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RESEARCH LETTER

Bleeding disorder of unknown cause & unclassified bleeding disorders at US hemophilia treatment centers

Bleeding disorder of unknown cause (BDUC) is a diagnostic category encompassing patients with an abnormal bleeding tendency yet normal hemostatic evaluation. Patients typically present with mucocutaneous predominant bleeding symptoms clinically indistinguishable from other mild bleeding disorders, including platelet function defects and von Willebrand disease [1]. Diagnosis rests on careful history taking, assisted by administration of a validated Bleeding Assessment Tool (BAT), along with laboratory testing to rule out possible inherited or acquired bleeding disorders. Genetic testing is not necessary for diagnosis, and the yield of next-generation sequencing of genes associated with coagulation and platelet disorders is low in patients with unexplained bleeding [2]. While formal diagnostic criteria have not been established, BDUC is increasingly diagnosed in clinical practice. Current US National Bleeding Disorder Foundation Medical and Scientific Advisory Council recommendation suggests that patients with BDUC be followed at hemophilia treatment centers (HTCs) [3]. We sought to examine trends in BDUC diagnosis at US Hemophilia Treatment Center Network (USHTCN) as well as our own center.

Community Counts is a public health surveillance program funded through the Centers for Disease Control and Prevention that tracks bleeding disorders at the 146 USHTCN sites [4]. Registered patients with unclassified bleeding disorders are reported as "Blood coagulation disorder without specific diagnosis." As of March 31, 2023, Community Counts has reported 2673 patients with unclassified bleeding disorders. This diagnosis comprises 2.1% of unique registered patients. The majority of these patients are female (69%) and diagnosed in adolescence or early adulthood. Seventy-seven percent of these patients are White, and 10% are Black or African American; 23% are of Hispanic, Latino/a, or Spanish origin. Ninety-eight percent of patients were insured (Table). Between 2012 and 2022, the number of annual active patients (patients who receive care in person or by telemedicine at an HTC) with the disorder increased from 184 to 495 (Figure). This represents a 170% increase compared to a 70% increase in the overall HTC population over the 10-year period. The reported prevalence at USHTCN sites would place it on par with other rare bleeding disorders in the United States, including factor XI deficiency (1921 patients) or platelet storage pool disorders (3814 patients).

Examining data from our own center, we see how changes in practice patterns significantly affect the number of patients with BDUC diagnosed and registered. Prior to 2020, single-digit numbers of patients with unclassified bleeding disorder were registered annually at our center. New registrations increased sharply in 2020 and have continued to increase, with 57 new patients registered in 2022 (Figure). This change reflects increased recognition of the disorder, standardization of practices around diagnosis and management, and an increasing referral network. All new patients presenting for evaluation of a potential bleeding disorder are evaluated in a standardized fashion, which includes administration of BAT and recording of the BAT score. Diagnosis of BDUC is considered for patients with abnormal BAT scores and normal hemostatic testing results; at our center, testing includes at minimum a complete blood count, prothrombin time/activated partial thromboplastin time, von Willebrand antigen and activity, factor VIII, fibrinogen, platelet function assay, platelet aggregometry, and platelet electron microscopy. Patients diagnosed with BDUC are subsequently registered in the HTC and scheduled for follow-up visits every 2 years.

While trends in BDUC registration have not previously been reported in the United States, our experience is comparable to that in other international sites. In the United Kingdom, the number of patients with unclassified bleeding disorders has increased sharply since 2012 and accounted for 2.65% of registered patients in HTCs as of 2019. As of February 2021, 1061 patients with unclassified bleeding disorders were registered in the United Kingdom [5]. Individual centers have amassed sizable cohorts of patients with BDUC. The Vienna Bleeding Biobank has collected clinical and laboratory data on 246 patients with BDUC [6], and a tertiary medical center in the Netherlands reported on a cohort of 228 patients [7].

At present, BDUC remains a small but growing segment of the bleeding disorder population in the USHTCN. As we have seen in our center, changes in practice patterns can significantly increase the diagnosis and registration of patients with BDUC. Despite significant increases in recent years, BDUC may still be significantly underrecognized and reported in Community Counts data. No specific criteria for BDUC or unclassified bleeding disorder exist within the American Thrombosis and Hemostasis Network data set, which site data coordinators use to submit data for Community Counts. Patterns and practices around diagnosis may differ between centers, biasing the representation of these patients in a national sample. Individual, high-reporting centers are thus overrepresented. Critical observational data, including International Society on Thrombosis and

TABLE Characteristics of patients with unclassified bleeding disorder registered at US Hemophilia Treatment Center Network sites from January 2012 to March 2023.

Characteristic	Values, *n* (%)
Sex	
Male	831 (31)
Female	1842 (69)
Age	
<2 y	118 (4)
2-10 y	580 (22)
11-19 y	838 (31)
20-44 y	614 (23)
45-64 y	302 (11)
65+ y	221 (8)
Race	
American Indian/Alaska Native	40 (1)
Asian	83 (3)
Black or African American	263 (10)
Native Hawaiian or other Pacific Islander	9 (0)
White	2055 (77)
More than 1 of these	34 (1)
Unknown	189 (7)
Ethnicity	
Hispanic, Latino/a, or Spanish origin	605 (23)
Non-Hispanic, -Latino/a, or -Spanish origin	1930 (72)
Unknown	138 (5)
Insurance status	
Insured	2627 (98)
Uninsured	22 (1)

Source: Centers for Disease Control and Prevention Community Counts population profile [4].

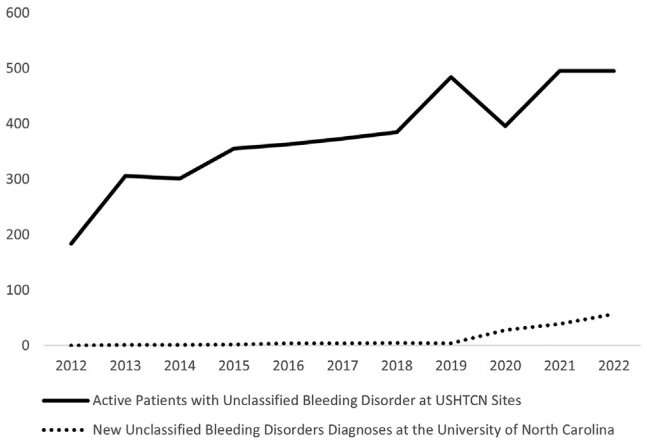

FIGURE Trends in unclassified bleeding disorder diagnosis and registration. Source: Centers for Disease Control and Prevention Community Counts population profile and American Thrombosis and Hemostasis Network dataset. USHTCN, US Hemophilia Treatment Center Network.

Haemostasis BAT score, are not routinely captured. Patients diagnosed with BDUC may be seen on an ad hoc basis and not formally registered at HTCs. Furthermore, many patients with potential bleeding disorders may never be evaluated by a hematologist—bleeding symptoms, particularly in marginalized communities, may go uninvestigated. Virtually all registered patients at USHTCN sites with unclassified bleeding disorders have medical insurance, suggesting that uninsured patients have greater difficulty accessing diagnostic hematology services necessary for diagnosis.

Inclusion of BDUC in HTCs will likely continue to increase the total bleeding disorder population served, creating new challenges and opportunities for center staff. Women, who may have needs specific to menstruation and reproductive health, make up a significant majority of the patient population. Genetic counseling and physical therapy, core components of hemophilia care, are less applicable as part of routine clinical care for these patients. Integrating BDUC into existing HTC care models is a sensible approach when patient numbers are small but should be critically examined as populations increase. Alternate care models may be appropriate; for example, patients with hereditary hemorrhagic telangiectasia may receive care in Hereditary Hemorrhagic Telangiectasia Centers of Excellence, which operate outside of HTCs due to the differing integrative care needed of these patients (eg, access to subspecialty otolaryngology and interventional radiology, among others).

Establishing the prevalence of BDUC is fundamental to further defining the role of the HTC in caring for this population and evaluating alternative care models. Implicitly embedded in the question of prevalence is a more fundamental question regarding the diagnosis itself: To what extent does an individual patient's bleeding phenotype need to deviate from population norms in order to qualify as a bleeding disorder? Abnormal cutoff values for the International Society on Thrombosis and Haemostasis BAT are based on 95% population means among healthy men and women [8] and have been shown to increase with normal aging [9]. Careful clinical judgment is needed on the part of the clinician to determine which patients should be followed longitudinally for bleeding disorder on the basis of their history.

One of the strongest rationales for BDUC as a diagnostic label, in addition to reflecting a clinical reality, is it allows for cohort definition for future research. Improved registry reporting is critical to better understand the natural history of the disorder, including risk of subsequent bleeding events and hemostatic management needs. A well-defined and surveilled cohort is also essential for conducting future mechanistic studies into the pathophysiology of bleeding in BDUC. Within the structure of the USHTCNs and existing surveillance databases, we have a significant opportunity to enhance our understanding of this disorder and improve care for patients. At the same time, existing comprehensive care models should be continually evaluated as the patient population with BDUC expands while being cognizant of resource utilization and divergent care needs.

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AUTHOR CONTRIBUTIONS

C.B. contributed to the project conception, data collection, analysis and interpretation of results, and manuscript preparation. N.S.K. and A.M. contributed to project conception, interpretation of results, and manuscript preparation. K.K. contributed to projection conception, data collection, analysis of results, and manuscript preparation.

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N.S.K. receives grant support from the National Heart, Lung, and Blood Institute, National Institutes of Health. He chairs the grant review committee for Novo Nordisk and has a leadership role on the International Society on Thrombosis and Haemostasis Council. He has participated on advisory boards for Pfizer and BioMarin. A.M. receives royalties from UpToDate and does unpaid consulting and committee work for the Foundation for Women & Girls with Blood Disorders. K.K. has no relevant disclosures. C.B.'s research is partially supported by a National Research Service Award predoctoral/postdoctoral traineeship from the Agency for Healthcare Research and Quality sponsored by the Cecil G. Sheps Center for Health Services Research, the University of North Carolina at Chapel Hill (grant number T32-HS000032). Community Counts is a project supported by cooperative agreement NU27DD000020 awarded to the American Thrombosis and Hemostasis Network in partnership with the US Hemophilia Treatment Center Network. The cooperative agreement is an annual financial assistance award totaling $4,300,000 that is 100% funded by the Centers for Disease Control and Prevention (CDC) and the US Department of Health and Human Services. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the CDC, the Department of Health and Human Services, the American Thrombosis and Hemostasis Network, or the US Hemophilia Treatment Center Network. Data reported in this publication were collected through Community Counts: CDC Public Health Surveillance Project for Bleeding Disorders.

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