Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO

A United Kingdom Haemophilia Centre Doctors’ Organization (UKHCDO) guideline approved by the British Committee for Standards in Haematology Peter W Collins,1 Elizabeth Chalmers,2 Daniel Hart,1 Ian Jennings,4 Ri Liesner,5 Savita Rangarajan,6 Kate Talks,7 Michael Williams8 and Charles R. M. Hay9

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Introduction

Acquired coagulation inhibitors result from immune-mediated depletion or inhibition of a coagulation factor. Inhibitors are most commonly directed against factor VIII (FVIII) and von Willebrand factor (VWF) and inhibitors against other coagulation factors are only occasionally reported. Since the publication of previous guidelines (Laffan et al, 2004; Pasi et al, 2004; Hay et al, 2006) substantial new data has been published on acquired FVIII inhibitors, necessitating updated guidelines. The rarity of acquired inhibitors to other coagulation factors means that limited information is available to guide management and the treatment strategies suggested are necessarily by consensus and often extrapolated from data derived from FVIII inhibitors. Inhibitors to VWF will not be covered because a revised von willebrand disease (VWD) guideline is in preparation (Laffan et al, 2004; Pasi et al, 2004).

Basic principles

Patients should be registered, and treated jointly with a Comprehensive Care Haemophilia Centre (CCC) experienced in the management of inhibitors (National Service Specification available at www.ukhcdo.org). CCCs must provide 24-h access to senior clinicians with experience in inhibitor management and laboratory services for the measurement of factor levels and inhibitor titres. An underlying cause of the acquired inhibitor should be sought and patients should be investigated for autoimmune disease and malignancy. Patients should be offered inclusion in appropriate clinical trials and reported to registries. UK patients must be registered with the National Haemophilia Database.

Recommendation

1 Patients with acquired coagulation factor inhibitors should be treated jointly with haemophilia centres experienced in the management of inhibitors and, in
the UK, registered with the National Haemophilia Database (Grade 2c).

Acquired haemophilia A (AHA) has an incidence of about 1-5/million/year and presents most commonly in the elderly at a median age of 75–80 years (Collins et al, 2004, 2007; Knobl et al, 2012). Other inhibitors are much less common. AHA is associated with polymyalgia, rheumatoid arthritis, systemic lupus erythematosus (SLE) and other autoimmune diseases, malignancy, pregnancy and pemphigoid. No association is identified in about half of patients (Green & Lechner, 1981; Morrison & Ludlam, 1995; Collins et al, 2007). Inhibitors to other coagulation factors have been associated with auto-immune disease and malignancy (Hay, 2012).

The mortality associated with AHA has been reported to be between 8% and 42% (Green & Lechner, 1981; Morrison et al, 1993; Hay et al, 1997; Delgado et al, 2003; Collins et al, 2007). In recent studies, 3–12% of deaths were attributed to the effects of immunosuppression and infection whilst 3–8% were attributed to bleeding (Collins et al, 2007; Knobl et al, 2012).

**Diagnosis**

**Clinical**

An acquired inhibitor should be considered in patients with recent onset of abnormal bleeding. Patients usually present to clinicians with limited experience of the disorder and diagnosis and appropriate treatment is often delayed. Severe and life-threatening bleeding is common in AHA, although, in contrast no haemostatic treatment is required in 25%–33% of cases (Lottenberg et al, 1987; Collins et al, 2007; Knobl et al, 2012). Some patients present without clinical bleeding. The severity of bleeding at presentation does not predict future bleeding and patients remain at risk of fatal bleeding until the inhibitor has been eradicated (Collins et al, 2007).

The clinical features of AHA differ from those of congenital haemophilia because bruising, retroperitoneal, muscle, gastrointestinal and urogenital bleeding are common whereas haemarthroses are uncommon (Morrisson et al, 1993; Hay et al, 1997; Delgado et al, 2003; Collins et al, 2007; Knobl et al, 2012). Fatality is associated with gastrointestinal, intracranial and retroperitoneal bleeds (Collins et al, 2007). Compartment syndromes and critical compression of nerves and blood vessels may be seen. There is limited information on the clinical features associated with inhibitors to other coagulation factors and this will be covered in specific sections of this guideline.

Acquired haemophilia A has been reported in association with antiocoagulation and anti-platelet agents and diagnosis may be delayed because the bleeding is assumed to be caused by these agents (Uggla et al, 2003; Dragnani et al, 2004; Haj et al, 2004; Vadikolia et al, 2007). Excessive bruising or unexpected bleeding in patients on antiocoagulants should be further investigated.

**Laboratory diagnosis**

Diagnosis of acquired coagulation factor inhibitors, and their differentiation from other coagulation abnormalities, requires specialized investigation, often necessitating referral to a reference laboratory. When investigating abnormal clotting times in patients presenting with bleeding, it is important to exclude treatment with anticoagulant therapy. See Fig 1 for further details.

Typical laboratory findings are of abnormal coagulation screening tests that do not correct with normal plasma, either with an immediate or incubated mix. The pattern of abnormality of screening tests depends on the specificity of the inhibitor (Fig 1). The diagnosis is confirmed by assays of specific factors and demonstration of an inhibitor in the Bethesda assay for FVIII or, for other factors, a modification of the Bethesda assay. In all cases, the Nijmegen modification should be employed to improve assay sensitivity. In the absence of a time-dependent inhibitor, it is possible to perform a Bethesda assay without the incubation step.

A lupus anticoagulant (LA) should be excluded as a cause of apparently reduced coagulation factor levels (Keeling et al, 2012), especially in the absence of bleeding. Acquired coagulation factor inhibitors may co-exist with a LA, especially antibodies to prothrombin. In some cases an inhibitor to one factor may interfere with the assay of other coagulations factors. This is best documented with FVIII inhibitors, where all intrinsic factors may apparently be low due to inhibition of FVIII in the intrinsic factor-deficient plasma, but this finding could equally apply to any inhibitor. In these cases serial dilution will result in correction of the non-specifically reduced factors whilst the specifically reduced factor will remain low. Thus it is important that factor assay design includes multiple dilutions of test plasma, and an evaluation of linearity against the calibration curve.

In some cases, for example for defects of fibrin polymerization, thromboelastometry may be useful. Some highly specialized laboratories may extend investigation to global assays, such as thrombin generation, but this is not recommended outside research studies.

**Inhibitors to FVIII.** FVIII inhibitors are time- and temperature-dependent and mixing studies with normal plasma may demonstrate inhibition on incubation that is not present immediately after mixing. Inhibitors to other coagulation factors have not been reported to be time-dependent. Enzyme-linked immunosorbent assay (ELISA)-based assays have been reported for FVIII inhibitor detection, which may avoid interference by LAs. Chromogenic FVIII assays may be used, because LAs do not interfere with this assay.

It is often difficult to define the titre of an acquired FVIII inhibitor due to the complex kinetics, whereby the pattern of inactivation is non-linear, and may therefore lead to the inhibitor potency being underestimated. It is usual to report the dilution that most closely inhibits half the FVIII after
If recombinant B domain-deleted porcine FVIII becomes available, inhibitor titres to this product should be performed. The laboratory investigation of other acquired inhibitors will be covered in appropriate sections.

Recommendations

1. The diagnosis of AHA should be considered if acute or recent onset of bleeding is accompanied by an unexplained prolonged activated partial thromboplastin time (aPTT) (Grade 1C).

2. Acquired inhibitors for other clotting factors may be considered if acute or recent onset of bleeding is accompanied by unexplained prolonged screening tests [prothrombin time (PT), aPTT or thrombin time (TT)] that fail to correct with normal plasma (Grade 2C).

Diagnostic and treatment delay

Delay in diagnosis and treatment is common, putting patients at unnecessary risk of severe bleeding, especially if invasive procedures are undertaken. In AHA, delays were more than 12 d in 25% and more than 4 weeks in 10% of cases and occurred both between the onset of bleeding and investigation and the finding of a prolonged aPTT and diagnosis (Knobl et al, 2012).

Coagulation laboratories should have algorithms in place that ensure appropriate investigation of abnormal coagulation screening tests, especially of an isolated prolonged aPTT. If the aPTT does not correct with normal plasma and the LA is negative, factor levels should be done. A possible algorithm is suggested (Fig 1) which can be adapted to local needs. Systems should be in place to inform clinicians of the potential

Fig 1. Investigation of acquired coagulation factor inhibitors. TT, thrombin time; PT, prothrombin time; aPTT, activated partial thromboplastin time; FBC, full blood count; LA, lupus anticoagulant; DIC, disseminated intravascular coagulation; VWF:RCo, ristocetin cofactor activity. 1Correction tests/mixing studies – these can be difficult to interpret. For markedly prolonged PT or aPTT, correction to within the reference range may not occur with a moderate/severe factor deficiency. Conversely, a low titre inhibitor may be diluted by addition of normal plasma to give partial correction in mixing studies. It is possible for LA to coexist with a factor deficiency. 3Patients on oral direct inhibitors may also develop acquired inhibitors – attention to the pattern of screening test results (e.g., a prolongation of the aPTT out of proportion to the PT in a patient on Coumadin therapy) is required. 4In a patient with a bleeding history and normal aPTT, or prolonged aPTT and normal factor assays, a 2-stage or chromogenic assay for FVIII coagulant activity (FVIII:C) should be considered.
significance of abnormal results and to ensure further investigations are performed rapidly to confirm or refute the diagnosis. Haematologists should take responsibility for managing the bleeding manifestations of the disease as soon as a diagnosis is suspected.

**Recommendations**

1. Coagulation laboratories should have algorithms that ensure timely and appropriate investigation of abnormal coagulation screening tests, especially of an isolated prolonged aPTT (Grade 2C).

2. Laboratories should urgently inform clinicians of the potential significance of abnormal results (Grade 2C).

**Treatment of acquired coagulation factor inhibitors**

Reviews and consensus treatment guidelines on the treatment of AHA have been published (Hay et al, 2006; Huth-Kuhne et al, 2009; Collins, 2011).

**Avoiding iatrogenic bleeding**

Patients should not be exposed to invasive procedures unless they are essential because uncontrollable bleeding may result even from minor procedures. The efficacy of available haemostatic agents is unpredictable and none are universally effective. Even for procedures that would normally be considered unsuitable for delay, the pros and cons of operating in the presence of an inhibitor should be weighed against the risks of conservative management until FVIII levels have increased.

Venepuncture and the placement of a venous cannula may also lead to severe bleeding and should be kept to a minimum. Some centres do not allow ward phlebotomists to take blood, in which case samples are taken by haemophilia centre staff. Ward staff should be educated about the risk of inducing bleeds and blood pressure and blood glucose monitoring are only performed if clinically indicated. Patients should be protected against the risk of falls when mobilizing. Intramuscular injections are contraindicated.

**Recommendation**

1. Invasive procedures should only be undertaken if unavoidable and venepuncture should be kept to a minimum (Grade 1C).

**Treatment of bleeding in AHA**

Treatment of bleeding should be supervised by a clinician experienced in the treatment of patients with inhibitors because bleeds may be very severe and prompt haemostatic control is required to reduce morbidity and mortality. In contrast, many patients do not require haemostatic therapy (Collins et al, 2007; Baudo et al, 2012) and, because of the increased risk of thrombosis associated with bypassing therapy, some bleeds, for example subcutaneous bleeds, may be best managed conservatively.

If haemostatic treatment is required it should be with a bypassing agent (Baudo et al, 2012). The available bypassing agents are recombinant factor VIIa (rFVIIa) (Novoseven®, Bagsvaerd, Denmark) and the activated prothrombin complex concentrate (aPCC) Factor Eight Inhibitor Bypassing Activity (FEIBA). Data on the haemostatic efficacy and side effects of bypassing agents in patients with AHA relate to these products and can not necessarily be extrapolated to other rFVIIa molecules or aPCCs.

Treatment with human FVIII concentrates is less efficacious than bypassing agents unless combined with immunoadsorption (Baudo et al, 2012). Desmopressin may increase FVIII levels in some patients, although this treatment may be contraindicated in some patients due to comorbidities (Mudad & Kane, 1993; Franchini & Lippi, 2011). Previously, plasma-derived porcine FVIII was shown to be efficacious in treating bleeding in AHA (Morrison et al, 1993).

**Bypassing agents.** Most data on the treatment of bleeds for patients with FVIII inhibitors relate to congenital haemophilia and focus on haemarthroses (Collins et al, 2013). The autoantibodies that cause AHA have different properties to the allo-antibodies associated with congenital haemophilia and the bleeding pattern differs. In particular, haemarthroses are uncommon. This means that data derived from patients with congenital inhibitors cannot necessarily be extrapolated to AHA.

A retrospective study of AHA patients treated with rFVIIa combined data from three sources that had variable inclusion criteria: a compassionate use programme (Hay et al, 1997), the Hemophilia and Thrombosis Research Society Registry and the published literature. It reported on 139 patients and 182 bleeds (Sumner et al, 2007). In the 103 episodes where rFVIIa was used as first-line therapy, treatment was effective or partially effective in 95% of cases (Sumner et al, 2007). Similar results were reported to the European Acquired Haemophilia (EACH2) registry, where 159 prospectively collected bleeds treated first-line with rFVIIa resolved in 92% of cases (Baudo et al, 2012). In EACH2, 64 bleeds were treated first-line with FEIBA with 93% resolution (Baudo et al, 2012). In a retrospective study of FEIBA in 34 patients, moderate bleeds had 100% and severe bleeds 76% haemostatic control at a median of 48 h (Sallah, 2004). When used in 57 surgeries, rFVIIa was reported as effective or partially effective in 86% of cases (Sumner et al, 2007).

The haemostatic efficacy of rFVIIa and FEIBA has not been compared directly in AHA. However, an analysis of data in the EACH2 registry, which controlled for bleed and patient characteristics by propensity score matching, found that the two
agents were indistinguishable [odds ratio (OR) 1.0, 95% confidence interval (CI) 0.23–4.44] (Baudo et al, 2012). In congenital haemophilia A, studies that compared rFVIIa and FEIBA for treatment of haemarthroses also suggest similar efficacy (Astermark et al, 2007; Young et al, 2008).

Either bypassing agent can be used as first-line treatment for bleeding in AHA. The choice of agent will depend on knowledge of the patient’s previous response, convenience of dosing, use of plasma-derived products and cost. If response to first-line therapy is inadequate, the alternative bypassing agent may be successful and should be tried at an early stage. The initial dose of rFVIIa should be 90 μg/kg every 2 h and for FEIBA 50–100 μg every 6–12 h with a maximum dose of 200 μg/kg/d. A period of treatment at reduced dose and frequency after initial bleed control is often needed to prevent recurrence and must be assessed on a case-by-case basis.

Factor VIII and desmopressin. In EACH2, after matching for bleed and patient characteristics, the likelihood of haemostatic failure was lower with bypassing agents compared to FVIII or desmopressin (OR 0.15, 95% CI 0.04–0.53, P = 0.003) (Baudo et al, 2012).

Human FVIII—Most patients with AHA are resistant to human FVIII and, even if the inhibitor titre is low, the response is unpredictable and the Bethesda assay is not predictive of FVIII recovery. Human FVIII is usually neutralized with an early rapid parabolic reduction to a low level, which is sometimes followed by a slower, second disappearance-phase resulting in a low level of residual FVIII activity that may persist for several hours (Gawryl & Hoyer, 1982). The FVIII level is not a good guide to clinical response. The administered dose of FVIII must be sufficient to overcome the inhibitor and provide an adequate haemostatic level. Although formulae have been suggested for calculating the dose, the inaccuracies inherent in the laboratory measurement of inhibitor titres in AHA make these, at best, very rough approximations. If FVIII is used, a large initial dose is likely to be required with regular boluses or continuous infusion and regular monitoring of plasma FVIII level and clinical response is required. If a poor response is observed an early change to an alternative product is required.

Human factor VIII and immunoadsorption—The use of high dose human FVIII (100 iu/kg/d) in combination with immunoadsorption may result in haemostatic FVIII levels and rapid control of severe bleeding, despite high anti-FVIII inhibitor titres (Zeitler et al, 2006a, 2010). This treatment strategy may be useful as first-line therapy or if bypassing agents have failed, although it is available in only a very limited number of centres (Guillet et al, 2001; Freedman et al, 2003).

Desmopressin—Some patients with a low titre inhibitor (<2 Bethesda units, BU) and baseline FVIII above 5 iu/dl may respond to desmopressin infusion: clinical response, however, is unpredictable and haemostatic efficacy is not as good as that seen with bypassing agents (Mudad & Kane, 1993; Francini & Lippi, 2011; Baudo et al, 2012). Desmopressin may be useful to treat minor bleeds but careful laboratory and clinical monitoring of response is required.

Porcine FVIII—In AHA, the inhibitor titre to porcine FVIII is usually 5–10% that of the human titre (Morrison et al, 1993) and so porcine FVIII may achieve haemostasis in situations where human FVIII is ineffective. Plasma-derived porcine FVIII has proven efficacy in AHA (Morrison et al, 1993) but is no longer available. The use of a recombinant B-domain deleted porcine FVIII is currently under investigation in AHA.

Tranexamic acid—Tranexamic acid is a useful adjunct therapy, especially for mucosal bleeds. It should be considered for all bleeds apart from renal tract bleeding. Concerns about concomitant use of tranexamic acid with FEIBA exist but reports of complications are very rare and many clinicians use tranexamic acid in combination with FEIBA (Holmstrom et al, 2012). Topical tranexamic acid may be useful for oral or skin bleeding.

Intravenous immunoglobulin—The use of intravenous immunoglobulin (IVIG) as an adjunct to other haemostatic measures is approved in the current UK IVIG clinical guidelines for patients with acquired inhibitors of coagulation factors and life or limb threatening haemorrhage that has failed to respond to other therapies, although there is only very limited data supporting its efficacy (http://www.ivig.nhs.uk/documents/dh_129666.pdf). Outcome data on the efficacy for this indication will be available in the future as part of the demand management of IVIG use in the UK.

Management of invasive procedures

Invasive procedures should only be performed at CCCs. Treatment options include the use of bypassing agents or immunoadsorption with FVIII infusion. Haemostasis cannot be guaranteed and life-threatening bleeding may result.

Thrombosis

Treatments with either rFVIIa or FEIBA is associated with arterial and venous thrombosis and the incidence of thrombosis appears to be higher than when these agents are used in congenital haemophilia A. This is probably due to risk factors associated with the age and the often complex clinical status of these patients.

A review of patients with AHA treated with rFVIIa reported 12 thrombotic events, predominantly arterial, in 139 patients (8·6%) (Sumner et al, 2007). EACH2 reported 11 thrombotic events (seven arterial and four venous) in
patients treated with a haemostatic agent and two in patients not treated with a haemostatic agent. There were 5/174 (2.7%) events associated with rFVIIa, 3/63 (3.6%) with FEIBA, 0/70 with FVIII or desmopressin and in three cases the haemostatic agent was not reported (Baudo et al., 2012). Although a causal relationship between bypassing agents and the reported thrombotic events cannot be established, caution is required and the decision to use a bypassing agent is not straightforward.

Treatment of significant bleeding should not be withheld because the benefit of early control of severe bleeding clearly outweighs the risk of thrombosis. However, careful consideration should be given to minor bleeds, such as subcutaneous haemorrhage, which often resolve spontaneously.

The use of rFVIIa at doses higher than 90 μg/kg has been shown to be safe and efficacious for the treatment of haemarthroses in congenital haemophilia (Santagostino et al., 2006; Young et al., 2008). Dose escalation should be considered only in exceptional circumstances in patients with AHA because higher dose rFVIIa has not been shown to be safe in this patient group or efficacious for treating the types of bleeds associated with AHA (Huth-Kuhne et al., 2009). However, in the management of severe bleeds unresponsive to conventional doses, escalation may be justifiable on a case-by-case basis. The use of combined rFVIIa and FEIBA should be avoided (Ingerslev & Sorensen, 2011) except in life or limb-threatening situations unresponsive to each agent alone (Teitel et al., 2007).

Remission is often associated with high FVIII levels and, because patients are likely to have other risk factors for venous thrombosis, they should be assessed and treated with appropriate venous thromboprophylaxis if indicated.

**Monitoring response to haemostatic agents**

No laboratory tests have been validated for monitoring haemostatic response of bypassing agents in AHA. FVIII levels can be measured and global haemostatic assays used but results do not necessarily correlate with haemostatic efficacy (Dehmel et al., 2008) and should only be used as part of a clinical trial. Monitoring of response is primarily clinical, supported by measurement of haemoglobin and appropriate imaging.

**Recommendations**

1. If indicated, bleeding should be treated without delay using rFVIIa or FEIBA (Grade 1B). Not all bleeds need haemostatic treatment and many subcutaneous bleeds can be managed conservatively. If the initial bypassing agent is ineffective the other should be tried at an early stage (Grade 2C).

2. The use of rFVIIa at doses higher than 90 μg/kg is not recommended except as rescue therapy because of the increased risk of thrombosis (Grade 2C).

3. FVIII replacement combined with plasmapheresis and immunoadsorption can be considered for severe bleeding or if first-line therapy is unsuccessful (Grade 2B).

4. Tranexamic acid should be considered for all bleeds and especially those involving mucosal surfaces (Grade 2C).

5. Once in remission, patients should be assessed for the risk of venous thrombosis and given prophylaxis if indicated (Grade 2C).

**Eradication of the inhibitor in AHA**

Immunosuppression to eradicate an inhibitor should be started as soon as the diagnosis has been made, to reduce the time a patient is at risk of bleeding (Collins et al., 2007), although haemostatic control should be the priority in the acute setting. The choice of immunosuppressive regimen needs to take into account the comorbidities of the patient. Patients should be monitored closely for evidence of infection.

Reports on the effectiveness of immunosuppression are difficult to interpret because of the use of variable endpoints and definitions in different studies. Reports are likely to reflect more severely affected patients and publication bias of good outcomes (Collins & Percy, 2010; Collins, 2011). One study reported a spontaneous remission in 25% of patients after a median 19 months follow up, although there was significant associated morbidity and two patients died of bleeding (Lottenberg et al., 1987); this finding has not been replicated.

Meta-analyses have identified older age and underlying malignancy as risk factors for mortality (Delgado et al., 2003; Bitting et al., 2009). Patients presenting with higher FVIII levels and lower inhibitor titres are more likely to respond to immunosuppression but the relationship is too weak to be the basis for treatment decisions (Collins et al., 2007). The median time to remission following the start of immunosuppression is about 5 weeks (Collins et al., 2007, 2012).

**Immunosuppressive regimens.** Routine first-line treatment in many centres is with either steroids alone or steroids combined with a cytotoxic agent (Huth-Kuhne et al., 2009).

**Steroids and cytotoxic agents—**The most robust analysis of first-line immunosuppression comes from the EACH2 registry of 331 patients. Patients treated with prednisone alone were compared to those treated with prednisone and oral cyclophosphamide. The groups were matched by logistic regression and a propensity score for age, gender, inhibitor titre, FVIII level and underlying aetiology. The study reported an OR of 3.25 (95% CI 1.51–6.96), \( P < 0.001 \), of achieving a stable remission using combined therapy compared to prednisone, despite the prednisone-alone arm receiving a higher dose of steroids (Collins et al., 2012).
A non-randomized, prospective, national consecutive cohort study compared patients treated with steroids versus steroids and cytotoxics. The design of this study reduced selection bias although the groups were not matched for presenting characteristics. The 34 patients treated with steroids had 76% complete remission (CR) at a median of 49 (95% CI, 31–62) days compared to 78% CR at 39 (34–57) days for the steroids and cytotoxics group (Collins et al, 2007).

A meta-analysis of 20 studies reported that the use of steroids and cyclophosphamide resulted in more patients achieving CR compared to steroids alone (Delgado et al, 2003). A more recent meta-analysis of 32 non-randomized studies (including the 20 previous studies) found that patients receiving combination immunosuppression had a reduced OR of 0.04 (95% CI 0.01–0.23), for persistent, acquired haemophilia when compared to those receiving no immunosuppression, and an OR of 0.38 (95% CI 0.14–0.94) for steroid therapy alone (Bitting et al, 2009).

The only prospective randomized study enrolled 31 patients (Green et al, 1993). This study is often interpreted as providing evidence to support the addition of cyclophosphamide to steroids if a CR has not been achieved by 3 weeks. The study data, however, do not provide evidence that this strategy is superior to any other.

Despite reports showing that patients treated first-line with a combination of steroids and cyclophosphamide were more likely to achieve a CR than steroids alone, the final outcome in terms of survival and sustained remission is the same in all large studies (Delgado et al, 2003; Collins et al, 2007, 2012).

Regimens involving combination immunosuppression have been reported to have high success rates but without comparative groups the results must be treated with caution because numbers are very small (Lian et al, 2002).

Rituximab—Rituximab is becoming a common treatment for AHA but there are no data to support the contention that alone, or with other agents, it results in more patients achieving remission or a more rapid response to treatment.

A literature review of 71 patients treated with rituximab and a variety of other immunosuppressive agents reported a response rate of over 90%, however, reporting bias towards good outcomes is likely and no controls were included (Franchini & Lippi, 2008). A more recent study reported that 42 patients treated with rituximab had similar outcomes to 44 control patients treated with cyclophosphamide and steroids (Sperr et al, 2007). EACH2 reported that 25 of 39 (64%) patients treated with rituximab and another immunosuppressive agent achieving a stable remission compared to 2/83, 70% treated with steroids and cyclophosphamide (Collins et al, 2012). Of the patients treated with rituximab alone 5/12 (42%) had a stable remission (Collins et al, 2012).

Based on current data, rituximab is not associated with more rapid remission. The 30 patients who responded in the EACH2 registry had a median (inter-quartile range) time to a negative inhibitor of 65 (29–144) days, which is a slower response compared to other regimens (median time to remission 32–40 d) (Collins et al, 2012). In a study of 12 patients treated with rituximab alone 75% achieved CR but with a median (interquartile range) time to remission of 106 (26–184) days (Boles et al, 2011).

Some patients who are resistant to standard first-line regimens respond to second-line rituximab (Collins et al, 2012). There is no evidence to support the use of rituximab in patients with high titre inhibitors, as has been suggested by some authors (Aggarwal et al, 2006).

Calcineurin inhibitors—The combination of ciclosporin or tacrolimus and steroids has been reported as successful first-line treatment with stable remission in 10/11 (91%) patients at a median of 3 weeks, though no controls were reported in this study (Pardos-Gea et al, 2012). A number of cases have been reported in which ciclosporin has induced CR following failed first-line therapy (Pfliegler et al, 1989; Schulman et al, 1996; Au et al, 2004; Haj et al, 2004).

Intravenous immunoglobulin—The available evidence does not support the use of IVIG as a single agent or in combination with steroids and cytotoxics as an immunosuppressive agent. The UKHCOO and EACH2 studies both showed no benefit for adding IVIG to other immunosuppression as first-line therapy (Collins et al, 2007, 2012) and a literature review reached the same conclusion (Delgado et al, 2003).

Factor VIII immune tolerance. FVIII in conjunction with immunosuppressive agents has been reported. The lack of controls in these studies means that the role of FVIII is difficult to assess. A study of daily infusion of FVIII (30 iu/kg/d for 1 week, 20 iu/kg/d for a second week and 15 iu/kg/d for a third week) combined with intravenous cyclophosphamide and methylprednisolone reported CR in 95% of 20 patients after a median 4-7 weeks, compared to 67% remission at a median of 28-3 weeks in six historical controls treated with steroids ± cyclophosphamide (Nemes & Pitlik, 2003).

A report of patients treated with 3 weekly infusions of FVIII combined with vincristine, cyclophosphamide and steroids resulted in a 92% CR rate in 12 patients after 1–3 courses (Lian et al, 1989). The same group later reported six patients who were treated with vincristine, cyclophosphamide and steroids without FVIII and found 83% remission after 1–7 courses (Lian et al, 2002). The effect of FVIII is unclear because the intensity of immunosuppression was greater than for many other protocols (Lian et al, 1989, 2002). Taken together these reports are insufficient to conclude that immune tolerance with FVIII is beneficial in AHA and the high cost of FVIII in these protocols must be taken into account.
Immunoadsorption, factor VIII and immunosuppression. A cohort of 35 patients with severe bleeding was treated with a combination of oral cyclophosphamide 1–2 mg/kg daily, prednisolone 1 mg/kg daily, immunoadsorption on day 1–5 weekly, IVIG 0.3 g/kg day 5–7 weekly and FVIII 100 IU/kg daily. Rapid control of bleeding was reported with an undetectable inhibitor at a median of 3 d (95% CI 2–4) and CR in 88% of patients at a median of 14 d (95% CI 12–17) (Zeitler et al, 2006b). The same group has published updated data on 67 patients with similar outcomes (Zeitler et al, 2010). Although no control patients are reported and the cost of the FVIII is high, this treatment appears to be useful for controlling bleeding and rapidly induces remission in responders.

Relapse. Studies with adequate follow up report a relapse rate of 10–20%. In the UKHCDO study, relapse was reported in 20% of 102 patients at a median of 7–5 months (range 1 week to 14 months) (Collins et al, 2007). This finding was confirmed by EACH2, which reported relapse in 18% of those treated first-line with steroids, 12% for steroids and cyclophosphamide and 1% in those treated with rituximab, after a median of 4 months (Collins et al, 2012).

Most patients (70%) achieved a second CR although some required long-term maintenance immunosuppression (Collins et al, 2007, 2012). Patients should be educated about symptoms and signs of recurrence and advised to report symptoms of bleeding or bruising early. The risk of relapse of pregnancy-related AHA is described below.

Adverse events. Adverse events are common, with high rates of infection, neutropenia, diabetes mellitus and psychiatric illness. In recent studies 3–12% of deaths have been attributed to the effects of immunosuppression, primarily through infection (Collins et al, 2007, 2012).

Second-line immunosuppressive therapy. Failure of first-line therapy should be considered after 3–5 weeks if the FVIII level is not increasing and the inhibitor titre not falling. In patients not responding to first-line steroids a cytotoxic agent, a calcineurin inhibitor or rituximab can be considered. If a patient fails first-line treatment with rituximab, then steroids, cytotoxics agents or calcineurin inhibitors may be successful. Mycophenolate mofetil may be a useful alternative although there are no reports in the literature of using this drug in AHA. Resistant cases may respond to high dose FVIII, immunosuppression and immunoadsorption or more intensive combination chemotherapy. In EACH2, 44/83 (53%) of evaluable patients achieved a stable remission with second-line therapy with combinations of a variety of immunosuppressive agents (Collins et al, 2012).

Conclusions on inhibitor eradication. There is consensus that immunosuppression aimed at eradicating the inhibitor should be started as soon as the diagnosis of AHA has been made. The combination of cyclophosphamide and steroids probably results in a higher CR rate than steroids alone but long-term outcome, in terms of survival and disease-free survival is not affected by the choice of first-line therapy in all large studies. Until further data become available it is not possible to make definitive recommendations and first-line therapy is at the discretion of the clinician based on the clinical circumstances and taking into account the potential side effects of each treatment.

1 Patients with AHA should start immunosuppression as soon as the diagnosis is made (Grade 1B).

2 Immunosuppression should be initiated with prednisolone 1 mg/kg/d either alone or combined with cyclophosphamide 1–2 mg/d orally (Grade 1B).

3 Rituximab can be considered as first-line therapy if standard immunosuppression is contraindicated, but may have limited efficacy if used as a single agent (Grade 2B).

4 If there is no response within 3–5 weeks, second-line therapies should be considered. The most common second-line treatment is with rituximab combined with other agents. Alternative options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols. (Grade 2B).

5 IVIG is not recommended as treatment for inhibitor eradication (Grade 1B).

6 Patients should be followed up at least monthly for the first 6 months because relapse is common (Grade 2B).

7 Patients with a past history of acquired haemophilia should have a coagulation screen, or preferably a FVIII level measured before any invasive procedures (Grade 2C).

8 When the FVIII level is normal, patient should be assessed for the risk of venous thrombosis and receive thromboprophylaxis if appropriate (Grade 2B).

Pregnancy-associated AHA

AHA is a very rare complication of pregnancy, reported in 1:350 000 births in the UK (Collins et al, 2007) and in 20 cases over 15 years in 42 specialist Italian centres (Italian Association of Haemophilia Centres (AICE) (2006). Patients present at a median of about 3 months postpartum but can present up to a year following delivery (Hauser et al, 1995; Italian Association of Haemophilia Centres (AICE) (2006); Michiels et al, 1997; Solymoss, 1998; Nemes et al, 2010). Seven patients out of 42 cases in the EACH2 registry had evidence of an ante-partum inhibitor (Nemes et al, 2010).

Retrospective reviews have reported a longer time to remission compared to AHA caused by other aetiologies, although this was not seen in the 42 patients reported to EACH2 (Nemes et al, 2010). Conversely, spontaneous remissions can occur (Hauser et al, 1995; Italian Association of Haemophilia Centres (AICE) (2006); Solymoss, 1998).
Treatment with immunosuppressive agents should take into account the age of the patients and the potential side effects of drugs in women of child bearing age (Hay et al, 2006). Rituximab has been used successfully but there are no data to suggest that it is superior to other treatment modalities (Dedeken et al, 2009; Nemes et al, 2010).

Relapse in subsequent pregnancies appears to be relatively uncommon but women should be warned that this is a possibility. A number of small studies report a variable risk of relapse, ranging from three women in whom relapse occurred in four of six subsequent pregnancies (Solymoss, 1998) to no relapses reported in nine subsequent pregnancies (Coller et al, 1981) and none in four patients reported by an Italian Registry (Italian Association of Haemophilia Centres (AICE) (2006). The antibody may affect the FVIII level of the fetus and this must be anticipated at the time of delivery (Ries et al, 1995; Lulla et al, 2009).

Treatment of bleeds should follow the principles outlined for AHA in general (Hauser et al, 1995; Italian Association of Haemophilia Centres (AICE) (2006); Solymoss, 1998) but caution about the risk of venous thromboembolism associated with bypassing agents in the postpartum period should be borne in mind when recommending treatment.

**Recommendation**

1. Cyclophosphamide and other alkylating agents should be avoided, if possible, in women of reproductive age. (Grade 2B).

**Inhibitors of other coagulation factors**

Information on the clinical presentation, treatment of bleeds and eradication of coagulation factor inhibitors other than FVIII is anecdotal and each patient should be assessed individually. Some inhibitors are asymptomatic despite causing significant abnormalities on laboratory testing. Patients presenting with bleeding should be treated with immunosuppression but a period of observation may be considered in asymptomatic cases because some inhibitors are transient or asymptomatic. In patients who require immunosuppression the regimens used for FVIII autoantibodies may be tried. For a detailed review with extensive references see (Hay, 2012).

Haemostatic treatment options vary depending on the specificity of the inhibitor (Table I). Factor levels can be measured to assess laboratory response to the inhibitors but there are limited data regarding adequate haemostatic levels. Repeated infusions of prothrombin complex concentrate (PCC) or FEIBA, to overwhelm an inhibitor, may lead to the accumulation of other coagulation factors, potentially increasing the risk of thrombosis (Mulhare et al, 1991). Sustaining a target factor level to overcome an inhibitor will be more readily achieved by increasing the frequency of infusions rather than increasing the dose.

Fresh frozen plasma (FFP) is likely to be ineffective in most cases because it will not be feasible to infuse sufficient volume to overwhelm the inhibitor and increase factor levels without risking circulatory overload. FFP or coagulation factor concentrates may be considered in association with plasmapheresis or immunoabsorption.

**Inhibitors to fibrinogen, fibrin formation and polymerization**

Acquired autoimmune antibodies may interfere with fibrin formation, polymerization and stabilization with factor XIII (FXIII) in a variety of ways. Autoantibodies may complex with fibrinogen or fibrin inhibiting fibrin polymerization, and polyclonal autoantibodies may inhibit the release of fibrinopeptide or affect FXIIIa stabilization (Hay, 2012).

**Table I. Haemostatic treatment for acquired coagulation factor inhibitors.**

<table>
<thead>
<tr>
<th>Factor VIII fibrin polymerization</th>
<th>Factor V</th>
<th>Factor VII</th>
<th>Factor IX</th>
<th>Factor X</th>
<th>Factor XI</th>
<th>Factor XIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>rFVIIa or FEIBA</td>
<td>Fibrinogen concentrate</td>
<td>Platelets ± FFP</td>
<td>rFVIIa or FEIBA</td>
<td>FEIBA</td>
<td>FXIII concentrate</td>
</tr>
<tr>
<td>Second-line</td>
<td>FEIBA or PCC</td>
<td>FEIBA</td>
<td>rFVIIa, FVII</td>
<td>FEIBA</td>
<td>FEIBA</td>
<td>FXIII concentrate and immunoadsorption</td>
</tr>
<tr>
<td>Other options</td>
<td>Alternative bypassing agent</td>
<td>Fibrinogen concentrate and immunoadsorption</td>
<td>FFP and immunoadsorption</td>
<td>Alternative bypassing agent</td>
<td>PCC or FEIBA and immunoadsorption</td>
<td>FXIII concentrate and immunoadsorption</td>
</tr>
<tr>
<td>Treatment less likely to be efficacious</td>
<td>FVIII and immunoadsorption</td>
<td>Cryoprecipitate ± immunoadsorption</td>
<td>FIX concentrate ± immunoadsorption</td>
<td>FEIBA or PCC and immunoadsorption</td>
<td>FXI concentrate ± immunoadsorption</td>
<td>Cryoprecipitate ± immunoadsorption</td>
</tr>
<tr>
<td>rFVIIa FEIBA FFP</td>
<td>rFVIIa FEIBA FFP</td>
<td>rFVIIa FFP</td>
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</tr>
</tbody>
</table>

rFVIIa, recombinant factor VIIa; FEIBA, factor VIII inhibitor bypassing activity; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.
Inhibitors affecting fibrin polymerization have been reported with monoclonal and polyclonal antibodies and are associated with monoclonal gammapathies (Lackner, 1973).

**Laboratory diagnosis.** Antibodies against fibrinogen or fibrin polymerization should be suspected when the aPTT, PT, TT, and reptilase time are prolonged and the Clauss fibrinogen is reduced. Mixing studies using the TT show significant prolongation with no correction after the addition of normal plasma. Thromboelastography or thromboelastometry may show reduced clot formation. Investigation for a paraprotein should always be performed.

**Clinical features.** Clinical features are variable but there may be severe, recurrent, and spontaneous bleeding associated with a high mortality. Gastrointestinal, genitourinary, pulmonary, and intraperitoneal bleeding often occur in combination with soft tissue haematomas and ecchymoses. Intracranial haemorrhage has also been described (Lorand et al, 2002).

**Haemostatic therapy.** For inhibitors that affect fibrinogen function or fibrin polymerization we suggest the use of fibrinogen concentrate as first-line therapy, potentially in combination with plasma exchange and immunoadsorption. Cryoprecipitate may be considered if fibrinogen concentrate is not available but high volumes are likely to be required. FFP is unlikely to be adequate treatment.

**Inhibitor eradication.** In patients with abnormal bleeding, immunosuppression should be started as soon as the diagnosis has been made. Regimens used to treat acquired FVIII inhibitors can be used and some data relating to corticosteroids, alkylation agents and rituximab have been reported (Tosetto et al, 1995; Lorand et al, 2002; Gregory & Cooper, 2006).

**Inhibitors to prothrombin and thrombin**

Most neutralizing autoantibodies against thrombin appear in patients exposed to topical preparations of bovine thrombin or fibrin glue during major surgery and these antibodies react mainly with bovine coagulation proteins. Prospective studies have found evidence of immunization to bovine thrombin and/or factor V (FV) in 30–50% of such patients (Banninger et al, 1993). Antibodies to bovine thrombin associated with fibrin glue may cause anaphylaxis if the patient is re-exposed to fibrin glue (Milde, 1989). Necker fibrin glue products contain human thrombin, thereby reducing the risk of antibody formation.

Other acquired inhibitors directed against human thrombin are usually associated with autoimmune conditions, monoclonal gammapathies or a polyclonal increase in immunoglobulin (Craddock et al, 1953; Frick, 1955; Perkins et al, 1970; Gabriel et al, 1987).

Some LAs cause acquired hypoprothrombinaemia-lupus anticoagulant syndrome (HLAS) and may cause severe bleeding (Fleck et al, 1988; Vivaldi et al, 1997). HLAS is most common following viral infection in children and should be considered in a child with a prolonged PT and aPTT and recent onset of bruising or bleeding. The low FII is often transient though the LA may take longer to resolve.

**Laboratory investigation.** An antibody against prothrombin would be expected to cause a prolonged PT and aPTT that do not correct with normal plasma and to have a normal TT. An antibody against thrombin would be expected to cause a markedly prolonged TT with a normal reptilase time. The Clauss fibrinogen assay is often normal in such patients due to a higher concentration of thrombin reagent and higher dilution of test plasma than in the thrombin time. The FII level will be low and the inhibitor titre can be estimated in a modified Bethesda assay.

Antiprothrombin antibodies are most commonly associated with antiphospholipid syndrome and this should be investigated appropriately (Keeling et al, 2012). ELISA for antiprothrombin antibodies may be useful.

**Clinical features.** Inhibitors to prothrombin or thrombin may be associated with bleeding (Strickler et al, 1988; Flaherty et al, 1989; Lawson et al, 1990; Banninger et al, 1993) or thrombosis but many are asymptomatic despite significant laboratory abnormalities (Mollica et al, 2006).

**Haemostatic therapy.** We suggest using FEIBA to partially overwhelm the inhibitor and also to potentially provide some bypassing activity, especially if the inhibitor prevents activation of prothrombin to thrombin and the action of thrombin. Alternatively, PCC may be used to overwhelm the inhibitor whilst monitoring prothrombin and factor VII, IX and X levels. Hypoprothrombinaemia associated with a LA is often due to increased clearance of prothrombin and in these cases a PCC can be used with regular monitoring of factor levels. Combination with plasmapheresis may be considered for resistant cases. rFVIIa is less likely to be efficacious, because its mode of action is through activation of prothrombin.

**Inhibitor eradication.** If the patient is experiencing abnormal bleeding, immunosuppressive regimens used for AHA can be considered.

**Inhibitors to factor V (FV)**

Neutralizing autoantibodies to FV usually occur in older people and have been reported in association with $\beta$ lactam oraminoglycoside antibiotics or malignancy. Approximately two-thirds develop following topical bovine thrombin or fibrin glue. Haemorrhagic complications usually occur after repeated exposures to bovine thrombin products. The prognosis is gen-
erally good and patients exposed to bovine thrombin appear to have a better prognosis than idiopathic inhibitors. Autoimmune inhibitors may disappear spontaneously within a few months (Feinstein, 1978; Knobl et al, 1997).

Laboratory investigation. An inhibitor to FV should be suspected when a prolonged aPTT and PT do not correct with mixing studies. FV activity will be low. The titre of the antibody can be estimated with a modified Bethesda assay. The dilute Russell viper venom time (dRVVT) is likely to be prolonged but no correction with excess of phospholipid will be seen, allowing differential diagnosis from LA. Contamination of a blood sample with EDTA will mimic a FV inhibitor – testing a fresh sample or measurement of K+ in the sample can exclude such an error (Favaloro et al, 2006).

Clinical features. Bleeding manifestations are similar to those of congenital FV deficiency and range from mild epistaxis or gingival bleeding, to life-threatening retropertitoneal haemorrhage (Emori et al, 2002). Other presentations include haematospermia, haematuria, and severe gastrointestinal bleeding. The severity of bleeding varies considerably and may correlate with the FV level. Some patients have no bleeding even with surgery, despite markedly abnormal laboratory findings. The bleeding phenotype may be related to the susceptibility of FV in the platelet alpha granule to be neutralized (Chediak et al, 1980; Nesheim et al, 1986). Severe bleeding complications have been observed with an anti-FV antibody that was present in both the patient’s plasma and platelets (Ajzner et al, 2003). A hypercoagulable state was described in a woman with an antibody that blocked the FVa cleavage sites causing severe activated protein C resistance (Kalafatis et al, 2002).

Haemostatic therapy. Patients can often be managed with FFP and platelets transfusions because platelets can bypass some inhibitors (Chediak et al, 1980). Salvage therapies for unresponsive bleeds includes high volumes of FFP and plasmapheresis with extracorporeal immunoabsorption (Tribl et al, 1995) or bypassing agents. FEIBA might be predicted to be more efficacious than rFVIIa in this situation. High dose IVIG has also been used (de Raucourt et al, 2003).

Inhibitor eradication. Because autoimmune FV inhibitors may disappear spontaneously over weeks to months, it is uncertain whether immunosuppressive regimens affect the natural history. Regimens used to treat FVIII inhibitors may be tried.

Inhibitors to FVII

Acquired FVII inhibitors may inhibit function or accelerate clearance and have been described in association with the use of antithymocyte globulin in aplastic anaeemia, the use of penicillins, cephalosporins and interleukin-2, sepsicaemia, pancreatitis and malignancy, such as multiple myeloma. A specific autoimmune antibody has been isolated from the plasma of a patient with acquired immunodeficiency syndrome (AIDS) who had a concurrent lupus-like anticoagulant. Whether these are genuine or chance associations is unknown (Hay, 2012).

Laboratory investigation. Typical findings will be of an isolated prolonged PT that does not correct with normal plasma. In these cases it is particularly important to exclude a LA. The FVII level will be low and the inhibitor titre can be estimated with a modified Bethesda assay.

Clinical presentation. The pattern of bleeding may be severe and intracranial haemorrhage is reported. Haemarthroses are uncommon in both congenital and autoimmune FVII deficiencies, for overview see (Hay, 2012).

Haemostatic treatment. We suggest first-line treatment with FEIBA because it activates coagulation without the need for FVII. Other options include rFVIIa, FVII concentrates and PCC although these are less likely to work unless a dose sufficient to overwhelm the inhibitor can be given. FFP is unlikely to be efficacious. If these strategies are unsuccessful, plasmapheresis with or without concomitant intravenous immunoglobulin may be considered.

Inhibitor eradication. Anecdotal reports suggest that eradication of the associated underlying disease state is important and recovery may be seen after tumour regression following chemotherapy (Weisdorf et al, 1989). Standard immunosuppressive regimens can be used.

Inhibitors to factor IX (FIX)

FIX auto-antibody inhibitors are associated with diseases similar to those underlying acquired FVIII inhibitors and have similar bleeding patterns (Lechner, 1971; Largo et al, 1974; Miller et al, 1978; Collins & Gonzalez, 1984).

Laboratory diagnosis. Typical findings are of an isolated prolonged aPTT that does correct with normal plasma. Auto-antibodies to FIX are immediate-acting. The specificity of the inhibitor can be confirmed with a FIX assay, and the degree of inhibition can be quantified using a modified Bethesda assay.

Haemostatic treatment. We suggest first-line treatment with either rFVIIa or FEIBA using regimens recommended for acquired FVIII deficiency. If bleeding is not controlled the alternative bypassing agent should be used. Treatment with high doses of FIX concentrate or a PCC is less likely to be efficacious. Unlike anti-FIX inhibitors in congenital haemophilia B, anaphylaxis has not been described although very few patients have been treated and close observation of patients is required.
Inhibitor eradication. Many inhibitors resolve spontaneously within a few months and it is not clear whether the natural history is altered by immunosuppressive therapy. The use of corticosteroids, with or without high-dose IVIG, has been reported anecdotally to be successful (Mazzucconi et al., 1999). If these are unsuccessful, similar regimens for the treatment of resistant AHA can be tried.

Inhibitors to factor X (FX)

Although acquired FX deficiency is usually associated with amyloidosis, there are occasional reports of acquired FX deficiency caused by an inhibitor to FX, with 34 cases included in a recent review (Lee et al., 2012). These cases presented with sudden onset of bleeding and possible underlying diseases were described. The causative relationship is not certain but 38% had evidence of respiratory infection and 24% had a malignancy, including four patients with acute myeloid leukaemia (Lee et al., 2012).

Laboratory diagnosis. Coagulation screens are likely to show a prolonged PT and aPTT that do not correct with normal plasma. The TT and fibrinogen will be normal. The DRVVT may also be prolonged and does not correct with normal plasma or phospholipid. Plasma FX activity will be reduced and the inhibitor titre can be estimated with a modified Bethesda assay.

The main differential diagnosis is FX deficiency associated with increased absorption due to systemic amyloidosis. In this situation the PT and aPTT correct with normal plasma and there will be no evidence of an inhibitor. In systemic amyloidosis, other coagulation factors, such as factors VII, IX and V and VWF may be reduced (Mumford et al., 2000).

Clinical features. The commonest reported bleeding in 34 cases was gastrointestinal followed by haematuria. Other bleeding included ecchymoses, mucosal bleeds and in three cases haemarthrosis. There was no bleeding in 29% at presentation. The bleeding severity or pattern did not correlate well with the FX level but all patients with a level <1 iu/dl had active bleeding (Peuscher et al., 1979; Currie et al., 1984; Mulhare et al., 1991; Lankiewicz & Bell, 1992; Rao et al., 1994; Matsunaga & Shafer, 1996; Lee et al., 2012).

Haemostatic treatment. Case studies report very poor haemostatic responses to FFP and vitamin K (Hay, 2012). Similarly, there are several reports where PCCs and rFVIIa have not been effective. rFVIIa is unlikely to be efficacious because its mode of action is through activation of FX and although apparently effective in some reports of splenectomy (Boggio & Green, 2001), two patients with amyloidosis-associated FX deficiency bled excessively following splenectomy despite the use of rFVIIa, one had a baseline FX of 3 iu/dl and the other had a baseline of 6 iu/dl (Thompson et al., 2010).

Good haemostatic control has been reported in one patient treated with Autoplex aPCC (Henson et al., 1989). However, thrombotic complications can occur with such concentrates, including cerebral infarction (Mulhare et al., 1991).

We suggest that bleeds are treated first-line with FEIBA, partially to overwhelm the inhibitor and provide FX activity and also potentially to supply an additional bypassing effect. If a PCC is used to overwhelm the inhibitor and replace the FX it may need to be used with immunoadsorption. Close laboratory monitoring of the FII, FVII, FIX and FX levels is required to sustain adequate FX levels whilst avoiding excessively high FII, VII and IX levels.

Inhibitor eradication. Treatment of underlying disease appears to be important for the eradication of acquired FX inhibitors. Immunosuppression using regimens used to treat AHA can be used but it is unclear whether these alter the natural history of the disease.

Inhibitors to factor XI (FXI)

Autoimmune antibodies to FXI are typically associated with an underlying collagen vascular disease, such as SLE, but have some reports of association with haematological malignancy, autoimmune gastrointestinal diseases or treatment with phenothiazines. The bleeding pattern is unpredictable and haemorrhage is often absent (Castro et al., 1972; Krieger et al., 1975; Canoso et al., 1977; Vercellotti & Mosher, 1982; Reece et al., 1984; Goldsmith & Silverman, 1985; Goodrick et al., 1992; Billon et al., 2001; Kyriakou et al., 2002).

Laboratory investigation. Patients with FXI inhibitors typically have an isolated prolonged aPTT that does not correct with normal plasma. Plasma FXI activity is low and the inhibitor titre can be estimated with a modified Bethesda assay. Often, acquired FXI inhibitors are asymptomatic and are detected when coagulation is tested for some other reason.

Haemostatic treatment. We suggest that bleeding should be treated with rFVIIa (Billon et al., 2001) or FEIBA with regimens similar to those used for AHA. If this is unsuccessful, FXI concentrates potentially with immunoadsorption could be considered.

Inhibitor eradication. Acquired FXI deficiency is often not associated with bleeding and so immunosuppression may not be indicated for all patients. In those with bleeding, regimens used to treat AHA can be used. Inhibitor eradication has been observed following corticosteroid therapy in patients with SLE (Vercellotti & Mosher, 1982) and chemotherapy for CLL (Goodrick et al., 1992).
Inhibitors to FXIII

Acquired inhibitors to FXIII have been reported to neutralize FXIII activation by thrombin, transamidase activity or block FXIII binding sites on fibrin (Boehlen et al, 2013; Hay, 2012).

Laboratory diagnosis. Screening coagulation tests such as the aPTT, PT, TT and fibrinogen level, are usually normal, although the thromboelastogram may be abnormal (Hsieh & Nugent, 2008). Clot solubility tests may be abnormal, although sensitivity is poor. Plasma FXIII activity assays, either based on ammonia release or amine incorporation, usually show FXIII levels <3%; neutralizing antibodies can be detected using mixing studies, although binding assays may be required to detect non-neutralizing antibodies. Variable inhibitors to FXIII can usually be detected in vitro with mixing tests, using patient plasma or purified IgG fraction to inhibit the cross-linking of α chains of fibrin in normal plasma.

Clinical features. The bleeding pattern of acquired FXIII deficiency may be more severe than congenital FXIII deficiency and includes haemarthroses, haematoma, menorrhagia, surgical bleeding, poor wound healing and recurrent miscarriage. Intracranial bleeds appear to be common (Nakamura et al, 1988; Gris et al, 1992; Lorand et al, 2002). For review of bleeding symptoms see Boehlen et al (2013).

Haemostatic treatment. Large doses of FXIII concentrate are likely to be the safest and most effective treatment option (Gootenberg, 1998; Boehlen et al, 2013), potentially in combination with plasma exchange and immunoadsorption. Cryoprecipitate has also been used successfully (Gregory & Cooper, 2006). Thrombotic complications have been reported (Boehlen et al, 2013).

Inhibitor eradication. In patients with abnormal bleeding, immunosuppression should be started as soon as the diagnosis has been made. Regimens used to treat acquired FVIII inhibitors can be used and some data relating to corticosteroids, alkylating agents and rituximab have been reported (Tosetto et al, 1995; Lorand et al, 2002; Gregory & Cooper, 2006). A possible immunosuppression strategy has been proposed (Boehlen et al, 2013).

Recommendations

1 Patients with a recent onset of bleeding should be investigated for acquired inhibitors of coagulation. Referral to a specialist laboratory may be required (Grade 2C).

2 Patients with a confirmed acquired factor inhibitor should be managed jointly with a haemophilia centre experienced in the management of inhibitors (Grade 2C).

3 Some patients with acquired factor inhibitors (other than FVIII) who are asymptomatic may not require treatment because some inhibitors are transient and others do not cause clinical bleeding, despite significant laboratory abnormalities (Grade 2C). Patients with clinical evidence of bleeding should be immunosuppressed to attempt to eradicate the inhibitor with the same regimens used to treat FVIII inhibitors (Grade 2C).

4 Haemostatic therapy depends on the specificity of the inhibitor. We suggest using the treatment options outlined in Table I (Grade 2C).

Disclaimer

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