bjh guideline

The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation

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Summary

The revised UKHCDO factor (F) 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 FIX 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 Bethesda Units/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 FVIII/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 (factor VIII inhibitor bypassing activity) and recombinant activated FVII (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 1 mg/kg/d ± cyclophosphamide. In the absence of a response to these agents within 6 weeks, second-line therapy with Rituximab, Ciclosporin A, or other multiple-modality regimens may be considered.

Keywords: diagnosis, management, factor VIII/IX inhibitors.

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Since the publication of the previous guideline on the detection and management of factor (F) 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 that 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, FVIII and FIX, inhibitors, antibodies, alloantibodies, auto-antibodies, rVIIa, Novoseven, FEIBA, PCC, Rituximab, management. Recommendations were based on reports with the highest levels of evidence (Agency of Health Care Policy and Research, 1992; Appendix 1).

Diagnosis and investigation of FVIII and FIX 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 FVIII concentrates in previously untreated patients (PUPs) with severe haemophilia A

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demonstrated 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, 90th centile 26 EDs, $n = 76$; Lusher *et al*, 1993, 2003; Bray *et al*, 1994; Rothschild *et al*, 1998). Inhibitor development is less common in patients who have received >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 (Rizza *et al*, 2001; Hay & Lee, 2002). The development of FIX inhibitors may be associated with life-threatening anaphylactic reactions (Warrier, 1998).

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 activated partial thromboplastin time (APTT)-based or Bethesda-based method. A possible APTT method has been described (Ewing & 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). FVIII/IX half-life measurement is the most sensitive way to detect an inhibitor. FVIII/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).

FVIII/IX recovery

FVIII/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 (White *et al*, 1998; Morfini, 2003). 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 min 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 & Berntorp, 2001; Morfini, 2003) but can vary slightly according to product. Recombinant FVIII has similar recovery values e.g. Recombinate mean (±standard deviation, SD) 2·6 (±0·5) IU/dl/IU/kg and Advate 2·4 (0·5; Tarantino *et al*, 2004).

FIX IVR values are lower than those of FVIII because FIX has a much larger volume of distribution. Plasma-derived FIX IVR values range from 0·7 to 1·7 (Morfini, 2003; Gascoigne *et al*, 2004) 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 <1-year-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 1–6 years 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 FIX 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 years, 0·79 in boys aged 10–19 years and 0·88 in men aged 50–56 years (Bjorkman *et al*, 2001).

There are minor differences when recovery is calculated using one or two-stage assays and recovery may be 20–30% higher when the chromogenic assay method is used (Lee *et al*, 1996). Pharmacokinetic studies of B-domain deleted recombinant FVIII (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 years old (Morfini *et al*, 2003).

FVIII/FIX half-life studies

When measuring half-life, it is essential to continue sampling for at least 48 h post-infusion in order to take account of both the distribution half-life and the elimination half-life (Bjorkman & Carlsson, 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 & Montoro, 1997). A number of different computer software programs are available to analyse the data but may give different estimates of pharmacokinetic parameters. Recent Secondary Standard for Coagulation Working Group 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 FVIII or 75 IU/kg of FIX are infused after a washout period of at least 72 h 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 min, 30 min, 3, 6, 9 and 24 h with additional sampling at 28 and 32 h for FVIII and 48 and 72 h for FIX (Lee *et al*, 2001). In practice, however, this number of samples may not be feasible.

The mean terminal half life ($T^1/_2$) for plasma derived FVIII concentrates in adults has been reported to range between 10 and 15 h (Bjorkman & Berntorp, 2001; Morfini, 2003) and values obtained with recombinant FVIII are similar; Recombinate mean $T^1/_2$ 14·7 h (Morfini, 2003) and 11·2 h (Tarantino *et al*, 2004), Refacto (chromogenic assay with Refacto standard) mean 10·05 h (Morfini *et al*, 2003). The Antihaemophilic Factor (Recombinant), Plasma/Albumin Free Method (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 – $r = 0{\cdot}34$, $P = 0{\cdot}02$ under the age of 6 years (Blanchette *et al*, 2004; Tarantino *et al*, 2004; aged 1–6 years mean (±SD) 9·84 h (±1·88); aged: 10–65 years; mean: 11·98 h (±4·3); range: 8·38–17·96).

FIX concentrates usually have a much longer $T^1/_2$ than FVIII, but reports vary widely, with mean values for plasma-derived FIX concentrates ranging from 7 to 34 h (White *et al*, 1997; Ewenstein *et al*, 2002; Berntorp & Bjorkman, 2003). Recombinant FIX has been reported to have a mean $T^1/_2$ of 16·8–20 h (White *et al*, 1997; Bjorkman *et al*, 2001; Ewenstein *et al*, 2002). The $T^1/_2$ 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 (Green *et al*, 1991; Hay & Lee, 2002) 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' FVIII mutations or major deletions of the FIX 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 non-sense mutations (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 FVIII molecule associated with a very high-risk inhibitor development (Hay & 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 & 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).

Laboratory 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 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 evidence.

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 FIX 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 FVIII 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 FVIII. 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 FVIII 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 FVIII (100–200 IU/kg/day) may achieve tolerance more rapidly than low-dose (25–50 IU/kg 3 × weekly), the outcome is similar in good-risk patients (starting inhibitor titre <10 Bethesda Units (BU)/ml and peak titre <200 BU/ml; Mauser-Bunschoten *et al*, 1995; Brackmann *et al*, 1996; Kroner, 1999; 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 http://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; Mauser-Bunschoten *et al*, 1995; Rocino & de Biasi, 1999; Smith *et al*, 1999; DiMichele *et al*, 2002). Experience with above 50 patients in the International Immune Tolerance Study indicates that it takes a median of 3 months to decline to this level (unpublished observations).

There is conflicting evidence that tolerance may be more readily achieved using low-purity FVIII. Kreuz *et al* (1996) reported six patients resistant to ITI with high-purity FVIII who were successfully tolerised when changed to low-purity FVIII. It has been suggested either that impurities in low-purity concentrate are immunosuppressive or that von Willebrand factor (VWF) 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 *versus* low-purity FVIII for ITI suggests that the outcome is superior when low-purity FVIII concentrates are used (W. 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 FVIII and success-rates quoted for low purity concentrates are generally similar to those published for high-purity and recombinant products (Mauser-Bunschoten *et al*, 1995; Brackmann *et al*, 1996; Batlle *et al*, 1999; Rocino & de Biasi, 1999; Smith *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 FVIII at the present time. Convincing controlled data is required before the use of low-purity FVIII for immune tolerance can be recommended.

Although the definition of successful ITI is accepted to be the restoration of normal pharmacokinetics established after a 3-day washout period, the failure of ITI is more difficult to define. Most patients achieve tolerance within 6–12 months but a resistant minority may take 1–3 years or more to achieve tolerance (Kreuz *et al*, 1995; Brackmann *et al*, 1996). 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 6-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 *et al*, 2002), and it is probably reasonable in such patients to abandon ITI after 6–9 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 (Carcao *et al*, 2004; Mathias *et al*, 2004). This experimental approach cannot be recommended as first line therapy at the present time.

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*, 1998). For that reason, the first 20 or so FIX infusions should be administered in the hospital setting. Should transfusion 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 FIX dose is reduced or the treatment discontinued. Regimens analogous to all of those described for FVIII inhibitors have all been used in haemophilia B, including low- and high-dose FIX, and a modified Malmo regimen.

Recommendations

Immune Tolerance Induction is recommended for patients with severe congenital haemophilia A and a confirmed FVIII or FIX 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 desmopressin (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 FVIII inhibitors

Products available for the treatment of bleeding in patients with FVIII/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 FVIII, reducing their FVIII baseline to <1 IU/dl (Hay *et al*, 1998). In other cases the antibody may not react with the patient's mutant FVIII and their baseline FVIII 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 FVIII. Patients with persistently low-titre inhibitors <2 BU/ml will respond to increased doses of human FVIII and may remain on home-therapy with FVIII. It is common clinical experience that inhibitors of up to 5 BU/ml may be overcome by very large doses of human FVIII. FVIII is reserved for life and limb-threatening emergencies in patients who have a brisk anamnestic response to this product.

Porcine FVIII. Porcine FVIII (Hyate:C; Speywood, UK) has been withdrawn. Its use was reviewed in the previous guideline (Hay *et al*, 2000). Recombinant porcine FVIII 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, 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 *et al*, 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 *et al*, 1983; Tjonnfjord, 2004).

Recent experiments suggest that the active moiety of FEIBA may be a complex of activated FX and prothrombin (Turecek

et al, 2004). Traditionally, the dose of APCCs has been adjusted clinically, un-informed by laboratory monitoring, although 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 h.

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, 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 FVIII 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 FVIII.

Recombinant FVIIa (rVIIa). Clinical experience with rVIIa has been reviewed by Lusher *et al* (1998a)) and Lloyd Jones *et al* (2003). A dose of 90 Bg/kg rVIIa has been shown to control 70–100% of bleeding episodes. Between one to three bolus doses of 90 Bg/kg given three-hourly have typically been used as home treatment for haemarthrosis and mild bleeding episodes (Key, 1998; Santagostino *et al*, 1999). Key (1998) reported rVIIa to be effective in 92% of episodes after a mean of 2·2 doses, although 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 Bg/kg has tended to be used there are few dose-finding studies. A randomised dose comparison has shown that 35 Bg/kg had similar efficacy to 70 Bg/kg for haemarthroses but that the 70 μg/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 FVIII and IX inhibitors undergoing surgery showed that 90 Bg/kg was more effective than 35 Bg/kg (Shapiro *et al*, 1998).

More recently the use of much larger doses has been considered (Kenet *et al*, 2003; Hedner, 2004; Parameswaran *et al*, 2005). Kenet *et al* (2003) 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 Bg/kg and a 97% response-rate with doses >200 Bg/kg. Clinical trials comparing standard 90 Bg/kg and 'mega-dose' 300 Bg/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 h (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, disseminated intravascular coagulation and other thromboses have been associated with its use. These are rare, occurring with a frequency of 2·5 to 8×10^5 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 & Kenet, 2004; Aledort, 2004, 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 FVIII. High responders have inhibitor levels >5 BU/ml and exhibit a brisk anamnestic response following FVIII exposure. Although the choice of 5 BU/ml as the cut-off is arbitrary, clinical experience suggests that patients with inhibitors >5 BU are completely refractory to FVIII. 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

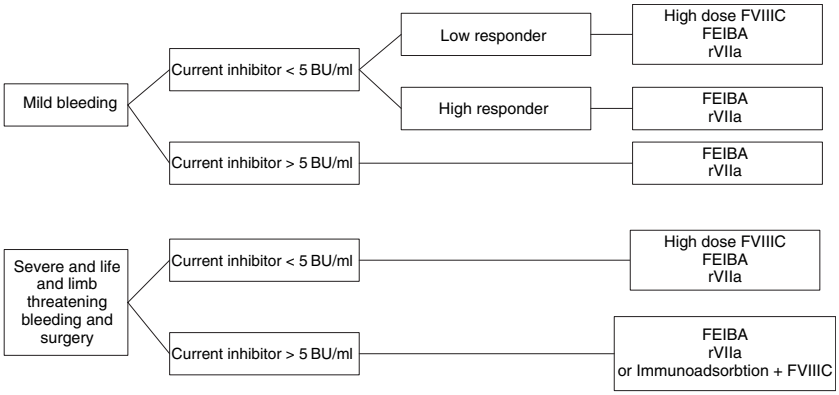

Fig 1. Treatment algorithm for bleeding in patients with congenital haemophilia and inhibitors.

there is no response to one bypassing agent, then the alternate may be used.

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

For patients in whom it is difficult to achieve satisfactory levels of FVIII, 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 FVIII 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 FVIII assays. If the initial antibody titre is >5 BU/ml human FVIII is unlikely to be effective without removal of antibody by plasmapheresis or immunoadsorption.

If inhibitor levels are too high for satisfactory levels of FVIII 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 FVIII (Freedman *et al*, 2003; Rivard *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 synergies (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 FVIII, 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 suggests that FEIBA may be the more useful prophylactic agent. Indeed, Hilgartner *et al* (2003) demonstrated limited efficacy of FEIBA 50–100 U/kg three 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 90 μg/kg b.d. 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 200 μg/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, FVIII may be considered. Such treatment is easily monitored and, if satisfactory FVIII levels can be maintained, efficacy should be assured. An anamnestic response may render FVIII ineffective in high responders after as little as 3–4 d 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 (Negrier *et al*, 1997; Goudemand *et al*, 2004; Tjonnfjord, 2004). Tjonnfjord (2004) described 15 minor and six major surgical procedures conducted with FEIBA 200 U/kg/d 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*, 2003). 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 Bg/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 FVII coagulant activity (FVII:C) levels did not predict success (Santagostino *et al*, 2001). A prospective study using a rate of 50 Bg/kg/h achieved plasma VII:C 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 Bg/kg with higher bolus doses. Surgery with this product is usually conducted using the licensed dose of 90 μg/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. **Major haemorrhage may be treated with FVIII 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 FVIII or rVIIa and FEIBA in combination.(grade C, level IV).**

Surgery. **FVIII 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 FVIII 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 FVIII or VWF but inhibitors to all other coagulation factors have been described. Guidelines for the diagnosis and management of acquired von Willebrand disease (VWD) have recently been published (Laffan *et al*, 2004; Pasi *et al*, 2004). Acquired haemophilia A (Green & 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*, 2004, 2005). Acquired haemophilia A has an equal sex distribution, presenting most commonly in the elderly at a median age of 70–80 years (Green & Lechner, 1981; Lottenberg *et al*, 1987; Morrison *et al*, 1993; Delgardo *et al*, 2003, unpublished UKHCDO data). Although acquired haemophilia A is commonly associated with pregnancy, malignancy, pemphegoid, rheumatoid arthritis, systemic lupus erythematosus and other autoimmune diseases, no clinical association is identified in about half the patients (Green & Lechner, 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 (Lottenberg *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 & 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).

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 the *Treatment of bleeding in congenital haemophilia A and FVIII inhibitors*, 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 (Lottenberg *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 randomised studies in the area. The only published study shows that 30% of patients treated with prednisolone 1 mg/kg/d 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 its 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/d 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 50–150 mg/d (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 d (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 FVIII in combination with immunosuppression improves the response rate but no controlled trials have been performed (Nemes & Pitlik, 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 was reported to be well tolerated and to achieve 80% complete remission 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 2 g/kg given over 2–5 d although some patients received concomitant steroids (Sultan *et al*, 1984; Green & Kwaan, 1987; Struillou *et al*, 1993; Schwartz *et al*, 1995; Dykes *et al*, 2001). A large retrospective study showed no benefit for high-dose immunoglobulin when added to prednisolone or cytotoxics (unpublished UKHCDO data).

Ciclosporin A. There are a number of case reports that ciclosporin A, either alone or in combination with other immunosuppression, successfully abolished an inhibitor after failure of first line therapies. Conventional doses of 10–15 mg/kg/d 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*, 1996).

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 1–2 mg/kg/d, prednisolone 1 mg/kg/d, large volume immunoadsorption days 1–5 weekly, intravenous immunoglobulin (IVIG) 0·3 g/kg; days: 5–7 weekly and FVIII 100 U/kg/d. They report rapid control of bleeding with an undetectable inhibitor at a median of 3 d (95% confidence interval 2–4) and complete remission in 88% of patients at a median of 14 d (95% confidence interval 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%) achieve 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 FVIII 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 (S. Solymoss, personal communication), however Coller *et al* (1981) reported no relapses in 9 subsequent pregnancies

and the Italian Registry reported 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 FVIIa, activated prothrombin complex concentrate and porcine FVIII. There are no comparative studies but the efficacy and risk of adverse events of these products appear to be similar. Porcine FVIII 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 75 U/kg was given 8 or 12 hourly. Adverse events were uncommon and there were no thrombotic complications (Sallah, 2004).

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

FVIII concentrate. Most patients with acquired haemophilia are resistant to FVIII replacement. The pharmacokinetics of FVIII are unpredictable in this condition and the Bethesda assay is not predictive of FVIII recovery and clinical response to human or porcine FVIII. Human FVIII 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 FVIII 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 HSG93(30) (grade C recommendation based upon level IV evidence).

Bleeding should be treated without delay, using rFVIIa, aPCC or porcine FVIII (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 randomised trials, immunosuppression should be initiated with Prednisolone 1 mg/kg/d either alone, combined with cyclophosphamide 50–100 mg/d orally or larger doses as an iv pulse. Cyclophosphamide and other alkylating agents 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 Ciclosporin A, multiple immunosuppressive agents and modified Malmo or Bonn regimens. Further studies are required before Rituximab can be considered a first-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 this guideline.

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Appendix

Appendix 1. 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
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 addressing 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

