

Emergency Department Visits in Children With Hemophilia

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Background. The pediatric emergency department (ED) management of bleeding and other complications of hemophilia constitutes an increasingly important component of hemophilia therapy. This retrospective study examined the overall ED use by children with hemophilia in a single center, with a particular aim to investigate visits related to injury or bleeding, and those related to blood stream infection in patients with a central venous catheter (CVC). **Methods.** Electronic medical records of patients with hemophilia presenting to Children's Hospital of Michigan ED were reviewed. Different categories of ED visits over a 5-year period (January 2006–December 2010) were examined. **Results.** There were 536 ED visits from 84 male patients (median age 4 years, range 0–21) with hemophilia over the 5-year period. The reasons for ED visits were: injury or bleeding (61.2%); suspected CVC-related infection (11.8%); causes unrelated to hemophilia (19.2%); and routine clotting factor

infusion (7.8%). Eighteen visits from six patients were secondary to injury or bleeding in a patient not yet diagnosed with hemophilia. An intracranial hemorrhage was detected in five visits. Overall, 5.4% of all visits represented distinct episodes of bloodstream infection. **Conclusion.** The pediatric ED is an indispensable component of the overall hemophilia care, because: (1) patients with potentially lethal problems such as ICH or CVC-related infection may present to the ED for their initial management; (2) previously undiagnosed patients with hemophilia may also present to the ED for their first bleeding episodes, initiating the diagnostic investigations; (3) the ED provides after-hours treatment service for many episodes of injury or bleeding, and also for clotting factor infusion. *Pediatr Blood Cancer* 2013;60:1188–1191.

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INTRODUCTION

The hemophilias are X-linked congenital bleeding disorders, and the two major categories are hemophilia A (factor VIII deficiency, seen in 1 in 5,000 male births) and hemophilia B (factor IX deficiency, seen 1 in 30,000 male births) [1]. Despite the fact that medical management of hemophilia is undertaken by a team of experts at specialized centers and the use of prophylactic clotting factor infusions at home, many patients with hemophilia still continue to seek medical attention for injuries or bleeding complications in the emergency department (ED). An emerging cause of ED visits among patients with hemophilia is infections related to central venous catheters (CVCs). These are used for prophylactic clotting factor infusions given at home, or immune tolerance induction therapy in patients with hemophilia who have developed neutralizing antibodies against clotting factors (inhibitors).

In this retrospective study, we examined the overall ED use by patients with hemophilia in a single center, particularly in order to examine visits related to an injury or bleeding, or a bloodstream infection in patients with CVC.

MATERIALS AND METHODS

This study was approved by the Human Investigation Committee of Wayne State University. Electronic medical records of all ED visits to Children's Hospital of Michigan were reviewed for all patients with hemophilia, aged 0–21 years, presenting over a 5-year period, between January 1st, 2006 and December 31st, 2010. Patients presenting to the ED were identified mainly through the medical records department, which provided a list of all encounters in the ED with the ICD-9 codes 286.0 and 286.1 for congenital factor VIII and factor IX deficiencies, respectively. In addition, the patients listed at our hemophilia care center were screened for ED visits during the study period.

Data collected included age at presentation, type of hemophilia, degree of severity of hemophilia, inhibitor status, and reason for presentation. Severity of hemophilia was classified as severe, moderate, or mild for factor levels <1%, 1%–5%, or 5%–25%,

respectively. A patient with inhibitor was defined as a patient with a positive inhibitor titer ≥ 0.6 Bethesda Unit/ml with Nijmegen modification when applicable, either at the time of the ED visit or in the past.

ED visits were categorized as visits related to: (1) injury or bleeding; (2) evaluation for a suspected CVC-related infection, including fever or positive blood culture in a patient with CVC; (3) general pediatric causes unrelated to hemophilia; and (4) routine clotting factor infusion. The injury or bleeding category encompassed history of trauma to a body part; fall, fight, or motor vehicle accident without referencing a specific body part; swelling or pain in a body part with a suspicion for bleeding, even when there is no history of an identifiable episode of trauma; and visible bruising or bleeding. For patients who had head CT imaging, these results were also examined for the presence of ICH, subcutaneous hematoma of the scalp, and other findings. Positive blood cultures were considered a contamination if the cultures grew a known skin contaminant [2] (e.g., *Staphylococcus epidermidis*) and both the repeat cultures before antibiotic treatment and the peripheral cultures remained negative.

RESULTS

Demographics

The medical records department identified 83 patients with ICD-9 codes for hemophilia who presented to the ED during the study period. Six of these were excluded because of erroneous coding (congenital deficiencies of factors V, VII, and XIII in three patients; combined factor V and VIII deficiency in one patient;

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plasminogen activator inhibitor-1 deficiency in one patient; and malingering in one patient). Our hemophilia treatment center list included 100 patients as of end of 2011, and we identified additional 31 patients with hemophilia that were not in the list provided by the medical records department; however, only six of these had visited the ED during the study period. Therefore, in total, there were 536 ED visits from 84 male patients (75 with hemophilia A and 9 with hemophilia B) over the 5-year period.

The median presentation age for ED visits was 4 years (range 0–21), while the mean age was 6.7 years. Racial or ethnic origin was Caucasian for 33 patients, African American for 40 patients, Hispanic for 2 and other (Middle Eastern, Asian) for 9. Eighty of the patients were followed at our institution; the other four were followed at outside centers. Five patients also had other chronic conditions: sickle cell anemia in two patients and Down syndrome, Crohn disease, and myelomeningocele in one patient each. Serologic information was available for the 79 patients followed at our center, and these patients were seronegative for Human Immunodeficiency Virus-1 (HIV-1). HIV infection was negative by history for the four patients followed at outside institutions and one patient who was more recently diagnosed. Distribution of ED visits per year was as follows: 85 (2006); 111 (2007); 108 (2008); 124 (2009); and 108 (2010).

Hemophilia Type and Severity

Among patients with hemophilia A, there were 52 patients with severe disease, 9 with moderate and 10 with mild. The disease severity was unknown in 4 patients. Among patients with hemophilia B, 3 were severely affected, 4 moderate, and 2 mild.

ED Visits in General

Whereas 26.2% (n = 22) of the patients visited the ED only once during the study period, the patient with the highest number of visits had 43 ED visits (median three visits per patient). Patients with hemophilia A constituted 86.6% (n = 464) of all ED visits whereas patients with hemophilia B constituted 13.4% (n = 72) of the visits. In visits where severity was known (98.5% of total, n = 528); severe, moderate, and mild hemophilia comprised 70.3%, 21.2%, and 8.5% of the ED visits, respectively.

The reasons for ED visits were as follows: 61.2% (n = 328) were for injury or bleeding; 11.8% (n = 63) for evaluation of a suspected CVC-related infection; 19.2% (n = 103) for pediatric causes unrelated to hemophilia; and 7.8% (n = 42) for routine clotting factor infusion for inability to infuse at home. Routine factor infusions category included 17 patients whose parents were yet in the process of learning intravenous access and infusion, and included visits either for prophylactic infusions or on demand infusions for previously diagnosed bleeding episodes (i.e., the ED visit was not for the bleeding problem).

ED Visits for Injury or Bleeding

Visits for injury or bleeding comprised the most common reason for an ED visit in hemophilic patients. These episodes were to the following body sites: extremities (n = 143); back (n = 4); abdomen (n = 10); chest (n = 5); gastrointestinal (n = 3); genitourinary (n = 10); oral (n = 30); ocular (n = 5); and facial-cranial region (n = 90). In addition, cases of headache

(without a history of cranial injury) with concern for intracranial bleeding (n = 6); CVC-related bleeding/swelling (n = 5); post-circumcision bleeding (n = 6); epistaxis (n = 4); injury to multiple sites (n = 6); and one infant who presented with lethargy and vomiting, who was subsequently discovered to have bilateral iliopsoas muscle hematoma and intracranial bleeding; were also included within this category.

Eighteen of the visits from six patients were because of a bleeding episode in patients not yet diagnosed with hemophilia. These visits were for circumcision site bleeding (n = 3), post-surgical abdominal hematoma (n = 1), extremity injury (n = 11), head injury (n = 2), and oral bleeding (n = 1). Three of these patients visited the ED for bleeding symptoms only once prior to being diagnosed with hemophilia; the other three visited the ED 2, 4, and 16 times for bleeding symptoms prior to being diagnosed with hemophilia.

Evaluation for ICH

Computerized tomographic (CT) examination of the head was undertaken in 86 of the visits from 43 patients. (One patient with moderate hemophilia B had 11 cranial CT examination requests from ED visits during the study period.) Reasons for obtaining the CT examination included either suspected or definite trauma to the facial-cranial region (n = 77) or other symptoms such as headache (n = 6), lethargy (n = 1), pallor (n = 1), and vomiting (n = 1). In six patients with head injury, the cranial CT examination was deferred because of a normal neurologic examination; none of the six were subsequently found to have ICH.

Cranial CT examinations yielded negative results in 43% (n = 37); scalp soft tissue swelling/hematoma in 39.5% (n = 34); and other results in 11.6% (n = 10) of the studies. Other results included nasal fracture; scalp defect; encephalomalacia; and arachnoid cyst. Overall, only 5.8% (n = 5) of the cranial CT examinations showed ICH. These patients had presented with head trauma (n = 3), vomiting (n = 1), and headache (n = 1). Table I summarizes the clinical presentation of cases with ICH.

Evaluation for a Suspected CVC-Related Bloodstream Infection

Sixty-three visits were for the evaluation for a suspected CVC-related bloodstream infection: either because of fever in a patient with CVC (n = 53) or because of positive results of a blood culture drawn earlier from a CVC (n = 10). Thirty-three of the blood cultures were positive; however, only 29 of these represented distinct episodes of bloodstream infections (5.4% of all visits). Two of the cultures were repeat draws after a positive culture drawn in the ED the day before, and two were skin contaminants, that included coagulase-negative *Staphylococci* from a surveillance blood culture on an asymptomatic patient and nutritionally deficient *Streptococci* from a febrile patient with symptoms suggestive of a viral upper respiratory infection. A peripheral culture that grew *Staphylococcus hominis* was also excluded based on these criteria, although the simultaneous central blood culture that grew *Serratia plymuthica* was included.

The 29 distinct episodes of bloodstream infections represented 46% of all visits for a suspected CVC-related bloodstream infection, and were from 22 febrile visits and seven recalls for a new

TABLE I. Clinical Characteristics of the Patients With Intracranial Hemorrhage

Age	Disease	Presentation	Abnormal neurologic findings	CT findings
7 months	Severe hemophilia A no inhibitors not on prophylaxis	Vomiting, concomitant bilateral iliopsoas muscle hematoma on ultrasonographic study (trauma not reported)	None	Large left temporal lobe hematoma
4 years	Severe hemophilia A no inhibitors not on prophylaxis, sickle cell anemia	Head injury, fever, vomiting, jerking of right arm, headache	Decreased strength in the right arm	Extra-axial hemorrhage along left parietal convexity
6 years	Severe hemophilia A no inhibitors receiving prophylaxis	Head injury, lethargy	Occipital contusion; altered mental status	Small right frontal parenchymal hematoma; posterior occipital subcutaneous hematoma; linear fracture of occipital bone
15 years	Severe hemophilia A past history of inhibitors receiving prophylaxis prior history of intracranial hemorrhage	Headache, photophobia	None	Subdural hemorrhage along left cerebral convexity; encephalomalacia
17 years	Severe hemophilia B no inhibitors receiving prophylaxis	Head injury, headache	None	Small extra-axial hemorrhage anterior to the left frontal lobe

positive blood culture. These episodes were from nine patients, all with severe hemophilia A (six with inhibitors). These cultures grew single gram-positive bacteria in 12 cases, single gram-negative bacteria in 10, and multiple organisms, including two with *Candida* species, in seven cases.

DISCUSSION

The ED of hospitals constitutes an indispensable component of the pediatric hemophilia care, as it serves as a *de facto* after-hours clinic for bleeding complications, injuries, and routine clotting factor infusions. A patient with undiagnosed hemophilia may first seek medical attention for bleeding in the ED, and therefore the ED visit may also be important in making a timely diagnosis for hemophilia patients. Two previous studies, one from the 1980's and the other from 1998, analyzed ED visits of hemophilia patients [3,4]. In the earlier study, 126 ED visits were noted (for bleeding or injury only) in a single center over a 10-year-period [3]. In the latter study, which included both pediatric and adult ED visits to 25 hospitals, 125 visits were noted over a 1-year-period (64.8% for bleeding episodes) [4]. Since then, many more patients are being treated with prophylactic infusions at home, which is now considered the standard of care [5]. Some patients in these early surveys were afflicted with the HIV-1 infection, which is no longer a problem for the new generations of patients with hemophilia, and none of the patients in the current study were HIV-positive [6].

The annual rate of pediatric ED visits was 107.2 per year among patients with hemophilia in the current study, that is, an ED visit every 3–4 days. Compare this high rate to a previous survey of ED use among children enrolled in Michigan's Children's Special Health Care Services (CSHCS), which revealed 148 visits from hemophilia patients between January 1998 and June 1999 in the entire state of Michigan [7]. This difference could be explained by the fact that our ED is part of a hemophilia

center, and our patient population may not be representative of patients with hemophilia presenting to a general ED.

Bleeding or injury were the most common cause of ED visits among hemophilia patients in our study, comprising 61.2% of all visits. This category was also the most common reason for ED visits among two earlier surveys of hemophilia patients [3,4]. Injury without signs of bleeding was also included in this category, as muscle, joint, or tissue bleeding is an anticipated outcome of injury in patients with hemophilia, and injuries require treatment with clotting factor infusions even in the absence of clinical symptoms.

During the study period, six previously undiagnosed patients visited the ED 18 times for injury or bleeding episodes. Although rare (~3.6 visits per year), the emergency physician should be vigilant for patients presenting with unusual bleeding episodes, and a detailed personal and family history of bleeding should be obtained in such cases. However, there may be no family history of hemophilia, either because of a lack of affected members, or because of a *de novo* mutation (approximately one-third of cases) [8]. Most undiagnosed hemophilia patients initially present to the ED, and it is not uncommon for the patient to see a doctor several times before finally being diagnosed with the hemophilia [9]. Appropriate screening tests include: complete blood count; prothrombin time; activated partial thromboplastin time (aPTT); and fibrinogen. Isolated prolongation of aPTT suggests hemophilia, and factor VIII and IX activity should be obtained in such cases in addition to testing for a circulating anticoagulant and von Willebrand disease. It is also important to realize that some patients with mild hemophilia may present with no or only minimal prolongation of the aPTT [10].

All patients suspected to have a bleeding disorder should be evaluated by a pediatric hematologist. The bleeding episode itself could provide clues to the ED physician: persistent bleeding, drop in hematocrit during the bleeding episode, bleeding where the severity is disproportionate to the trauma, or bleeding at unusual

sites are all suspicious for a bleeding disorder. Early suspicion of a bleeding disorder, and timely referral for hematologic evaluation are important in preventing ongoing musculoskeletal damage, or even a fatal outcome, from bleeding episodes in patients with hemophilia.

ICH, the most dreaded complication of hemophilia, was fortunately rare in our study: five patients, representing 0.9% of all hemophilia visits to the ED, over a 5-year period. ICH occurs in 3–10% of the hemophilia population after the neonatal period [11], and is more common among patients with severe hemophilia, those with inhibitors, or those with a history of prior ICH [12]. Prophylactic factor treatment is one of the measures that can be used to reduce the risk of post-neonatal ICH (in patients without an inhibitor) [12,13]. ICH can occur without a history of head trauma [11–13]. In two of the visits we noted, there was no history of head trauma, and all of these patients had severe hemophilia.

Cranial CT imaging is an important tool for evaluation for ICH in patients presenting with head trauma; however, it should be used judiciously as it exposes the child to cranial radiation, as for the child who had 11 cranial CT examinations [14]. Obviously, it is difficult to arrive at good guidelines for selecting patients with hemophilia and head injury who could be observed alone without obtaining a cranial CT. The emergency physician, in consultation with the hematologist, should take into account multiple factors, including the mechanism and severity of the injury; loss of consciousness after the injury; presenting symptoms; physical examination findings; and disease-associated factors such as the severity of hemophilia, presence of inhibitors, and prophylactic treatment; in order to formulate a judicious management plan. Factor infusion to correct to 100% activity level should be provided without delay [15].

CVC-related infections occur in 44% of patients with hemophilia with CVCs according to a meta-analysis (pooled incidence of 0.66 per 1000 catheter-days), and requires prompt medical attention and institution of antibiotic therapy once blood cultures have been obtained [16,17]. Evaluation for a suspected CVC-related bloodstream infection (fever or positive blood culture) constituted 11.8% of all ED visits in patients with hemophilia in the current study. We included fever in a patient with hemophilia without a CVC within general pediatric visits, because we wanted to examine the impact of CVC use in patients with hemophilia separately.

Patients with inhibitors have been noted to have a higher risk of infection [16][18], and interestingly six of the nine patients that did have positive blood cultures either had inhibitors or had a past history of inhibitors. Patients with inhibitors commonly are candidates for daily immune tolerance induction treatment or may need to receive bypassing agents (e.g., recombinant human factor VIIa) several times a day for bleeding episodes, and therefore may have to access the CVC more frequently than patients receiving factor infusions for prophylaxis or on demand treatments. Additionally, patients with inhibitors may develop bleeding around the port, which may predispose to a CVC infection [19]. In fact, the presence of an inhibitor was noted to be the strongest predictor for a CVC infection in a previous study [20]. Gram-positive bacteria,

especially *Staphylococcus aureus* or *S. epidermidis*, are the most commonly cultured organisms in CVC-related bloodstream infections of patients with hemophilia [21].

The emergency physician should note that a significant proportion (42%) of febrile visits in children with hemophilia with a CVC resulted in a significant bloodstream infection in the current study. CVC-related infections can cause serious complications (such as septic arthritis or bacterial endocarditis, etc.) [21], or prove fatal in patients with hemophilia, as reported in a patient with hemophilia A and an inhibitor who presented with *S. aureus* bacteremia [22]. Fever in a patient with hemophilia with CVC is therefore a serious symptom, and necessitates commencing empirical antimicrobial treatment as soon as possible while awaiting culture results.

In conclusion, the pediatric emergency physician is commonly challenged not only with hemorrhagic complications of hemophilia, but also with suspected CVC-related bloodstream infections in febrile patients. Although less common, undiagnosed patients with hemophilia may also present with their first hemorrhagic episode to the ED. The emergency physician therefore should be knowledgeable not only in the management of the complications of hemophilia, but also in the investigation of a suspected bleeding disorder.

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