Received: 13 August 2024 | Accepted: 4 September 2024

https://doi.org/10.1016/j.rpth.2024.102572

ORIGINAL ARTICLE

Periprocedural hemostatic prophylaxis and outcomes in bleeding disorder of unknown cause

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Handling Editor: Dr Michael Makris

Abstract

Background: Bleeding disorder of unknown cause (BDUC) is a diagnostic category encompassing patients with a clear bleeding phenotype but without identifiable abnormality on hemostatic testing. The optimal management of hemostasis in BDUC patients prior to invasive procedures and childbirth is uncertain.

Objectives: Our objective was to characterize periprocedural hemostatic prophylaxis and bleeding outcomes in patients with BDUC.

Methods: We conducted a retrospective cohort study of adult patients with BDUC at 2 academic medical centers. Following diagnosis of BDUC, subsequent surgical procedures and childbirths were analyzed using a combination of registry data and manual chart review.

Results: We identified 127 patients with mean age of 39.9 years (SD = 16.6); the majority of patients were female (91.3%). Forty-eight major procedures, 70 minor procedures, and 19 childbirths were analyzed. Antifibrinolytic monotherapy was advised for 57% of major procedures, 59% of minor procedures, and 67% of childbirths. Perioperative platelet transfusion was recommended in 26% of major procedures and 9% of minor procedures in combination with other hemostatic agents. Major or clinically relevant nonmajor bleeding occurred in 4.1% (4/98) of procedures with prophylaxis and 10% (2/20) of procedures without prophylaxis. Postpartum hemorrhage occurred in 26% (5/19) of deliveries.

Conclusion: In this multiinstitution experience, we found overall low rates of hemostatic complications in procedures completed with hemostatic prophylaxis, although preventing hemorrhage in childbirth and gynecologic procedures remain unmet needs.

KEYWORDS
bleeding disorder of unknown cause, blood coagulation disorders, hemorrhagic disorders, postoperative hemorrhage, postpartum hemorrhage, unclassified bleeding disorder

Essentials

- Optimal periprocedural hemostatic management is uncertain in bleeding disorder of unknown cause.
- We analyzed hemostatic prophylaxis and outcomes of 118 procedures and 19 childbirths.
- Antifibrinolytics were the most common prophylaxis; bleeding rates were low in treated patients.
- Preventing hemorrhage in childbirth and gynecologic procedures remain unmet needs.

1 | INTRODUCTION

Bleeding disorder of unknown cause (BDUC) is an increasingly recognized diagnostic category that encompasses patients with a clear bleeding tendency but without identifiable abnormality on hemostatic testing [1,2]. Up to 60% of patients presenting to a tertiary center for hemostatic evaluation are ultimately diagnosed with BDUC [1], with bleeding assessment tools (BATs) (including the International Society on Thrombosis and Haemostasis BAT [ISTH] [3] and the condensed MCMDM1VWF BAT [4]) playing an important role in establishing an abnormal bleeding tendency.

BDUC is a women's health issue: 66% to 87% of the BDUC population is female [1] and women with strong bleeding histories are far less likely than men to have a detectable abnormality on laboratory testing [5]. Women with BDUC frequently report heavy menstrual bleeding and postpartum hemorrhage, along with easy bruising, and excessive postsurgical bleeding [1].

The bleeding phenotype in BDUC may resemble that of other mild bleeding disorders, including von Willebrand disease or intrinsic platelet defect. Along with menorrhagia and mucocutaneous bleeding, postsurgical bleeding is commonly reported in BDUC. Hematologists and hemophilia treatment center staff are commonly involved in the periprocedural management of BDUC patients.

While recognition and diagnosis of BDUC are increasing, significant uncertainty exists regarding the optimal management of these patients prior to invasive procedures. A recently published communication from the ISTH Scientific and Standardization Committee (SSC) on "von Willebrand factor, platelet physiology, and women's health issues in thrombosis and haemostasis" suggests a staged approach to prophylactic treatment with antifibrinolytic agents, desmopressin acetate (DDAVP), and platelet transfusion versus observation alone, based on perceived individual and procedural bleeding risks [1,6]. However, minimal clinical evidence is available to guide management, with few retrospective case series reported in the literature [7–9].

Prior research has suggested that BAT scores may be associated with higher risk of spontaneous bleeding events, but less is known about periprocedural bleeding [10]. Thus, the objective of this study was to characterize periprocedural hemostatic prophylaxis and bleeding outcomes in patients with BDUC.

2 | METHODS

2.1 | Study design

We conducted a retrospective analysis using 2 observational patient cohorts. Cohort 1 (University of North Carolina [UNC]) consisted of patients identified using the UNC patient cohort in the American Thrombosis and Hemostasis Network dataset and supplemental chart review from 2015 to 2022. Cohort 2 (KNG) consisted of patients at Queen's University in Kingston, ON, 2006-2023, with 100 sequentially reviewed BDUC patients subject to a screening procedure. We documented patients' demographic characteristics and condensed MCMDM-1 bleeding score as determined by the treating hematologist at the time of diagnosis. Following a diagnosis of BDUC, outcomes of subsequent surgical procedures and deliveries were evaluated. All hemostatic treatments provided were at the discretion of the treating physician in the absence of any prespecified treatment protocol or established guidelines. This study was approved by the institutional review boards at both participating centers.

2.2 | Patient selection

Patients meeting the following criteria were included: 1) completion of a structured bleeding assessment; 2) completion of core diagnostic testing per institutional practices (at minimum complete blood count, prothrombin time/activated partial thromboplastin time, platelet function assay, von Willebrand antigen and activity, factor (F)VIII activity, platelet function assay, platelet aggregometry and secretion); 3) clinician assessment as documented in the medical record that is consistent with BDUC without further diagnostic work-up; and 4) age at diagnosis ≥18 years. In contrast to the ISTH SSC definition of BDUC [6], the evaluation of FIX and FXI was not explicitly required in our protocol, although patients were required to have a normal activated partial thromboplastin time and prothrombin. Assessment of platelet secretion, recommended in the SSC communication, was required for this study. Structured bleeding assessment was performed with the condensed MCMDM-1 bleeding score as opposed to the ISTH-BAT as per institutional practice at the time of the study.

2.3 | Outcomes and covariates

Our primary outcome was the composite of major or clinically relevant nonmajor bleeding by ISTH criteria [11,12]. Clinically relevant nonmajor bleeding includes bleeding that prompts clinical intervention, hospitalization or a higher level of care, or face-to-face evaluation. Postpartum hemorrhage was defined as cumulative blood loss ≥1000 mL or blood loss accompanied by signs or symptoms of hypovolemia per the American College of Gynecology Practice Bulletin [13], along with any bleeding that resulted in red cell transfusion or acute surgical intervention. Bleeding was assessed by chart review of operative notes, progress notes, discharge summaries, and telephone notes in the perioperative period. Our primary exposure variable was hemostatic treatment prior to surgery or procedure. This was assessed by administration of any one of the following products, alone or in combination, as documented in the electronic health record: DDAVP, tranexamic acid, aminocaproic acid, platelets, fresh frozen plasma, cryoprecipitate, or other hemostatic agent. Our covariates of interest were age, sex (sex assigned at birth), bleeding score, and procedure type (major vs minor). Bleeding score was recorded at the initial encounter using the MCMDM-1 bleeding questionnaire. Procedures were classified as major or minor using criteria adapted from previous clinical trials in von Willebrand disease [14,15]. Major surgical procedures included orthopedic, abdominal, gynecologic/genitourinary, head and neck, neurosurgical/spinal, or cardiovascular surgery, as well as complicated dental extraction. Additionally, any surgery requiring general or spinal anesthesia was considered major. Minor surgical procedures included simple skin procedures, ophthalmologic procedures, endoscopy (with or without biopsy), hemorrhoidectomy, simple dental extraction, arthroscopy, skin/soft tissue biopsy, and simple vascular procedures.

2.4 | Analysis plan

Descriptive statistics were performed on all variables to determine frequency of categorical variables and distribution as well as means and standard deviations among normally distributed continuous variables. Peripartum outcomes were analyzed separately from periprocedural outcomes. Using prophylactic treatment as a binary variable (received/not received), we calculated the proportion of bleeding events in patients who received prophylactic hemostatic treatment versus those who did not receive prophylactic treatment, stratified by procedure type. Multivariable logistic regression was used to model prophylactic choices and bleeding events and calculate odds ratios. Bleeding score was additionally evaluated as a predictor of bleeding events. Patients with incomplete hemostatic outcome data were excluded from the analysis. Statistical analysis was completed using Stata (StataCorp. 2021. Stata Statistical Software: Release 17, StataCorp LLC). The 2-sided threshold for statistical significance was set at $P < .05$.

3 | RESULTS

A total of 200 patients were screened for eligibility (100 patients at each site). Of these 200 patients, 73 did not meet inclusion criteria due to incomplete hemostatic evaluation (n = 28), age <18 at the time of diagnosis (n = 30), or alternate diagnosis established (n = 15), resulting in 127 patients available for analysis. Among these 127 patients, 80 had a documented procedure between diagnosis and conclusion of chart review (Figure; CONSORT diagram). Follow-up time varied between participants and the most recent available records were analyzed.

3.1 | Patient characteristics

BDUC patients in our cohort were predominantly female (91.3%), with a similar sex breakdown between the UNC and KNG cohorts. Mean MCMDM-1 bleeding score was 9.7 (SD = 3.9) and the mean age was 39.9 (SD = 16.6) at the time of initial diagnosis. Race and ethnicity data were collected only at the UNC cohort site: 78.7% of patients were White and 10% were Black or African American, while 4.3% of patients were of Hispanic, Latino/a, or Spanish origin (Table 1).

3.2 | Bleeding phenotype at diagnosis

All patients included in this analysis had an overall bleeding score and bleeding domain subscores documented in the medical record at the time of diagnosis, allowing for the characterization of historical bleeding symptoms. The most common bleeding symptom reported at diagnosis was menorrhagia (88.1% of patients; 96.5% of female patients), followed by cutaneous bleeding (73.0%), oral cavity bleeding (58.7%), bleeding with tooth extraction (54.8%), and surgical bleeding (53.2%). Fifty-eight per cent of female patients had experienced prior self-reported postpartum bleeding, which includes all bleeding requiring medical attention (MCMDM BAT score ≥1). Muscle hematoma and hemarthrosis were uncommonly reported (11.1% and 1.6%, respectively).

3.3 | Procedures and hemostatic prophylaxis

A total of 53 major procedures, 76 minor procedures, and 21 childbirths were completed between diagnosis and the end of the follow-up period. Of these, 48 major procedures, 70 minor procedures, and 19 childbirths had complete hemostatic outcome data. Details of procedures and categorization can be found in Supplementary Table S1.

The most common treatment combinations across all procedures and deliveries were antifibrinolytic agents (tranexamic acid or aminocaproic acid) (Table 2). Antifibrinolytic monotherapy was advised

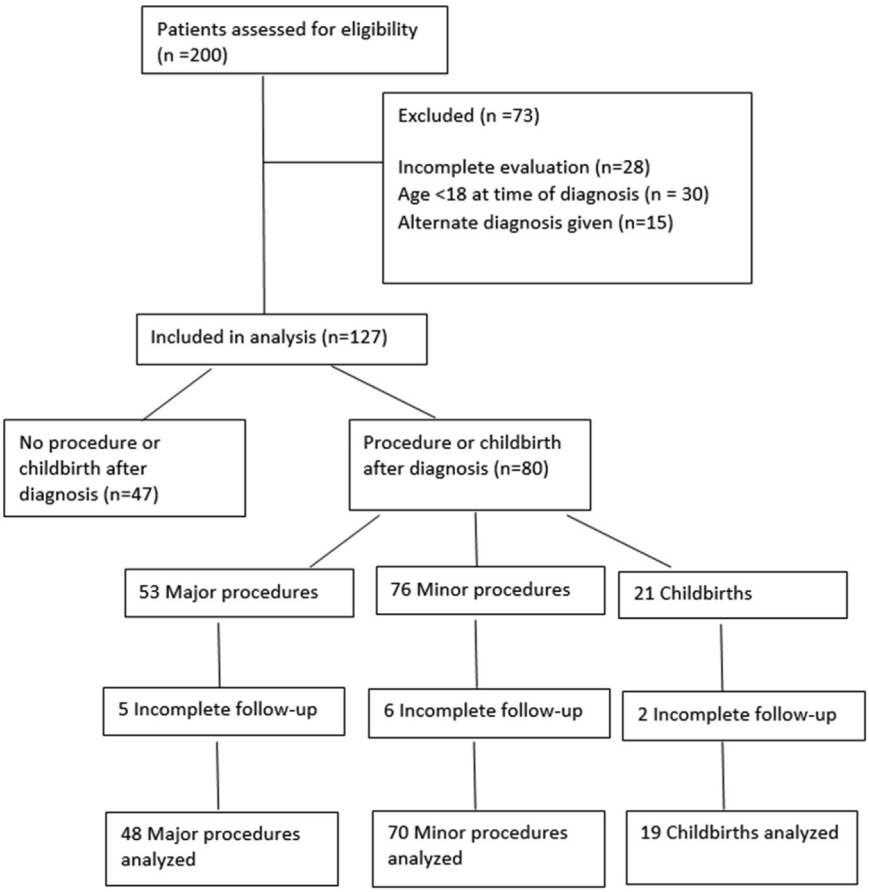

FIGURE Bleeding disorder of unknown cause patient CONSORT (Consolidated Standards of Reporting Trials) diagram.

for 57% of major procedures, 59% of minor procedures, and 67% of childbirths.

Perioperative platelet transfusion was recommended in 26% of major procedures and 9% of minor procedures in combination with other hemostatic agents. Practice patterns differed between centers, with the majority of prophylactic DDAVP and all platelet transfusions occurring at the UNC site. Within the UNC cohort, major procedures were more likely to be treated with platelet transfusion compared with minor procedures (unadjusted OR, 6.36; 95% CI, 2.20-18.37; adjusted for bleeding score, age at diagnosis, gender; OR, 6.14; 95% CI, 2.10-17.95). Bleeding score, however, was not associated with the decision to prescribe platelets in either adjusted or unadjusted models (unadjusted OR, 1.00; 95% CI, 0.89-1.12; adjusted OR, 1.01; 95% CI, 0.89-1.15).

In 8% of major procedures, 21% of minor procedures, and 14% of childbirths, no hemostatic prophylaxis was given. In one major procedure, prophylactic antifibrinolytics or other agents were not recommended due to significant vascular risk factors. In the remaining cases, a hematologist was either not consulted prior to procedure, or hemostatic recommendations from hematology were not followed. While many of these procedures were minor dermatologic or ophthalmologic procedures, this group included a total hip arthroplasty (complicated by significant bleeding) and thoracic laminectomy (no bleeding complications).

3.4 | Bleeding outcomes

Major or clinically relevant nonmajor bleeding was observed in 10.4% of major procedures (5/48), 1.4% of minor procedures (1/70), and 26% of childbirths (5/19) for which complete outcomes data were available (Table 3). Bleeding occurred in 4.1% (4/98) of procedures conducted with hemostatic prophylaxis compared with 10% (2/20) of procedures conducted without any hemostatic prophylaxis. Out of the 2 childbirths without hemostatic prophylaxis, one was complicated by bleeding. Bleeding complicated 23.5% (4/17) of childbirth where prophylaxis was provided.

Details of bleeding events are documented in Supplementary Table S2. Three of the 6 procedural bleeding events were during gynecologic procedures (2 dilations and curettages, 1 hysteroscopic cervical lysis of adhesions and endometrial sampling). The difference in proportions for procedural bleeding did not reach threshold for statistical significance (2-sided test of proportions $P = .27$, regression analysis controlled for age, bleeding score, procedure classification,

TABLE 1 Patient demographic characteristics at diagnosis.

Demographic characteristic	Total (*N* = 127)	UNC (*N* = 70)	KNG (*N* = 57)	*P* value[a]
Age at diagnosis (y)	39.9 (16.6)	42.5 (16.5)	36.6 (16.4)	.047
Bleeding score	9.7 (3.9)	9.5 (4.3)	9.9 (3.5)	.55
Sex assigned at birth				.22
Female	116 (91.3%)	62 (88.6%)	54 (94.7%)	
Male	11 (8.7%)	8 (11.4%)	3 (5.3%)	
Race[b]				
American Indian or Alaska Native		1 (1.4%)		
Asian		2 (2.9%)		
Black or African American		7 (10.0%)		
Multiracial		1 (1.4%)		
Unknown		4 (5.7%)		
White		55 (78.6%)		
Ethnicity[b]				
Hispanic, Latino/a, or Spanish origin		3 (4.3%)		
Not Hispanic, Latino/a, or Spanish origin		64 (91.4%)		
Unknown		3 (4.3%)		

KNG, Queen's University in Kingston; UNC, University of North Carolina.
[a]*P* values were computed using *t*-tests for continuous variables and chi-squared for categorical variables.
[b]Race and ethnicity were data collected only at the UNC site.

and study site *P* = .051). Bleeding score as a continuous variable was not associated with the occurrence of bleeding events (OR, 0.92; 95% CI, 0.74-1.16, adjusted for age, prophylaxis, procedure classification, and study site; adjusted OR, 0.95; 95% CI, 0.7-1.27).

3.5 | Other adverse outcomes

Two of 13 patients (15%) who received DDAVP developed hyponatremia requiring additional intervention. In one case, a patient received DDAVP prior to laparoscopic hysterectomy with a drop in serum sodium from 137 to 121 mmol/L postoperatively associated with neurologic symptoms. She was managed with hypertonic saline in the surgical intensive care unit with the resolution of symptoms. In the other case, a patient had an asymptomatic drop in sodium to 127 mmol/L that did not require intervention.

One patient who received tranexamic acid prior to hysterectomy was diagnosed with a pulmonary embolism 2 weeks after her surgery. Her postoperative course was notably complicated by vaginal vault cellulitis that required readmission to hospital. The patient was subsequently diagnosed with a prothrombin gene mutation.

No adverse reactions to platelet transfusion were described.

TABLE 2 Hemostatic prophylactic regimens in major procedures, minor procedures, and childbirth.

Hemostatic prophylaxis	Major procedures *n* (%)	Minor procedures *n* (%)	Childbirth *n* (%)
Antifibrinolytic alone	30 (57%)	45 (59%)	14 (67%)
Antifibrinolytic + DDAVP	4 (8%)	6 (8%)	0 (0%)
Antifibrinolytic + platelet transfusion	5 (9%)	4 (5%)	3 (14%)
Antifibrinolytic + DDAVP + platelet transfusion	9 (17%)	3 (4%)	0 (0%)
None	4 (8%)	16 (21%)	3 (14%)
Other	1 (2%)	2 (3%)	1 (5%)

DDAVP, desmopressin acetate.

TABLE 3 Major and clinically relevant nonmajor bleeding events in patients receiving and not receiving hemostatic prophylaxis.

Procedure type	Overall bleeding events (%)	Bleeding events (%) with hemostatic prophylaxis	Bleeding events (%) without hemostatic prophylaxis
All procedures	6/118 (5.1%)	4/98 (4.1%)	2/20 (10%)
Major procedures	5/48 (10.4%)	4/44 (9%)	1/4 (25%)
Minor procedures	1/70 (1.4%)	0/54 (0%)	1/16 (6.3%)
Childbirth	5/19 (26%)	4/17 (23.5%)	1/2 (50%)

4 | DISCUSSION

In this study, we identified and characterized the periprocedural outcomes in 137 procedures and childbirths from a retrospective cohort of 127 patients with BDUC. This study forms the largest BDUC procedural cohort to date and the first in North America to our knowledge. In our multiinstitution experience, procedural bleeding rates remain low (major bleeding = 1%; clinically relevant nonmajor bleeding = 3.1%) in patients who received hemostatic prophylaxis, with the most commonly administered prophylactic strategy being tranexamic acid monotherapy. No significant bleeding complications were seen in minor procedures treated prophylactically; among 44 major procedures with prophylaxis, 3 clinically relevant nonmajor bleeding events (6.8%) and 1 major bleeding event (2.3%) were observed. We observed over twice the proportion of bleeding events in patients who did not receive hemostatic prophylaxis compared with patients who did receive prophylaxis. While this difference did not reach statistical significance in our small sample, it is suggestive of a potential impact meriting exploration in future studies.

Postpartum hemorrhage as evaluated by estimated blood loss as well as need for acute surgical intervention or transfusion in our study was high even in patients who received hemostatic prophylaxis, and half the procedural bleeding events were in gynecologic procedures. Hemorrhage occurred in patients who received tranexamic acid alone as well as tranexamic acid combined with platelet transfusion. Retained products of conception were associated with bleeding in 3 out of 5 cases of postpartum hemorrhage. Obstetric hemorrhage is by nature multifactorial, influenced by structural and uterine factors in addition to coagulopathy. Improved management of BDUC patients during obstetric and gynecologic procedures remains an unmet need.

The results of our study are presented in comparison with previously published cohorts of BDUC patients (Table 4). We note that methodological differences in identifying and classifying BDUC patients and outcomes, as well as procedural mix, make direct comparisons challenging. The proportion of procedural bleeding in our study was similar to those reported by McDonald et al. [9] but lower than that reported by Obaji et al. [8] and Veen et al. [7]. In a study by Mehic et al. [16], 23 of 107 patients experienced postsurgical bleeding after a diagnosis of BDUC; however, it is unclear how many total surgical procedures were conducted during the study period. The majority of these procedures were classified as moderate bleeding risk and a minority of patients (20%) received prophylaxis. The high occurrence of postpartum hemorrhage in this population is consistent with findings by MacDonald et al. [9], Veen et al. [7], and Castle et al. [17], though again note that exact definitions of postpartum hemorrhage are not standardized and vary between prior studies [7,9,17]. In our combined cohort study with multiple years of data collection and standardized outcome assessment, we were able to examine bleeding events in major procedures, minor procedures, and childbirth with a larger sample size than achieved by prior studies.

Prophylactic strategies varied both by procedure type and treating institution. Heterogeneity in treatment strategies is expected as procedures occurred prior to the publication of any consensus treatment guidelines. Antifibrinolytic alone was used in the vast majority of procedures at the KNG site, while DDAVP and/or platelet transfusion was commonly utilized at UNC for major procedures. Although the number of bleeding events was low overall, we did not see an association between bleeding score measured as a continuous variable and bleeding events. Four major procedures were performed without hemostatic prophylaxis due to non-communication with the hemophilia treatment center. This finding likely reflects both broader system-wide challenges in caring for patients with bleeding disorders as well as a lack of familiarity with BDUC among proceduralists.

The impact of a prophylactic strategy on resource utilization, health care costs, and risk of adverse medication effects should be considered. Platelet transfusion in particular is a limited resource that should be used judiciously. We did not quantify health care costs in this study but do note that coordinating outpatient infusions and transferring procedures to the inpatient setting requires significant resources, and procedures are at times delayed to allow for such hemostatic planning. Two patients did develop hyponatremia as a result of DDAVP, including one who required intensive care unit management. Hyponatremia is a known risk and perioperative fluid restriction is typically recommended, however, this may be challenging to enforce in an operative setting. Further investigation into the risks of DDAVP in this patient population is warranted. While one patient who received tranexamic acid developed a postoperative pulmonary embolism, we note this patient had other mitigating factors (postoperative infection with readmission, inherited thrombophilia) and that the favorable safety profile of tranexamic acid has been established in large randomized controlled trials in childbirth [18], trauma [19], and surgery [20].

Strengths of this study include the design of the retrospective cohort. While data collection was completed prior to the publication

TABLE 4 Comparison of retrospective cohort studies in bleeding disorder of unknown cause.

All procedures			
Study	**Number of procedures**	**Proportion of bleeding events with hemostatic treatment**	**Proportion of bleeding events without hemostatic treatment**
Obaji 2016 [8]	74	8/74 (11%)	NA
MacDonald 2020 [9]	69	4/69 (5.8%)	NA
Veen 2021 [7]	53	7/29 (24%)	8/24 (33%)
Berkowitz 2024	118	4/98 (4.1%)	2/20 (10%)
Major procedures			
Study	**Number of procedures**	**Proportion of bleeding events with hemostatic treatment**	**Proportion of bleeding events without hemostatic treatment**
MacDonald 2020 [9]	16	0/16 (0%)	NA
Veen 2021 [7]	7	1/4 (25%)	0/3 (0%)
Berkowitz 2024	48	4/44 (9%)	1/4 (25%)
Childbirth			
Study	**Number of deliveries**	**Postpartum hemorrhage with hemostatic prophylaxis**	**Postpartum hemorrhage without hemostatic prophylaxis**
Obaji 2016 [8]	4	0/4 (0%)	NA
MacDonald 2020 [9]	13	3/13 (23%)	NA
Veen 2021 [7]	26	1/2 (50%)	11/24 (46%)
Castle 2022 [17]	39	13/33 (39%)	5/6 (83%)
Berkowitz 2024	19	4/17 (23.5%)	1/2 (50%)

NA, not applicable.

of ISTH SSC communication on BDUC [6], we note that the inclusion criteria align closely with the recommended laboratory evaluation. Some prior analyses have aggregated both procedures preceding and following a diagnosis of BDUC [17], and thus may demonstrate a regression to the mean bias. We avoided this pitfall by only considering bleeding events after a diagnosis of BDUC was established. Additionally, through careful chart review including assessment of outside records, we were able to capture certain procedures where the hemophilia treatment center was not involved in periprocedural planning.

This study does carry several limitations. While this study was conducted across 2 academic medical centers, periprocedural recommendations still reflect the practice patterns of a relatively small number of hematologists. All clinical and outcome data were collected via chart review. The condensed MCMDM-1 bleeding score, rather than the bleeding score currently endorsed by the ISTH-BAT, was captured clinically at the time of diagnosis at study sites and thus used for analysis. Non-White patients are not well represented, which may reflect the systemic hurdles required for such patients to be evaluated by a hematology subspecialist and receive a diagnosis of BDUC. Also of note, 28 patients were excluded from the cohort analysis given incomplete hemostatic work-up—chiefly, absence of platelet aggregation testing, which can be hard to coordinate even at subspecialty centers. As hemostatic outcomes were assessed by chart review, incomplete outcomes were noted in 13 procedures (8.7% of procedural sample). Exclusion of missing data may overestimate bleeding, as we would expect bleeding events to be more frequently documented in the medical record and communicated back to the treated hematologist as opposed to nonbleeding events.

With increasing diagnoses and recognition of BDUC, more evidence is needed to support strategies for empiric hemostatic interventions prior to procedures and deliveries. Our study lends support to the recently published communication from the ISTH SSC advocating for the use of hemostatic prophylaxis, particularly antifibrinolytics, prior to invasive procedures and highlights potential unmet needs for gynecologic and obstetric procedures [6]. While we report the largest observational cohort study to date, increasing procedural case reports of BDUC in the literature by 50%, our findings are limited by sample size and event rate. Efforts to standardize and improve registry reporting among hemophilia treatment centers may improve the quantity and quality of real-world evidence to support periprocedural treatment strategies in BDUC, as well as future prospective clinical trials.

ACKNOWLEDGMENTS

Support for this study was provided by the Foundation for Women and Girls with Blood Disorders Promoting Excellence in Women's

Health: Optimal Management of Women and Girls with Bleeding Disorders: Special Research Award. C.B. is additionally supported by a National Bleeding Disorders Foundation-Takeda Clinical Fellowship Award and received support from 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).

AUTHOR CONTRIBUTIONS

C.B., A.M., and N.S.K. contributed to the initial project conception. C.B., K.K., S.G., J.G., and P.D.J. contributed to data collection. C.B., A.M., V.M., J.G., N.S.K., and P.D.J. contributed to the planning, analysis, and interpretation of results.

RELATIONSHIP DISCLOSURE

C.B., A.M., S.G., V.M., K.K., and J.G. have no relevant disclosures. N.S.K. has acted as a consultant to Pfizer and Centessa/Apcintex and Chairs an investigator sponsored studies grants program for Novo Nordisk. P.D.J. has received research funding from Bayer and consultancy fees from Band/Guardian Therapeutics, Star/Vega Therapeutics, Roche, and Biomarin.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102572