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REVIEW

Management of acute hemorrhage in patients with hemophilia or von Willebrand disease in the emergency department

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Abstract

Patients with hemophilia or von Willebrand disease may present to the emergency department (ED) with life-threatening bleeding, as severe hemorrhage can lead to hemodynamic instability and bleeding in the central nervous system, throat, and neck. Thus, inappropriate, or delayed management could lead to serious treatment-related complications or even death, and therefore, emergency medical staffs should be well-equipped with the latest knowledge to properly and timely treat these patients. The goal of treatment in emergency settings is to achieve hemostasis by replacing clotting factor levels, prevent hemodynamic instability, and prompt initiation of further specialized treatments. In this study, we searched Medline, PubMed, Embase and Google Scholar for papers addressing hemophilia- and Von Willebrand disease (VWD)-related bleeding and factors in emergency settings to determine evidence-based approaches for managing severe hemorrhage in these patients in the ED.

Keywords

Hemophilia; von Willebrand disease; Hemorrhage; Bleeding; Emergency medicine

1. Introduction

Patients with hemophilia who experience bleeding complications are often initially managed in the emergency department (ED) [1], whereby the caregivers must understand the pathophysiology, clinical presentation and management strategies of these disorders to properly treat these patients. At ED presentations, the severity level of both hemophilia A and B can be classified into mild, moderate or severe based on the plasma levels of factor VIII or IX (Table 1) [2]. Hemophilia rarely affects females, and emergency professionals should consider hemophilia in male patients presenting with easy bruising, spontaneous bleeding (without apparent reasons) or bleeding after minimal trauma. In this paper, we reviewed the evidence-based approaches to managing acute hemorrhage in patients with hemophilia or von Willebrand disease (VWD) in the emergency department.

2. Methods

We searched Medline, PubMed, Embase and Google Scholar for papers on emergency medicine plus hemophilia- and VWD-related bleeding and factors. An experienced emergency physician and a hematologist with more than 20 years of clinical and academic practice in a university and tertiary care hospital reviewed and integrated the results of these studies based on their reported diagnosis and treatment.

3. ED Clinical Presentations

The most common ED clinical presentations for hemophilia are hemarthrosis and muscle hematoma (Table 2) [2]. Trauma is a common cause of hemophilic bleeding that can occur from 8 hours up until 1 to 5 days after the event [3, 4]. If left untreated or treatment is delayed, the blood loss can lead to hypovolemic shock and death. All severely affected patients with $<1\%$ of normal VIII or IX levels have delayed and impaired clot formation [5, 6]. The emergency clinical presentations of hemophilia A and B are practically indistinguishable.

Hemarthrosis, one of the most common complications of hemophilia, should be managed as a moderate to severe bleeding condition. It is characterized by acute joint pain, swelling and a limited range of motion. It is more common in hinged joints (*i.e.*, ankles, knees, and elbows) and less common in multiaxial joints (*i.e.*, shoulders, wrists and hips). Early diagnosis, treatment and prevention could help preserve joint functions. Muscle hematomas should be managed as a mild to moderate condition, except for those occurring in large muscles such as quadriceps and iliopsoas, as these could lead to life-threatening hemorrhages. Patients with muscle hematomas usually present to the ED with pain, decreased range of motion and nerve impingement [2]. Bleeding in large muscles, if left untreated, may result in hypovolemic shock or compromise neurovascular structures leading to compartmental syndrome and even death [5]. Inadequate treatment may lead to the formation of a pseudotumor which increases the risk of bleeding,

TABLE 1. Classification of severity for hemophilia A and B.

Severity of disease	Clotting factor level (percent of normal)	Bleeding characteristics
Mild	6–49%	Bleeding after serious injury, trauma or surgery; women may experience menorrhagia or postpartum hemorrhage
Moderate	1–5%	Bleeding after injuries
Severe	<1%	Bleeding after injuries; spontaneous bleeding, often in the joints and muscles

Created by authors. Source: National Hemophilia Foundation, Hemophilia A and Hemophilia B. hemophilia.org [2].

TABLE 2. Frequency of bleeding at different sites [2].

Site of bleeding	Approximate frequency (%)
Hemarthrosis	70–80
Muscles	10–20
Other major sites	5–10
Central nervous system	<5

making treatment even more challenging.

Life-threatening hemophiliac presentations include bleeding in the central nervous system (CNS), retroperitoneum or oropharyngeal spaces, which require immediate treatment. Intracerebral hemorrhage is the most serious complication observed in patients with hemophilia and has a high mortality rate [7]. It should be considered in any patient who presents to the ED with acute headache, progressive nausea, vomiting, seizures, decreased level of consciousness, or focal neurologic deficits. However, it should be noted that some patients may also present with clinically silent hemorrhages that are detected only after imaging. Importantly, intracranial hemorrhage can occur immediately or days to weeks post-trauma. Thus, replacement factors should be started immediately, and non-contrast head computed tomography (CT) should be arranged for triage.

Hemorrhages at the iliopsoas and retroperitoneal regions can cause a large accumulation of blood, forming a large mass that can damage the femoral nerve and persistent femoral nerve neuropathy [8]. Hematuria is common in hemophiliacs, usually mild, and requires no specific treatment. Patients with hemophilia can present with any complications related to acute or recurrent bleeding [9].

4. Diagnosis and evaluation

4.1 Laboratory investigations

Initial laboratory investigation to assess the severity of bleeding in patients includes complete blood count, activated partial thromboplastin time (aPTT), prothrombin time (PT) and factor levels [10] (Table 3). Patients with VWD may have a normal or prolonged aPTT depending on the levels of factor VIII. Type 2B VWD usually consists of normal PT and mild thrombocytopenia. Screening tests can be used to assess the quantity and function of the von Willebrand factor. In patients with hemophilia, aPTT is usually prolonged, whereas PT and platelet counts are normal. The presence of thrombocytopenia or prolonged PT suggests a different diagnosis. However, in certain patients, such as those with mild hemophilia, aPTT can be normal. Also, considering conditions such as stress may increase factor VIII levels and lead to the normalization of aPTT; thus, a normal aPTT may not completely exclude the diagnosis of hemophilia, especially in mild hemophilia B.

TABLE 3. Emergency department laboratory investigations for hemophilic patients with bleeding.

Test	VWD	Hemophilia
Platelet count	Low	Normal
Activated partial thromboplastin time (aPTT)	Normal or prolonged	Prolonged[a]
Prothrombin time (PT)	Normal	Normal

[a]*Stress may increase factor VIII levels, leading to normalization of aPTT. Thus, a normal aPTT cannot completely exclude the diagnosis of hemophilia, especially in mild hemophilia B. VWD: Von Willebrand disease.*

In cases of abnormal bleeding accompanied by prolonged aPTT or PT, mixing studies are useful first-line tools to determine the cause of the prolongation. These studies use relatively simple techniques by mixing the patient's plasma with normal plasma and determining whether the bleeding indices have normalized to investigate which clotting factor(s) is deficient [11]. This then guides further evaluation using specific, costlier and more time-consuming assays to determine the type of factor deficiency and factor activity level. Generally, a diagnosis of hemophilia A is confirmed when the factor VIII activity level is below 40% of the normal level or a pathogenic factor VIII gene mutation is found [10]. Similarly, an activity level of factor IX below 40% of the normal level or pathogenic factor IX gene mutation is required to make a diagnosis of hemophilia B. Mixing studies that fail to normalize aPTT indicate an alternative diagnosis such as acquired factor inhibitors that may have developed during pregnancy or secondary to conditions such as systemic lupus erythematosus, rheumatoid arthritis, or malignancy, or as a result of drug reactions [10]. Bleeding resulting from acquired factor inhibitors is usually severe and may constitute a medical

TABLE 4. Imaging modality according to a patient's presentation.

Conditions	Imaging modality
Headache, vomiting, seizure, head trauma, neurological deficit, decreased level of consciousness	Non-contrast brain CT
Abdominal pain with hemodynamic instability	CT abdomen with contrast
Suspected retroperitoneal bleeding	
Pains in large muscles	Muscle CT with contrast
Joint pain with reduced joint mobility (suspected hemarthrosis)	Point-of-care musculoskeletal ultrasound (POC-MSKUS)
Chest trauma with suspected hemothorax	Chest x-ray and ultrasound
Marked hematuria or renal trauma	Renal ultrasound/cystoscopy

CT: computed tomography.

emergency. The Bethesda Assay can be used to confirm the presence of factor inhibitors [12].

4.2 Imaging

The imaging modality selection should be based on a patient's presentation, history and physical findings (Table 4).

Non-contrast head CT should be performed for patients with known hemophilia or VWD and a history of headache, vomiting, seizure, head trauma, neurological deficit, or decreased level of consciousness. Contrast CT is recommended when soft tissue or retroperitoneal bleeding is suspected [13]. Point of care musculoskeletal ultrasound (POC-MSKUS) is the preferred modality for hemarthrosis if the patient has suggestive symptoms as it is noninvasive, time-saving, does not require sedation and can detect soft tissue and bony changes over time. However, it requires technical expertise. If hemothorax is suspected, the preferred imaging modality is chest x-ray, while bedside ultrasound may be used to detect minimal hemothorax. Chest CT is preferred if lung parenchymal bleeding is suspected.

5. Management of hemophilia

5.1 General principles

Initial stabilization, control of bleeding and replacement of specific factors are the main treatments for the emergency management of bleeding in hemophilic patients. The main objective is to quickly elevate clotting factor levels to achieve hemostasis. Upon patient arrival, a peripheral intravenous access should be established, and blood should be drawn for typing and screening. Specific factor concentrates are the mainstay of treatment. For patients presenting with bleeding, the bleeding site should be controlled. Transfusion of packed red blood cells for hemorrhagic shock should be started. For patients with active life-threatening bleeding, fresh frozen plasma (15 mL/kg) can be given if factor concentrates are not immediately available. The emergency physician should have a low threshold for administering factor replacement to patients with bleeding and coordinate care with the patient's hematologist. For patients with severe bleeding, especially in the head, neck and gastrointestinal tract, factor replacement should be started immediately, even before diagnostic imaging is completed. Intramuscular injections should be avoided. Tetanus vaccine can be subcutaneously administered if needed.

5.2 Special considerations for airway management

Manipulation of the airway and intubation in a hemophilic patient can cause trauma, submucosal hemorrhages, and immediate airway obstruction. Emergency physicians should perform airway management with great precautions to avoid any minor airway trauma. Endotracheal intubation in hemophilic patients should be recognized as a dangerous procedure and should be performed by the most experienced healthcare professional in airway management to minimize the number of attempts and risks of trauma and bleeding. Difficult airway carts should be ready and prepared in case needed. Awake fiberoptic intubation, video-assisted laryngoscope, or bronchoscopy can be used to avoid multiple attempts and possible airway trauma. These should be performed using endotracheal tubes with a flexible and soft distal tip should be used to prevent trauma and/or airway bleeding. Nasal intubation is contraindicated in any hemophilic patient needing intubation [14]. If a patient develops progressive tongue hematomas, prompt tracheostomy in an operative room must be considered [15]. For neck trauma and cervical hematoma, ultrasound is helpful to detect the cricothyroid membrane, and awake fiberoptic intubation can be successfully performed [15, 16].

5.3 Hemodynamic issues and vascular access

Intravenous access should be given by the most experienced personnel to avoid hematoma formation. Smaller-gauge catheters (*i.e.*, 22 gauge in adults and 24 gauge in children) should be used unless there is a need for aggressive fluid resuscitation. If peripheral access is not possible and the patient requires immediate fluid resuscitation, femoral central venous access should be tried. Central venous catheterization should be performed under ultrasound guidance, which is the standard of care and is familiar to most emergency physicians [17].

5.4 Pain management

The type of pain management in people with hemophilia should depend on the cause of the pain. Usually, pain

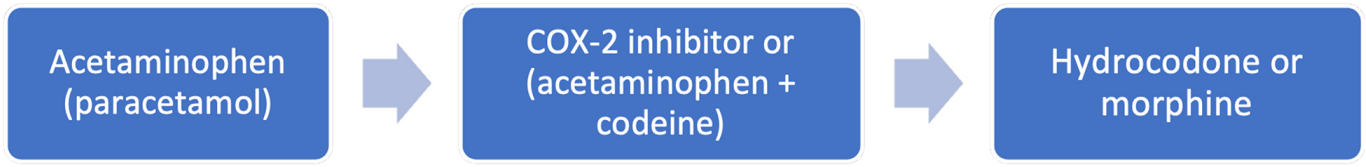

FIGURE 1. Management of pain in patients with hemophilia.

treatment should start with simple analgesic drugs and advance as required (Fig. 1). Rest, cold compression and immobilization are useful adjunctive therapies for acute joint or muscle bleeds. Intramuscular injections should be avoided. Acetaminophen (paracetamol) is the first-choice drug for pain control. Cyclooxygenase (COX)-2 inhibitors such as celecoxib or meloxicam can be used if acetaminophen is ineffective. Codeine, hydrocodone or morphine can be used if acetaminophen and COX-2 inhibitors are ineffective. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided. If the pain persists, the patient should be referred to a pain management team [18].

5.5 Factor Replacement

Factor replacement is the preferred treatment for prophylaxis and acute bleeding episodes in hemophilia patients: recombinant factor VIII for hemophilia A patients and recombinant factor IX for hemophilia B patients (Table 5). ED staff should administer patients' factors if available. Ideally, the factor should be administered within one hour of presentation. The desired factor activity is based on the location/system involved: 30–50% activity for mild bleeding, 50–100% activity for moderate to severe bleeding, and 100% activity for severe to life-threatening bleeding. The dosing of factors should be based on the desired factor activity and body weight. For hemophilia A, dosing should be based on the desired rise in factor concentration multiplied by the patient's weight (kg), multiplied by the volume of distribution, approximated at 0.5 dL/kg. For example, an average 72 kg patient with life-threatening bleeding will require a bolus of 3600 units of factor VIII to raise factor VIII activity by 100%. Subsequent doses would be given at intervals of approximately one half-life of the infused factor, approximately 8 to 12 hours for standard factor VIII products. Typically, doses can be given after every 12 hours for several days. Another approach is to give a continuous infusion of factor VIII after the initial bolus at a dose of 4 units/kg/hour [19]. This approach can be employed in the ED, where factor levels can be checked at intervals to allow consistent levels and decrease factor utilization. For hemophilia B patients, the empiric dose of factor IX for moderate to severe bleeding is generally 100–120 International Units/kg, which typically raises factor levels to approximately 80–100% of the normal level and can be estimated using the following equation: Factor IX required (International Units) = weight (kg) $\times$ 1 $\times$ (% factor activity desired). The factor should be administered intravenously over 1–2 minutes. Subsequent doses can be given at intervals of approximately one half-life of the infused product, typically after 24 hours for standard products and 54–104 hours for longer-lasting ones at half the initial doses. A continuous infusion of 6 units/kg/hours can maintain the factor activity achieved by the initial bolus [19]. This method has several advantages, such as maintaining consistent factor levels, decreasing monitoring frequency and reducing factor utilization. The duration of factor replacement therapy should be individualized based on the extent of bleeding, need for surgery, site of bleeding and response to initial therapy (Table 1). For example, factor replacement prophylaxis can be given to reduce mortality in hemophilic patients with intracranial hemorrhage or head trauma, while factor VIII therapy can be given to those with greater than 50% activity level, even with a normal head CT, for at least 3 days [7].

Hemarthrosis is a common presentation in EDs. Hemophilia A patients with hemarthroses may require approximately 25 units/kg of factor VIII to raise factor VIII levels by 50%. In comparison, hemophilia B patients require 50–60 units/kg of factor IX to raise factor IX by a similar level. Some patients with hemarthroses may require several days of therapy and bed rest to control the bleeding and reduce re-bleeding risks; hence, the need for additional doses and duration of therapy should always be individualized.

If factor VIII concentrate is not available, cryoprecipitate may be used as an alternative to treat acute hemophilia A [3]. For an adult patient, 10–12 units of cryoprecipitate can be administered every 12 hours, and for children, 1 unit per 6 kg of body weight can be administered every 12 hours. Cryoprecipitate should be given through a standard blood filter at a rate of 4–6 mL/min. As cryoprecipitate does not contain factor IX, it is not recommended for treating hemophilia B [3, 20].

Desmopressin (DDAVP) can be used to treat minor bleeding in hemophilia A patients [2]. One dose of desmopressin can last up to 6 hours [21–23]. The recommended dose is 0.3 μg/kg intravenously over 15–30 minutes or 300 mcg intranasally for adult patients weighing >50 kg [23]. Desmopressin is not a useful treatment for bleeding in patients with hemophilia B [24]. Clinical improvement, normal PTT and optimal factor VIII activity levels are good indicators of clinical response.

The levels of circulating antibodies should be checked in patients with no response despite factor VIII administration. Adverse effects of factors VIII and IX are rare and include simple allergies ranging from injection site reactions to anaphylaxis, cough, headache, diarrhea and abdominal pain but can be successfully managed in the ED [1, 2].

5.6 Acquired Hemophilia

Most patients with acquired hemophilia present with bleeding from the skin, mucosa, gastrointestinal or genitourinary tracts, while hemarthrosis is rare [25, 26]. Although a diagnosis of acquired hemophilia is not generally made in the ED, it should be considered in patients with persistent bleeding and

TABLE 5. Treatment choices for prophylaxis and acute bleeding episodes in the setting of hemophilia.

Type of hemophilia	Treatment	Dose		
Hemophilia A	Recombinant factor VIII (in unit)	Desired factor activity level based on the bleeding severity	Mild 30–50% Moderate 50–100% Severe 100%	Patient weight (kg) × (% desired factor activity) × 0.5 dL/kg
	If factor VIII concentrate is not available:			
	Cryoprecipitate	10–12 units every 12 hours		
	Desmopressin (DDAVP)	0.3 μg/kg intravenously over 15–30 minutes or 300 mcg intranasally for patients weighing >50 kg		
Hemophilia B	Recombinant factor IX	Severe bleeding, 80–100%	Patient weight × Desired factor activity level	

unexplained high aPTT. The initial treatment of acquired factor inhibitors in the ED is aimed at controlling the bleeding, for which one of the following treatments can be given: [26–31]

• Bolus injection of recombinant activated factor VIIa (rFVIIa) at a dose of 90–120 μg/kg every 2–3 hours until hemostasis is achieved.

• Bolus injection of activated prothrombin complex concentrates (aPCC), such as FEIBA (Anti-Inhibitor Coagulant Complex), at a dose of 50–100 IU/kg every 8–12 hours to a maximum of 200 IU/kg/day.

• Recombinant factor VIII and DDAVP.

The choice of treatment option depends on the severity of the bleeding and inhibitor titers. For patients with severe bleeding and a high titer of inhibitors ($\geq$ 5 Bethesda units (BU)), aPCC or rFVIIa are superior to recombinant factor VIII (which cannot be given in high enough amounts to overcome the inhibitors) [32]. The choice between rFVIIa and aPCC should depend on local expertise and cost considerations as no comparative clinical trials have been done [33]. Almost 93% of bleeding cases in hemophilic patients with alloantibody inhibitors respond to recombinant factor VIIa [30]. Commercially available recombinant human factor VII (rFVIIa) includes NovoSeven, SevenFact and aPCC such as FEIBA. rFVIIa and FEIBA are life-saving, but these products may occasionally be prothrombotic [31]. Patients with severe bleeding but a low titer of inhibitors can be treated with high doses of recombinant factor VIII concentrates [25, 34]. However, since rFVIIa and aPCC are superior, they are widely recommended as first-line therapy [26]. Due to the overall superior efficacy of rFVIIa and aPCC, DDAVP is rarely recommended but can be useful in certain patients presenting to the ED with non-life-threatening bleeding and low-titer inhibitors, in whom DDAVP can be subcutaneously administered, typically at a dose of 0.3 mcg/kg for 3–5 days to achieve hemostasis [25].

Acquired hemophilia due to inhibitors directed against clotting factors other than VIII is rare. Prothrombin inhibitors may be suspected in patients presenting to the ED with antiphospholipid syndrome and bleeding rather than thrombosis. Treatment with high-dose corticosteroids has demonstrated conflicting results in achieving hemostasis [27, 35]. The infusion of fresh frozen plasma at 15 to 20 mL/kg can be used to raise prothrombin levels and stop bleeding. Inhibitors against thrombin can cause fatal hemorrhage [36], which may necessitate plasma exchange. Generally, management using factors V, VII, IX, X, XI and XIII inhibitors depend on the bleeding severity and consists of plasma exchange in fatal hemorrhages and immunosuppressive agents such as cyclophosphamide and corticosteroids. In addition, platelet transfusion may be administered in severe hemorrhage resulting from factor V inhibitors [37]. Plasmapheresis is another second-line option [38].

6. Management of acute bleeding in VWD

The treatment of active bleeding in VWD patients necessitates stabilization, similar to other ED patients. The management approach includes treatment with von Willebrand factor (VWF) concentrates or DDAVP (Table 6), which may be accompanied by other nonspecific therapies such as antifibrinolytic agents and topical therapies [39].

6.1 VWF concentrates

VWF concentrates are indicated for major bleeding in VWD patients or bleeding into a closed space, such as intracranial or joint bleeding (Table 6). VWF concentrates are available as plasma-derived products or recombinants (rVWF). Plasma-derived products contain factor VIII, which is linked to an increased risk of thrombosis [40]. However, the treatment efficacy and risks of adverse effects are similar. The loading dose of plasma-derived products is 40–60 units/kg for major bleeding and 30–60 units/kg for minor bleeding [41]. Maintenance doses with 20–40 units/kg every 8–24 hours may be required. The duration of therapy may range from a single dose for minor bleeding to up to 14 days after significant bleeding or surgery [42]. rVWF is administered at 40–50 IU/kg for minor bleeding and 60–80 IU/kg for major bleeding [43]. Factor VIII at a dose of 50 units/kg should be used with the initial rVWF dose to raise factor VIII by 100 IU/dL [43]. Subsequent doses of rVWF can be given at 40–60 units/kg every 8–24 hours.

TABLE 6. Management of bleeding in patients with von Willebrand disease.

Treatment	Loading dose		Maintenance dose	Duration/comments
	Minor bleeding [41]	Major bleeding [41]		
Plasma-derived products	30–60 units/kg	40–60 units/kg	20–40 units/kg every 8–24 hours may be required	Single-dose for minor bleeding and for up to 14 days after significant bleeding or surgery [42]
Recombinant von Willebrand factor (rVWF)	40–50 IU/kg [43]	60–80 IU/kg [43]	Subsequent doses of rVWF can be given at 40–60 units/kg every 8 to 24 hours An infusion rate of 2–15 units/kg/hour can be used [45]. Continuous infusion is also used in patients with acquired VWD and patients with alloantibodies against infused VWF	Continuous infusion of VWF concentrates can reduce the clearance of infused products and decrease the total therapeutic dose and cost by as much as 50% [44]
Factor VIII	50 units/kg			Should be used with the initial rVWF dose to raise factor VIII by 100 IU/dL [43]

VWD: Von Willebrand disease.

Continuous infusion of VWF concentrates at a rate of 2–15 units/kg/hour can reduce the clearance of infused products, lower the total therapeutic dose and reduce cost by as much as 50% [44, 45]. Continuous infusion is also used in patients with acquired VWD and alloantibodies against infused VWF. Adverse effects include thrombosis, allergic reactions, and inhibitor development.

6.2 Desmopressin (DDAVP)

DDAVP at a recommended dose of 0.3 μg/kg can be given as an intravenous infusion over 30 min and is generally reserved for minor bleeding. For type 1 VWD, the emergency physician should enquire if patients have had desmopressin before and if they have responded to it, or review prior documentation whenever possible [1, 46]. For patients with mild bleeding, intranasal desmopressin may be adequate. The adult dose is two puffs of the 150 μg/mL nasal preparation and one puff for pediatric patients [47]. Dosing may be repeated in 12–24 hours. Tachyphylaxis, a diminished response to desmopressin after repeated dosing, may be observed from the second dose and limit the usefulness of desmopressin in patients who require prolonged resuscitation of factor levels [48, 49]. It should be noted that desmopressin-induced hyponatremia may occur. Therefore, electrolytes and fluid intake should be monitored, and 3% of sodium chloride over 48 h can be used to correct the hyponatremia. Patients with known heart disease should be monitored for symptoms of acute coronary ischemia [50].

6.3 Other therapies

Fresh frozen plasma (FFP) is only recommended for life- or limb-threatening bleeding when no factor is available [38]. Platelet transfusion may be appropriate for individuals with thrombocytopenia. Antifibrinolytic agent tranexamic acid (TXA) can be used alone or in conjunction with desmopressin or VWF replacement therapy at a dose of 15 mg/kg three times daily or orally at a typical dose of 15–25 mg/kg three times daily [51]. Adverse effects of TXA include nausea, vomiting and abdominal pain and should be avoided in patients with a history of thromboembolic disease [52]. Topical TXA can be used for skin or mucosal bleeding [53, 54]. Cryoprecipitate can be used without desmopressin or replacement VWF, at a dose of 10–12 units every 12 hours for adults and 1 unit per 6 kg of body weight every 12 hours for children [3, 20, 52].

7. Consultations and dispositions

7.1 Consultations

These depend on the response to therapy, type of bleeding and severity of the underlying disease. Disposition and follow-up should be determined in conjunction with the hematologist whenever possible. Clinicians should determine if a patient will have access to factors after discharge and instruct them to follow up with their hematologist in outpatient. Repeated assessment of factor levels should be made to determine responsiveness to the medication [55].

7.2 Hospital admission

Admission is required for all severe conditions, including patients with any one of the following conditions: circulatory shock, deep lacerations, injuries in noncompressible tissue such as mouth, neck, eye, mouth, and spinal column; major trauma, and CNS bleeding with head trauma.

8. Conclusion

The cornerstone of managing acute hemorrhage in hemophiliac patients is to immediately initiate treatment with factor concentrates, even before completing diagnostic workups, particularly in patients with serious or life-threatening hemorrhages.

Some guidelines suggest that clinical assessment should not exceed 15 minutes from the time of arrival at the ED, and the initiation of treatment for bleeding should not exceed 30 minutes. Therefore, it may be necessary to give available factor concentrates before considering specific factors to urgently stop bleeding in previously undiagnosed patients.

AUTHOR CONTRIBUTIONS

All authors participated in data collection, analysis and report writing. ZAA—conceptualized and drafted the study protocol. ZAA, WAA and WSA—screened abstracts and articles for inclusion. ZAA—assessed the screened articles' quality. ZAA—developed and performed the search strategy. ZAA, WAA and WSA—drafted the manuscript, and all authors contributed to this study revision. ZAA—takes overall responsibility for the study. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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