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# BLEEDING DUE TO ACQUIRED COAGULATION INHIBITORS

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Acquired coagulation inhibitors are auto antibodies directed against components of the haemostatic system with their neutralization and/or accelerated clearance from the plasma. Some of them neutralize proteins involved in the regulation of thrombus formation, with thrombotic tendencies due to inactivation of natural anticoagulants such as protein C, protein S<sup>1,2</sup> or of the vWF cleaving protease ADAMS 13<sup>3,4</sup>; on the other hand, auto antibodies directed against procoagulant factors such as FVIII (in over 98% of the cases) cause a bleeding tendency such as acquired haemophilia that is the object of this presentation.

The yearly incidence of acquired haemophilia varies between 0.1 and 1.0 case per million in the general population, but, likely, not all affected patients are included in the published surveys<sup>5</sup>. Acquired haemophilia is commonly associated with a variety of clinical conditions such as autoimmune diseases, solid tumours, lymphoproliferative diseases, and pregnancy but in 50% of the cases occurs in previously healthy people<sup>5,6</sup>. The median age at presentation varies between 65 and 78 years but typically there are two peaks of age of onset: in the young adult, mainly in women who develop this complication in the post-partum period, and in the elderly, usually with no underlying disease with equal distribution between sexes<sup>5-7</sup>.

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. Patients often present to physicians with no experience in this setting with delayed diagnosis and suboptimal treatment. The diagnosis is suggested by the clinical picture

and confirmed by the laboratory tests. The sudden onset of clinically significant bleeding without family and personal history with a prolonged APTT, not corrected by incubation at 37 °C for 2 hours with normal plasma, and with a normal prothrombin time are the diagnostic hallmarks<sup>8</sup>. The diagnosis is confirmed by FVIII assay and inhibitor titer determination.

The bleeding may be spontaneous but quite frequently is related to a trivial trauma or intervention (about 25% of the cases). Occasionally patients with an overlooked prolonged APTT before surgery are referred to specialized centers because of critical perioperative bleeding during procedures carried out because of misdiagnosed compartmental syndromes. At presentation bleeding may be mild and did not require treatment but, in the majority of cases (over 67%), is major and the management may be very demanding because of the severity and the presence of comorbidities<sup>5,7</sup>. Severe bleeding is reported in 85% of the patients in the EACH registry<sup>6</sup>. The clinical phenotype does not correlate with FVIII level or inhibitor titre; co-morbidities may influence the clinical phenotype. The bleeding pattern of acquired haemophilia is rather different of that of 'classical' hereditary hemophilia. In more than 80% of the patients, hemorrhages of the skin, mucous membranes, muscles and soft tissues are observed, whereas haemarthroses are unusual. Particularly harmful are progressive retroperitoneal hematomas or large intramuscular bleeding with compartmental syndromes and compression of nervous and vascular structures. Bleeding related mortality rate is high, ranging from 7.9% to 22%, mainly within the first few weeks after presentation, related to invasive procedures carried out to control bleeding, delay in diagnosis, inadequate

replacement therapy. Therefore early diagnosis and treatment are essential <sup>8</sup>. The management is directed to the control of the bleeding and the suppression of the inhibitor. No high-level evidence support management recommendations for patients with acquired haemophilia. Data are derived from observational and retrospective studies, including a limited number of patients with different primary clinical conditions. Data generated in patients with congenital haemophilia may occasionally be used to support treatment decisions. Most treatment recommendations must generally rely on the clinical experience of physicians who have managed patients with this disorder. Control of acute bleeding is the immediate priority. The criteria of choice of the anti hemorrhagic treatment are the site and the entity of bleeding, the potential side effects of haemostatic agents, the benefits and the costs of treatment. By-passing agents are the recommended first-line therapy. Both recombinant activated factor VIIa (Novo Seven) and factor eight inhibitor bypassing activity (FEIBA) have proved effective in the treatment of hemorrhagic manifestation. Neither of these agents is effective in all patients and no high-level evidence exists for the use of one product in preference to the other. The dosage is largely based on experience in congenital hemophilia and no data are available on the duration of treatment. Management is generally based on the clinical assessment because there are no validated laboratory tests to determine the therapeutic level <sup>8</sup>.

The experience with FEIBA in acquired hemophilia is very limited: 4 reports with 66 patients <sup>9-12</sup>. The effectiveness is high (control of bleeding in 76-89% of the episodes), but anamnestic response is observed in about 8% of the cases <sup>13</sup>. The response rate with Novo Seven is also high: 83% as first line and 66% as salvage therapy <sup>14</sup>. In the EACH registry bleeding control with FEIBA and Novo Seven is reported in 93.7% of the bleeding episodes for both arms (odds ratio (95% CI) 1.0 (0.24-4.18) (p=1) with no difference in bleeding resolution <sup>13</sup>. Thromboembolic complications are rare and their relation to the treatment is controversial because of concomitant confounding factors (e.g. stroke, cancer, surgery, pregnancy, liver failure, congestive heart failure, coronary artery disease). With the use of by-passing agents cardio-vascular risk for age, co-morbidities and co-medications should be kept in mind. Caution should also be used when evaluating patients in whom tissue factor may be expressed (e.g. advanced atherosclerotic disease,

crush injury, septicaemia or DIC). Risks, benefits and costs of treatment must be carefully weighed on an individual basis <sup>8</sup>.

The optimal therapeutic strategy for inhibitor eradication is not yet been defined. For the last two decades the immunosuppressive regimen most successfully applied have included corticosteroid therapy alone or in combination with cyclophosphamide. The response rate reported in the literature is variable: corticosteroids 42-70%, corticosteroids + cyclophosphamide 50-84% <sup>8</sup>. A retrospective registry in the UK showed no difference in inhibitor eradication or disease-free survival between the two therapies and neither inhibitor titre nor FVIII level was significantly associated with outcome <sup>3</sup>. At variance in the EACH registry a higher proportion of patients achieved complete remission with steroids and a cytotoxic (predominantly cyclophosphamide) (77%) than those treated with steroids alone (58%) (P<0.005). Relapse was most common after initial treatment with steroids alone (19%) and stable complete remission after first line treatment was highest after steroids plus a cytotoxic (67%) than steroids alone (48%) <sup>15</sup>.

Recent reports have shown promising results in eradicating inhibitors with aRituximab at a common dose used in non Hodgkin lymphoma. A recent literature review based on uncontrolled studies or case reports suggests that this drug may be useful in treating acquired haemophilia patients, with remission obtained in 79% of patients (N=43) and no reported cases of opportunistic infections <sup>16</sup>. At present this drug is recommended as second line therapy if cyclophosphamide and/or corticosteroids have failed or were contraindicated <sup>8</sup>.

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

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