15 years, fewer than 20% of postpubertal girls and adolescents with heavy menstrual bleeding underwent screening for von Willebrand disease in this cohort. Increased clinician awareness and adherence to recommended screening recommendations may increase diagnosis of von Willebrand disease.

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Heavy menstrual bleeding is a common complaint in postpubertal girls and adolescents and can cause decreased quality of life as well as major health problems including iron deficiency anemia, need for hospitalization, and transfusion in severe cases.^{1–4} Among girls and adolescents with heavy menstrual bleeding, up to 20% may have an underlying bleeding disorder.⁵ However, bleeding disorders remain an underrecognized and undertreated condition in females.⁶

Von Willebrand disease, defined as a quantitative or qualitative deficiency of von Willebrand factor, is the most common bleeding disorder in females with an estimated prevalence of 1.6 million in the United States.⁶ Heavy menstrual bleeding is the most common symptom among females with von Willebrand

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disease, occurring in up to 93% of patients.⁷⁻⁹ Onset of heavy menstrual bleeding at menarche is often the first sign of von Willebrand disease in affected patients.¹⁰ Early diagnosis of von Willebrand disease allows for additional treatment strategies for heavy menses if needed and prophylaxis for bleeding during future surgical procedures or childbirth. As early as 2001, the American College of Obstetricians and Gynecologists (ACOG) published the recommendation to screen adolescents with menorrhagia for von Willebrand disease.¹¹ In a later Committee Opinion, ACOG refined this recommendation by advising screening for bleeding disorders in adolescents reporting heavy menstrual bleeding in combination with one or more of the following: menses longer than 7 days or bleeding through a pad or tampon in 2 hours, anemia, a family history of a bleeding disorder, and history of bleeding after a hemostatic challenge (ie, tooth extraction, surgery, delivery).¹⁰

Although these guidelines have been in place for more than 15 years, the uptake of von Willebrand disease screening in clinical practice is unknown. Our team has previously found that screening was performed in only a minority of Ohio Medicaid patients (fewer than 15% with heavy menstrual bleeding and fewer than 25% with severe heavy menstrual bleeding).¹²

In the present study, we used a longitudinal health care insurance claims database to assess the frequency of von Willebrand disease screening in a nationally representative sample of females aged 10–17 years with heavy menstrual bleeding and examine patient- and health care provider-level factors that predict screening. We hypothesized that the overall frequency of von Willebrand disease screening in this population would be low and that distance to specialty care would be the most important factor that affects screening.

MATERIALS AND METHODS

In this retrospective cohort study, we used the Truven Health MarketScan Research Databases, a family of research databases, which include the medical prescription claims of more than 109 million total covered lives across the United States as well as Medicaid data on 8.6 million patients from 14 states from 2011 to 2013. Although all patient identifiers are removed to protect patient privacy, all health information during periods of eligibility is linked using a unique member identification number, allowing for patient-level longitudinal analysis without the need for complex algorithms. The MarketScan Databases contain patient demographics and physi-

cian and facility claims from more than 100 payers and are representative of all 50 states of the U.S. commercially insured population.¹³ The database captures any insurance-claimed care that the patient receives regardless of the facility in which the patient presents. Additionally, the database includes the same comprehensive claims for Medicaid patients (from 14 states representing all regions of the country). Because all data are already deidentified and collected for administration purposes, this study did not qualify as human subject research and was considered exempt by the Nationwide Children's Hospital institutional review board.

Our study population drew from a database of girls aged 10–17 years with a diagnosis of heavy menstrual bleeding based on the presence of one inpatient or two outpatient codes consistent with heavy menstrual bleeding (International Classification of Diseases, 9th Revision [ICD-9] 626.2, 626.3, 626.8) (Table 1). We were specifically interested in patients with a new diagnosis of heavy menstrual bleeding, so patients were required to have 6 months of continuous enrollment in the MarketScan Databases before the first appearance of one of the previously mentioned ICD-9 codes. Additionally, patients were required to have 12 months of continuous enrollment after the first heavy menstrual bleeding diagnosis to encompass an adequate time for diagnostic workup. We were interested in both patients with a diagnosis of heavy menstrual bleeding and those with severe heavy menstrual bleeding. As a result of the limitations of using an administrative database and similar to our study of Medicaid patients in central and southeast Ohio,¹² we defined severe heavy menstrual bleeding as heavy menstrual bleeding plus one of the following clinical features appearing in the 12 months after the first diagnosis: 1) inpatient stay with heavy menstrual bleeding as the primary discharge code or anemia (ICD-9 280.x, 285.1, 285.9) as the primary discharge code and heavy menstrual bleeding as the secondary discharge code, 2) evidence of iron deficiency anemia (ICD-9 280.0, 280.8, 280.9), or 3) evidence of blood transfusion (ICD-9 9900, 9902, 9904, 9907) (Table 1). We defined von Willebrand disease screening as the presence of a laboratory claim for VWF:Ag, VWF:RCo plasma levels, or both within the 12 months after the first appearance of a heavy menstrual bleeding ICD-9 code.

We were most interested in investigating the patient- and facility-level characteristics that we hypothesized would be associated with the frequency and likelihood of von Willebrand disease screening in this population. We collected the following from the MarketScan Databases: 1) patient age, 2) health care



Table 1. International Classification of Diseases, 9th Revision Code Descriptions

ICD-9 Code	Description
626.2	Excessive or frequent menstruation
626.3	Excessive menstruation at puberty
626.8	Other disorders of menstruation and other abnormal bleeding from the female genital tract
280.0	Iron deficiency anemia secondary to blood loss (chronic)
280.8	Other iron deficiency anemias
280.9	Iron deficiency anemia, unspecified
285.1	Acute posthemorrhagic anemia
285.9	Anemia, unspecified
99.00	Procedure code for perioperative autologous transfusion of whole blood or a blood component
99.02	Procedure code for transfusion of previously collected autologous blood
99.04	Procedure code for transfusion of packed cells
99.07	Procedure code for transfusion of other serum

ICD-9, International Classification of Diseases, 9th Revision.

provider type seen at the first visit for heavy menstrual bleeding, 3) whether the patient was living in a metropolitan statistical area (used as a proxy for urban vs rural inhabitation), and 4) approximate travel time from the patient's metropolitan statistical area to the nearest hemophilia treatment center. These factors were found to be significant in our pilot work with Ohio Medicaid data¹² and are known factors that predict the use of health services in behavioral models.¹⁴

In the United States, a metropolitan statistical area is a geographic region with a relatively high population density and close economic ties throughout the area. These regions are not incorporated as cities or towns, nor do they have legal administrative divisions such as counties or separate entities such as states. To estimate travel time to the nearest hemophilia treatment center, we used ArcMap software to calculate the distance between the metropolitan statistical area and the nearest hemophilia treatment center (Fig. 1). Metropolitan statistical area data were not available for Medicaid patients. The MarketScan Database provided pooled data from approximately 8 million Medicaid patients in 14 states, but does not provide data on geographic location of Medicaid patients.

Frequencies were calculated to describe the sample. Bivariate analyses using the χ^2 test were performed initially to examine relationships between the independent factors and von Willebrand disease screening. Logistic regression including the a priori identified variables listed was used to assess the factors related to the occurrence of von Willebrand disease screening. Independent variables with a *P* value $\leq .20$ in bivariate analyses then were entered into a multivariable logistic regression model using $\alpha = 0.05$. Outcomes from the logistic regression models are expressed as odds ratios (ORs).

With an anticipated sample size of more than 19,000 adolescents with heavy menstrual bleeding, we were able to estimate percentages within 1% and detect ORs of at least 1.5, the smallest OR deemed clinically relevant, with more than 99% power. We set a low threshold for our OR to ensure that we were able to identify as many factors as possible that could potentially affect von Willebrand disease screening.

RESULTS

The database identified 202,000 postpubertal girls and adolescent females. Of these, 56,000 (27%) had a diagnosis of heavy menstrual bleeding at least one time during the study period. Nearly three fourths were excluded because they did not have either one inpatient or two outpatient codes for heavy menstrual bleeding (Fig. 2). There were 23,888 girls and adolescents between the ages of 10 and 17 years who met our inclusion criteria and were diagnosed with heavy menstrual bleeding between 2011 and 2013 (Table 2). The most common health care provider types seen at the first visit for heavy menstrual bleeding were obstetrician-gynecologists (28% [6,609/23,888]) and family practice (13% [3,001/23,888]). There were 986 of 23,888 patients (4%) who met the study definition for severe heavy menstrual bleeding. Fewer than 1 in 10 (8% [1,936/23,888]) of the total population and fewer than one in five females who met our criteria for severe heavy menstrual bleeding (16% [160/986]) were screened for von Willebrand disease.

Patients who were younger at the time of presentation with heavy menstrual bleeding were screened more often than older patients (risk difference for screening percentage of young [10–13 years old (13.9%) vs 14–17 years old (6.4%)] 7.5%, 95% CI



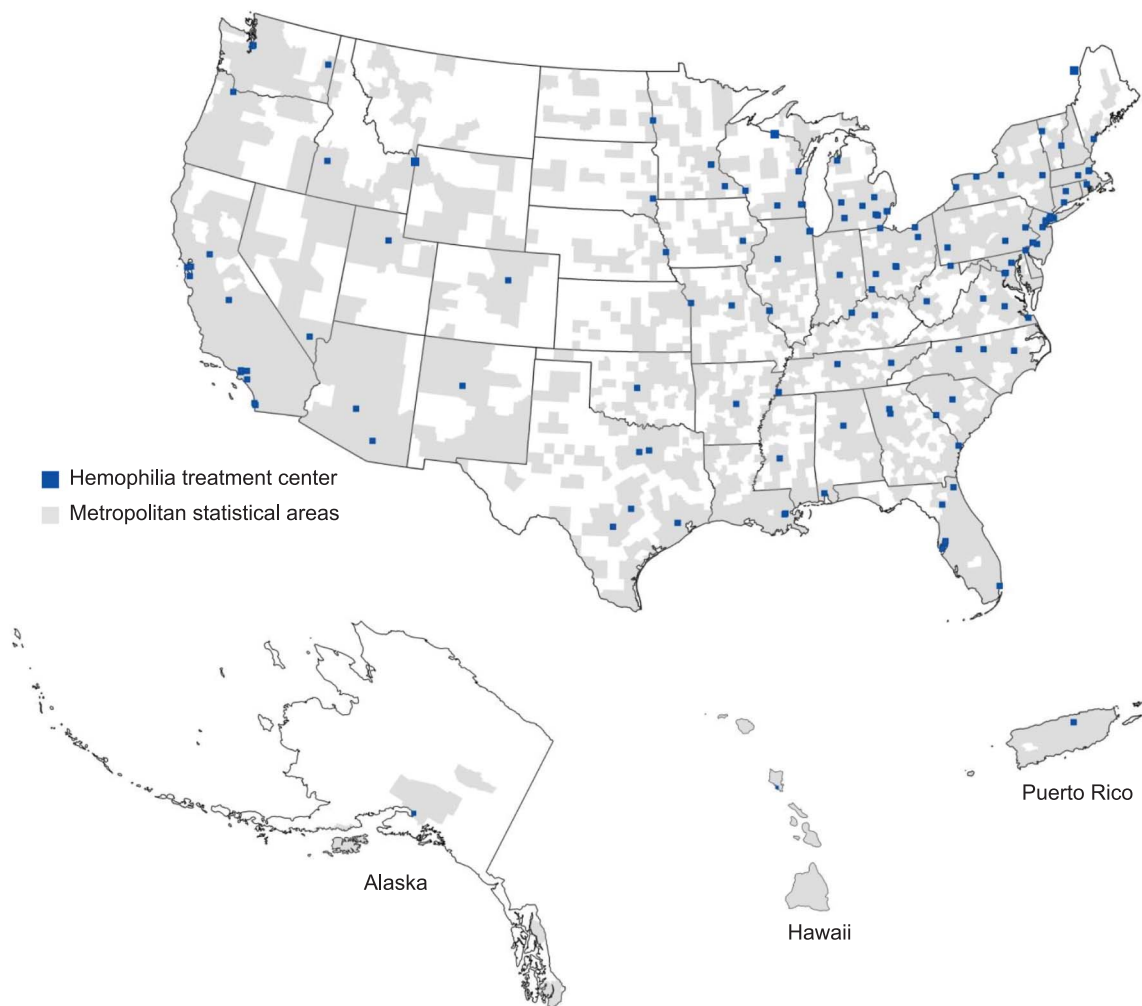


Fig. 1. Hemophilia treatment centers and metropolitan statistical areas, United States, 2013. Jacobson. *Von Willebrand Disease Screening in Females With Menorrhagia*. *Obstet Gynecol* 2018.

6.5–8.5%, $P < .001$). Patients admitted for heavy menstrual bleeding, those with a diagnosis of iron deficiency anemia, and those who underwent testing for iron deficiency anemia were screened more often for von Willebrand disease (risk difference screening percentage, respectively, 7.0%, 95% CI 3.0–11.0%, $P < .001$; 8.5%, 95% CI 6.0–11.0%, $P < .001$; 15.6%, 95% CI 14.7–16.4%, $P < .001$) (Table 3). Having a blood transfusion was not significantly associated with von Willebrand disease screening.

Logistic regression analysis showed that girls and adolescents meeting our criteria for severe heavy menstrual bleeding had a significantly increased likelihood of undergoing von Willebrand disease screening (16.2% vs 7.8%, OR 1.58, 95% CI 1.31–1.91) when compared with females who did not meet our criteria for severe heavy menstrual bleeding. Patients who underwent testing for iron deficiency ane-

mia had the highest likelihood of being screened for von Willebrand disease (18.3% vs 2.8%, OR 7.08, 95% CI 6.32–7.93) (Table 4).

There were 17,095 females with private insurance, of whom more than 80% lived within a metropolitan statistical area. We had metropolitan statistical area data for 16,654 patients (only 2.6%, 441 had missing codes). Metropolitan statistical area data were not available for Medicaid patients. Privately insured patients were screened more often than Medicaid patients (risk difference screening percentage 2.3%, 95% CI 1.6–3.0%, $P < .001$). Logistic regression analysis showed that privately insured patients were significantly more likely to be screened for von Willebrand disease than Medicaid patients (8.8% vs 6.5%, OR 1.66, 95% CI 1.47–1.87). Among those who were privately insured, adolescents living within a metropolitan statistical area were more likely to be



Identification

Females aged 10–17 years in Truven Health MarketScan Research Databases (n=202,000)

Patients excluded due to inadequate inpatient or outpatient ICD-9 codes (n=146,088)

Screening

Patients with 1 or 2 outpatient codes for heavy menstrual bleeding (ICD-9 626.2, 626.3, 626.8) (n=55,912)
Private insurance patients: 41,053
Medicaid patients: 14,859

Patients excluded due to inadequate prediagnosis enrollment period (n=15,399)

Eligibility

Patients with 6 months continuous enrollment before first heavy bleeding diagnosis (n=40,513)

Patients excluded due to inadequate postdiagnosis enrollment period (n=16,625)

Included

Adolescent females included in final analysis with 12 months of continuous enrollment after first heavy bleeding diagnosis (n=23,888)

Fig. 2. Flow diagram of data extracted from the Truven Health MarketScan Research Databases. ICD-9, International Classification of Diseases, 9th Revision.

Jacobson. Von Willebrand Disease Screening in Females With Menorrhagia. *Obstet Gynecol* 2018.

screened than those living outside a metropolitan statistical area (9.5% vs 5.5%, OR 1.64, 95% CI 1.38–1.95).

When looking at health care provider type, we found that patients seeing family practice providers at the time of initial diagnosis of heavy menstrual bleeding were less likely to undergo von Willebrand disease screening when compared with patients seeing obstetric–gynecologic providers (3.2% vs 6.0%, OR 0.43, 95% CI 0.34–0.54). Patients seeing acute care providers (10.4% vs 6.0%, OR 1.22, 95% CI 1.03–1.44) and pediatricians (12.0% vs 6.0%, OR 1.21, 95% CI 1.02–1.42) at the time of initial diagnosis were modestly more likely to undergo screening when compared with patients seeing obstetric–gynecologic providers (Table 4). There were 6,310 patients in whom the health care provider type at initial diagnosis of heavy menstrual bleeding was “other” or “missing.” Other health care provider types included other subspecialty surgeons such as otolaryngologists. A missing health care provider type indicates that the diagnosis code was associated with a laboratory

encounter that could not be linked back to a specific health care provider.

We calculated the approximate travel time to the nearest hemophilia treatment center in all patients who lived within a metropolitan statistical area (n=13,475). Of these, more than one third (36%) had to travel longer than 1 hour to get to the nearest hemophilia treatment center (Table 2). Patients living in a metropolitan statistical area who were less than 1 hour to the nearest hemophilia treatment center were more likely to undergo von Willebrand disease screening than patients living further from a hemophilia treatment center (10.7% vs 7.6%, OR 1.37, 95% CI 1.19–1.56) (Table 4).

DISCUSSION

In 2001, ACOG recommended screening adolescents with heavy menstrual bleeding since menarche for von Willebrand disease. The refined recommendations, published in 2013, better defined what a diagnosis of heavy menstrual bleeding entails and included recommendations for screening in



Table 2. Demographics of Postpubertal Girls and Adolescents With Heavy Menstrual Bleeding (N=23,888), Truven Health MarketScan Research Databases, 2011–2013

	n (%)
Screened for von Willebrand disease	
Yes	1,936 (8.1)
Admitted for heavy menstrual bleeding	
Yes	306 (1.3)
Iron deficiency anemia diagnosis	
Yes	864 (3.6)
Blood transfusion	
Yes	110 (0.5)
Severe HMB	
Yes	986 (4.1)
Underwent iron deficiency anemia testing	
Yes	8,228 (34.4)
Age (y)	
10	208 (0.9)
11	736 (3.1)
12	1,666 (7.0)
13	2,751 (11.5)
14	4,035 (16.9)
15	5,186 (21.7)
16	5,433 (22.7)
17	3,873 (16.2)
Insurance type	
Commercial	17,095 (71.6)
Medicaid	6,793 (28.4)
Health care provider	
Acute care	2,732 (11.4)
Internal medicine	2,394 (10.0)
Family practice	3,001 (12.6)
Obstetrics–gynecology	6,609 (27.7)
Pediatric	2,842 (11.9)
Other or missing	6,310 (26.4)
Metropolitan statistical area (among 17,095 privately insured)*	
Living in a metropolitan statistical area (urban)	13,475 (78.8)
Living outside of a metropolitan statistical area (rural)	3,179 (18.6)
Missing metropolitan statistical area	441 (2.6)
Minutes from a hemophilia treatment center [†]	
Less than 60	8,641 (64.1)
60 or more	4,834 (35.9)

HMB, heavy menstrual bleeding.

* No metropolitan statistical area information is available for patients with Medicaid coverage.

[†] Available for 13,475 living in a metropolitan statistical area.

adolescents reporting heavy menstrual bleeding and any of the following: 1) menses lasting more than 7 days or bleeding through a pad or tampon in 2 hours, 2) a personal history of anemia, 3) a family history of a bleeding disorder, or 4) a personal history of abnormal bleeding after a hemostatic challenge. In this study of a national claims database, we found that

of 27,888 postpubertal girls and adolescent girls (10–17 years) with a diagnosis of heavy menstrual bleeding, 8% were screened for von Willebrand disease. Because ACOG's recommendations do not provide a definition for severe heavy menstrual bleeding and given the limitations of using an administrative database, we elected to use the following criteria to define severe heavy menstrual bleeding: a diagnosis of heavy menstrual bleeding plus a hospital admission for menstrual bleeding, a diagnosis of iron deficiency anemia, or evidence of a blood transfusion. Among those patients who met our criteria for severe heavy menstrual bleeding, the screening rate was modestly better (16% were screened for von Willebrand disease). Our study demonstrated that despite published recommendations, von Willebrand disease screening was rarely performed as part of the evaluation of postpubertal girls and adolescents with heavy menstrual bleeding in the United States. The following patient characteristics were significantly associated with a higher frequency of von Willebrand disease screening: inpatient admission for heavy menstrual bleeding, diagnosis of iron deficiency anemia, testing for iron deficiency anemia, younger age at presentation with heavy menstrual bleeding, commercial insurance, an obstetrician–gynecologist as opposed to a family practice provider at the initial encounter for heavy menstrual bleeding, geographic location within a metropolitan statistical area, and travel time less than 1 hour to the nearest hemophilia treatment center. Additionally, patients who underwent testing for iron deficiency anemia, regardless of having a subsequent diagnosis of iron deficiency anemia, had a significantly increased likelihood of undergoing von Willebrand disease screening. Even among patients living within a metropolitan statistical area, the distance to the nearest hemophilia treatment center remained modestly predictive of their likelihood to be screened for von Willebrand disease.

There are important limitations of our study design to consider. We were not able to account for ethnicity, family history of bleeding disorders, medical history, and medications because these data were not available in Truven Databases. Additionally, if ICD-9 diagnosis codes for heavy menstrual bleeding were recorded incorrectly or not recorded at all, this may have misidentified or omitted some patients. Strengths of our database include a large and diverse population representative of the U.S. population. To minimize concerns about selection bias and external validity, we oversampled commercially insured patients to have the largest possible sample. Although we do not know the states that were



Table 3. Association Between von Willebrand Disease Screening and Patient and Health Care Provider Characteristics Among All Adolescents, the Subset of Privately Insured Patients, and the Subset of Privately Insured Patients Living Within a Metropolitan Statistical Area

	All Patients (N=23,888)		Privately Insured Patients (n=16,654) *		Privately Insured Patients Living in a Metropolitan Statistical Area (n=13,475) [†]	
	% Screened	P	% Screened	P	% Screened	P
Overall % screened	8.1		8.8		9.5	
Admitted for heavy menstrual bleeding		<.001		<.001		<.001
Yes	15.0		17.0		16.9	
No	8.0		8.7		9.4	
Iron deficiency anemia diagnosis		<.001		<.001		<.001
Yes	16.3		18.3		19.0	
No	7.8		8.5		9.2	
Blood transfusion		.153		.160		.446
Yes	11.8		13.3		12.3	
No	8.1		8.7		9.5	
Severe heavy menstrual bleeding		<.001		<.001		<.001
Yes	16.2		18.1		18.7	
No	7.8		8.4		9.2	
Underwent iron deficiency anemia testing		<.001		<.001		<.001
Yes	18.3		20.2		21.6	
No	2.8		3.0		3.2	
Age (y)		<.001		<.001		<.001
10	22.6		22.7		24.0	
11	17.5		19.2		21.1	
12	14.3		16.3		17.5	
13	12.0		13.2		14.9	
14	9.2		10.0		10.9	
15	6.6		6.9		7.1	
16	5.5		5.9		6.6	
17	4.7		5.3		5.7	
Insurance type		<.001				
Commercial	8.8		NA		NA	
Medicaid	6.5					
Health care provider		<.001		<.001		<.001
Acute care	10.4		10.2		11.5	
Internal medicine	6.9		9.7		10.1	
Family practice	3.2		3.5		3.8	
Obstetrics–gynecology	6.0		6.2		6.7	
Pediatric	12.0		13.0		13.3	
Other or missing	10.4		12.9		14.2	
Metropolitan statistical area				<.001		
Living in a metropolitan statistical area (urban)	NA		9.5		NA	
Living outside of a metropolitan statistical area (rural)			5.5			
Minutes from a hemophilia treatment center						<.001
Less than 60					10.7	
60 or more					7.6	

NA, not applicable.

* These 16,654 patients are a subset of the 23,888 adolescents.

† These 13,475 patients are a subset of 16,654 privately insured patients.

represented by the Medicaid patients, we do know that the 14 states are representative of each region in the United States. Although we did not have geographic data for publicly insured patients, we hypothesize that distance barriers are as important (if not

more) for publicly insured patients. In our prior work with Ohio Medicaid data, distance was a factor that affected screening frequency.¹²

Because bleeding disorders in women tend to be less severe than hemophilia, it can be more difficult



Table 4. Adjusted Odds Ratio of von Willebrand Disease Screening in Postpubertal Girls and Adolescents With Heavy Menstrual Bleeding, Multivariable Logistic Regression Model

Variable	OR	95% Wald Confidence Limits
Full model, adjusted for other variables in the model (N=23,888)		
Age (y)	0.82	0.79–0.84
IDA testing (yes vs no)	7.08	6.32–7.93
Severe HMB (yes vs no)	1.58	1.31–1.91
Insurance type (private vs Medicaid)	1.66	1.47–1.87
Health care provider		
Acute care vs obstetrics–gynecology	1.22	1.03–1.44
Family practice vs obstetrics–gynecology	0.43	0.34–0.54
Internal medicine vs obstetrics–gynecology	1.06	0.87–1.30
Pediatrician vs obstetrics–gynecology	1.21	1.02–1.42
Missing or other vs obstetrics–gynecology	1.31	1.14–1.51
Privately insured patients (n=16,654)		
Urban vs rural*	1.64	1.38–1.95
Privately insured patients living in an MSA (n=13,475)		
Less than 60 min away from an HTC vs more than 60 min away†	1.37	1.19–1.56

OR, odds ratio; IDA, iron deficiency anemia; HMB, heavy menstrual bleeding; MSA, metropolitan statistical area; HTC, hemophilia treatment center.

* Available only for privately insured patients (unavailable for all Medicaid patients); from a model with n=16,654 adjusted for age, IDA testing, severe HMB, and health care provider.

† Available only for privately insured patients living within a metropolitan statistical area; from a model with n=13,475 adjusted for age, IDA testing, severe HMB, and health care provider.

for physicians and patients to recognize symptoms, and the average time to diagnosis can be as long as 4–16 years.^{15–17} Although patients in our study who met criteria for severe heavy menstrual bleeding were more likely to be screened than nonsevere patients, the screening rate remained less than one in five and was lower than our prior report of Ohio Medicaid patients.¹² Females with bleeding disorders are more likely to undergo hysterectomy and also undergo hysterectomy at an earlier age than women without bleeding disorders.¹⁸ Early recognition of von Willebrand disease can help prevent subsequent bleeding episodes during pregnancy, postpartum hemorrhage, bleeding during surgical procedures, and potentially unnecessary hysterectomies.

The multiple other causes of heavy menstrual bleeding can be a barrier to diagnosing von Willebrand disease. Anovulatory and dysfunctional uterine bleeding is commonly seen in adolescents, and these diagnoses may discourage the health care provider from testing for a bleeding disorder if he or she makes the assumption that these diagnoses are the cause of heavy menstrual bleeding. A personal or family history of heavy menstrual bleeding; postpartum hemorrhage; iron deficiency requiring therapy or transfusion; unusual, unexpected, or excessive surgical bleeding; unexplained or frequent epistaxis; oral bleeding; or easy bruising should further prompt health care providers to screen for von Willebrand

disease.^{5,19} Additionally, validated bleeding scores have been published and can be used in clinical practice but are not without limitations, especially if used in adolescents.⁵ In a recent North American Society of Pediatric and Adolescent Gynecology committee opinion, recommendations for acute treatment of heavy menstrual bleeding in adolescents were to first address symptomatic anemia or severe bleeding with blood products if needed. Then high-dose estrogen-only, progesterone-only (if estrogen is contraindicated), or combined contraceptive pills can be used to stabilize the endometrium, resulting in bleeding cessation. Iron deficiency should be corrected with supplementation, either oral or intravenous.⁵

It is essential to understand how to interpret von Willebrand disease results that warrant hematology referral and also recognize testing limitations and factors that may affect testing accuracy. A concern for possible von Willebrand disease arises when there is low von Willebrand factor antigen, activity (ristocetin cofactor), or both or when the platelet function analysis (closure time) is prolonged, because this test was developed as a screening test for von Willebrand disease. Von Willebrand disease screening is highly specific (greater than 98%) for von Willebrand disease, but sensitivity is much lower as a result of various conditions that may affect testing. Many centers send out these tests to commercial laboratories, which can cause falsely low levels as



a result of delays in processing and elevated sample temperature. Anemia and high-dose estrogen therapy, which is commonly used to treat severe heavy menstrual bleeding, can increase von Willebrand factor antigen and activity.²⁰ Von Willebrand disease testing should be postponed until a patient is off high-dose estrogen therapy. Standard or low-dose estrogen treatment would be much less likely to interfere with von Willebrand disease testing, and we routinely screen for von Willebrand disease in patients on standard-dose combined contraceptives in clinical practice. Von Willebrand factor is an acute-phase reactant and may also be elevated in the setting of illness or stress. Thus, a hematology referral may be warranted should a clinical history of bleeding be present, even if test results are negative. Von Willebrand factor antigen, activity levels above the upper limit of normal, or both are rarely clinically significant and do not warrant hematology referral unless there are persistent and otherwise unexplainable bleeding concerns.

In conclusion, our study demonstrates that despite more than 15 years of ACOG recommendations, approximately 90% of postpubertal girls and adolescents with heavy menstrual bleeding are not being screened for von Willebrand disease. We showed that a variety of health care providers are the “first responders” for girls and adolescents with heavy menstrual bleeding, which emphasizes the need for increased awareness of von Willebrand disease among all health care providers taking care of adolescent females and recognition that heavy menstrual bleeding is the most common and often the first bleeding symptom in young women with von Willebrand disease.

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