

# Acquired Hemophilia A: Clinical Features, Surgery and Treatment of 34 Cases, and Experience of Using Recombinant Factor VIIa

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Acquired hemophilia A is rare, but life-threatening disorder caused by autoantibody against factor VIII. As it is useful to gather more data on epidemiology, clinical pictures and therapy of it, we evaluated relevant medical findings in 34 acquired hemophiliacs from Dec 1999 to Dec 2007. Eight patients (23.5%) had low titers (<10 Bethesda Unit BU) and 26 patients (76.5%) had high titers of inhibitors (>10 BU). The mean of inhibitors was  $548.38 \pm 359.27$  SD BU. The most common hemorrhagic symptoms were hematoma 21 (33.33%), ecchymosis 16 (25.39%), hemarthrosis

8 (12.69%), hematuria 6 (9.52%), menorrhagia 4 (6.34%), compartment syndrome 3 episodes (4.76%). The eliminator therapies were recruited according to titers of inhibitor and types of bleeding and it's results were 27 efficient treatments (79.4%), 5 partial efficient treatment (14.7%) and two treatments inefficient (5.9%). Elimination therapy using steroid alone or with combination can terminate complete remission in most cases.

**Keywords:** acquired hemophilia A; factor VIII inhibitor; hemorrhage; inhibitor elimination; surgery management

## Introduction

Acquired hemophilia (AH) is a rare hemorrhagic disorder that causes severe and life-threatening situation with a high potential for significant bleeding problems and an inhibitor-related mortality rate of 7.9% to 22%.<sup>1-3</sup> It is caused by the spontaneous formation of inhibitory antibodies to coagulation factor VIII. The autoantibodies are primarily of the immunoglobulin (Ig)G class, with IgG4 heavy chains, and are directed against single epitopes on the factor VIII molecule (A2 domain, A3 domain, and most often

C2 domain, whereas alloantibodies are usually directed against both the A2 and C2 domains and sometimes against A3 domain).<sup>4,5</sup> The antibodies display type 2 inactivation kinetics. It characterized by the finding of residual factor VIII activity in plasma in the face of variable titers of antibody. It is unlike that characterizing alloantibody formation in congenital hemophilia A. The patients with inhibitor may have severe bleeding out of proportion to that expected for the concentration of plasma factor VIII activity.<sup>6</sup> Up to 80% of cases occur in older people, and although AH may be associated with a variety of concomitant disorders that were recognized at the time the autoantibody was diagnosed such as rheumatoid arthritis, peripartum, malignancy, systemic lupus erythematosus, some dermatologic disease, multi-transfusion patients, and secondary to drug reactions, up to 50% of reported cases are idiopathic as no underlying disease can be detected.<sup>2,7-9</sup> Spontaneous remission is often observed for the pregnancy and postpartum-related AH where the majority of

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inhibitors disappear spontaneously after an average time of 30 months.<sup>8</sup> Treatment options for acute hemorrhagic episodes in patients with low-titer inhibitors ( $\leq 5$  Bethesda unit [BU]) include human factor VIII concentrate and 1-deamino-8-D-arginine vasopressin (DDAVP).<sup>10</sup> The activated prothrombin complex concentrate (aPCC) products are used to reach hemostasis in patients with high-titer inhibitors ( $>10$  BU).

The clinical pictures are mainly disperse, soft tissue bleeds, and unlike congenital bleeding disorders, joint hemorrhages are rare.<sup>11</sup> The autoantibodies give refractoriness to therapy with factor VIII and factor IX concentrates. Bypassing agents such as activated recombinant factor VII (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) and aPCC (factor eight inhibitor bypassing activity [FEIBA]; Baxter AG, Vienna, Austria) have been used successfully in the management of hemorrhage in patients with AH.

The management of acute hemorrhagic episodes in patients with AH has been hampered by the lack of prospective surveys due to rare nature of disorder.<sup>2</sup> However, rarity of AH necessitates the wider collection of data from available sources to improve overall understanding and knowledge about patients and treatment. The objective of current retrospective study was to evaluate and report the experiences on clinical presentations, treatment, and surgical managements of diagnosed cases in our geographic region.

## Patients and Methods

A retrospective survey was conducted between December 1999 and December 2007 in hemophilia centre, at Imam Khomeini Hospital, Tehran. The diagnosis of AH was based on the demonstration of an isolated prolongation of the activated partial thromboplastin time (APTT), not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study), associated with a normal prothrombin time (PT), reduced factor VIII level, and formal evidence of a factor VIII inhibitor by Bethesda assay method in a patient with no previous personal or family history of bleeding. Overall, 34 patients diagnosed during the past 8 years entered the study. Some of them have been referred to our center by other hospitals in Tehran or various cities. Everyone of them had been checked for the presence of lupus anticoagulant in their blood.

From the hemorrhagic symptoms, which are cited in Table 1, bruising and petechia were not asked because of unreliability of these symptoms as reported by patients or denying milder symptom such as petechia. For bleeding resulted in hematoma focused on the abnormal hemorrhage which presented with swelling and ecchymoses findings not stopped with compression and have needed medical intervention.

On the subject of epistaxis without trauma that did not stopped with compression and needed intervention was regarded positive. Bleeding after toothbrushing was asked directly from patients that have had bloody saliva after brushing in their mouth. For hematuria, macroscopic red color urine appearance and microscopic observation of red blood cells more than normal were regarded positive. In connection with gastrointestinal (GI) bleeding, patients with melena regarded positive. Retroperitoneum bleeding was confirmed by sonography reports. About bleeding after surgery, severe bleeding that needed blood preparation transfusion was regarded positive.

Treatment options were based on management of bleeding episodes and elimination of inhibitors. The choice of treatment was based on clinical presentations and severity of hemorrhages. For severe and life-threatening bleeding rFVIIa and for minor and non-life-threatening bleeding aPCC (FEIBA) were administered.

For acute hemorrhagic episodes, clinical response was assessed as treatment efficient, partially efficient, inefficient, and patient died. For surgical procedures, patients were evaluated as no bleeding or bleeding less than normal (efficient), equivalent to normal bleeding (partial efficient), or greater than normal bleeding (inefficient). Safety was assessed by undesirable episode reporting throughout the treatment period.

## Elimination of Inhibitor

After treatment initial bleeding episodes, the following regimens were used according to inhibitor titers and clinical presentations in patients in hope of inhibitor elimination:

- Prednisolone alone (1-2 mg/kg daily).
- Prednisolone combined with cyclophosphamide (1-2 mg/kg daily)  $\pm$  immunoglobulin (1-2 g/kg over 2-5 days).
- Immunoglobulin alone.
- Two patients did not require any immunosuppressive therapy.

**Table 1.** Hemostatic and Demographic Characteristics of 34 Individuals With Acquired Hemophilia A

Patient Number	Sex/ Age	Factor VIII:C (%)	APTT (S)	Inhibitor Level (BU)	First Clinical Presentation	Underlying Disease
1	F/28	1	93	16	Hematoma and compartment syndrome	Postpartum (vaginal delivery)
2	F/22	7	79	11.3	Bleeding after dental extraction	Postpartum (vaginal delivery)
3	F/27	4	45	6.5	Postsurgical hematoma in leg and ecchymosis	Postpartum (vaginal delivery)
4	F/27	2	78	170	Menorrhagia and compartment syndrome	Postpartum (vaginal delivery)
5	F/32	8	45	2	Menorrhagia and ecchymosis	Postpartum (vaginal delivery)
6	F/31	3	96	46	Ecchymosis and knee hemarthrosis	Postpartum (vaginal delivery)
7 <sup>a</sup>	F/38	<1	98	1600	Hematoma and hemarthrosis	Postpartum (cesarean)
8	F/30	3	45	34	Hematoma	Postpartum (vaginal delivery)
9 <sup>a</sup>	F/22	<1	150	469	Hematoma	Postpartum (vaginal delivery)
10	F/20	7	67	16	Ecchymosis and hematoma	Postpartum (vaginal delivery)
11	F/13	<1	107	9	Hemarthrosis and hematoma	Idiopathic
12	F/58	2	73	12	Hematoma and hematuria	Idiopathic
13	F/62	<1	100	273	Menorrhagia and hematuria	Rheumatoid arthritis
14	F/65	<1	69	25	Ecchymosis and hematuria	Rheumatoid arthritis
15 <sup>a</sup>	F/49	<1	82	120	Ecchymosis and GI bleeding	Rheumatoid arthritis
16	F/60	<1	60	128	Hematoma and compartment syndrome	Rheumatoid arthritis
17	F/57	1	93	16	Hemarthrosis and ecchymosis	Myasthenia gravis
18	F/37	2	54	5.5	Ecchymosis and hemarthrosis	Idiopathic
19	F/25	1	93	16	Muscle hematoma and ecchymosis	Idiopathic
20	F/53	4	78	6.5	Ecchymosis and hematoma in moth	Hyperthyroid
21	F/46	8	56	7	Menorrhagia	Idiopathic
22	F/37	5	65	16	Hematoma and hematuria	Idiopathic
23	M/68	<1	87	573	Ecchymosis, hematoma, and hematuria	Drugs induced
24	M/73	<1	64	120	Ecchymosis and mouth bleeding	Bronchial asthma
25	M/60	4	89	39	Hemarthrosis and hematuria	Malignant tumor
26	M/68	<1	54	500	Hematoma, ecchymosis, and epistaxis	Bronchial asthma
27	M/65	<1	57	125	Hematoma and hematuria	Rheumatoid arthritis
28	M/55	7	67	16	Mouth bleeding	Idiopathic
29	M/63	2	49	26	Hematoma	Idiopathic
30 <sup>a</sup>	M/82	1	64	54	Hematoma	Idiopathic
31 <sup>b</sup>	M/70	1	83	25	Hematoma and hemarthrosis	Malignant tumor
32	M/53	<1	95	9	Ecchymosis and hematoma	Idiopathic
33 <sup>a,b</sup>	M/55	<1	92	1100	Hematoma and ecchymosis	Bronchial asthma
34	M/35	<1	95	6	Hematoma and hemarthrosis	Idiopathic

NOTES: APTT = activated partial thromboplastin time; BU = Bethesda unit; GI = gastrointestinal; S = second.

<sup>a</sup> The cases that underwent surgery.

<sup>b</sup> Deaths.

## Results

Among 34 individuals who diagnosed with factor VIII inhibitor included in survey, 12 were male and 22 were female, with mean age of  $55.34 \pm 17.02$  SD years. The minimum and maximum ages of them were 13 and 82 years, respectively. Of the 34 patients, 8 (23.5%) had low titers of inhibitors (<10 BU) and 26 (76.5%) had high titers of inhibitors (>10 BU). All of them had negative result for lupus anticoagulant. The median of inhibitors was 25, with a range of 2 to 1600 BU. The underlying disorders in current group included the following: 10 cases with postpartum (29.41%), 11 (32.35%) were idiopathic, 5 with rheumatoid arthritis (14.70%), 3 with

bronchial asthma (8.82%), 2 with malignancy tumors (5.88%), 1 with myasthenia gravis (2.94%), 1 secondary to drug (Phenobarbital; 2.94%), and 1 with hyperthyroidism (2.94%). Among 63 primary clinical presentations (Table 1), the most common hemorrhagic symptoms were hematoma 21 (33.33%), ecchymosis 16 (25.39%), hemarthrosis 8 (12.69%), hematuria 6 (9.52%), menorrhagia 4 (6.34%), compartment syndrome 3 episodes (4.76%), mouth bleeding 2 (3.17%), GI bleeding 1 (1.58%), 1 post-dental extraction hemorrhage (1.58%), and epistaxis 1 (1.58%). The majority of affected individuals (79.5%) had bleeding from more than 1 site. Subdural and intracerebral bleeding were not observed in any cases.

**Table 2.** The Inhibitor Elimination Therapy Program for 34 Patients With Acquired Factor VIII Inhibitor

Type of Treatment	Number of Patients	Complete Remission, n (%)	Partial Remission, n (%)	Failure, n (%)
Prednisolon (1-2 mg/kg)	8	6 (75)	1 (12.5)	1 (12.5)
Prednisolon + IVIG (1-2 g/kg over 2-5 days)	4	3 (75)	1 (25)	0 (0)
Prednisolon + cyclophosphamide (1-2 mg/kg/d)	11	8 (72.7)	2 (18.1)	1 (9.1)
Prednisolon + cyclophosphamide + IVIG	8	7 (87.5)	1 (12.5)	0 (0)
IVIG	1	1 (100)	0 (0)	0 (0)
No treatment	2	2 (100)	0 (0)	0 (0)
Total	34	27 (79.4)	5 (14.7)	2 (5.9)

NOTE: IVIG = intravenous immunoglobulin.

For elimination of inhibitor, after treatment initial bleeding episodes, eliminator therapies were recruited according to titers of inhibitor and types of hemorrhages (Table 2). The final results of induction were 27 efficient treatments (79.4%), 5 partial efficient treatment (14.7%), and 2 treatments inefficient (5.9%). The majority of patients who achieved efficient treatment received steroid alone or in combination. Most of the patients respond to immunosuppressant within 4 to 6 weeks. Six patients relapsed and experienced new bleeding episodes, which required further treatment. After 12 to 24 months follow-up, the median time needed to achieve first complete remission was 3 months (range 0.5-8 months) and the median time of treatment was 4 months (range 1-18 months).

The mortality rate was 5.9% in one case due to advanced underlying disease and the other due to uncontrolled bleeding.

### Monotherapy Using rFVIIa, NovoSeven

A 13-year-old girl (case # 11) was referred from the North of country to our hospital and admitted in emergency department. She had severe ecchymosis, severe pain, and haematoma in left leg and hemarthrosis after trauma with restriction of movement. From her medical history, it was revealed that she had experienced spontaneous bleeding during last month. She had no underlying disorder and did not consume any drug. Her hemostatic tests were as follows: antiphospholipids and lupus anticoagulant tests were negative, APTT 107s, factor VIII level < 1%, normal von Willebrand antigen (vWF:Ag), normal Ristocetin cofactor, and 9 BU of inhibitor. For controlling her bleeding, rFVIIa was administered (90 µg/kg) every 2 hours immediately for 24 hours and followed every 4 hours for 48 hours in combination with tranexamic acid (15 mg/kg). A

month later, she checked again and prednisolon (60 mg/kg) plus cyclophosphamide (1 mg/kg) were administered for 2 months to eradicate inhibitor. At last visit (16 months later), factor VIII inhibitor was <0.5 BU.

### Monotherapy Using FEIBA

A 62-year-old woman (case # 13) was referred to our hospital with severe menorrhagia and hematuria. She had no family or past history of bleeding tendency. Antiphospholipids and lupus anticoagulant tests were negative. Her hemostatic tests were as follows: APTT 100s, factor VIII level < 1%, and 273 BU of inhibitor. A single dose of FEIBA (50 U/kg) was administered once receiving tests result and establishing diagnosis. This dosage was repeated every 12 hours for 2 days that started 12 hours after primary dose. It continued once per day for 2 days. The hemostatic response to FEIBA was assessed as efficient.

### Surgery Managements

During the last 8 years, 5 individuals with AH underwent 7 operation procedures (3 urgent surgeries and 4 elective surgeries) successfully (Table 3). Hemostasis was controlled by administering coagulation bypassing agents (rFVIIa, NovoSeven, and aPCC; FEIBA). Three urgent surgeries included 1 tracheostomy (case 33) through obstruction of the air way, and 2 surgeries intervention in a 22-year-old postpartum case (case 9) due to compartment syndrome. Four elective surgeries comprised 2 cataract surgeries (case 30), 1 cesarean section (case 7), and 1 cholecystectomy (case 15). The following data were collected: type of surgical procedures performed, treatment regimen, ability to achieve hemostasis, and adverse events as thrombophilia tendency.

**Table 3.** Hemostatic Treatments Overview for Surgical Procedures Using aPCC and rFVIIa Therapy

Patients	Sex/ Age (Years)	Inhibitor Level (BU) <sup>a</sup>	Procedures Treatment	Preoperative Treatment	Intraoperative Treatment	Outcome	Postoperative	Outcome	AE
1	F/22	469	Compartment syndrome	rFVIIa	rFVIIa	Partially efficient	rFVIIa + TA	Efficient	No
2	M/55	1100	Tracheotomy	rFVIIa	rFVIIa	Efficient	rFVIIa + TA	Efficient	No
3	F/49	120	Cholecystectomy	rFVIIa	rFVIIa	Efficient	rFVIIa + TA	Efficient	No
4	F/38	1600	Cesarean section	rFVIIa	rFVIIa	Partially efficient	rFVIIa + TA	Efficient	No
5	M/82	54	Cataract	aPCC	aPCC	Efficient	aPCC	Efficient	No

NOTES: AE = adverse effect; aPCC = activated prothrombin complex concentrates; BU = Bethesda unit; rFVIIa = recombinant activated factor VII (NovoSeven); TA = tranexamic acid.

<sup>a</sup> Inhibitor level related to first time of diagnosis.

The protocol for prevention of surgical bleeding involved the administration of rFVIIa at a dose of 90 µg/kg intravenously (IV), 2 hourly for 12 doses (24 hours) and 4 hourly for 8 doses (32 hours). It was followed by 90 µg/kg 4 to 6 hourly until the bleeding resolved and wound healed (range 8 hours to 12 days treatment). Tranexamic acid was routinely administered at a dose of 15 mg/kg IV or oral route.

There were no intraoperative bleeds in any of the 7 procedures. Two patients required blood transfusion. Efficacy of rFVIIa therapy was assessed by demonstrating a shortening of the PT and by measuring the FVII:C level.

Moreover, treatment regimens were well tolerated by all patients. All of them were cautiously monitored for clinical signs of adverse effects (AEs) including thrombophilia and diffuse intravascular coagulation (DIC). No AE was observed in patients with AH who received Prednisolon alone or in combination.

## Discussion

Acquired hemophilia A may be an underestimate, given the obscurity in making the diagnosis. Many of the individuals with low-titer inhibitors may be unrecognized unless patients undergo surgery or trauma. The mortality rate of AH has been estimated to be 7.9% to 22%,<sup>12,13</sup> and most death take place in first few weeks after appearance. The age distribution of AH is usually biphasic with a minor pick between 20 and 30 years (postpartum) and a chief pick in age of 68 to 80 years. Acquired hemophilia affects both sexes equally; female dominate in the younger age group for the reason that is associated with pregnancy, whereas males composite the

greater part of affected individuals over the age of 60 years.<sup>14</sup>

Postpartum AH usually occurs in women within 3 months of deliverance, most frequently after the initial delivery and usually does not reoccur with consequent pregnancies.<sup>15</sup> Inhibitor may pass the placenta and may continue for up to 3 months in the fetus and causing bleeding problem.<sup>16</sup>

Therapeutic regimes attract attention to 3 points, the treatment of bleeding manifestation, treatment of underlying disease, and elimination of inhibitor. It has been shown that rFVIIa is clinically safe and effective in first and second line of treatments for severe bleeding episodes as Hay et al<sup>17</sup> reported high response rate (88% after 8 hours and 92% after 24 hours) in a multicenter survey.

Diverse treatment modalities have been proposed for elimination of factor VIII inhibitor. Patients may respond to corticosteroid, cyclophosphamide, or combination of the current 2 drugs. In addition, high doses of intravenous gammaglobulin have been reported as effective in a limited number of cases. Holme et al<sup>11</sup> have reported effective management of bleeds and immune therapy in 14 patients with AH and immune therapy to eradicate autoantibodies in Norway. Eight severe hemorrhages were treated with aPCC and 10 patients received corticosteroids and cyclophosphamide as immunotherapy within 6 months. Of them, 5 achieved complete remission. Nigrier et al<sup>18</sup> reported their experiences on using aPCC in 14 patients to be effective in 81% of bleeds.

Mortality rate in our study was 5.9% (2 cases with age 55 and 70 years) in group under study that was less than similar report by Collins et al.<sup>19</sup> Overall, 94.1% of patients achieved complete or partial remission.

In analysis outcome of 4 immunosuppressive treatment regimens administered to 31 patients including

prednisolone alone (n = 8, 1-2 mg/kg), prednisolone plus intravenous immunoglobulin (IVIg; n = 4, 1-2 g/kg over 2-5 days), prednisolone plus cyclophosphamide (n = 11, 1-2 mg/kg/d), and prednisolone + cyclophosphamide + IVIg (n = 8, 1-2 g/kg over 2-5 days), it was revealed that there were no differences in outcome proportion of prednisolone alone or in combination with IVIg and prednisolone equal to 75%, 75%, and 72.7%, respectively.

Two cases with low titers of inhibitors (2 and 6 BU) did not undergo treatment because low-titer inhibitors tend to disappear and remission occurs spontaneously within months. The results of current survey suggest that surgical procedures can be safely performed in patients with acquired inhibitor using administration of aPCC and rFVIIa therapy for control of hemorrhage perioperatively. Combination therapy may be beneficial in controlling bleeding episodes in cases with AH in which monotherapy is ineffective, but it should be administered under caution and close monitoring.

The gap whether more and aggressive treatment or administration of new generation of drug such as rituximab remained to be elucidated in well-designed clinical trial. Rituximab is a chimeric monoclonal antibody against cluster of differentiation (CD20). Cluster of differentiation (CD20) is widely expressed in B cells, from early pre-B cells to later in differentiation, but it is absent in plasma cells. Few minutes after rituximab infusion, more than 90% of circulating B cells are deleted. In vitro studies have demonstrated high sensitivity of memory B cells than other B cell subsets to rituximab, whereas other surveys have shown rituximab-resistant B cell population. The exact mechanism of rituximab on memory B cells and role of repopulation B cells are in discussion contentiously.<sup>20</sup>

Mainly clinical benefit of B cell depletion using rituximab is thought to be related to deletion of memory B cells. Taken together, its administration results in undetectable inhibitor titer. Indeed, the effect of rituximab-related B cell depletion on hemophiliacs with inhibitor is widely unknown. Further clinical surveys are in process to understand the effect of rituximab on B cell deletion and the immune system that needs more studies and time.

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