Clin. Lab. 2019;65:XXX-XXX

CASE REPORT

Acquired Hemophilia A: Three Cases and Review of the Literature

H. El Bayed Sakalli, W. Matrane, Z. El Hamzaoui, B. Oukkache

Ibn Rochd Hospital Center, Laboratory of Hematology, Casablanca, Morocco

SUMMARY

Background: **Acquired hemophilia A (AHA) is an autoimmune disease caused by autoantibodies against coagulation factor VIII. It is a rare and potentially fatal and often underestimated pathology, mainly in the elderly person and for whom the rapidity of the diagnosis and the initiation of the background treatment are necessary. We reported three cases diagnosed in our hospital.**

Methods and Results: **First case: A 55-year-old man, without personal or familial hemorrhagic case history. Admitted to the hospital with anemic and hemorrhagic cutaneous syndromes. His treatment included transfusion support, concentrate F VIIIa, and corticosteroids with good clinical evolution.**

Second case: An 82-year-old man, without case history, admitted with cutaneous mucosal hemorrhagic syndrome with hemorrhage of the puncture sites. Good evolution with treatment based on NovoSeven, corticosteroid, and cyclophosphamide in addition to transfusion support.

Third case: A 52-year-old man, was followed for 3 years for pemphigoid. He was hospitalized for surgical treatment of an extensive and painful hematoma of the anterior aspect of the right leg following a fall and treated with corticosteroid and NovoSeven.

Conclusions: **Although rare, AHA must be diagnosed early, and may, at any time, commit to the vital prognosis by the appearance of serious hemorrhagic complications.**

(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2019.190140)

Correspondence:
Hind El Bayed Sakalli
Laboratory of Hematology
Hospital Center Ibn Rochd
Casablanca
Morocco
Phone: +212 22 661483661
Email: h.esakalli@gmail.com

Case Report accepted March 21, 2019

KEY WORDS

acquired hemophilia A, factor VIII, inhibitor antifactor FVIII, hemorrhage

INTRODUCTION

Acquired hemophilia A is an autoimmune disease that affects the adult more readily and is caused by the appearance of autoantibodies to factor VIII [1].

The first description by Lozier et al. dates back to 1940 [2]. It is a rare disease with an annual incidence of 1 to 2 cases per million inhabitants [3,4]. Acquired inhibitors against coagulation factor VIII (FVIII), also termed acquired haemophilia A, neutralize its procoagulant function and result in severe or often life-threatening bleeding. These inhibitors are antibodies arising in individuals with no prior history of clinical bleeding. Auto-FVIII antibodies are usually polyclon-

al immunoglobulins with neutralizing capacity, and their appearance often results in serious bleedings and requires different treatments [5].
It is a diagnostic and therapeutic emergency evoked in the presence of a hematoma in the context of associated autoimmune disease [6]. We report three cases diagnosed in our hematology laboratory at the University Hospital Ibn Rushed Casablanca.

CASES REPORTS

Case report 1

A 55-year-old man, father of a single son, with a past history for chronic fundal antrum gastritis, without a personal or familial hemorrhagic history. The patient presented in February 2016 with the following symptoms: an episode of macroscopic hematuria; a hematoma of the right buttock measuring 4 x 8 mm visualized by the echography with a notion of spontaneous resorption, one month later he was admitted with anemic syndrome, and digestive hemorrhagic syndrome with melena. During his hospitalization the patient developed a hematoma of the left arm and a hemarthrosis of the right ankle, reveal mucocutaneous pallor, no petechiae, no adenopathy, no fever; the remainder of the examination was normal. Laboratory studies were performed and showed a hemoglobin at = 53 g/L; level of white blood cells at = 10,2 g/L, and platelets were normal.
The prothrombin was normal at = 77% (normal = 70 - 140%), and the aPTT was prolonged = 89 seconds (28S) relative to control.
The repeat aPTT values remained high. Following this result, mixing studies was performed with the patient plasma, but the prolonged aPTT failed to correct completely. The patient had a low plasma factor VIII level of 3% (Table 1). The plasma VIII inhibitors were also detected and the titer value was found to be 14 Bethesda units.
Other exams were done: negative autoimmune balance; scanning of the whole body without argument for a neoplasia or a deep infectious focus; HIV serology, HCV serology, HBC negative serology; oeso-gastroduodenal fibroscopy: Chronic fundal antrum gastritis with moderate intestinal metaplasia and presence of helicobacter pylori. Initially, transfusion support alone was put in place. He was started on corticosteroid treatment against factor VIII. The treatment with injections of concentrated FVIII with corticosteroid therapy 1 mg/kg/day resulted in hematoma regression and hemarthrosis resorption.

Case report 2

An 82-year-old man, without a specific pathological history, was admitted to the hospital with a cutaneous mucosal hemorrhagic syndrome with hemorrhage at the puncture sites, hemorrhagic syndrome, reevaluated mucinous pallor, and bruising at the level of the sampling sites. Laboratory studies were performed and showed anemia at 70 g/L, hyperleukocytosis, hyperlymphocytosis, and thrombopenia at 100 g/L, a myelogram was performed and showed: 42% lymphocytes on rich marrow, polyclonal with immunophenotyping. The conclusion was a lymphoproliferative syndrome. In the presence of non-regression of hemorrhage, the hemostasis tests showed: the prothrombin was normal at = 94% (normal = 70 - 140%) and the aPTT was prolonged = 106 seconds (28S) relative to control.
The repeat aPTT values remained high. Following this result, mixing studies were performed with the patient plasma, but the prolonged aPTT failed to correct completely. The patient had a low plasma factor VIII level of 7% (Table 2). Plasma VIII inhibitors were also detected and the titer value was found to be 16 Bethesda units.
Other exams were done: negative immune assessment, abdominal echography, and TAP scanner did not show abnormalities.
The patient was admitted to emergency. He received corticosteroid treatment (1.5 mg/kg/day) and cyclophosphamide (1 mg/kg/day), showing no improvement. Injection of NovoSeven with a dose of 50 µg/kg/day, and maintenance of corticosteroid therapy resulted in the disappearance of clinical signs and the standardization of his hemostasis assessment (Table 3).

Case report 3

A 52-year-old man was followed for 3years for pemphigoid, treated with corticosteroids. He was hospitalized for surgical treatment of an extensive and painful hematoma of the anterior aspect of the right leg following a fall. Laboratory studies were performed and showed a hemoglobin at = 63 g/L; level of white blood cells at = 15 g/L, and thrombopenia at = 20 g/L. The prothrombin was normal at = 87% (normal = 70 - 140%) and the aPTT was prolonged = 52 seconds (28S) relative to control.
The repeat aPTT values remained high. Following this result, mixing studies were performed with the patient plasma but the prolonged aPTT failed to correct completely, the patient had a low plasma factor VIII level of 3% (Table 4). Plasma VIII inhibitors were also detected and the titer value was found to be 17 Bethesda units, all consistent with acquired hemophilia. He was treated successfully with recombinant human factor VIII (NovoSeven) and oral corticosteroids.

DISCUSSION

We report three cases with acquired hemophilia A, whose main characteristics are in agreement with the data available in literature; however, some points are different than data published. Our three cases were men; two of them were aged less than 60 years old, the third was aged 82 years old (> 65 years old) age described in the literature as an element of poor prognosis, which is not the case of our patient who evolved well.
In our observations, FVIII > 2% and inhibitor level < 20

Table 1. Assessment of hemostasis of the patient 1.

Hemostasis tests	Results	Reference values
TP	77%	70 - 140 %
aPTT	89 S	28 +/- 5 S
Fibrinogen	3.7 g/L	2 - 4 g/L
Bleeding time	8 min	< 10 min
VWF	133%	50 - 140%
F VII	75%	70 - 140%
F VIII	3%	70 - 140%
F IX	75.4 %	50 - 140%
Mixing Test	79.1 s (Presence the CCA)	
Research the CCA anti F VIII bay method Bethesda	31%	
Titration the CCA anti F VIII	14 Bethesda units	

Table 2. Hemostasis assessment of the patient 2 before treatment.

Hemostasis test	Results	Reference values
TP	94%	70 - 140%
aPTT	106 S	28 +/- 5 S
Fibrinogen	3.9 g/L	2 - 4 g/L
Bleeding time	10 min	< 10 min
F VIII	7%	70 - 140%
F IX	109%	50 - 140%
Mixing Test	Presence the CCA	
Titration the CCA anti F VIII	16 Bethesda units	

Table 3. Hemostasis assessment of Patient 2 after treatment.

Hemostasis test	Results	Reference values
TP	89%	70 - 140%
aPTT	30 S	27 +/- 5 S
Fibrinogen	2.8 g/L	2 - 4 g/L

Table 4. Hemostasis assessment of Patient 3.

Homeostasis test	Results	Reference values
TP	87%	70 - 140%
aPTT	52 S	28 +/- 5 S
Fibrinogen	3.1 g/L	2 - 4 g/L
Bleeding time	10 min	< 10 min
F VIII	3%	70 - 140%
F IX	72%	50 - 140%
Mixing test	Presence the CCA	
Titration the CCA anti F VIII	17 Bethesda units	

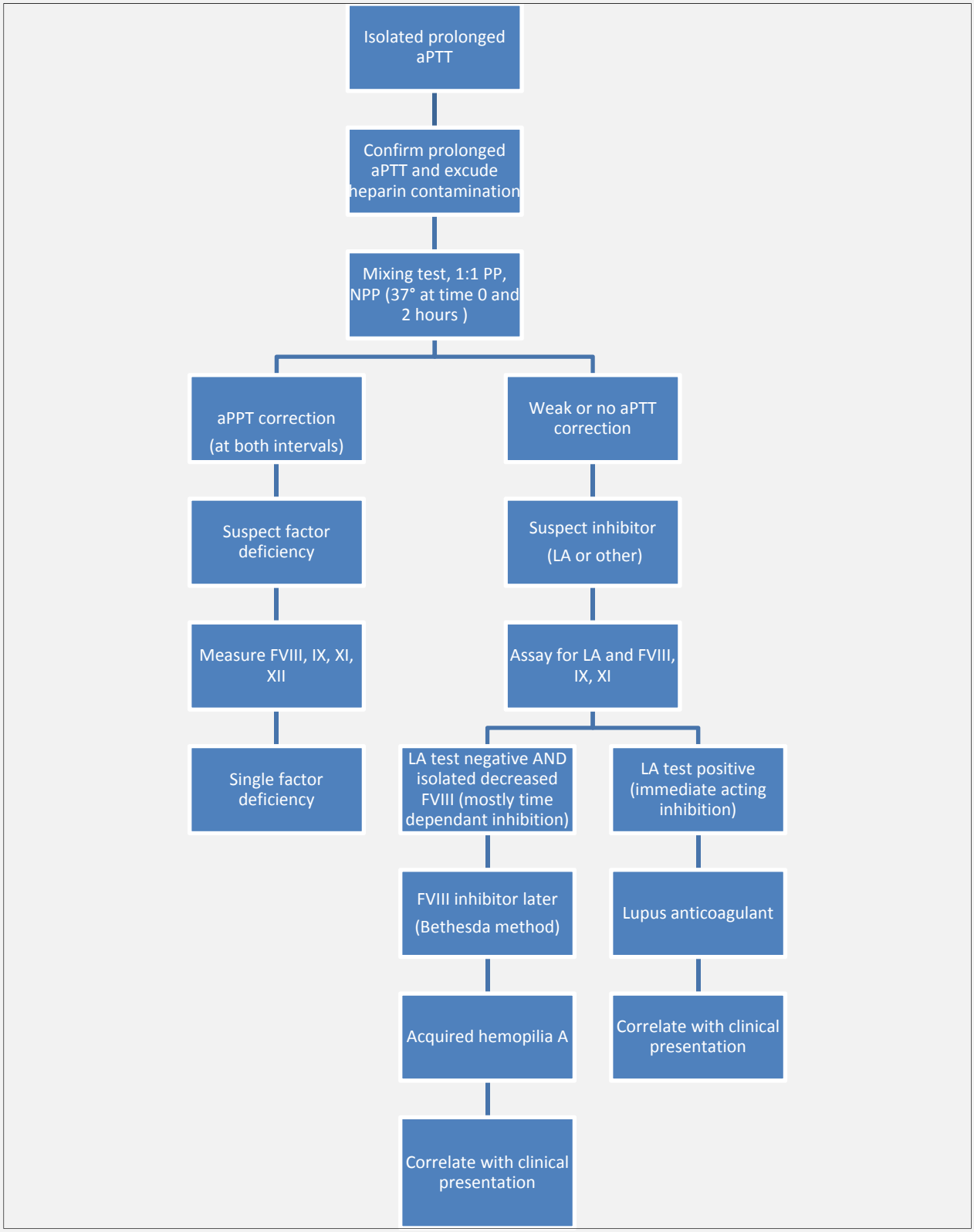

Figure 1. A diagnostic algorithm for the laboratory diagnosis of acquired hemophilia A.

Bethesda units were independent predictors of overall survival and can define a patient with better prognosis. This verdict is compatible with a study that has been done by Andreas Tiede et al. They reported the results of a German, Austrian, and Swiss registry (GTH-AH study) of acquired hemophilia and identify prognostic factors that may guide the choice of immunosuppressive treatment (IST) to eradicate the autoantibody contributing to the outcome of the syndrome [6,7].

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by immunoglobulin G antibodies that bind to specific domains on the factor (F) VIII molecule, partially or completely neutralizing its coagulant function [8]. It occurs in approximately one person per million each year and can cause life-threatening bleeding [9]. The hemorrhagic syndrome is violent, sometimes noisy, with no antecedents of coagulopathy [6]. It constitutes a therapeutic urgency that must be recognized quickly to evoke before any hemorrhagic syndrome in a field of autoimmunity [6]. The purpose of our study is to focus in this rare ailment.

The incidence of the acute hemophilia is low. A subjacent cause is noticed in 50% of the cases: post-partum, autoimmune disorders, cancer, and sometimes malignant blood disorders [2,3].

AHA is likely underdiagnosed and misdiagnosed in real-world clinical practice [10]; however, there are several types of antifactor VIII autoantibodies, some are "neutral" and do not entail any consequence, the others neutralize or inhibit the factor VIII and others hydrolyze its activity [3]. Indeed in 2008, Wootla et al. showed that some antibodies were capable of hydrolyzing VIII [3,11]. This hydrolysis is linked to the IgG fraction of the antibodies and is 4 times greater in acquired hemophilia A than in healthy persons [3,11]. Moreover, in persons carrying HAA, a proportion of hydrolysis contributes to the inactivation of factor VIII and is probably an exacerbation of a physiological catalytic immune response. In 2010, the same authors showed that some HAA autoantibodies were capable of hydrolyzing factor IX, thus activating it, allowing a potential restoration of the thrombin generation [3,13]. The typing of the heavy and light chains mainly found the subclass IgG1 and IgG4 [6,10,13].

Most often, the diagnosis is clinically evoked in the presence of unusual, spontaneous bleeding, ecchymotic layers, hypothermic hematomas mimicking an erythema nodosum [14,15]. Acquired hemophilia, as revealed by cutaneous-mucosal bleeding, is a rare disease more commonly seen in adults. In dermatology, acquired hemophilia has been reported in association with pemphigoid, in which case the prognosis is consistently very poor, with pemphigus vulgaris [15,16].

Only the exploration of the aPTT will make it possible to orientate the biologist towards the search of anti-antifactor VIII antibodies, in fact the biological diagnosis of the anti-antifactor VIII antibody is based on the following triad:

1. Prolonged activated partial thromboplastin time (aPTT) uncorrected by mixing test.
2. The decrease of factor VIII less than 30%.
3. The presence of circulating anticoagulant antibody, specific antifactor VIII titrated by the Bethesda method (titer greater than 0.4 Bethesda units) [6,10, 14].

However, other explorations are sometimes necessary during acquired hemophilia either for diagnostic purposes or in order to exclude the differential diagnoses [6,17].

Treatment of acquired hemophilia is two-pronged. The immediate priority is to control acute bleeding with bypassing agents [18,19]. The treatment includes two aspects: first, treatment of the hemorrhagic complications and, second, elimination of the autoantibodies [18]. Thus the management of hemorrhagic complications predominantly prolonged activated partial thromboplastin time (aPTT) includes prothrombin complexes, or factor VII [20]. The principal products available for the treatment of bleeding episodes are activated prothrombin complex concentrates (such as FEIBA^{R}Factor eight inhibitor by passing activity, which contains activated factors VII, IX, and X) or recombinant activated factor VII (NovoSeven) [13,19,21]. Retrospective AHA studies showed that the overall efficacy of the two bypass agents (rFVIIa and FEIBA) represented approximately 90%.The efficacy of both agents is very similar and the choice of product and dose is determined by the site and severity of the bleeding. It should be noted that even extensive cutaneous purpura does not necessarily require treatment [1,19,22].

The concentrates of factor VIII may be administered only if the antibody is said to be saturable, that is to say, a titer of less than 5 UB/mL [6,23].

However, the implementation of an immunosuppressive treatment to eliminate the autoantibody is far from being standardized, although the international recommendations propose a prednisone-immunosuppressive combination [18].

CONCLUSION

Acquired hemophilia A is a rare disease associated with hemorrhagic complications which can be serious or even fatal. Therefore, the diagnosis must be promptly evoked to palliate the hemorrhagic emergency and detect the associated disease. Once the diagnosis is made, an appropriate treatment must be put in place immediately. Good collaboration between clinicians and laboratory staff is imperative, particularly in patients without clinical signs of blood.

Authors' Contributions:

Both authors contributed to the bibliographic research and the writing of this manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Interest:
The authors declare no competing interest.

References:

1. Chaari M, Sassi M, Galea V, Gerotziafas GT, Elalamy I. [Acquired haemophilia A in prepartum: Case report and literature review]. Rev Med Interne. 2012 Jul;33(7):401-4 (PMID: 22658166).

2. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organization. Blood 2007;109:1870-7 (PMID: 17047148).

3. Le Cam-Duchez V. [Acquired A hemophilia and lymphoproliferative diseases: A literature review]. Rev Med Interne 2015; 36(12):834-9. https://www.sciencedirect.com/science/article/pii/S0248866315006402

4. Mannucci PM. Autoimmune haemophilia. Blood Transfus 2008; 6:6-7 (PMID: 18661917).

5. Elezovic I. Acquierd haemophilia syndrome: pathophysiology and therapy. Serbian archives of Medicine.2010 Jan,138 Suppl 1: 64-8 (PMID: 20229686).

6. Shetty S, Behav M, Ghosh K. Acquired hemophilia a diagnosis, etiology, clinical spectrum and treatment options .Autoimmun rev. 2011 (PMID: 21115138).

7. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/201 study. Blood 2015;125(7):1091-7 (PMID: 25525118).

8. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. J Blood Med. 2015;6:143-50 (PMID: 26056504).

9. Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: systematic review and meta-analysis. Blood Coagul Fibrinolysis. 2009 Oct;20(7):517-23 (PMID: 19644360).

10. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol. 2017 Jul;92(7):695-705 (PMID: 28470674).

11. Wootla B, Nicoletti A, Patey N, et al. Hydrolysis of coagulation factors by circulating IgG is associated with a reduced risk for chronic allograft nephropathy in renal transplanted patients. J Immunol 2008;180:8455-60 (PMID: 18523313).

12. Wootla B, Christophe OD, Mahendra A, et al. Proteolytic antibodies activate factor IX in patients with acquired hemophilia. Blood 2011;117:2257-64 (PMID: 21131590).

13. Mulliez SM, Vantilborgh A, Devereese KM. Acquired hemophilia: a case report and review of the literature. Int J Lab Hematol. 2014;36:398-407 (PMID: 24750687).

14. Graveleau J, Trossaërt M, Leux C, et al. [Acquired hemophilia A. A monocentric retrospective study of 39 patients]. Rev Med Interne 2013;34(1):4-11. https://www.sciencedirect.com/science/article/pii/S0248866312011071

15. Wendling. D, Bertrand M A. Hémarthroses et hémophilie acquise: à propos de 2 observations .Rev Rhumatisme 2003;70:1118-1121. https://www.sciencedirect.com/science/article/pii/S1169833003001406

16. Tiede A, Hofbauer CJ, Werwitzke S, et al. Anti-factor VIII IgA as a potential marker of poor prognosis in acquired hemophilia A: results from the GTH-AH 01/2010 Study. Blood. 2016;127:2289-97 (PMID: 26912467).

17. Collins P, Baudo F, Huth-Kühne A, et al. Consensus recommendations for the diagnosis and treatment of acquired haemophilia A. BMC Res Notes.2010;3:161 (PMID: 20529258).

18. Collins PW. Treatment of acquired hemophilia A. J Thromb Haemost. 2007 May;5(5):893-900 (PMID: 17461924).

19. Baudo F, Collins P, Huth-Kuhne A, et al. Management of bleeding in acquired hemophilia A: Results from the European Acquired Haemophilia (EACH2) registry. Blood. 2012;120:39-46 (PMID: 22618709).

20. Sumner MJ, Geldziler BD, Pedersen M, Seremetis S. Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. Hemophilia 2007;13:451-61S (PMID: 17880429).

21. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. J Thromb Haemost. 2012 Apr; 10(4):622-31 (PMID: 22321904).

22. Baudo F, Caimi T, de Cataldo F. Diagnosis and treatment of acquired haemophilia. Haemophilia. 2010;16:102-6 (PMID: 20536992).