A mong the autoimmune diseases that affect human blood, hemolytic anemia and autoimmune thrombocytopenia are the most frequent and the best known from a diagnostic and therapeutic point of view. More seldom, autoantibodies may develop against components of the hemostasis system. Some of them neutralize proteins involved in the regulation of thrombus formation, causing acquired thrombotic tendencies due to autoantibodies inactivating naturally occurring anticoagulants such as protein C and protein S, or the von Willebrand factor cleaving protease ADAMTS13. On the other hand, autoantibodies directed against procoagulant factors cause a bleeding tendency, such as acquired hemophilia A due to the development of anti-factor VIII (FVIII) autoantibodies (autoantibodies against procoagulant factors other than FVIII are rare).

Acquired hemophilia has a yearly incidence of no more than one case per million in the general population, and affects not only patients with pre-existing autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, myasthenia, Sjögren syndrome, hyperthyroidism and others) but also (and more frequently) previously healthy people. Typically, there are two peaks of age of onset of acquired hemophilia: in the young adult, mainly in women who develop this condition in the post-partum period; and in the elderly, usually with no underlying disease. Acquired hemophilia is much more clinically severe than congenital hemophilia, and is more difficult to diagnose, also because cases are seen in an array of clinical settings that are not usually equipped to tackle them. Even the specialized center, however, sees a very limited number of cases, so that it is difficult to acquire a truly wide experience in acquired hemophilia. It is not surprising, therefore, that nine experts from three continents chose to put together their experiences in an article meant to provide consensus recommendations on the diagnosis and treatment of acquired hemophilia. Their recommendations are clear and concise, and our only major disagreement regards the writing of a similar manuscript for non-specialist physicians. We disagree, because the only useful advice that can be given to them is to refer the patient immediately to the closest hematology center. With no major disagreement with Huth-Hühne et al., we chose to compare their recommendations for the treatment of bleeding episodes and eradication of the autoantibodies with those made very recently by Franchini and Lippi in a “How I Treat” article in Blood.

Treatment of bleeding in acquired hemophilia

Both the articles recommend bypassing agents as first-line therapy, and both list recombinant activated factor VII (rFVIIa) and factor VIII inhibitor bypassing activity (FEIBA) as the products of choice. The recommended dosages and schedules of administration are very similar: bolus injections of rFVIIa, 90 μg/kg every 2-3 hours (Franchini and Lippi mention the possible usage of dosages up to 120 μg/kg), and 50-100 μg/kg FEIBA every 8 to 12 hours. (Huth-Kühne et al recommend not exceeding a maximum daily dosage of 200 IU/kg). On the whole, it would appear that both agents are able to control as many as 80-90% of bleeding episodes (spontaneous and post-traumatic), even though there is no face-to-face comparison. The recommended bolus dosages are similar, even though the authors’ choice is mainly transferred from the experience gained with congenital hemophilia complicated by FVIII inhibitors (alloantibodies). In the latter, the current prevailing regimen, supported by randomized trials, is to give a single large dose (270 μg/kg) rather than repeated smaller doses. It would be of interest to use this high-dosage bolus regimen also in acquired hemophilia, even though in these severe patients, who are almost always admitted to hospital, the use of a single dose is not as critically convenient as it is for home self-treatment in congenital hemophilia. The international group mentions the possibility of using sequentially both rFVIIa and FEIBA, but the experience gained in congenital hemophilia with this combination is still too small to postulate its use in acquired hemophilia. According to the reports in the literature, there is little evidence in favor of either product over the other, but Franchini and Lippi declare their preference for rFVIIa for a higher perceived viral safety. Both products are indeed convincingly safe, but rFVIIa does not cause the anamnestic response of anti-FVIII, sometimes observed after FEIBA that contains some FVIII. Lack of an anamnestic response is not so critical in acquired hemophilia as it is in congenital disease, because in the latter a rise in inhibitor titer may render difficult or delay the start of eradication through immune tolerance. Finally, both the articles state that the risk of thrombotic complications, owing to the hypercoagulable state induced by both rFVIIa and
FEIBA, is greater in acquired hemophilia than in congenital hemophilia, due to the older age of the patients and the thrombotic tendency often associated with the underlying clinical conditions.

Both the articles are also proposing, but with lower priority, methods of treatment that increase FVIII to levels capable of overcoming the inactivation exerted by the autoantibody, and both discuss the role of FVIII containing concentrates. This treatment is recommend- ed only when the antibody level is low, and Franchini and Lippi set the threshold at 5 Bethesda units. Both the articles recommend a loading dose of FVIII, tailored upon the antibody titer and meant to neutralize it, followed by additional doses meant to increase plasma FVIII to the levels necessary to handle any bleeding episode. In the context of low-titer antibodies, Franchini and Lippi are more enthusiastic than Huth-Kühne et al. on the use of desmopressin, given at the standard dose of 0.3 µg/kg for 3–5 days.

We agree with their favorable experience in a few selected cases.

**Inhibitor eradications**

Both the articles state that attempts to eradicate the inhibitor should be aggressively pursued, owing to the severity of bleeding episodes and the costs and risks associated with the forementioned treatments. Franchini and Lippi point out very appropriately that the first attempt to attain this goal is the cure of the associated condition or disease, that would lead to the disappearance of the inhibitor. This approach is not easily applicable in the absence of an underlying condition or disease, as in the elderly, but is typically applicable in the post-partum period. Even though it may take several weeks after delivery for the inhibitor to disappear, a conservative approach based upon the actual and prompt treatment of bleeding is warranted in these women, and any attempt to eradicate the antibody with immunosuppressive agents should be delayed and ultimately implemented only in the rare cases of persisting antibodies. Other diseases in which the antibody may disappear upon treatment are some hematologic malignancies, solid cancers, inflammatory bowel disease and drug-associated cases. However, as mentioned above, the antibodies developing in elderly patients with no underlying diseases are the epitome of those that warrant eradication with immunosuppressive agents. This therapeutic approach is justified by the high risk of death due to intracranial and retroperitoneal bleeding in these frail elderly individuals, but a balance must always be made with the concomitant risk of immunosuppression and related infections.

Both the articles emphasize that antibody eradication is the only aspect of the management of acquired hemophilia that is evidence-based, albeit only on the results of a small randomized trial of 31 patients. They were initially treated with prednisone at a daily dose of 1 mg/kg for three weeks, and more than one-third responded with the eradication of the antibody. Patients unresponsive after the initial course were then randomized to receive the same dose of prednisone for six additional weeks, oral cyclophosphamide alone (2 mg/kg per day) or cyclophosphamide plus prednisone.

Approximately half of the patients initially unresponsive to prednisone alone responded to one of the two cyclophosphamide regimens. The only significant contribution after this seminal study comes from a non-randomized but large surveillance study carried out in the United Kingdom by Collins et al., who found no significant difference between patients treated from the onset with steroids alone, or with a combination of steroids and other immunosuppressive agents. With these studies as background, the recommendations of Franchini and Lippi and those of Huth-Kühne et al. are similar. Both favor the combination of daily prednisone (1 mg/kg) plus cyclophosphamide (1.5–2 mg) for at least four weeks. We definitely prefer to start with corticosteroids alone for at least one month, and to resort to cyclophosphamide only in case of failure, because we were appalled by recent data that infections related to the use of immunosuppressive agents are the main cause of death in patients with acquired hemophilia. More recently, there has been an increasing tendency to use rituximab for eradication therapy, usually after failure of the forementioned immunosuppressive regimens but sometimes also as first therapy. Several reports of single cases or small series give promising results, using the dosages and the schemes of treatment adopted in patients with B-cell non–Hodgkin’s lymphomas. Eradication of the inhibitor was observed in approximately 90% of cases, even though the follow-up was usually too short to rule out re-appearance of the autoantibody when B-cells circulate again. In both the forementioned articles rituximab is recommended as second-line therapy only if cyclophosphamide and/or corticosteroids have failed or were contraindicated. We agree with these recommendations, because rituximab is very expensive and not without side effects, besides being used off-label in acquired hemophilia.

**Conclusions**

Acquired hemophilia is so rare that it is unlikely that large randomized therapeutic trials will ever be feasible in this severe and life-threatening disease. The available data are usually based on case reports or small uncontrolled trials, or on review articles that turn out to be as informative as the small studies that have generated them. Hence, it is convenient for the general hematologist that two recent articles produced by an array of recognized experts make similar therapeutic recommendations. Some progress can be expected in the near future. We are not convinced that the larger and more-evidence based use of rituximab will substantially change the rate of eradication of the autoantibodies, already high with the means currently available. In terms of treatment of bleeding episodes, we hope that the forthcoming availability of recombinant B-domainless FVIII of porcine origin, that is usually poorly inactivated by human autoantibodies, will increase the number of patients that can be effectively treated with replacement therapy of the deficient coagulation factor.
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