TREATMENT OF HEMOPHILIA

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ACQUIRED HEMOPHILIA

Revised edition

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WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL

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Table of Contents

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Summary

Classical hemophilia is an inherited coagulation disorder caused by a deficiency of either factor VIII or factor IX. It is usually associated with bleeding problems from an early age, and bleeding into joints is a typical feature. Acquired hemophilia is a rare condition that is due to the production of autoantibodies, in adult life, which inactivate factor VIII. Typical clinical manifestations of the acquired form are extensive cutaneous purpura and internal hemorrhage: bleeding into the joints is not a prominent feature. Both sexes are affected and there may be identifiable underlying conditions. Diagnosis is based on the finding of a low factor VIII level associated with the presence of a time-dependent inhibitor in the plasma. Treatment of the condition involves the use of an activated prothrombin complex concentrate (e.g., FEIBA) or recombinant activated factor VII (NovoSeven) to control bleeding episodes. In addition, immunosuppression with steroids is usually effective at reducing inhibitor production and bringing about a sustained rise in the factor VIII level. The monoclonal antibody rituximab may also be used for suppression of autoantibody production.

Clinical features

The classical form of hemophilia results in a congenital bleeding tendency associated with a reduction in the factor VIII (or factor IX) level. Like colour blindness, the inheritance of hemophilia is sex-linked. Males are predominantly affected by the severe form of hemophilia, which is transmitted by carrier females who do not usually have significant bleeding problems themselves. By contrast, acquired hemophilia is typically a disorder of middle age and occurs equally in both sexes. It is due to the development of autoantibodies directed against factor VIII and the resulting reduction in factor level is associated with a significant bleeding tendency.

However, the pattern of bleeding seen in acquired hemophilia is quite distinct from that seen in the more common congenital form. Whereas bleeding into joints (hemarthrosis) is the hallmark of severe congenital hemophilia, this is unusual in acquired hemophilia where the principal manifestations are bleeding into skin (purpura) and soft tissues. Figures 1 and 2 illustrate typical examples of extensive purpura due to acquired hemophilia.

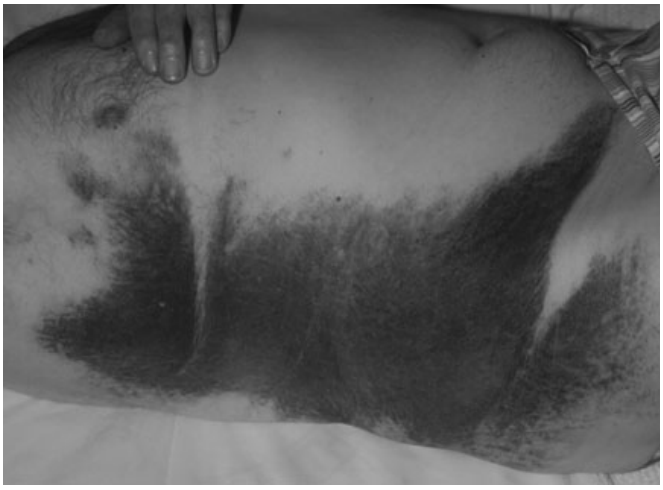

FIGURE 1. Extensive purpura over the flanks of a 62 year-old man with acquired hemophilia.

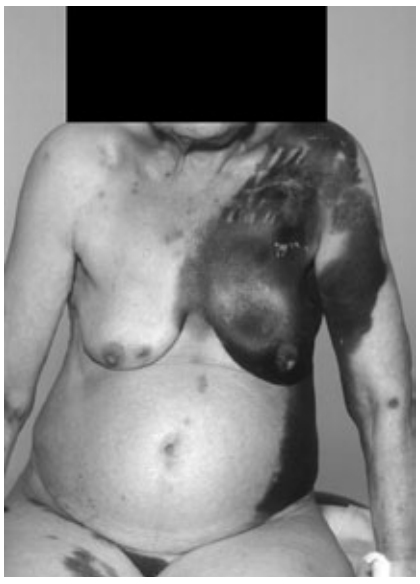

FIGURE 2. Extensive purpura over the chest and abdomen of a 78 year-old woman with acquired hemophilia.

The reason for the completely different bleeding pattern in acquired hemophilia remains unknown; there is no demonstrable impairment of platelet function. In a survey of 24 cases treated in a single centre over a 28-year period, purpura and soft tissue hemorrhage were the presenting problems in the overwhelming majority (23) of cases [1]. Bleeding into soft tissues can worsen rapidly into a compartment syndrome. Other presentations included hematuria (4 cases), gastrointestinal bleeding (2 cases), and prolonged postpartum bleeding (4 cases). This study also emphasized the potential life-threatening nature of the condition as 3 patients (11% of the cohort) died directly of bleeding complications. Other studies have demonstrated a similar clinical presentation and mortality in the range of 8-22%, with the highest risk being within the first few weeks after presentation [2].

It There is often an underlying medical condition associated with this acquired hemophilia. An association with other autoimmune conditions, malignant disease, certain drugs, and pregnancy has been recognized in various surveys. In approximately half of all cases, there is no obvious underlying cause and the condition is labelled as idiopathic.

Epidemiology

Acquired hemophilia is significantly rarer than the inherited form, affecting around 2 per million of the population [2]. As with the conventional inherited form, it appears in all ethnic groups and has a worldwide prevalence. The condition is often not recognized or mistaken for other acquired bleeding disorders such as disseminated intravascular coagulation (DIC). Case presentations within institutions and conferences can help to increase local awareness of the disorder among healthcare professionals in other disciplines.

Acquired hemophilia typically presents in middle age and beyond. It rarely arises in childhood, where the presence of an inhibitor on laboratory screening of a previously healthy child is much more likely caused by the presence of a lupus anticoagulant (antiphospholipid antibody). In an analysis of pooled data from 20 surveys encompassing 249 patients, the median age of patients reported with acquired hemophilia was 64, with a range of 8-93 years [3]. In a prospective national study from the United Kingdom, the median age at diagnosis was 78 years; only 15% were less than 65 years-old at the time of diagnosis [2]. An underlying diagnosis such as cancer, autoimmune disease, or pregnancy was identified in 40% of patients in this series.

Laboratory diagnosis

The typical findings of acquired hemophilia are a prolonged activated partial thromboplastin time (APTT) and a low factor VIII level. The thrombin and prothrombin times are normal, as are both the platelet count and function. Mixing studies can be used to demonstrate the presence of a time-dependent inhibitor of factor VIII. Details of the methodology for the screening of plasma samples for inhibitory antibodies to factor VIII and their quantification can be found in sections 28 and 34 of the WFH laboratory manual, *Diagnosis of Haemophilia and Other Bleeding Disorders* [4]. It is important to distinguish anti-factor VIII inhibitors from the more commonly encountered antiphospholipid antibodies (or "lupus anticoagulant"). In such cases, no correction of the baseline APTT will be seen immediately after mixing text plasma with normal plasma.

The antibodies in acquired hemophilia are invariably directed towards factor VIII and not factor IX. The antibodies are usually polyclonal IgG4 antibodies (rarely IgM or IgA). Most antibodies bind to the 44-kD A2 domain and/or the 72-kD C2 domain of factor VIII, and do not fix complement.

The kinetics of the interaction between factor VIII and the inactivating antibody in acquired hemophilia are unusual and differ from the usual pattern seen in congenital hemophilia complicated by inhibitor development. The profile shows a non-linear inactivation pattern (type II kinetics), with some residual factor VIII activity identifiable even after incubation at high concentrations of antibody for some time. The lack of complete inactivation of factor VIII even at high concentration is due to the fact that antibodies in acquired hemophilia may react with factor VIII to form a complex with some residual factor VIII activity. What this means in practice is that patients with acquired hemophilia may have measurable factor VIII baseline levels even in the presence of high titer inhibitory antibodies. There is therefore a poor correlation between

the measureable factor VIII level and bleeding severity in acquired hemophilia, as opposed to what is seen with congenital hemophilia. A patient with acquired hemophilia and a factor VIII level of, say, 5% can still have serious hemorrhagic episodes.

Clinical management

Acquired hemophilia is a rare disorder and the potential for significant bleeding problems is high. It is therefore recommended that such patients be managed in specialist hemophilia units, which have the necessary expertise and blood products available.

It needs to be remembered that many of the patients with this condition are elderly and frail, and may thus be particularly vulnerable to the adverse effects of treatment with steroids such as diabetes mellitus, psychosis, osteoporosis, and cataract development. There may well also be ethical issues involved in decisions regarding how far to pursue investigations for underlying pathology and getting truly informed consent, as well as the cost of treatment. At the very least, a thorough medical history, physical examination with a limited panel of blood tests, and radiological studies should be conducted to identify any underlying condition.

Recent medication use should be carefully reviewed as the development of acquired hemophilia has been reported as a very occasional adverse reaction to certain drugs. Drugs that have been implicated in published case reports include antibiotics (such as penicillin, sulphonamides and ciprofloxacin), immune-modifying drugs (interferon, fludarabine), psychotropic drugs (phenytoin, flupentixol, zuclopenthixol), and the antiplatelet agent, clopidogrel. However, this is by no means an exhaustive list and the possibility that any recent drug could have provoked the bleeding disorder must be considered. Many elderly patients may be prescribed medications that can exacerbate the bleeding tendency in acquired hemophilia through inhibition of platelet function, for e.g. anti-inflammatory drugs for osteoarthritis or aspirin or clopidogrel for cardiac disease.

Treatment of acquired hemophilia is two-pronged [5]. The immediate priority is to control acute bleeding with bypassing agents. Immunosuppression should then be used to control antibody production. Human factor VIII is likely to be very rapidly inactivated by a significant titer of inhibitory antibody and therefore of no practical use, even at high doses.

Treatment of acute bleeding

The principal products available for the treatment of bleeding episodes are activated prothrombin complex concentrates (such as FEIBA, which contains activated factors VII, IX, and X) or recombinant activated factor VII (NovoSeven). 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 do not necessarily require treatment.

FEIBA is a plasma-derived concentrate which is subjected to dry heat vapour treatment and nanofiltration. Doses in the range of 50-100 units every 8-12 hours are given by intravenous infusion, but it is important not to exceed a total of 200 units/kg within a 24-hour period as this may be associated with a risk of venous thromboembolism. Tranexamic acid should not be given together with this agent.

A recent retrospective survey of 34 patients with acquired hemophilia documented an overall complete response rate of 86%, with a typical dosage regime of 75 units/kg given every 8-12 hours [6]. The median number of doses required to control a severe bleed was 10, compared to a median of 6 doses for an episode classified as “moderate”. There is no easy way to monitor the response to FEIBA in the laboratory and clinical judgement must be relied on.

Recombinant activated factor VII is an alternative agent, which has the advantage of freedom from the risk of transmission of blood-borne viruses and other pathogens. A review of its use in acquired hemophilia reported an efficacy rate of 95% in 139 patients when used as first line therapy [7]. A typical dose regime would be 90-120 μg/kg administered every 3 hours until bleeding is controlled. Tranexamic acid may be safely used in combination with recombinant activated factor VII to inhibit fibrinolysis and thus enhance hemostasis. As with FEIBA, laboratory monitoring is not easy and response to treatment is best assessed on purely clinical grounds. Shortening of the prothrombin time (PT) will be observed after administration of recombinant activated factor VII.

There are published case reports of venous and arterial thrombosis associated with both bypassing agents, although the risk is arguably lower with recombinant activated factor VII [8,9]. It is difficult to quantify the risk in the light of such isolated case reports but caution seems warranted in the treatment of patients with documented cardiovascular risk factors. As mentioned above, tranexamic acid should not be given in conjunction with FEIBA.

Clinical trials are currently underway to determine the efficacy of recombinant porcine factor VIII in both congenital and acquired hemophilia. Its use is based on the rationale that the structure of porcine factor VIII is sufficiently similar to the human form to have some hemostatic effect, but sufficiently different to be less susceptible to inactivation by circulating antibodies.

Suppression of inhibitor formation

While hemostatic agents are administered to control actual bleeding episodes, some form of immunosuppressive treatment also needs to be given in order to suppress production of the underlying inhibitory antibody. It is recommended that immunosuppressive therapy be initiated as soon as the diagnosis of acquired hemophilia is established [2,5].

The usual treatment involves administration of prednisolone (prednisone) at a dose of 1 mg/kg combined with cyclophosphamide 50-100 mg/day orally. Azathioprine is an alternative immunosuppressive agent. Treatment should be continued for up to two months, with regular review.

Most patients will respond well to such a combination of treatment. However, relapse is not uncommon once the drugs are stopped or the dose reduced. Patients should be followed up for at least one year after treatment. Monitoring of the APTT alone is usually quite sufficient if more sophisticated laboratory facilities are not available [5]. A relapse rate of 20% was observed in the U.K. cohort after a median time of 7.5 months (range: 1 week–14 months) [2]. This is potentially problematic as it is not feasible to continue this treatment in the long-term. One option is to use periodic pulses of steroid therapy to maintain a satisfactory factor VIII level, but the use of other immunosuppressive agents should also be considered.

It has become clear in recent years that rituximab may be a valuable agent in managing acquired hemophilia [10]. This anti-CD20 monoclonal antibody is primarily used in the management of lymphoma because of its affinity for B lymphocytes. However, it has been successfully applied in the management of various autoimmune conditions, including autoimmune thrombocytopenia.

The usual treatment regime involves four separate intravenous infusions of 375 mg/m² each, administered at weekly intervals. It is generally well tolerated and a clinical response is typically seen within a week of the first infusion, with a rise in factor VIII level and a corresponding fall in inhibitor titer. However, rituximab is not licensed by any of the major regulatory authorities for the treatment of acquired hemophilia and its off-label use to treat this condition is likely to need prior approval in many institutions. There is now general consensus that the use of rituximab should be considered in cases where patients prove resistant to first line therapy or in patients in whom steroids and/or cytotoxics are best avoided. Some groups now take the view that the use of rituximab should also be considered as initial therapy in cases where the initial antibody titer is high.

A course of rituximab is likely to prove much cheaper than extended treatment with bypassing agents. A significant rebound with high factor VIII levels has been seen in some patients who have received immunosuppression. For this reason, international guidelines recommend that consideration be given to thromboprophylactic measures in vulnerable immobile patients [5].

Mycophenolate is another immunosuppressive agent that has been recently reported to be both effective and well tolerated in a small number of patients with acquired hemophilia, in whom other treatments do not work. [11]. Its use should be regarded as experimental for the time-being and considered only in patients who do not respond to conventional treatment.

Cyclosporin has also been used in several cases [12], and appears effective particularly when systemic lupus erythematosus is the underlying disorder. Long-term treatment will require appropriate monitoring of plasma levels in order to minimize toxicity. Cyclosporin is contraindicated in renal failure.

Modern guidelines no longer recommend infusions of immunoglobulin or DDAVP as treatment options [5]. A meta-analysis of 249 cases showed a complete remission rate of 74% after a median follow-up of 12 months [3]. The inhibitor-related mortality rate was 11%. Poor prognostic features identified in the review were: age at diagnosis (<65 better than ≥ 65 years; achievement of a complete remission (yes better than no); nature of underlying disease (malignant disease worse than others).

Postpartum acquired hemophilia

This category deserves special mention as it has some distinct features. Postpartum development of acquired hemophilia is a rare but serious complication of pregnancy. The bleeding tendency is often severe and often requires immediate treatment. However, the prognosis is good: in a review of 51 cases the overall outcome was favourable, with 97% survival at two years [13].

Three deaths due to bleeding occurred amongst these patients at 1, 5, and 36 months. This survey showed the highest risk applied after first pregnancy. The median age of the women was 28 years and the average onset of symptoms was two months after delivery. Persistent vaginal bleeding was the most common symptom, reported in 17 of the 51 cases. The antibody titer is often high in postpartum hemophilia and the median inhibitor titer in this series was 20 Bethesda units (BU). The probability of complete remission (CR=absence of the inhibitor and normalization of factor VIII activity) was almost 100% at 30 months.

It seems that all postpartum inhibitors will eventually disappear spontaneously over a period of months. Giving a course of immunosuppression hastens recovery by a few months but does not affect the overall response rate. The median time to achieve complete remission for patients who received no treatment was 16 months, compared with 12 months with steroids alone and 8 months with immunosuppression ± steroids. The physician has to decide in individual cases whether the possible beneficial effect of immunosuppressive therapy may outweigh the small but definite risk of this treatment. In view of the length of time it takes for the inhibitor to disappear, women should be advised to use some form of contraception until remission is achieved.

The limited data available suggest that recurrence of the inhibitor during subsequent pregnancies is possible but by no means inevitable. A recurrence rate of 0/11 pregnancies was reported in an early international survey [14]. Data from the Italian registry of acquired hemophilia showed similar results, with a recurrence rate of 0/4 [15]. The only study to document any cases of recurrence was a survey of centres in North America [16]. Three of 14 women with postpartum acquired hemophilia were documented as having had 6 subsequent pregnancies. There was an anamnestic response during 4 of these and no recurrence in the other 2.

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Glossary

Activated partial thromboplastin time (APPT): A test that measures blood clotting ability.Taken together with a normal prothrombin time, prolonged APPT is the most useful screening test for detecting deficiencies of factors VIII, IX, XI, and XII.

Activated prothrombin complex concentrate (APCC): Plasma-derived concentrate that contains many activated clotting factors. These activated clotting factors can bypass certain stages in the coagulation process and are used to treat people with factor VIII or factor IX inhibitors.

Anamnestic response: An immune system mechanism in which the memory of a previous encounter with a foreign substance triggers the formation of antibodies. The rapid increase in inhibitor titer levels as a result of an infusion with clotting factor is one example.

Antibody: A protein produced by the immune system that attacks foreign substances in the body.

Autoantibody: An antibody that attacks a person's own healthy tissue.

Bethesda units (BU): A measurement for the level of an inhibitor in the blood. The BU level indicates the potency of the inhibitor and can be used to determine the effectiveness of factor infusions.

Compartment syndrome: A condition in which increased pressure (caused, for example, from bleeding) in an enclosed area of the body restricts the circulation and can damage nerves, blood vessels, and tissues.

Congenital: Present at birth. It refers to traits or conditions that are inherited or occur during gestation up to the moment of birth.

Cutaneous: Relating to the skin.

Half-life: The time is takes for infused factor to lose half of its potency.

Hematuria: Blood in the urine caused by bleeding in the kidneys or bladder.

Hemorrhage: A general term for bleeding, either internally or on the surface, with significant blood loss. It may be brought on by injury to blood vessels or by a deficiency of certain necessary blood elements such as factor proteins or platelets.

Hemarthrosis: Bleeding into a joint cavity, such as the shoulder, elbow, hip, knee, or ankle.

Idiopathic: Occurring without a known cause.

Inhibitor: Antibodies made by the body to fight off things it sees as foreign which prevent, or inhibit, the functioning of a substance, such as a blood factor protein.

Porcine factor VIII: Factor VIII concentrate made from the blood of pigs, mainly used to treat people with factor VIII inhibitors.

Postpartum: After childbirth.

Prothrombin time (PT): A test that measures blood clotting ability. Prolonged PT may be an indicator of anticoagulants or deficiencies in factors I (fibrinogen), II (prothrombin), V, VII, and X.

Purpura: A condition characterized by bleeding into the skin.

Recombinant: The process of manufacturing proteins using genetic engineering technology. Recombinant proteins are synthetic copies of proteins found in human blood plasma.

Titer: The standard measure of the strength or concentration of a component per volume of a solution.