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Acquired hemophilia: a critical bleeding syndrome

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A 69 year old man attended the emergency department because of severe abdominal pain of acute onset. At physical examination the patient had clinical signs of acute abdomen; he had been on prednisone for twelve months for a polymyalgia syndrome. No cutaneous or mucosal bleeding was evident. The family and personal history was not significant for a bleeding tendency. Relevant laboratory data included: Hb 11.5 g/dL, WBC $8.0 \times 10^9/L$ with normal differential count, platelets $182 \times 10^9/L$; liver and renal function tests normal; prothrombin time (PT) ratio 1.05, activated partial thromboplastin time (APTT) ratio 1.9. The abdominal ultrasound showed an image in the left iliac fossa interpreted as an aneurysm of the left iliac artery (Figure 1). At surgery an ileo-psoas hematoma was found and severe intra- and post-operative bleeding ensued. On arrival at our department Hb was 5.5 g/dL despite previous transfusion of numerous units of red blood cells and fresh-frozen plasma. Platelet count was $156 \times 10^9/L$; WBC $12.2 \times 10^9/L$ with normal differential count; PT ratio 1.29; APTT ratio 2.3; factor (FVIII) 2.5%; human and porcine antiFVIII inhibitor 63 and 3 Bethesda units (BU)/mL, respectively.

The significant clinical findings at initial presentation are the signs of acute abdomen and the APTT ratio of 1.9. An increased APTT ratio in an adult patient with a negative family and personal history for bleeding should always raise the suspicion of the presence of an inhibitor, especially when surgery is considered. The ultrasound image of the left iliac fossa in this setting could suggest the presence of a hematoma. In clinical practice FVIII inhibitors are the most frequent type of inhibitor. The laboratory investigations carried out in this patient confirmed this diagnosis.

Acquired hemophilia (AH) is a rare clinical syndrome characterized by the sudden onset of bleeding, either spontaneous or after surgery or trauma, usually severe (87% of the cases) and often fatal (8–22%).¹⁻⁴ The deple-



Figure 1. The abdominal ultrasound image of the left iliac fossa interpreted as an aneurysm of the left iliac artery.

tion of factor VIII, and much less frequently of factor IX, is mediated by specific autoantibodies, directed against functional epitopes. This neutralizes the FVIII and/or its accelerates its clearance from the plasma.⁵ The incidence of AH varies between 0.1 to 1.0 per million/population per year, although it is likely that not all affected patients are included in the published surveys.^{1,2,6,7} The median age at presentation is 65 years with equal sex distribution except in the younger group because of the cases related to pregnancy.^{1-4,8,9}

AH is commonly associated with a variety of clinical conditions: autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, asthma), solid tumours, lymphoproliferative diseases, drug hypersensitivity and pregnancy but in 50% of the cases is idiopathic^{1,3,8-12} (Table 1). Pregnancy is a frequent concomitant condition (7–21%),^{1-4,7-9} in general the inhibitor occurs in the first pregnancy¹³⁻¹⁷ and does not recur, although recurrence in the subsequent pregnancies was reported in some series.¹⁸ Five to 15% of the patients have a concomitant malignancy, three times more frequently in males than in females, without a definite relation to the tumor type although AH is more common in solid tumors than in lymphoproliferative diseases.^{3,8,19-21} Tumor specific therapy in general is not associated with the disap-

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Table 1. Clinical conditions associated with acquired FVI-II/FIX inhibitors.

Clinical conditions	Green D ¹ %	Morrison AE ³ %	Bossi P ⁸ %	Baudo F ⁹ %
Number of patients	215	65	34	96
Idiopathic	46.1	52.5	47.1	46.8
Autoimmune disorders	20.4	21.5	17.6	16.6
Drug related	3.0	5.6	2.9	0
Pregnancy and post-partum	11.0	7.3	8.9	21.0
Malignancies	13.5	5.5	14.6	9.4
Other	1.5	11.8	8.8	6.2

pearance of the inhibitor; if therapy is effective low titer inhibitors, especially in the early stages, are more likely to disappear than high titer ones.¹⁹⁻²¹

Our patient had been on steroids for one year because of a polymyalgia-syndrome; the etiology and pathogenesis are not well understood but its relevance to the appearance of the anti FVIII inhibitor is questionable.

The diagnosis of AH is suggested by the clinical picture and confirmed by the laboratory tests. Usually severe bleeding or diffuse bruising occurs either spontaneously or following minor trauma or after a procedure (positioning of an intravenous catheter, surgery, intramuscular injections). Common sites of bleeding are the skin (large ecchymoses), the mucosae (epistaxis, gingivorrhagia, metrorrhagia), and the muscles; hemarthroses are unusual.^{3,8,19-21} If the bleeding occurs in critical sites, compression problems may ensue. Retroperitoneal hemorrhages are common and, if unrecognized, can be fatal.

In our patient the space-occupying image interpreted as an aneurysm was in fact due to a hematoma of the ileo-psoas muscle. The diagnosis might have been considered if the APTT ratio had not been overlooked.

A prolonged APTT, not corrected by incubation with normal plasma, with a normal prothrombin time is the hallmark of the laboratory diagnosis. Lupus anticoagulant (LA) and heparin in the plasma must be excluded. The presence of heparin is suggested by a prolonged thrombin time with normal reptilase time. The diagnosis is confirmed by the specific factor assay and by dosage of the inhibitor.^{2,11,12} The measurement of antiporcine factor VIII inhibitor is recommended. The inhibitor titer is poorly correlated with the clinical picture;⁸ therefore it is less valuable in guiding therapy than it is in patients with congenital hemophilia and inhibitor. A laboratory diagnostic algorithm is reported in Figure 2.

The mortality is high with the majority of deaths occurring within the first weeks after presentation. The high rate of death may be related to inappropriate invasive procedures (in the Italian Registry of Acquired Hemophilia [Registro Italiano Emofilia Acquisita - RIEA], 1/3 of the events occurred after surgery) carried out to control the bleeding, to a delay in diagnosis and to inadequate replacement therapy.⁹

Bleeding was controlled by replacement therapy with porcine FVIII concentrate. On day 7, while on treatment, the patient suffered an extensive hematoma of the chest wall. The APTT ratio was 1.9. The patient was treated with FEIBA and the bleeding subsided. On day 15 hematemesis and melena secondary to a bleeding duodenal ulcer, confirmed by gastroscopy, occurred; immuno-adsorption with Sepharose protein A and replacement therapy with porcine FVIII were successful. On day 30 the patient died because of the recurrence of massive hematemesis. At autopsy the source of the bleeding was identified as a small artery.

Therapeutic options

The aims of therapy are to control the bleeding and suppress the inhibitor.

Therapy to control the bleeding

No prospective randomized trials comparing the efficacy of various agents have been reported and none of the available agents is effective in all patients. Efficient hemostasis can be achieved with a variety of methods: normalization/correction of FVIII (human plasma-derived or recombinant FVIII concentrates, porcine concentrate, desmopressin), bypassing the inhibitor [activated prothrombin complex concentrate (FEIBA), recombinant activated FVII (rFVIIa)], neutralization of the inhibitor by idiotypic anti FVIII antibodies (high dose immunoglobulins), and removal of the inhibitor by immuno-adsorption or plasmapheresis. Combined modalities may be necessary. The selection criteria for the anti-hemorrhagic therapy are site and entity of bleeding, age, underlying disorders, co-morbid states, inhibitor titer, and cross-reactivity with porcine FVIII. Life-or limb-threatening bleeding must be treated aggressively. In minor bleeding (e.g. ecchymoses) observation is justified. The bleeding-related mortality rate approaches 15%, mainly due to early hemorrhagic complications; this fact underscores the importance of early diagnosis and treatment. The therapeutic agents and the recommended doses are reported in Table 2.

For minor bleeds with low inhibitor titers (<10 BU/mL) replacement with human FVIII concentrate is the treatment of choice.^{11,12,22} In AH, the anamnestic response is rare.^{17,18,23-26} The recovery and half-life of the infused FVI-II cannot be predicted because of the variable kinetics

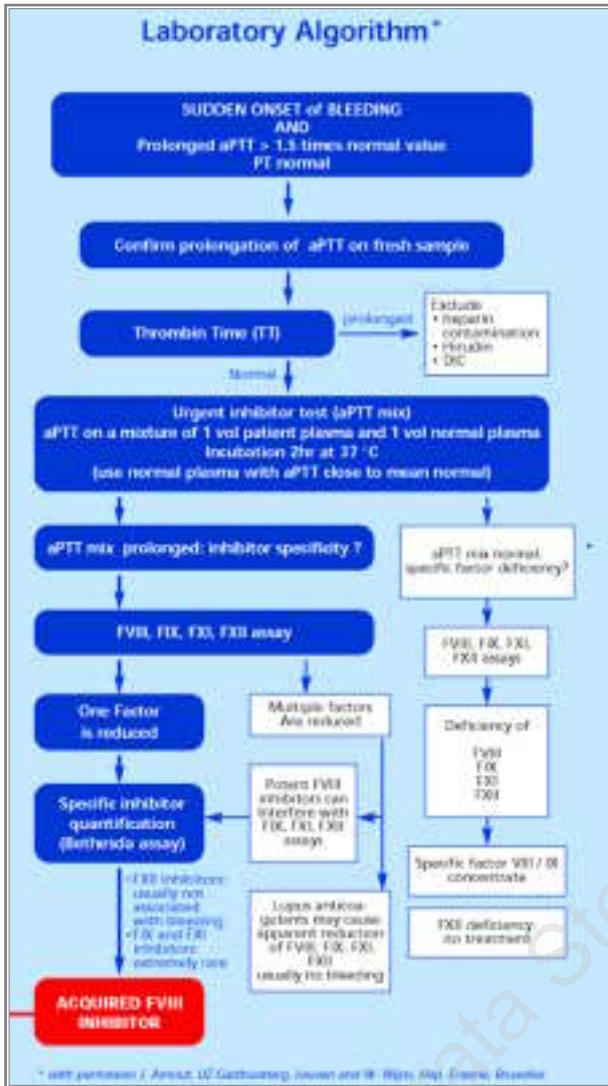


Figure 2. Laboratory algorithm for the diagnosis of FVIII inhibitor.

of FVIII.²⁵ Nevertheless its determination is clinically useful. A loading dose is given to neutralize the inhibitor and subsequent doses are then given by bolus or by continuous infusion to achieve and maintain the hemostatic level.^{25,26} Many FVIII concentrates with comparable therapeutic efficacy and safety are commercially available.

DDAVP (1-deamino-8-D-arginine) infusion results in a rapid increase of FVIII which is sufficient to treat minor bleeding.²⁷⁻²⁹ The tachyphylaxis phenomenon limits its use to 3 or 4 consecutive days. The well-known antidiuretic and vasomotor side-effects should be carefully considered in older patients.^{11,29}

High dose immunoglobulins induce complete or partial remission in 23-37% of the patients with low titer inhibitors.³⁰ Multiple courses are needed to obtain a sus-

tained response. The cost of this treatment is high.

rFVIIa has been a major advance in the treatment of bleeding in congenital hemophilia with high titer inhibitors (>10 BU/mL); however, efficacy and safety in AH are not well defined. Favorable reports in patients who failed to benefit from other treatments suggest that it could be used as first-line therapy. Disadvantages are its high cost, the lack of laboratory monitoring and its short half-life (6 hours) necessitating frequent administrations; thromboembolic complications are rare.³¹⁻³⁴

The mechanism of action of bypassing concentrate (FEIBA) is not fully understood. Efficacy is not predictable and laboratory monitoring is not satisfactory.³⁵⁻³⁷ Only clinical endpoints can be used to monitor treatment. Thromboembolic complications are possible.³⁸

FVIII autoantibodies have a low cross-reactivity with porcine FVIII; therefore a satisfactory hemostatic level may be obtained even in patients with high inhibitor titer.³⁹⁻⁴² Pyrexia, flushing, urticaria may occur during the initial infusion; severe anaphylactic reactions or thrombocytopenia are rarely observed with concentrates obtained by serial polyelectrolyte fractionation.⁴³⁻⁴⁶ The porcine FVIII concentrate is not available in Italy.

In particular clinical conditions (e.g. prior to surgery) effective hemostasis can be restored by removing the inhibitor by plasmapheresis or by immunoabsorption (staphylococcal protein A bound to sepharose or to silica matrix, sepharose-bound polyclonal sheep antihuman antibodies). Extracorporeal methods have only a temporary effect and replacement therapy with FVIII is needed immediately after the procedure. Simultaneous immunosuppression is needed because of the subsequent rebound in inhibitor titer. The need for special equipment and expertise limit its use but in the case of life-threatening hemorrhages, immunoabsorption may be lifesaving.⁴⁷⁻⁵¹

Immunosuppressive therapy

The aim of immunosuppressive therapy is to suppress of the inhibitor. Factors predicting a positive response are a low inhibitor level and a short interval between the appearance of the inhibitor and the start of therapy.^{11,12,52,53} Prednisone, cyclophosphamide, azathioprine, vincristine, and cyclosporine are all currently used as monotherapy or in combination. There are no prospective, controlled clinical trials to evaluate their efficacy. The available studies are retrospective and include a limited number of patients with different clinical conditions. On the other hand it would be difficult to carry out sufficiently powered prospective, controlled studies to evaluate the efficacy of the different therapeutic agents. Efficacy is also difficult to assess because of the possibility of spontaneous remissions (mainly in children, post partum or drug-associated cases).^{6,13} Severe

Table 2. Agents used and recommended dose in the treatment of acute bleeding in acquired hemophilia.

Agents	Initial dose	Subsequent doses
Human FVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
Porcine FVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
rFVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
DDAVP	0.3 µg/kg	0.3 µg/kg/day
High dose Ig	1 or 0.4 g/kg	1 or 0.4 g/kg for 2 or 5 consecutive days
APCC	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or c.i.
rFVIIa	90 µg/kg	90 µg/kg every 3-6 hours or 10-20 µg/kg/h by c.i.

and life-threatening hemorrhages may occur in 80-90% of patients in the course of the disease, suggesting that immunosuppressive therapy must be started as soon as the diagnosis is established.^{54,55}

Immunosuppressive treatment with steroids alone is the initial preferred treatment. In children, in post-partum women and in drug-associated cases complete disappearance of the inhibitor was reported in 33-96% of the patients.^{1,9,56,57} The patients unresponsive to steroids were treated with chemotherapeutic agents alone or combined with steroids with an overall response rate of 58-80%.^{1,9,57} The relapse rate averaged 23% but a second remission was obtained in 90% of the patients with combined therapy.^{9,56} Different strategies may be suitable for different subgroups of patients.³ A *watch and wait* approach may be appropriate for children, pregnancy-related and drug-associated cases; combined immunosuppressive therapy is indicated for idiopathic, autoimmune and malignancy-related cases. Current evidence from the literature suggests that prednisone at a dose of > 1 mg/kg per day for a minimum of three

weeks induces inhibitor disappearance in 1/3 of the patients, generally in those with low titer inhibitors, but that sustained remission after prednisone discontinuation is rare; cyclophosphamide (2 mg/kg per day) combined with prednisone and/or vincristine, azathioprine, induces complete and continuous remissions in a high percentage of cases (78-92%) provided that the therapy is continued until the inhibitor disappears completely and that it is administered at adequate doses.^{11,12,52} Previous experience in hemophiliacs emphasized the importance of carrying out the treatment according to hematologic tolerance.⁵⁸

Immune tolerance is an accepted and effective treatment in patients with congenital hemophilia and inhibitor but has rarely been applied in AH. Evidence of its effectiveness and safety was provided by the Budapest protocol (human FVIII combined with cyclophosphamide and methylprednisolone).⁵⁹ A complete and sustained remission was reported in more than 90% of the patients. Similar results were reported by the Heidelberg and Bonn groups which used a modified Malmö protocol (immunoabsorption, high doses of FVIII, cyclophosphamide and corticosteroids).^{60,61} Very recently promising results have been reported with the anti-CD20 monoclonal antibody (rituximab)^{62,63} and 2-chlorodeoxyadenosine.⁶⁴

The majority of cases of acquired hemophilia occur in general hospitals and bleeding manifestations may be life-threatening. In the presence of an unexplained often severe hemorrhage with an abnormally prolonged APTT it is important to seek immediate specialist advice. A prolonged APTT is often observed and overlooked. Because of the rarity of the disorder, the complex treatment and the potential risk of severe bleeding, these patients should be managed in the hemophilia centers or under their supervision.

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Addendum

The European Registry on Acquired Hemophilia has recently been activated on Internet: www.eachregistry.org.

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