The Diagnosis and Management of Factor VIII and IX Inhibitors: A Guideline from the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)

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Summary:

The revised UKHCDO factor VIII/IX Inhibitor Guidelines (2000) are presented. A schema is proposed for inhibitor surveillance which varies according to the severity of the haemophilia and the treatment type and regimen used. The methodological and pharmacokinetic approach to inhibitor surveillance in congenital haemophilia has been updated. Factor VIII/IX genotyping of patients is recommended to identify those at increased risk.

All patients who develop an inhibitor should be considered for immune tolerance induction (ITI). The decision to attempt ITI for factor IX inhibitors must be carefully weighed against the relatively high risk of reactions and the nephrotic syndrome and the relatively low response rate observed in this group. The start of ITI should be deferred until the inhibitor has declined below 10 BU/ml, where possible. ITI should continue, even in resistant patients, where it is well tolerated and so long as there is a convincing downward trend in the inhibitor titre.

The choice of treatment for bleeding in inhibitor patients is dictated by the severity of the bleed, the current inhibitor titre, the previous anamnestic response to factor VIII/IX, the previous clinical response and the side-effect profile of the agents available. We have reviewed novel dose-regimens and modes of administration of FEIBA and rVIIa and the extent to which these agents may be used for prophylaxis and surgery.

Bleeding in acquired haemophilia is usually treated with FEIBA or rVIIa. Immunosuppressive therapy should be initiated at the time of diagnosis with Prednisolone 1mg/kg/day +/- cyclophosphamide. In the absence of a response to these agents within 6 weeks, second-line therapy with Rituximab, Cyclosporine A, or other multiple-modality regimens may be considered.

INTRODUCTION:

Since the publication of the previous guideline on the detection and management of factor VIII inhibitors (Hay *et al,* 2000), significant diagnostic and therapeutic advances have taken place. The UK Haemophilia Doctors Organisation (UKHCDO) has therefore revised and updated those sections of the earlier guideline covering areas of clinical practice which we felt had developed, to define best current practice internationally. Although all sections of the previous guideline have been reviewed, some sections required little revision whereas others required rewriting. For those areas which did not require revision, the reader is referred back to the previous guideline. The evidence-based approach used highlights the need for future clinical trials in areas where current treatment strategies are based on uncontrolled observations or where there is a dichotomy of clinical opinion.

Methods:

The guidelines were drafted by the UKHCDO Inhibitor Working Party and circulated to the Executive Committee of the UKHCDO for consultation. Members of UKHCDO and its working parties make an annual declaration of interest to UKHCDO and to their Hospital Trusts.

Relevant scientific papers were identified using Pubmed, using index terms H(a)emophilia, factor VIII and IX, inhibitors, antibodies, alloantibodies, auto-antibodies, rVIIa, Novoseven, FEIBA, PCC, Rituximab, management. Recommendations were based on reports with the highest levels of evidence (AHCPR 1992, Appendix 1).

Diagnosis and investigation of factor VIII and IX inhibitors:

General strategy for inhibitor surveillance

The frequency of testing for inhibitors in haemophilia A and B should reflect the type and severity of haemophilia, the regimen of factor concentrate replacement (prophylactic or on-demand), and the extent of prior exposure to factor concentrate. Prospective studies of recombinant factor VIII concentrates in previously untreated patients (PUPs) with severe haemophilia A demonstrate that although inhibitors may arise at any time in the patient's life, the majority develop early, after a median of 10 exposure days (EDs) (range 3 – 69 EDs, 90th centile

26 EDs, n = 76) (Bray *et al*, 1994; Lusher *et al*, 1993; Lusher, 2003; Rothchild *et al*, 1998). Inhibitor development is less common in patients who have received more than 150 EDs of factor concentrate replacement (McMillan *et al*, 1988). Inhibitors are also less frequent in individuals with haemophilia B (Sultan, 1992) and patients with milder forms of haemophilia A (Hay and Lee, 2002; Rizza *et al*, 2001). The development of FIX inhibitors may be associated with life threatening anaphylactic reactions (Warrier, 1998a).

Laboratory assessment in inhibitor screening

The approach to screening for inhibitors will be dependent on the treatment regimen used by the patient. Individuals on prophylaxis whose trough FVIII or FIX levels are >1 IU/dl do not warrant further screening tests for inhibitors. Screening for inhibitors is normally conducted using an APTT-based or Bethesda-based method. A possible APTT method has been described (Ewing and Kasper, 1982) but each laboratory must standardise this test independently and determine what they consider to be an abnormal result. Recently, a screening method that is both simpler and more sensitive than the Bethesda Assay has been reported (Keeling *et al*, 2005). Factor VIII/IX half life measurement is the most sensitive way to detect an inhibitor. Factor VIII/IX recovery is probably more sensitive than screening assays or Bethesda methods.

FVIII inhibitor and FIX inhibitor quantification.

The reader is referred back to the previous guideline (Hay *et al*, 2000). It is no longer recommended that inhibitors be routinely measured against porcine FVIII whilst this product is unavailable. If recombinant porcine FVIII concentrates become available, appropriate quantification of cross reactive inhibitors will be required.

Laboratory diagnosis of acquired haemophilia.

The reader is referred to the previous UKHCDO inhibitor guidelines (Hay *et al*, 2000).

Factor VIII / IX Recovery

Factor VIII/IX recovery can be determined from the peak factor level that occurs in the first hour following infusion. This figure should be reported as an incremental value, subtracting the pre-infusion level from the post-infusion and then it should be reported as 'adjusted *in vivo* recovery' (IVR) on a per-dosage basis as IU/ml or IU/dl per IU/kg (Lee *et al*, 2001). The practice of calculating expected recovery using a recovery constant and estimated plasma volume is no longer considered valid since this was originally calculated on early plasma derived concentrates and newer high-purity plasma derived and recombinant FVIII and FIX concentrates have different pharmacokinetic properties (Morfini, 2003; White *et al*, 1998). A pre-infusion sample should be taken (on which the inhibitor screen may also be performed, if required) and a post-infusion sample taken 15-30 minutes after the end of the infusion. The patient's weight is required to calculate the dose/kg given.

Normal adjusted IVR values for plasma derived FVIII for older children and adults are usually between 2.0 and 2.5 IU/dl / IU/kg (Bjorkman and Berntorp, 2001; Morfini, 2003) but can vary slightly according to product. Recombinant FVIII has similar recovery values e.g. Recombinate mean (SD) 2.6 (0.5) IU/dl / IU/kg and Advate 2.4 (0.5) (Tarantino *et al*, 2004).

Factor IX IVR values are lower than FVIII because factor IX has a much larger volume of distribution. Plasma-derived FIX IVR values range from 0.7 - 1.7 (Gascoigne *et al* 2004, Morfini, 2003) and Benefix from 0.46 – 1.38 IU/dl / IU/kg (White *et al*, 1997; Ewenstein *et al*, 2002).

Pharmacokinetic data of both FVIII and FIX in infants and young children are sparse, particularly in infants < 1yr old. Clinical data suggests that recovery in infants and children is lower than in adults. Recent data from the Advate study group showed that the mean (SD) IVR of children aged 1-6yrs was 1.89 (0.43), range 1.2 – 3.4 IU/dl/IU/kg, recovery correlating positively with body mass index. The mean recovery value was 20% lower than that of older children and adults using the same product, confirming suspicions that FVIII recovery is moderately reduced in small children (Blanchette *et al*, 2004). The situation is less clear for factor IX in patients with haemophilia B. Data from the Recombinant FIX Study Group (Shapiro *et al*, 2005) showed a mean IVR (SD) for Benefix in infants and small children of 0.68 (0.27) IU/dl / IU/kg. There was no difference in IVR between the age groups 1 month to

2 years and 2-12 years. A further study comparing pharmacokinetic data between different age groups observed a mean IVR of 0.61 IU/dl / IU/kg in boys aged 4-9 yrs, 0.79 in boys aged 10-19 yrs and 0.88 in men aged 50-56 yrs (Bjorkman *et al*, 2001).

There are minor differences when recovery is calculated using one or two-stage assays and recovery may be 20 to 30% higher when the chromogenic assay method is used (Lee *et al*, 1996). Pharmacokinetic studies of B-domain deleted recombinant factor VIII (BDDrFVIII, Refacto, Wyeth, USA) should be conducted using a chromogenic method or a one stage method using the Refacto standard for this product. A one-stage FVIII assay with a normal standard had a mean IVR 1.59 compared to 2.06 when measured using a chromogenic method with the Refacto laboratory standard in subjects > 12 yrs old (Morfini *et al*, 2003).

Factor VIII / FIX half-life studies:

When measuring half-life, it is essential to continue sampling for at least 48 hours post-infusion in order to take account of both the distribution half-life and the elimination half-life (Bjorkman and Carlssen, 1997). The problem of multiple half lives is overcome by analysing the data using a model-independent (non-compartmental) method. Although model-dependent analysis may also be used, this will not give the same result (Lee *et al*, 1990; Morfini *et al*, 1991; Pascual and Montoro, 1997). A number of different computer software programmes are available to analyse the data but may give different estimates of pharmacokinetic parameters. Recent SSC recommendations suggest that a series of simple linear regression models can reduce calculations involved but they emphasise that rigorous statistical analysis is required in order to assign the correct regression function (Lee *et al*, 2001).

In most half-life studies, 50 IU/kg of factor VIII or 75 IU/kg of factor IX are infused after a washout period of at least 72 hours or when the baseline factor level is reached (typically <1.0 IU/dl). To obtain the maximum information it is recommended that the following samples are taken; pre-dose, 15 mins, 30 mins, 3hrs, 6 hrs, 9 hrs, and 24 hrs with additional sampling at 28 and 32 hrs for FVIII and 48 and 72 hrs for FIX (Lee *et al*, 2001). In practice however this number of samples may not be feasible.

The mean terminal half life (T½) for plasma derived FVIII concentrates in adults has been reported to range between 10 and 15 hours (Bjorkman and Berntorp, 2001; Morfini, 2003) and values obtained with recombinant FVIII are similar; Recombinate mean T½ 14.7

hours (Morfini, 2003) and 11.2 hours (Tarantino *et al*, 2004), Refacto (chromogenic assay with Refacto standard) mean 10.05 hours (Morfini *et al*, 2003). The rAHF-PFM clinical study group compared pharmacokinetic data in adults and children and found a weak but significant positive correlation between half life and age – r = 0.34, p = 0.02 under the age of 6 (Blanchette *et al*, 2004; Tarantino *et al*, 2004) (aged 1-6 yrs mean (SD) 9.84 (1.88) hrs; aged 10-65 yrs mean 11.98 (4.3) hrs range 8.38-17.96).

Factor IX concentrates usually have a much longer T½ than FVIII, but reports vary widely with mean values for plasma derived factor IX concentrates ranging from 7 to 34 hrs (White *et al*, 1997; Ewenstein *et al*, 2002; Berntorp and Bjorkman 2003). Recombinant FIX has been reported to have a mean T½ of 16.8 to 20 hrs (White *et al*, 1997; Bjorkman *et al*, 2001; Ewenstein *et al* 2002). The T½ of rIX in infants and small children with haemophilia B is unknown (Shapiro *et al*, 2005).

Role of FVIII and FIX Gene Mutation Analysis

The risk of inhibitor development in haemophilia A and B has been shown to be related to the underlying FVIII or FIX gene mutation (Hay and Lee, 2002; Green *et al*, 1991) and a positive family history of inhibitor development (Astermark *et al*, 2001). Therefore, determination of an individual's FVIII or FIX gene mutation may help in the assessment of their risk for inhibitor development. This is particularly valuable for mild and moderate haemophilia A and haemophilia B, where inhibitor development has been shown to be strongly associated with inheritance of "high-risk" factor VIII mutations or major deletions of the factor IX gene. In haemophilia B the risk of inhibitor development is almost zero for single amino acid substitutions, while 50% of individuals with FIX inhibitors have gross deletions and the vast majority of the remaining patients have nonsense mutation (Green *et al*, 1991). Mild and moderate haemophilia A is usually caused by missense mutations. Most of these mutations are associated with very low inhibitor risk but some, especially those in the A2, C1 and C2 domains of FVIII may cause a conformational change in the factor VIII molecule associated with a very high risk inhibitor development (Hay and Lee, 2002). Data from the UK National Haemophilia Database shows that 28% of FVIII inhibitors reported in the UK over the past 12 years occur in mild and moderate haemophilia A (Rizza *et al*, 2001), with an incidence of 0.84 and 3.5 inhibitors per 1000 patients for mild/moderate and severe haemophilia A, respectively (Hay and Lee, 2002). Therefore,

knowledge of the underlying FVIII/FIX gene mutation will identify individuals at a high risk of inhibitor development and guide appropriate inhibitor screening.

Recommendations:

FVIII and FIX mutation analysis should be undertaken in all patients with haemophilia A and B, especially newly diagnosed patients (Grade B recommendation based on level IIb evidence).

Lab assessment of patients on prophylaxis can be performed by the measurement of trough FVIII/FIX levels, or estimation of the FVIII/FIX half-life. If the trough FVIII/FIX level is <1 IU/dL or there is a suboptimal recovery (see section..) then screening should be conducted using a sensitive inhibitor screening method or the Nijmegen modification of the Bethesda assay (Grade C recommendation based on level IV evidence).

Patients treated with on demand therapy should be screened for inhibitors using a sensitive screening method or the Nijmegen modification of the Bethesda assay (grade C recommendation based on level IV evidence0.

In severe and moderately severe haemophilia A, previously untreated patients should be screened for inhibitors after every 5th ED until the 20th ED, then 3 to 6 monthly up to 150 EDs then once every 12 months (Grade C recommendation based on level IV evidence).

Inhibitor screening should also be performed prior to invasive procedures, when the frequency of breakthrough bleeding increases, or when the clinical or laboratory response to factor concentrate replacement is poor. (Grade C recommendation based on level IV evidence)

In mild haemophilia A screening for inhibitors is recommended after intensive replacement therapy, especially in individuals with high risk mutations. (Grade B level III)

In severe and moderately severe haemophilia B the frequency of screening for inhibitors should be the same as for severe haemophilia A The first 20 infusions of factor IX should be administered where facilities for paediatric resuscitation are immediately available in patients with severe haemophilia B with a known high-risk mutation or when the mutation is unknown (grade B recommendation based on level III evidence).

B-domainless factor VIII should be measured using either a chromogenic assay or a one-stage assay using a specific, standard (Grade B recommendation based upon level IIb evidence).

New inhibitors should be centrally notified to the National Haemophilia Database.

Clinical Management of Inhibitor Patients:

Immune Tolerance Induction:

It is usually recommended that when patients with haemophilia A develop inhibitors, they are offered immune tolerance induction (ITI) to eliminate the inhibitor and restore normal clinical responsiveness to factor VIII. The procedure for immune tolerance induction is fully described in the previous guideline (Hay *et al*, 2000) and by Hay (2005), and so only newer issues and those issues that remain contentious are reviewed below.

There remains a lack of consensus in relation to several issues which are reviewed briefly below. These include the importance of the dose and the type of factor VIII used for ITI, the role of concomitant immunosuppressive treatments such as Rituximab and the definition of failure of ITI.

Single centre series and registries suggest that although high-dose factor VIII (100-200 IU/kg/day) may achieve tolerance more rapidly than low-dose (25-50 IU/kg 3 X weekly), the outcome is similar in good-risk patients (starting inhibitor titre <10 BU/ml and peak titre <200 BU/ml) (Kroner, 1999; Brackmann *et al*, 1996; Mauser-Bunschotten *et al*, 1995; DiMichele, 2003). Low dose regimens are less costly and may also be administered without using a central venous line, thus avoiding the risk of infection which may seriously jeopardise the outcome of ITI. Since the relative efficacy of high and low-dose regimens is disputed, this hypothesis is the subject of an ongoing international randomised clinical trial (Hay *et al*, 2000). For further details contact **haemophilia@man.ac.uk** or **www.itistudy.com** . In contrast, there is a broad consensus that high-dose ITI is more successful than low-dose in poor risk patients (starting inhibitor titre >10 BU/ml, peak titre >200 BU/ml) (Kroner, 1999).

Since it is widely accepted that patients with a starting inhibitor titre <10 BU/ml have a much better outcome than those with a higher titre, it is recommended to treat the patient waiting to start ITI with rVIIa on-demand until the inhibitor titre has declined to <10 BU before starting ITI (Mariani *et al*, 1994; DiMichele and Kroner, 2002; Mauser-Bunschotten *et al*, 1995; Smith *et al*, 1999; Rocino and di Biasi, 1999). Experience with over 50 patients in the International

Immune Tolerance Study indicates that it takes a median of 3 months to decline to this level (CRM Hay, personal communication).

There is conflicting evidence that tolerance may be more readily achieved using low-purity factor VIII. Kreuz reported six patients resistant to ITI with high-purity factor VIII who were successfully tolerised when changed to low-purity factor VIII (Kreuz *et al*, 1996). It has been suggested either that impurities in low-purity concentrate are immunosuppressive or that von Willebrand factor in the concentrate masks inhibitor epitopes in the concentrate leading to a longer half-life in the inhibitor patient. The preliminary data from an un-randomised controlled comparison of high-purity vs low-purity factor VIII for ITI suggests that the outcome is superior when low-purity factor VIII concentrates are used (Kreuz, personal communication). The number of subjects in this study is still small, however, and since the patient characteristics have not been presented, the data are difficult to interpret. Furthermore, there are no controlled data showing a significant difference in outcome of ITI for low and high-purity factor VIII and success-rates quoted for low purity concentrates are generally similar to those published for high-purity and recombinant products (Mauser-Bunschotten *et al*, 1995; Brackmann *et al*, 1996; Smith *et al*, 1999; Rocino and di Biasi, 1999; Batlle *et al*, 1999). This question is also addressed by the ITI study (above) and is the subject of a proposed international randomised clinical trial (the RESIST study). Most immune tolerance induction is conducted using recombinant factor VIII at the present time. Convincing controlled data is required before the use of low-purity factor VIII for immune tolerance can be recommended.

Although the definition of successful ITI is accepted to be the restoration of normal pharmacokinetics established after a three-day washout period, the failure of ITI is more difficult to define. Most patients achieve tolerance within six to 12 months but a resistant minority may take 1-3 years or more to achieve tolerance (Brackmann *et al*, 1996; Kreuz *et al*, 1995). It is probably reasonable to continue tolerance for this length of time if it is well tolerated and if there is a continued and convincing downward trend in the inhibitor titre. Should the inhibitor titre fail to decline over a six month, infection-free, period then consideration should probably be given to stopping ITI. At the other extreme, it is recognised that a minority of patients will be super-high responders whose inhibitors rise rapidly to >500 BU/ml after starting ITI and who usually have a poor outcome. Only 1 of 14 such patients reported to the North American registry successfully achieved tolerance (DiMichele and Kroner, 2002), and it is probably reasonable in

such patients to abandon ITI after six to 9 months if there is no evidence of a significant decline in inhibitor within that time.

There are anecdotal accounts of the second line use of Rituximab in patients who have failed conventional ITI. Mixed responses to Rituximab have been reported in these circumstances (Mathias, *et al* 2004; Carcao, *et al* 2004). This experimental approach cannot be recommended as first line therapy at the present time.

Immune tolerance induction (ITI) requires study on an international collaborative basis if we are to learn how it may be optimised and applied in the most cost-efficient way. ITI must be viewed as a long-term investment and compared with the cost of life-long treatment in the presence of a persistent high inhibitor titre.

Immune Tolerance in Haemophilia B:

ITI for haemophilia B should be carefully considered because of the relatively poor (25%) overall success rate and the high risk of complications, including anaphylaxis and sometimes irreversible nephrotic syndrome (Ewenstein *et al*, 1997; Warrier *et al*, 1998b). For that reason, the first 20 or so factor IX infusions should be administered in the hospital setting. Should trtansfusion reactions occur, ITI should probably be discontinued since steroids and antihistamines have limited value in suppressing them. Furthermore, the nephrotic syndrome that commonly accompanies the reactions is often not reversible when the factor IX dose is reduced or the treatment discontinued. Regimens analogous to all of those described for factor VIII inhibitors have all been used in haemophilia B including low- and high-dose factor IX, and a modified Malmo regimen.

Recommendations:

Immune Tolerance Induction is recommended for patients with severe congenital haemophilia A and a confirmed factor VIII or IX inhibitor and should be considered as early as possible after the presence of an inhibitor has been confirmed (Grade B recommendation, level of evidence IIB).

It is recommended that bleeding should be managed on-demand using rVIIa (Novoseven) prior to ITI to avoid an anamnestic rise in inhibitor titre. The start of ITI should be deferred if possible until the inhibitor titre has fallen below 10 BU/ml (and preferably

below 5 BU/ml), which usually takes 3-6 months (grade B recommendation based on level III evidence).

ITI should continue as long as there is a convincing downward trend in inhibitor titre but should be abandoned if there is no decrease over a period of at least six months (Grade B recommendation based on level III evidence).

Careful consideration should be given to immune tolerance in patients with haemophilia B, given the relatively poor response rate and the risk of anaphylaxis and the nephritic syndrome. (Grade B recommendation, level III evidence.)

Patients with mild haemophilia from kindreds with high-risk mutations should be treated with DDAVP wherever possible. Should they develop an inhibitor, a trial of bypass therapy on-demand should precede consideration of ITI, the success rate of which is low in this group. (Grade C recommendation, level IV evidence)

It is recommended that all patients undergoing ITI be entered into comparative clinical trials of ITI, or that data from their ITI procedure be included in one of the international registries of ITI (Grade B recommendation based on level III evidence).

ITI should be conducted under the supervision of a Haemophilia Comprehensive Care Centre, as defined by HSG93(30) (Grade C recommendation based on level IV evidence).

TREATMENT OF BLEEDING IN CONGENITAL HAEMOPHILIA A AND FACTOR VIII INHIBITORS:

Products available for the treatment of bleeding in patients with factor VIII/IX inhibitors:

A number of haemostatic agents are available for the treatment of bleeding in patients with congenital haemophilia and inhibitors. These treatment options are examined in detail in a recent systematic review (Lloyd Jones *et al*, 2003).

DDAVP:

DDAVP is ineffective in severe haemophilia but may have a role in the management of patients with mild haemophilia and inhibitors. If a patient with mild haemophilia develops an inhibitor the antibody usually cross-reacts with the patient's own factor VIII reducing their

factor VIII baseline to <1 IU/dl (Hay *et al*, 1998). In other cases the antibody may not react with the patient's mutant factor VIII and their baseline factor VIII activity is therefore unaffected. DDAVP may be effective in such cases and is the treatment of choice for minor bleeding episodes in patients with mild haemophilia and a high-risk mutation.

Human factor VIII:

Patients with persistently low-titre inhibitors <2 BU/ml will respond to increased doses of human factor VIII and may remain on home-therapy with factor VIII. It is common clinical experience that inhibitors of up to 5 BU/ml may be overcome by very large doses of human factor VIII. Factor VIII is reserved for life and limb threatening emergencies in patients who have a brisk anamnestic response to this product.

Porcine factor VIII

Porcine FVIII (Hyate:C, Speywood, UK.) has been withdrawn. Its use was reviewed in the previous guideline. Recombinant porcine factor VIII is currently in clinical trial but is unlicensed and not yet available for general use.

Prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCCs):

Prothrombin complex concentrates, containing varying amounts of factors II, VII, IX and X. PCCs are effective in approximately 50% of haemarthroses (Lusher *et al*, 1980). APCCs (FEIBA) have undergone some degree of activation during manufacture and so contain higher levels of activated factors. FEIBA was found to be more effective than PCC in a controlled comparison, with response-rates of 64% and 52% respectively (Sjamsoedin *et al*, 1981). Response rates with FEIBA have been reported to be as high as 80-90% (Hilgartner & Knatterud, 1983; Negrier *et al*, 1997). Negrier *et al* (1997) reported that FEIBA had controlled bleeding effectively after 95% of surgical procedures. Success-rates of 75% (3/4) and 95% (13/14) have also been reported in two prospective surgical studies (Hilgartner & Knatterud, 1983; Tjonnfjiord 2004).

Recent experiments suggest that the active moiety of FEIBA may be a complex of activated factor X and prothrombin (Turecek *et al*, 2004). Traditionally, the dose of APCCs

has been adjusted clinically, uninformed by laboratory monitoring, though the thrombin generation assay may offer this possibility in the future (Varadi *et al*, 2003). Thrombin generation assays suggest that FEIBA has an effective half-life of 4-7 hours.

The use of activated and non-activated prothrombin complex concentrates has been associated with isolated episodes of venous thromboembolism, myocardial infarction and disseminated intravascular coagulation (Chavin *et al,* 1988; Mizon *et al,* 1992; Lusher, 1994). This risk appears to be rare, with a frequency estimated at 4-8 events per 10^5 infusions (Ehrlich *et al*, 2002; Aledort, 2004; Aledort, 2005). This risk is greater in a surgical context, in the elderly, in the presence of advanced liver disease and pre-existing ischaemic heart disease and when very large doses are used. Since thrombotic risk factors were present in 83% of the cases reported, the extent of the risk attributable to FEIBA is unclear (Ehrlich *et al*, 2002). Isolated episodes of myocardial infarction and DIC have been reported in patients lacking these clinical risk factors, however, when treated with very large doses of PCCs or APCCs.

The recommended dose of FEIBA is 50-100 u/kg, with a maximum daily dose 200 u/kg. Concurrent anti-fibrinolytic therapy carries a theoretical risk of increased thrombogenicity and is generally avoided.

FEIBA contains some factor VIII and may induce an anamnestic response (Negrier *et al*, 1997). Although the efficacy of PCCs and aPCCs is independent of the inhibitor titre, such an anamnestic response may compromise the subsequent response to large doses of factor VIII.

Recombinant factor VIIa (rVIIa):

Clinical experience with rVIIa has been reviewed by Lusher (1998a) and Lloyd Jones (2003). A dose of 90 μg/kg rVIIa has been shown to control 70-100% of bleeding episodes. Between one to three bolus doses of 90 μg/kg given three-hourly have typically been used as home treatment for haemarthrosis and mild bleeding episodes (Key *et al*, 1998; Santagostino *et al*, 1999). Key (1998) reported rVIIa to be effective in 92% of episodes after a mean of 2.2 doses, though all patients received one further dose after a response had been noted. Santagostino *et al* (1999) reported that 40% of mild or moderate bleeding episodes responded to a single infusion and a further 40% responded to two infusions with a partial response in a further 11%. This study also showed a greater success-rate for treatments initiated early.

Although a standard dose of 90 μg/kg has tended to be used there are few dose finding studies. A randomised dose comparison has shown that 35μg/kg had similar efficacy to 70μg/kg for haemarthroses but that the 70 ug.kg was more effective for muscle haematomas (Lusher *et al*, 1998b). Larger doses may be required for serious bleeding or surgery, since a randomised study of 29 patients with factor VIII and IX inhibitors undergoing surgery showed that 90μg/kg was more effective than 35μg/kg (Shapiro *et al,* 1998).

More recently the use of much larger doses has been considered (Hedner, 2004; Parameswaran *et al*, 2005; Kenet *et al*, 2003). Kenet compared a continuous-infusion protocol with a single-bolus "mega-dose" rVIIa (300 μg/kg) in three young patients with haemophilia. Higher efficacy and a quicker resolution of haemarthroses were obtained with the mega-dose schedule. 114 of 244 bleeding episodes were treated with the mega-dose schedule and 95 (83%) responded to a single dose. Re-bleeding occurred in 11/114 (10%) but uniformly responded to a second dose. Parameswaran et al (2005) described a retrospective registry of patients treated with variable doses of rFVIIa and reported an 84% response-rate at doses < 200 μg/kg and a 97% response-rate with doses > 200 μg/kg. Clinical trials comparing standard 90 μg/kg and "mega-dose" 300 μg/kg are awaited.

The short half-life makes treatment with rVIIa very costly if administered over a prolonged period. Administration of rVIIa by continuous infusion (CI) would seem logical but there are no comparative studies of CI and bolus administration. A study comparing two CI regimens showed that 68 of 94 episodes responded within 6 to 12 hours (Kenet *et al*, 2000). An early uncontrolled review suggested good efficacy in 91% of continuous infusions (Schulman, 1998).

rVIIa has a good safety record (Roberts *et al*, 2004) but cases of myocardial infarction, stroke, DIC and other thromboses have been associated with its use. These are rare, occurring with a frequency of 2.5 to 8 X 10^5 infusions. Concomitant risk factors or concomitant use of PCCs were present in about 80% of these cases and so the attributable thrombotic risk is unclear (Abshire and Kenet, 2001; Aledort, 2004; Aledort, 2005). It is also thought to be safe to give anti-fibrinolytic agents concurrently with rVIIa and this may increase efficacy.

Management of bleeding in Haemophilia A:

The management of an acute bleed in an inhibitor patient is determined by the severity

of the bleed, the current inhibitor titre and the previous anamnestic response. Low responders have inhibitor levels of < 5 BU/ml and do not develop an anamnestic response following exposure to factor VIII. High responders have inhibitor levels > 5 BU/ml and exhibit a brisk anamnestic response following factor VIII exposure. Although the choice of 5 BU/ml as the cut-off is arbitrary, clinical experience suggests that patients with inhibitors > 5BU are completely refractory to factor VIII. Figure 1 suggests therapeutic options for different categories of patient and bleed. The likely efficacy, the risk of anamnesis, and product-safety should all be considered when selecting the most appropriate treatment. There is no convincing evidence that either Novoseven or FEIBA is clinically more effective or more thrombogenic than the other (Berntorp et al, 2005). Furthermore, it is a common clinical observation that patients who fail to respond to rVIIa may still respond to FEIBA and vice versa and that their response may vary from time to time (Berntorp et al, 2005). Therefore, the choice of product may be dictated by clinical efficacy and if there is no response to one bypassing agent, then the alternate may be used.

Minor Haemorrhage;

Higher than normal doses of factor VIII may be effective in low responders and the response to this treatment can easily be monitored with factor VIII assays. Human factor VIII should be reserved for life-threatening bleeding in high-responders as the expected anamnestic response may compromise the subsequent efficacy of factor VIII for serious bleeding.

For patients in whom it is difficult to achieve satisfactory levels of factor VIII, we recommend treatment of minor haemorrhages with FEIBA or rVIIa. FEIBA and rVIIa have not been compared in a randomised, controlled trial. rVIIa may be preferred in those high responders with a low initial titre who have previously developed an anamnestic response when exposed to FEIBA.

Major Haemorrhage.

Very large dose of factor VIII sufficient to overcome the antibody may be considered in patients with an initial antibody titre of <5 BU/ml, whether high or low responder. The response to therapy must be monitored using factor VIII assays. If the initial antibody titre is >5 BU/ml human factor VIII is unlikely to be effective without removal of antibody by

plasmapheresis or immunoadsorption.

If inhibitor levels are too high for satisfactory levels of factor VIII to be achieved, rVIIa or FEIBA should be used for major bleeding. If the patient fails to respond to rVIIa or FEIBA then the alternate may be used, possibly combined with antibody removal with plasmapheresis or protein adsorption followed by high dose factor VIII (Rivard *et al*, 2003; Freedman *et al*, 2003). rVIIa has been given in combination with FEIBA in patients with unresponsive bleeding, the rationale being that since their mode of action differs that they may synergise (Schneiderman *et al*, 2004). This approach has not been subjected to clinical trial and is theoretically more thrombogenic than the use of either product alone, but may be considered in patients with life-threatening unresponsive bleeding.

Prophylaxis

The short half-life of factor VIII, rVIIa and FEIBA in inhibitor patients have limited their usefulness as secondary prophylaxis. The longer half-life of thrombin generation observed with FEIBA when compared with rVIIa suggest that FEIBA may be the more useful prophylactic agent. Indeed, Hilgartner *et al*, (2003) demonstrated limited efficacy of FEIBA 50-100 u/kg 3 times weekly in reducing the rate of joint bleeding in 4 of 6 patients and the rate of joint deterioration in 7 of 16 joints. Kreuz *et al*, (2000) found that a more aggressive regimen of FEIBA 50-100 u/kg twice daily arrested joint deterioration and largely prevented bleeding in 5 patients. In contrast, Brackmann *et al*, (2000) found that rVIIa 90ug/kg BD did not influence the frequency of haemarthroses in five patients whereas a regimen of regular PCCs reduced the rate of bleeding by 50% in a further four. Two recent case reports of prophylaxis using rVIIa in the very high dose of 200ug/kg 6 to 12-hourly (Young *et al*, 2005), show rVIIa may be used for prophylaxis if given in high enough dose. These reports suggests that if bypass agents are used in large enough doses and are given sufficiently frequently, they may have a useful prophylactic effect, but at very considerable cost. Further studies are planned.

Surgery:

Surgery in haemophiliacs with inhibitors is a high-risk procedure which should not be undertaken lightly since no product can guarantee sustained haemostasis. Haemostasis must

be adequate perioperatively and for a period of days post-operatively, to facilitate wound healing. Elective procedures, in particular, need strong justification.

If the antibody titre is low, factor VIII may be considered. Such treatment is easily monitored and, if satisfactory factor VIII levels can be maintained, efficacy should be assured. An anamnestic response may render factor VIII ineffective in high responders after as little as 3-4 days but usually longer.

The main alternatives for high responders are FEIBA or rVIIa. Both FEIBA and rVII have been used successfully for surgery and many authorities believe that they may be used interchangeably since both seem to offer effective haemostasis in 80-90% of patients. (Goudemand *et al*, 2004; Tjonnfjord *et al*, 2004; Negrier *et al*, 1997). Tjonnfjiord (2004) has described 15 minor and six major surgical procedures conducted with FEIBA 200 U/kg/day without any severe or unexpected bleeding. Twenty further major orthopaedic procedures conducted using rVIIa in 17 and FEIBA in three have been reported (Rodriguez-Merchan *et al*, 2004). Excessive bleeding was observed in three of the patients treated with rVIIa.

A prospective uncontrolled study of rVIIa in surgery found that CI of 16.5 μg/kg/h did not produce reliable haemostasis (Smith *et al*, 2001). Another prospective uncontrolled study in severe haemorrhage or surgery reported that satisfactory haemostasis was obtained for 30 of 35 episodes (86%) with similar infusion rates but that FVIIC levels did not predict success (Santagostino *et al*, 2001). A prospective study using a rate of 50 μg/kg/h achieved plasma VIIC levels in excess of 30 IU/ml and achieved a good outcome in nine patients requiring major orthopaedic surgery although six need additional bolus doses (Ludlam *et al*, 2003). There have been no trials comparing CI with bolus doses in major surgery and no trials comparing standard bolus doses of 90 μg/kg with higher bolus doses. Surgery with this product is usually conducted using the licensed dose of 90 ug/kg 2-hourly, increasing the dose-interval after the first day or two.

Recommendations:

The management of an acute bleed depends on a clinical assessment of severity, knowledge of the inhibitor level and product(s) to which the patient has previously responded and whether the patient is a high or low responder. (Grade B recommendation based on level IIb evidence)

Minor haemorrhage: ***These may be managed with large doses of FVIII in low responders (Grade B level III). Otherwise FEIBA (Grade A, level Ib) or rVIIa should be used (Grade B, level III).***

Major haemorrhage ***may be treated with factor VIII if inhibitor titres are low enough to allow satisfactory plasma levels to be achieved (Grade B level III). Otherwise rVIIa or FEIBA is recommended (Grade C, level IV). If this fails, the alternate product may be used. An alternative approach is to use concomitant antibody removal using plasmapheresis or protein A adsorption and high-dose factor VIII or rVIIa and FEIBA in combination.(Grade C, level IV)***

Surgery: ***. Factor VIII can be used if satisfactory plasma levels can be achieved (Grade B level III). Otherwise rVIIa or FEIBA may be used (Grade C, level IV). If first-line therapy fails, then the alternate bypass agent may be used.***

All surgery in patients with factor VIII inhibitors should be conducted in a Haemophilia Comprehensive Care Centre. (Grade C, level IV)

Inhibitors in Haemophilia B:

The reader is referred to the previous UKHCDO inhibitor guidelines (Hay *et al*, 2000).

Acquired Haemophilia:

Introduction:

Acquired haemophilia is caused by auto-immune depletion or inhibition of a coagulation factor. The inhibitor is usually directed against factor VIII or VWF but inhibitors to all other coagulation factors have been described. Guidelines for the diagnosis and management of acquired VWD have recently been published (Pasi *et al*, 2004; Laffan *et al,* 2004). Acquired haemophilia A (Green and Lechner, 1981; Delgardo *et al*, 2003) leads to a potentially severe bleeding diathesis, often of sudden onset. The incidence of acquired haemophilia A is about 1.5 per million per year (Collins *et al*, 2005). Acquired haemophilia A has an equal sex distribution, presenting most commonly in the elderly at a median age of 70-

80 years (Delgardo *et al*, 2003, Lottenburg *et al,* 1987; Green and Lechner, 1981; Morrison *et al,* 1993, unpublished UKHCDO data). Although acquired haemophilia A is commonly associated with pregnancy, malignancy, pemphegoid, rheumatoid arthritis, SLE and other autoimmune diseases, no clinical association is identified in about half the patients (Green and Lechner, *et al* 1981; Morrison *et al*, 1993; Collins et al, 2005).

The clinical features of acquired haemophilia A differ from those of congenital haemophilia in that bruising, soft tissue, muscle bleeding, gastrointestinal and urinogenital bleeding are common manifestations whereas haemarthroses are not a prominent feature. Severe and life threatening bleeding is common but no haemostatic treatment is required in 25-33% of cases (Lottenburg *et al*, 1987, Collins *et al*, 2005). The mortality associated with acquired haemophilia A has been reported to be between 7.9% and 42% (Green and Lechner, 1981; Morrison *et al*, 1993; Hay *et al,* 1997, Delgardo *et al*, 2003, Collins *et al*, 2005). Deaths are attributable to bleeding, underlying illness, the age of the patient population and the side effects of immunosuppression (Collins et al, 2005 and Delgardo *et al*, 2003). Severe bleeding and haemorrhagic deaths may occur within the first few weeks after presentation but if the inhibitor is not eradicated severe and life threatening bleeds can occur at any time (Collins et al 2005 *et al*).

Treatment of Acquired Haemophilia:-

Elimination of the inhibitor should be attempted using immunosuppression, which is initiated as soon as the diagnosis has been established. Where successful, this restores haemostasis to normal.

Bleeding in acquired haemophilia should be treated aggressively, since there is a significant morbidity and mortality from haemorrhage. The options for haemostatic therapy are described below. The side effects of these agents are described in section 6, above.

Eradication of the inhibitor

Eradication of the inhibitor is important to restore normal haemostasis and minimize the length of time the patients is at risk of bleeding. Although about 25% of patients will achieve remission spontaneously without immunosuppression (Lottenburg *et al*, 1987) patients remain at risk of severe or life threatening bleeding until the inhibitor is eradicated, even if at presentation

they have relatively mild bleeding symptoms (unpublished UKHCDO data).

Steroids and cytotoxics: There is a lack of randomized studies in the area. The only published study shows that 30% of patients treated with prednisolone 1 mg/kg/day for 3 weeks achieve complete remission (CR). Randomisation at this point showed no difference in complete remission between patients who continued to be treated with prednisolone alone (CR 75%) or changed to cyclophosphamide (CR 50%) or a combination of prednisolone and cyclophosphamide (CR 50%) (Green *et al*, 1993). This study, however, did not have sufficient power to demonstrate a difference between the arms if one existed and did not continue treatment with prednisolone long enough to establish it effect, as the median time to remission is about 5 weeks (unpublished UKHCDO data).

Most other studies have reported retrospectively on single centre cohorts or collections of referral centre experience. Control patients have not been included and so all data must be treated cautiously. A meta-analysis has been performed on 20 of these studies (Delgardo *et al*, 2003) and a surveillance study in the UK has collected details on all patients with acquired haemophilia over a 2 year period.

The meta-analysis and the UKHCDO surveillance study both suggest that prednisolone 1 mg/kg/day results in the abolition of the inhibitor in approximately 60-70% of patients whilst 70-80% of patients respond to a combination of prednisolone and oral Cyclophosphamide 50-150mg/day (unpublished UKHCDO data and Delgardo *et al*, 2003). In both studies, however, the overall survival and disease free survival are the same for steroids and steroids plus cytotoxics (unpublished UKHCDO data and Delgardo *et al*, 2003). The median time to remission in the UKHCDO study was 35 days (range 2-360) and was the same for steroids and steroids plus cytotoxics. Other combinations of prednisolone with azathioprin or with cyclophosphamide and vincristine have been shown to be effective (Lian *et al,* 2002). Some authors suggest that the use of factor VIII in combination with immunosuppression improves the response rate but no controlled trials have been performed (Nemes *et al*, 2003 and Lian *et al*, 1989).

Alkylating agents may cause infertility, so prednisolone alone or combined with azathioprin may be preferred for patients with acquired haemophilia A associated with pregnancy. Some studies suggest that acquired haemophilia associated with pregnancy responds slowly to

immunosuppression (Hauser *et al*, 1995).

Rituximab: **When used as a first line therapy rituximab has been reported to be well tolerated and to achieve 80% complete remission when used as first-line therapy in 10 patients. No controls were included in the study. The two non responders achieved CR when cyclophosphamide was added to rituximab. Three patients relapsed but responded to further infusions of rituximab (Stasi *et al*, 2004).**

High-dose immunoglobulin: In some studies approximately 30% of patients with acquired haemophilia A have been reported to respond partially or completely to high-dose immunoglobulin 2g/kg given over two to five days although some patients received concomitant steroids (Struillou et al, 1993; Sultan *et al*, 1984; Schwartz *et al*, 1995; Green and Kwaan, 1987; Dykes *et al*, 2002). A large retrospective study shows no benefit for high dose immunoglobulin when added to prednisolone or cytotoxics (unpublished UKHCDO data).

Cyclosporin A: There are a number of case reports of cyclosporin A, either alone or in combination with other immunosuppression, successfully abolished an inhibitor after failure of first line therapies. Conventional doses of 10-15mg/kg/day to give normal therapeutic serum levels of 150-350 ng/ml have been used (Hart *et al*, 1988; Pfliegler *et al,* 1989; Schulman *et al*, 1996a).

Immunosuppression and immunoadsorption (modified Bonn/Malmo regimen) Zeitler et al (2005) reported 35 patients with acquired haemophilia and severe bleeding treated with a combination of oral cyclophosphamide 1-2mg/kg daily, prednisolone 1mg/kg daily, large volume immunoadsorption days 1-5 weekly, IVIG 0.3g/kg days 5-7 weekly and factor VIII 100u/kg daily. They report rapid control of bleeding with an undetectable inhibitor at a median of 3 days (95% CI 2-4) and complete remission in 88% of patients at a median of 14 days (95% CI 12-17). Although no control patients are reported, this treatment appears to achieve remission rapidly and should be considered for severely bleeding patients especially in those unresponsive to bypassing therapy.

Relapse

The relapse rate after first CR is about 20%. Most of these patients (70%) achieved a second CR (unpublished UKHCDO data) although some need long-term maintenance immunosuppression. Relapse of pregnancy related acquired haemophilia appears to be relatively rare but may occur and women should be warned of this possibility. The antibody may affect the factor VIII level of the fetus and this must be considered at the time of delivery. It has been of observed that in three women acquired haemophilia recurred in 4 of 6 subsequent pregnancies (Solymoss personal communication), however Coller et al (1981) reported no relapses in 9 subsequent pregnancies and the Italian Registry reports no relapses amongst four such patients (Baudo et al, 2003).

Treatment of Bleeding in Acquired Haemophilia:-

Options for first line treatment for bleeding episodes in patients with acquired haemophilia A include recombinant factor VIIa, activated prothrombin complex concentrate and porcine factor VIII. There are no comparative studies but the efficacy and risk of adverse events of these products appear to be similar. Porcine factor VIII is currently unavailable but both rFVIIa and aPCCs are widely used.

Activated Prothrombin Complex Concentrate: A retrospective study reported a complete response in 76% of severe and 100% of moderate bleeds. A median dose of 75u/kg was given 8 or 12 hourly. Adverse events were uncommon and there were no thrombotic complications (Sallah, 2004).

Recombinant factor VIIa: Hay (1997) reported the treatment of 60 bleeding episodes in 38 patients with acquired haemophilia A. These were generally severe bleeding episodes that had failed to respond to treatment with other blood-products. Efficacy was reported to be good for 75% bleeding episodes with a partial response in a further 17%. FVIIa was used as first line therapy in 14 bleeds and a good response was reported in all cases. Almost all responses occurred within 8-24 hours and so alternative therapy should be considered if a clinical response has not occurred within that time.

Desmopressin (DDAVP): If the inhibitor titre is low and residual factor VIII level measurable,

DDAVP may raise the circulating factor VIII activity sufficiently to treat minor non life-threatening bleeding (Chistolini *et al,* 1987; Mudad and Kane, 1993). The effect of DDAVP may be very transient and the factor VIII level should be monitored. DDAVP has no place in the management of patients with a very low factor VIII level.

***Factor VIII Concentrate*:** Most patients with acquired haemophilia are resistant to factor VIII replacement. The pharmacokinetics of factor VIII are unpredictable in this condition and the Bethesda assay is not predictive of factor VIII recovery and clinical response to human or porcine FVIII. Human factor VIII is usually neutralised with an early rapid parabolic reduction to a low level. This is sometimes followed by a slower second disappearance-phase such that a low level of residual factor VIII activity may persist for several hours. If used, close clinical and laboratory monitoring are required.

Recommendation:

The management of patients with acquired haemophilia should be supervised by Haemophilia Comprehensive Care Centres as defined by HSC 93(30) (Grade C recommendation based upon level IV evidence).

Bleeding should be treated without delay, using rFVIIa, aPCC or porcine factor VIII. (Grade B recommendation based on level IIb evidence).

It is recommended that immunosuppressive therapy be initiated as soon as the diagnosis of acquired haemophilia is established (Grade B recommendation based on level IIb evidence).

In the absence of randomized trials, immunosuppression should be initiated with Prednisolone 1 mg/kg/day either alone, combined with cyclophosphamide 50-100 mg/day orally or larger doses as an iv pulse. Cyclophosphamide and other alkylating agemnts should be avoided, if possible, in women of reproductive age. (Grade b recommendation based on level IIb evidence).

If there is no response within 6-8 weeks, second line therapies may be considered. These include Rituximab, and Cyclosporin A, multiple immunosuppressive agents and modified Malmo or Bonn regimens. Further studies are required before Rituximab can be considered 1st line therapy. (Grade C recommendation based on level V evidence).

Declaration of Interest:

All Members of the executive of the UKHCDO and UKHCDO working party members are obliged to present a declaration of interests to the Chairman of UKHCDO annually. None of the authors has any shareholding in any pharmaceutical company. None of the authors is acting as an advisor or consultant for any of the manufacturers in relation to products currently used for the treatment of factor VIII/IX inhibitors. Although all of the authors have been involved in clinical research with rVIIa and some with HYATE:C and FEIBA, none of these studies is ongoing.

Disclaimer:

Whilst every effort has been made to ensure that the advice and information in these guidelines is true and accurate at the time of going to press, neither the authors, UKHCDO, nor the publishers accept any legal responsibility for the content of the guideline.

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B Attock, T Baglin, Bolton-Maggs, S Brown, EA Chalmers, PW Collins, BT Colvin, D Creagh, G Dolan, N Goulden, J Hanley, CRM Hay, FGH Hill, DM Keeling, R Liesner, GDO Lowe, CA Ludlam, MCJC Mainwaring, M Makris, O McNulty, A Moosa, T Nokes, JK Pasi, SR Pavord, D Perry, M Richards, GF Savidge, Prof O Smith, RC Tait, K Talks, AE Thomas, CH Toh, B White, JT Wilde, AF Will, MD Williams, M Winter.

APPENDIX: LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS BASED ON AHCPR 1992:

Level:	Type of evidence.
Ia	Evidence obtained from meta-analysis of randomised studies.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study.
III	Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations:

Grade:	Recommendations:
A (Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency adessing the specific recommendation.
B (IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of the recommendation.
C (IV)	Requires evidence from expert committee reports or opinions and/or clinical

experience of respected authorities. Indicates absence of directly applicable studies of good quality.

10.0 REFERENCES:

Abshire T and Kenet G. (2004) Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *Journal of Thrombosis and Haemostasis*, **2**, 899-909.|

AHCPR. (1992) Acute pain management: operative or medical procedures and trauma (Agency of Health Care Policy and Research Publications). *US Dept of Health and Human Services.*

Aledort LM. (2004) Comparitive thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *Journal of Thrombosis and Haemostasis*, **2**, 1700-8.

Aledort LM. (2005) Comparitive thrombotic event incidence after infusion of recombinant factor VIIa vs factor VIII inhibitor bypass activity – reply to a rebuttal. *Journal of Thrombosis and Haemostasis*, **3**, 822.

Astermark J, Berntorp E, White GC, Kroner BL. (2001) The Malmo International Brother Study (MIBS): further support for genetic predisposition to inhibitor development in hemophilia patients. *Haemophilia*, **7**,267-72.

Batlle J, Lopez MF, Brackmann HH. (1999) Induction of immune tolerance with recombinant factor VIII in haemophilia A patients with inhibitors. *Haemophilia*, **5**, 431-5.

Berntorp E, Bjorkman S. (2003) The pharmacokinetics of clotting factor therapy. *Haemophilia*, **9**, 353-9.

Bjorkman S, Carlsson M. (1997) The pharmacokinetics of factor VIII and factor IX: methodology, pitfalls and applications. *Haemophilia*, **3**, 1-8.

Bjorkman S, Berntorp E. (2001) Pharmacokinetics of coagulation factors: clinical relevance for patients with haemophilia. *Clinical Pharmacokinetics*, **40**, 815-832.

Bjorkman S, Shapiro A, Berntorp E. (2001) Pharmacokinetics of recombinant factor IX in relation to age of the patients; implications for dosing in prophylaxis. *Haemophilia*, **7**, 133-139.

Blanchette V, Shapiro A, Liesner R, Hernandez F, Retzios AD, Schoth P, Fritsch S, Spotts G, Ewenstein BM.(2004)

Characterisation of the pharmacokinetics of rFVIII in young pre-school children, including an analysis of the influence of age and body weight. *Blood*, **104**, 842a, abstr 3084.

Baudo F, de Cataldo F. Italian Association of Haemophilia Centres (AICI): Registry of acquired factor VIII inhibitors (2003). Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice. *Brit J of Obstetrics and Gynaecology* 113; 11-314.

Berntorp E, Donfield S, Waters J, Mattson E, DiMichele DM, Gringeri A, Astermark J. (2005) The FEIBA Novoseven Comparoitive study (FENOC) – A randomised evaluation of bypassing agents in haemophilia complicated by inhibitors. *Blood,* **106**, 98a.

Brackmann HH, Oldenburg J, Swaab R. (1996) Immune tolerance for the treatment of factor VIII inhibitors – twenty years of the Bonn protocol. *Vox Sanguinis*, **70**, 30-5.

Brackmann HH, Effenberger E, Hess R, Schwaab R, Oldenburg J. (2000) Novoseven in immune tolerance therapy., *Blood Coagulation and Fibrinolysis*, **11**, (suppl 1) S39-S44.

Bray GL, Gomperts ED, Courter S, Gruppo R, Gordon EM, Manco-Johnson M, Shapiro A, Scheibel E, White G, Lee M. (1994) A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. The Recombinate Study Group. *Blood*, **83**, 2428-35.

Carcao M, St Louis J, Lacroix S, Stain AM, Rivard G and The Association of Hemophilia Clinic Directors of Canada. (2004) Rituximab for congenital hemophiliacs with inhibitors: a Canadian experience. *Haemophilia*, **10**, 57 (abstr 12 PO 28),

Chavin, S.I., Siegel, D.M., Rocco, T.A. (1988) Acute myocardial infarction during treatment with an activated prothrombin complex concentrate in a patient with factor VIII deficiency and a factor VIII inhibitor. *American Journal of Medicine*, **85**, 244-249.

Chistolini, A., Ghirardini, A., Tirindelli, M.C. (1987) Inhibitor to factor VIII in a non-haemophilic patient: evaluation of the response to DDAVP and the in vitro kinetics of factor VIII. *Neuve Revue Francaise Haematologie,* **29**, 221-224.

Coller BS, Hultin MB, Hoyer LW, Miller F, Dobbs JV, Dosik MH, Berger FR. (1981) Normal pregnancy in a patient with a prior postpartum factor VIII inhibitor: with observations on pathogenesis and prognosis. *Blood,* 58:619-24.

Collins P, Macartney N, Davies R, Lees S, Giddings J and Majer R. (2004) A population based, unselected, consecutive cohort of patients with acquired haemophilia A. British Journal of Haematology, **124**, 86-90.

Delgardo J, Jimenez-Yuste V, Hernandez-Navarro F and Villar A. (2003) Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. British Journal of Haematology, **121**, 21-35.

DiMichele DM. Kroner BL. (1999) Analysis of the North American Immune Tolerance Registry (NAITR) 1993-1997: current practice implications. ISTH Factor VIII/IX Subcommittee Members. *Vox Sanguinis*, **77** Suppl 1, 31-2.

DiMichele DM, Kroner B, and the North American Immune Tolerance Study Group. (2002) The North American Immune Tolerance registry: practices, outcomes, outcome predictors. *Thrombosis and Haemostasis,* 8752-7.

DiMichelle DM. (2003) Immune tolerance therapy dose as an outcome predictor. *Haemophilia*, **9**, 382-6.

Dykes AC, Walker ID, Lowe GDO and Tait RC. (2001) Combined prednisolone and intravenous immunoglobulin treatment for acquired factor VIII inhibitor: a 2-year study. *Haemophilia*, **7**,160-163.

Ehrlich HJ, Henzl MJ, Gomperts ED. (2002) Safety of factor VIII inhibitor bypass activity (FEIBA) 10-year compilation of thrombotic adverse events. *Haemophilia*, **8**, 83-90.

Ewenstein, B.M., Takemoto, C., Warrier, I., Lusher, J., Saidi, P., Eisle, J., Ettinger, L.J. and DiMichele, D.M. (1997) Nephrotic syndrome as a complication of immune tolerance in hemophilia B. *Blood*, **89**, 1115-1116.

Ewenstein BM. Joist JH. Shapiro AD. Hofstra TC. Leissinger CA. Seremetis SV. Broder M. Mueller-Velten G. Schwartz BA. Mononine Comparison Study Group. (2002) Pharmacokinetic analysis of plasma derived and recombinant FIX concentrates in previously treated patients with moderate or severe haemophilia B. *Transfusion*, **42**, 190-197.

Ewing, N., Kasper, C. (1982) In vitro detection of mild inhibitors to factor VIII in haemophilia. *American Journal Clinical Pathology*, **77**, 793-7.

Freedman J, Rand ML, Russel O, Davis C, Cheatley PL, Blanchette V and Garvey MB. (2003) Immunoadsorption may provide a cost effective approach to management of patients with inhibitors to FVIII. *Transfusion*, **43**, 1508-1513.

Gascoigne EW, Dash CH, Harman C, *et al*. (2004) A retrospective survey on the safety of Replenine, a high purity

factor IX concentrate. *Pharmacoepidemiology and Drug Safety*, **13**, 187-195.

Goudemand J, Tagariello G, LopacIUk F. (2004) Cases of surgery in high-responder haemophilia patients. *Haemophilia*, **10** (suppl 2), 46-9.

Green, D., Lechner, K. (1981) A survey of 214 non-hemophilic patients with inhibitors to factor VIII. *Thrombosis and Haemostasis*, **45**, 200-203.

Green, D., and Kwaan, C.H. (1987) An acquired factor VIII inhibitor responsive to high-dose gamma globulin. *Thrombosis and Haemostasis*, **57**, 521-2.

Green PM, Montandon AJ, Bentley , Giannelli F. (1991) Genetics and molecular biology of haemophilias A and B. *Blood Coagulation and Fibrinolysis*, **2**, 539-65.

Green, D., Rademaker, A.W., Briet, E. (1993) A prospective randomised trial of prednisolone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. *Thrombosis and Haemostasis,* **70**, 753-757.

Hart, H.C., Kraaijenhagen, R.J., Kerckhaert, J.A., Verdel, G., van de Wiel, A. (1988) A patient with a spontaneous factor VIII:C autoantibody: successful treatment with cyclosporin. *Transplant Proceedings*, **20**, (supplement 4), 323-8.

Hauser I, Schneider B and Lechner K. (1995) Post-partum factor VIII inhibitors. *Thrombosis and Haemostasis*, **73**, 1-5.

Hay, C.R.M., Negrier, C., Ludlam, C.A. (1997) The treatment of bleeding in acquired haemophilia with recombinant factor VIIa. *Thrombosis and Haemostasis,* **78**, 1463-67.

Hay C.R., Ludlam, C.A., Colvin, B.T., Hill, F.G., Preston, F.E., Wasseem, N., Bagnall, R., Peake, I.R., Berntorp, E., Mauser Bunschoten, E.P., Fijnvanaat, K., Kasper, C.K., White, G. & Santagostino, E. (1998) Factor VIII inhibitors in mild and moderate-severity haemophilia A. UK Haemophilia Centre Directors Organisation. *Thrombosis and Haemostasis,* **79,** 762-766.

Hay CR, Baglin TP, Collins PW, Hill FG, Keeling DM. (2000) The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO). *British Journal of Haematology*, **111**, 78-90.

Hay CR, Lee CA. (2002) Inhibitors. In: Roiguez-Merchan EC, Lee CA, editors. Inhibitors in patients with haemophilia: Blackwells.

Hay CRM. (2005) Inhibitors to factor VIII/IX: treatment of inhibitors – immune tolerance induction. Chapter 13 in Textbook of Hemophilia (eds: Lee CA, Berntorp EE, and Hoots WK. Blackwell).

Hedner U. (2004) Dosing with recombinant factor viia based on current evidence. *Seminars in Hematology*, **41**(Suppl 1), 35-9.

Hilgartner, M.W., Knatterud, G.L. and the FEIBA study group. (1983) The use of factor eight inhibitor by-passing activity (FEIBA Immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. *Blood,* **61**, 36-40.

Hilgarter M, Makiperna A, Dimichele DM. (2003) Long-term FEIBA prophylaxis does not prevent progression of existing joint disease. *Haemophilia*, **9**, 261-8.

Keeling D, Beavis J and Sukhu K. (2005) A simple inhibitor screen is more sensitive than a Bethesda assay in monitoring for the development of inhibitors in haemophilia A and B. *British Journal Haematology*, **128**, 885.

Kenet G, Lubetsky A, Gitel S, Luboshitz J, Varon D, Martinowitz U. (2000) Treatment of bleeding episodes in patients with hemophilia and an inhibitor: comparison of two treatment protocols with recombinant activated factor VII. Blood Coagulation Fibrinolysis, 11 (Suppl 1), S35-8.

Kenet, G., Lubetsky, A., Luboshitz, J. & Martinowitz, U. (2003) A new approach to treatment of bleeding episodes in young hemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven). *Journal of Thrombosis and Haemostasis,* **1,** 450-455.

Key, N.S., on behalf of the US rFVIIa Home Therapy Study Group. (1998) Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (novoseven) in haemophiliacs with inhibitors. *Thrombosis and Haemostasis,* **80**, 912-8.

Kreuz, W., Ehrenforth, S., Funk, M., Auerswald, D., Mentzer, J., Joseph-Steiner, J., Beeg, T., Klarmann, D., Scharrer, I., Kornhuber, B. (1995) Immune tolerance therapy in paediatric haemophiliacs with factor VIII inhibitors: 14 years follow-up. *Haemophilia*, **1**, 24-32.

Kreuz, W., Mentzer, D., Auerswald, G., Becker, S., Joseph-Steiner, J. (1996) Successful immunetolerance therapy of FVIII inhibitor in children after changing from high to intermediate purity FVIII concentrate. *Haemophilia*, **2**, (supple 1), 19.

Kreuz W, Escurich-Ettinghauser C, Martinez I, Mentzer D, Figura S, Klarmann D. (2000) Efficacy and safety of FVIII inhibitor bypassing activity (FEIBA) for long-term prophylaxis in patients with high-responding inhibitors. *Blood*, **96**, 265a, abs 1140.

Kroner BL. (1999) Comparison of the international immune tolerance registry and the north American Immune tolerance registry. *Vox sanguinis*, **77**, 33-37.

Laffan M, Brown SA, Collins PW**,** Cummin AM, Hill FGH, Keeling DM, Peake IR and Pasi KJ. (2004) Diagnosis of Von Willebrand disease. A guideline from the UK Haemophilia Centre Doctors' Organisation. *Haemophilia*, **10**, 199-217.

Lee,C.A., Barrowcliffe, T., Bray, G., Gomperts, E., Hubbard, A., Kemball-Cook, G., Lilley, P., Owens, D., Von Tilberg, L., Pasi, J. (1996) Pharmacokinetic in vivo comparison using 1-stage and chromogenic substrate assays with two formulations of Hemofil-M. *Thrombosis and Haemostasis,* **76**, 950-6.

Lee, M., Poon, W.Y., Kingdon, H. (1990) A two-phase linear regression model for biologic half-life data. *Journal of Laboratory and Clinical Medicine*, **115**, 745-8.

Lee M, Morfini M, Schulman S. The design and analysis of pharmacokinetic studies of coagulation factors. Factor VIII/IX SSC-ISTH 2001 recommendations at http:/www.med.unc.edu/isth/fviiipharmaco.htm

Lian, E.C.Y., Larcada, A.F., ChIU, A.Y.Z. (1989) Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. *Annals of Internal Medicine,* **110**, 774-778.

Lian EC. Villar MJ. Noy LI. Ruiz-Dayao Z. (2002) Acquired factor VIII inhibitor treated with cyclophosphamide, vincristine, and prednisone. *American Journal of Hematology*, **69**,294-5.

Lloyd Jones, M., Wight, J., Paisley, S. & Knight, C. (2003) Control of bleeding in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia,* **9,** 464-520.

Lottenberg, R., Kentro, T.B., Kitchens, C.S. (1987) A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. *Archives of Internal Medicine,* 147, 1077-1081.

Ludlam, C.A., Smith, M.P., Morfini, M., Gringeri, A., Santagostino, E. & Savidge, G.F. (2003) A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *British Journal of Haematology,* **120,** 808-813.

Lusher, J.M., Shapiro, S.S., Palascak, J.E., Rao, A.V., Levine, P.H., Blatt, P.M., and the Haemophilia study group. (1980) Efficacy of prothrombin complex concentrates in hemophiliacs with antibodies to factor VIII: a multicenter therapeutic trial. *New England Journal of Medicine*, **303**, 421-425.

Lusher JM, Arkin S, Abildgaard CF, Schwartz RS. (1993) Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. Safety, efficacy, and development of inhibitors. Kogenate Previously Untreated Patient Study Group. *New England Journal of Medicine,* **328**, 453-9.

Lusher, J.M. (1994) Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors: benefits and limitations. *Seminars in Haematology,* **31** (supp 4), 49-52.

Lusher, J.M., Ingerslev, J., Roberts, H., Hedner, U. (1998a) Clinical experience with recombinant factor VIIa. *Blood Coagulation and Fibrinolysis*, **9**, 119-28.

Lusher, J.M., Roberts, H.R., Davignon, G., Joist, J.H., Smith, H., Shapiro, A., Laurian, Y., Kasper, C.K., Mannucci, P.M., and the r FVIIa Study Group. (1998b) A randomised, double blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. *Haemophilia*, **4**, 790-98.

Lusher JM, Lee CA, Kessler CM, Beosian CL. (2003) The safety and efficacy of B-domain deleted recombinant factor VIII concentrate in patients with severe haemophilia A. *Haemophilia*, **9**, 38-49.

Mariani G, GhirardiniA, Belloco R. (1994) Immunetolerance in hemophilia. Principal results from the international registry. *Thrombosis and Haemostasis,* **72**, 155-8.

Mathias M. Khair K. Hann I. Liesner R. (2004) Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia. *British Journal of Haematology*, **125**, 366-8.

Mauser-Bunschoten, E.P., Niewenhuis, H.K., Roosendaal, G., van den Berg, H.M. (1995) Low-dose immune tolerance induction in haemophilia A patients with inhibitors. *Blood,* **86**, 983-988.

McMillan CW, Shapiro SS, Whitehurst D, Hoyer LW, Rao AV, Lazerson J. (1988) The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. *Blood*, **71**, 344-8.

Mizon, P., Goudemand, J., Jude, B. and Marey, A. (1992) Myocardial infarction after FEIBA therapy in a hemophilia-B patient with a factor IX inhibitor. *Annals of Haematology,* **64**, 309-311.

Morfini, M., Lee, M., Messori, A. (1991) The design and analysis of half-life and recovery studies for factor VIII and factor IX. Factor VIII/IX Standardisation Sub-Committee of the International Society for Thrombosis and Haemostasis *Thrombosis and Haemostasis,* **66**, 384-6.

Morfini M. (2003) Pharmacokinetics of factor VIII and factor IX. *Haemophilia*, **9** (suppl 1), 94-100.

Morfini M, Cinotti A, Bellatreccia A, Paladion E, Gringeri A, Mannuci PM and the Refacto-AICE study group. (2003) A multicentre pharmacokinetic study of the B-domain deleted recombinant factor VIII concentrate using difference assays and standards. *Journal of Haemostasis and Thrombosis*, **1**, 2283-2289.

Morrison, A.E., Ludlam, C.A., Kessler, C. (1993) Use of porcine factor VIII in the treatment of patients with acquired hemophilia. *Blood,* **81**, 1513-20.

Mudad, R., and Kane, W.H. (1993) DDAVP in acquired haemophilia A: case report and review of the literature. *American Journal of Haematology*, **43**, 295-299.

Negrier, C., Goudemand, J., Sultan, Y., Bertrand, M., Rothschild, C., Lauroua, P., and the members of the French FEIBA study group. (1997) Multicenter retrospective study on the utilisation of FEIBA in France in patients with factor VIII and factor IX inhibitors. *Thrombosis and Haemostasis*, **77**, 1113-119.

Nemes L and Pitlik E. (2003) Ten years experience with immune tolerance induction therapy in acquired hemophilia. *Haematologica*, **88** (supple 12) 106-110.

Parameswaran R. Shapiro AD. Gill JC. Kessler CM. HTRS Registry Investigators. (2005) Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia*, **11***,* 100-6.

Pasi KJ, Collins PW, Keeling DM, Brown SA, Cumming AM, Dolan GC, Hay CRM, Hill FGH, Laffan M and Peake IR. (2004) Management of Von Willebrand disease. A guideline from the UK Haemophilia Centre Doctors' Organisation. *Haemophilia*, **10**, 218-231.

Pfliegler, G., Boda, Z., Harsfalvi, J., Flora-Nagy, M., Sari, B., Pecze, K., Rak, K. (1989) Cyclosporin treatment of a woman with acquired hemophilia due to factor VIII inhibitor. *Postgraduate Medical Journal,* **65**, 400.

Rivard GE, St Louis J, Lacroix S, Champagne M and Rocks G. (2003) Immunoadsorption for coagulation factor inhibitors: a retrospective critical appraisal of 10 consecutive cases from a single institution. *Haemophilia*, **9**, 711-716.

Rizza CR, Spooner RJ, Giangrande PL. (2001) Treatment of haemophilia in the United Kingdom 1981-1996. *Haemophilia*, **7**, 349-59.

Roberts, H.R., Monroe, D.M., 3rd & Hoffman, M. (2004) Safety profile of recombinant factor VIIa. *Seminars in Hematology,* **41,** 101-108.

Rocino, A., de Biasi, R. (1999) Successful immune tolerance treatment with monoclonal or recombinant factor VIII concentrates in high responding inhibitor patients. *Vox Sanguinis*, **81**, 35-8.

Rodriguez-Merchan EC, Wiedel Jd J, Wallny T, Hvid I, Berntorp E, Rivard GE, Goddard Nj N, Querol F, Caviglia H. (2003) Elective Orthopaedic Surgery for inhibitor patients. *Haemophilia*, **9**, 625-31.

Rothschild C, Laurian Y, Satre EP, Borel Derlon A, Chambost H, Moreau P, Goudemand J, Parquet A, Peynet J, Vicariot M, Beurrier P, Claeyssens S, Durin A, Faradji A, Fressinaud E, Gaillard S, Guerin V, Guerois C, Pernod G, Pouzol P, Schved JF, Gazengel C. (1998) French previously untreated patients with severe hemophilia A after exposure to recombinant factor VIII : incidence of inhibitor and evaluation of immune tolerance. *Thrombosis and Haemostasis*, **80**, 779-83.

Sallah S. (2004) Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia*, **10**, 169-173.

Santagostino E. Gringeri A. Mannucci PM. (1999) Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. *British Journal of Haematology*, **104**,22-6.

Santagostino, E., Morfini, M., Rocino, A., Baudo, F., Scaraggi, F.A. & Gringeri, A. (2001) Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thrombosis and Haemostasis,* **86,** 954-958.

Schneiderman J, Nugent DJ, Young G. (2004) Sequential therapy with activated prothrombin complex concentrate and recombinant factor VIIa in patients with severe haemophilia and inhibitors. *Haemophilia* **10**, 347-51.

Schulman, S., Langevitz, P., Livneh, A., Martinowitz, U., Seligsohn, U., Varon, D. (1996a) Cyclosporin therapy for acquired factor VIII inhibitor in a patient with systemic lupus erythematosus. *Thrombosis and Haemostasis*, **76**, 344-346.

Schulman, S. (1998) Safety, efficacy and lessons from continuous infusion with rFVIIa. rFVIIa-CI Group. *Haemophilia,* **4,** 564-567.

Schwartz, R.S., Gabriel, D.A., Aledort, L.M., Green, D., Kessler, C.M. (1995) A prospective study of the treatment of acquired (autoimmune) factor VIII inhibitors with high dose intravenous gammaglobulin. *Blood,* **86**, 797-804.

Shapiro, A.D., Gilchrist, G.S., Hoots, W.K., Cooper, H.A., Gastineau, D.A. (1998) Prospective, randomised trial of two doses of rFVIIa (Novoseven) in haemophilia patients with inhibitors undergoing surgery. *Thrombosis Haemostasis*, **80**, 773-78.

Shapiro AD. Di Paola J. Cohen A. Pasi KJ. Heisel MA. Blanchette VS. Abshire TC. Hoots WK. Lusher JM. Negrier C. Rothschild C. Roth DA.. (2005) The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe haemophilia B. *Blood*, **105**, 518-525.

Sjamsoedin, L.J., Heijnen, L., Mauser-Bunschoten, E.P., van Geijswijk, J.L., van Houwelingen, H., van Asten, P., Sixma, J.J. (1981) The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with haemophilia A and antibodies to factor VIII. A double-blind clinical trial. *New England Journal of Medicine*, **305**, 717-21.

Smith, M.P., Spence, K.J., Waters, E.L., Berresford-Webb. R., Mitchell, M.J., Cuttler, J., Alhaq, S.A., Brown, A.A., Savidge, G.F. (1999) Immune tolerance therapy for haemophilia A patients with acquired factor VIII antibodies: comprehensive analysis of experience at a single institution. *Thrombosis and Haemostasis*, **81**, 35-8.

Smith, M.P., Ludlam, C.A., Collins, P.W., Hay, C.R., Wilde, J.T., Grigeri, A., Melsen, T. & Savidge, G.F. (2001) Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding. *Thrombosis and Haemostasis,* **86,** 949-953.

Stasi R. Brunetti M. Stipa E. Amadori S. (2004) Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood*, **103**,4424-8.

Struillou, L., Fiks-Sigaud, M., Barrier, J.H., Blat, E. (1993) Acquired haemophilia and rheumatoid arthritis: success of immunoglobulin therapy. *Journal of Internal Medicine,* **233**, 304-305.

Sultan, Y., Kazatchkine, M.D., Caisonneuve, P., Nydegger, U.E. (1984) Anti-idiotype suppression of autoantibodies to factor VIII (antihaemophilic factor) by high-dose intravenous immunoglobulin. *Lancet,* **ii**, 765-768.

Sultan Y. (1992) Prevalence of inhibitors in a population of 3435 hemophilia patients in France. French Hemophilia Study Group. *Thrombosis and Haemostasis*, **67**, 600-2.

Tarantino MD., Collins PW., Hay CR., Shapiro AD., Gruppo RA., Berntorp E., Bray GL., Tonetta SA., Schroth PC., Retzios AD., Rogy SS., Sensel MG., Ewenstein BM., RAHF-PFM Clinical Study Group. (2004) *Haemophilia*, **10**, 428-437.

Tjonnfjord GE. (2004) Activated prothrombin complex concentrate (FEIBA) Treatment during surgery in patients with inhibitors to FVIII/IX: the updated Norwegian experience. *Haemophilia*, **10** (suppl 2) 41-5.

Turecek, P.L., Varadi, K., Gritsch, H. & Schwarz, H.P. (2004) FEIBA: mode of action. *Haemophilia,* **10 (**Suppl 2**),** 3-9.

Varadi, K., Negrier, C., Berntorp, E., Astermark, J., Bordet, J.C., Morfini, M., Linari, S., Schwarz, H.P. & Turecek, P.L. (2003) Monitoring the bioavailability of FEIBA with a thrombin generation assay. *Journal of Thrombosis and Haemostastis,* **1,** 2374-2380.

Warrier, I. (1998a) Management of haemophilia B patients with inhibitors and anaphylaxis. *Haemophilia*, **4**, 574-576.

Warrier, I., Lenk, H., Saidi, P., Pollman, H., Tengborn, L., and Berntorp, E. (1998b) Nephrotic synome in hemophilia B patients with inhibitors. *Haemophilia,* **4**, 248-51.

White GC, Beebe A, Nielsen B. (1997) Recombinant factor IX, *Thrombosis and Haemostasis*, **78**, 261-265.

White GC, Shapiro A, Ragni M, Garzone P, Goodfellow J, Tubridy K, Couter S. (1998) Clinical evaluation of recombinant factor IX. *Seminars in Hematology*, **35** (suppl 2), 33-38.

Young G, McDaniel M and Nugent DJ. (2005) Prophylactic recombinant factor VIIa in haemophilia patients with inhibitors. *Haemophilia*, **11**, 203-7.

Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, Vetter H and Brackmann H. (2005) Treatment of acquired hemophilia by the Bonn-Malmo protocol: documentation of an in vivo immunomodulating concept. *Blood*, **105**, 2287-2293.

Figure 1:

Treatment algorithm for bleeding in patients with congenital haemophilia and inhibitors