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Guideline

THE DIAGNOSIS AND MANAGEMENT OF FACTOR VIII AND IX INHIBITORS: A GUIDELINE FROM THE UK HAEMOPHILIA CENTRE DOCTORS' ORGANIZATION (UKHCDO)

The expected incidence of inhibitors in severe haemophilia A and B approaches 33% and 3% respectively (Katz, 1996). The occurrence of this complication has significant clinical implications, as the response to treatment becomes uncertain, morbidity is increased and life expectancy reduced. Direct medical costs are much higher for inhibitor patients (Goudemand, 1998), as are direct non-medical costs to the patient, their family and to society as a whole. This must be fully recognized by commissioners or purchasers of haemophilia services.

Since the previous guideline on the detection and management of factor VIII inhibitors was published, significant diagnostic and therapeutic advances have taken place (Hay *et al*, 1996a). The UK Haemophilia Centre Doctors' Organization (UKHCDO) has therefore revised, updated and substantially rewritten the earlier guideline. In doing so, we have tried to define best current practice internationally, as reflected by the literature. We have avoided recommending one haemostatic product over another where no direct comparative trials have been conducted. Where marked national differences in clinical practice exist, in immune tolerance induction for example, we recommend the strategy for which the highest level of evidence exists. This evidence-based approach highlights the need for future clinical trials in areas where current treatment strategies are based on uncontrolled observations and 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 and editorial commentary. These include several members who practice only paediatric haematology and two members who are primarily general haematologists. Members of the working party make an annual declaration of interest to UKHCDO.

Relevant scientific papers were identified from Medline using the index terms h(a)emophilia, factor VIII and IX, inhibitors, antibodies, alloantibodies, autoantibodies and management [Agency of Health Care Policy and Research (AHCPR), 1992]. Recommendations were based on reports with the highest levels of evidence available (see Appendix).

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DIAGNOSIS AND INVESTIGATION OF INHIBITORS TO FACTORS VIII AND IX

Introduction and general strategy for inhibitor surveillance

Inhibitors develop in patients with severe haemophilia A after a median of 9–12 treatment days (Ehrenforth *et al*, 1992; Addiego *et al*, 1993; Lusher *et al*, 1993). Outbreaks of inhibitors among frequently treated adults normally considered to be at low risk of inhibitor development have also been reported in relation to changes in factor VIII concentrate manufacture (Peerlinck *et al*, 1993; Rosendaal *et al*, 1993; Rosendaal (1997). Therefore, patients should be screened more frequently during the early phase of treatment and following any change to a new and unestablished type of factor VIII concentrate. Patients with factor IX deficiency should be monitored in the same way.

In vitro laboratory tests for the detection and quantification of factor VIII antibodies will detect those neutralizing inhibitor antibodies that interfere with the function of factor VIII or IX. Factor VIII recovery and plasma half-life studies are required for the detection of inhibitor antibodies that reduce factor VIII survival and for the detection of very low-level inhibitors. Children on regular prophylaxis and lacking free antibody are an example of this.

Recommendation

Patients should be screened for inhibitors after every 5th exposure day or every 3 months until the 20th exposure day, every 6–12 months thereafter and prior to any surgical procedure. Patients should also be screened for inhibitors if the frequency of bleeding increases or if the clinical or laboratory response to replacement therapy is poor (grade B recommendation based on level III evidence).

If the clinical response or factor VIII increment are poor, an estimate of factor VIII recovery and/or half-life should be conducted, particularly if the inhibitor assay is negative (grade B recommendation based on level III evidence).

Screening for inhibitors is normally conducted using an activated partial thromboplastin time (APTT)-based or Bethesda method, but children on regular prophylaxis should be screened using factor VIII/IX recovery or half-life measurements (commonly peak and trough factor VIII/IX measurements in the first instance) (grade C recommendation based on level IV evidence).

Inhibitor screening using the activated partial thromboplastin time (APTT)

Factor VIII inactivation by inhibitors is time and temperature dependent (Lossing *et al*, 1977) and so the APTT of the

patient:pooled-plasma mixture should be measured immediately after mixing and after incubation.

The most widely used APTT screening method for factor VIII inhibitors compares the APTT of a patient:pooled-plasma mixture immediately after mixing and after 2 h incubation (Ewing & Kasper, 1982). Each laboratory must standardize this test independently and determine what they consider an abnormal result.

Recommendation

It is recommended that an APTT-based method should be used to screen patients for factor VIII inhibitors (level 1b recommendation based on grade A evidence).

Factor VIII inhibitor quantification

The Bethesda assay has been recommended as the standard method for measuring the factor VIII inhibitor titre (Kasper *et al*, 1975). The original Bethesda method may give false-positive results owing to loss of factor VIII activity caused by a pH shift and reduced protein concentration unrelated to the presence of an inhibitor. The Nijmegen modification of the assay avoids this pH shift (Verbruggen *et al*, 1995). False-positive results are eliminated by this modification, which has now been recommended by the International Society of Thrombosis and Haemostasis Factor VIII/IX Scientific Sub-committee (Giles *et al*, 1998).

The Bethesda assay can be modified to measure the degree to which an inhibitor inactivates porcine factor VIII using porcine factor VIII concentrate as substrate (Hyate:C, Ipsen, UK). This is diluted in haemophilic plasma to a concentration of 100 IU/dl and measured in a standard factor VIII assay using the usual reagents and standards.

Inhibitor quantification in factor IX deficiency

Factor IX inhibitory activity may be quantified using the Bethesda method, but omitting the two-hour incubation (Ewing & Kasper, 1982). There are no published data on the role of the Nijmegen modification for the quantification of factor IX inhibitors.

Recommendation

Factor VIII inhibitors should be quantified using the Nijmegen modification of the Bethesda assay (grade A recommendation based on level Ib evidence).

Factor VIII inhibitor titre should initially be quantified to both human and porcine factor VIII and, subsequently, if treatment with porcine factor VIII is contemplated (grade B recommendation based on level III evidence.) Factor IX inhibitors should be quantified using the Bethesda assay without an incubation period (grade B recommendation based on level III evidence).

Laboratory diagnosis of acquired haemophilia

The diagnosis is established by the demonstration of an isolated, time-dependent, prolongation of the APTT. Specific tests for the lupus anticoagulant should be negative. A marked reduction in factor VIII is commonly accompanied by more modest *in vitro* reductions in factor IX, XI and XII activity, which may create the false impression that the inhibitor is non-specific. This is a laboratory artefact caused by depletion of factor VIII in the substrate plasma, which may be 'diluted out' so that assays of increasing dilutions of the patient's plasma give progressively increasing factor IX, XI and XII levels while having no effect on the uniformly low factor VIII level. The inhibitor titre should be determined using both human and porcine factor VIII because factor VIII auto-antibodies usually exhibit little inhibitor activity against porcine factor VIII (Kasper, 1991; Fiks-Sigaud *et al*, 1993; Morrison *et al*, 1993). The Bethesda assay may underestimate inhibitor potency in acquired haemophilia because the second-order reaction kinetics result in the persistence of low levels of factor VIII, even after prolonged incubation. It has been suggested that, for consistency, in this situation, one should report the inhibitor titre calculated from the lowest dilution that results in approximately 50% residual factor VIII after the 2 h incubation (Kasper, 1991).

Recommendation

The diagnosis of acquired haemophilia should be based upon the clinical presentation, an isolated prolongation of the APTT that corrects initially with normal plasma, but which prolongs on incubation, a marked reduction in factor VIII concentration (usually $< 0{\cdot}01$ IU/ml) and an inhibitor measurable using the Bethesda Assay. Specific tests for the lupus anticoagulant should also be negative.

It is also recommended that the inhibitor in acquired haemophilia should be quantified using both human and porcine factor VIII, calculated from the lowest dilution that results in approximately 50% residual factor VIII (grade B recommendation based on level III evidence).

Factor VIII recovery

For pharmacokinetic studies in adult patients, samples are taken at several time-points up to 2 h after infusion to establish the peak factor VIII value. Recovery is calculated from the peak plasma factor VIII concentration using a formula that requires an estimation of plasma volume and which is unsuitable for paediatric use (Kjellman, 1984; Kasper, 1991; Morfini *et al*, 1991). In routine clinical practice, a single measurement taken 30–60 min after infusion is usually used. Factor recovery percentage should be calculated with reference to the recovery constant (k) for that product, as this constant may vary from one product to another. k is commonly taken as 2·0 for factor VIII and 1·0 for factor IX, but different values apply to some factor VIII concentrates and to recombinant IX (Benefix, Genetics Institute, USA).

Recovery percentage

= [(measured factor VIII/IX increment IU/dl)

/(expected factor VIII/IX increment IU/dl)] × 100

Expected factor VIII/increment (IU/dl)

= IU/kg infused × k.

Normal recovery values range from 75% to 100% (Kjellman, 1984). Recovery and half-life are commonly lower in

children. A factor VIII recovery as low as 66% and a half-life as low as 6 h may be observed in small haemophilic children lacking inhibitors.

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 factor VIII (BDDrFVIII, Refacto, Wyeth, USA) should be conducted using either the chromogenic method or a one-stage method that uses a specific standard or a thromboplastin optimized for this product. The standard one-stage factor VIII assay may underestimate BDDrFVIII recovery by 30–50%.

Recommendation

Factor VIII recovery should be based upon the difference in factor VIII concentration between a sample taken pre- and 30–60 min after infusion (grade C recommendation based on level IV 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).

Factor VIII recovery in children should be calculated using a simple formula that requires no estimate of plasma volume (grade B recommendation based upon level III evidence).

Factor VIII half-life studies

Factor VIII activity-time curves fit a biphasic two-compartment model. The initial decline in factor VIII is the distribution (disappearance) half-time and is complete within 4 h. The second slope of decay is the elimination half-life. The half-disappearance time is the time from infusion until the factor VIII concentration has fallen to 50% of the peak post-infusion level. Short half-life studies are influenced more by the distribution half-life than by the elimination half-life and so it is recommended that half-life studies are continued for at least 24–48 h after infusion.

Model-dependent or model-independent analysis may be used to analyse the data, but will not give the same results (Lee *et al*, 1990; Morfini *et al*, 1991). Different computer programmes used to analyse the same data set may also give different estimates of pharmacokinetic parameters. Although a non-compartmental model is less subject to this variability, it may give different results from a two-compartment model (Pascual & Montoro, 1997).

In most half-life studies, 50 U/kg of factor VIII or 75 IU/kg of factor IX are infused after a washout period of at least 72 h or when the baseline factor level is reached (typically $< 0{\cdot}01$ u/dl). Samples should be taken regularly for 48 h or until the factor activity has fallen to baseline levels. In the absence of a pharmacokinetic computer model, the elimination half-time should be calculated by linear least-squares regression analysis (Kjellman, 1984; Kasper, 1991). At least four sample-points are required to establish a log-linear phase (Kasper, 1991).

Recommendation

Half-life studies should be conducted after a wash-out period or when the factor VIII or IX level has reached baseline. A sample should be taken at 1 h, 4 h and at several points thereafter until the factor VIII activity has fallen to baseline (grade B recommendation based on level III evidence).

CLINICAL MANAGEMENT OF INHIBITOR PATIENTS

The two aspects of inhibitor management, inhibitor abolition through immune tolerance induction and the haemostatic management of bleeding episodes and surgery, will be reviewed separately. Immune tolerance induction (ITI) requires study on an international collaborative basis if we are to learn how this approach may be optimized and applied in the most cost-efficient way. ITI must be viewed as a long-term investment and the period of intensive treatment compared with the cost of life-long treatment in the presence of a persistent high inhibitor titre. Treatment of acute bleeding must be active and initiated early, as this aggressive approach should reduce patient morbidity or mortality and also reduce overall direct medical costs.

It is important that commissioners and treaters enter into partnership so that the clinical effectiveness, cost benefit and cost-effectiveness of immune tolerance and other treatment approaches are studied and analysed prospectively by national and international studies. The management of such patients should be supervised by a Haemophilia Comprehensive Care Centre, as defined in the NHS Executive Health Service Guidelines (HSG) 30 (1993).

Immune tolerance induction

Factor VIII inhibitors may be abolished in more than 80% of selected patients with severe haemophilia A ITI (Nilsson *et al*, 1988; Mariani *et al*, 1994; Kreuz *et al*, 1995; Mauser-Bunschoten *et al*, 1995; Brackmann, 1996; DiMichele *et al*, 1999, 2001). Successful ITI leads to normalization of the factor VIII half-life, a marked improvement in the patient's quality of life and a considerable reduction in the future cost of treatment.

Current knowledge of ITI for factor VIII and IX inhibitors is derived from uncontrolled series of patients treated using various factor VIII dose regimens and the results of three retrospective surveys of ITI. These surveys include the International Immune Tolerance Registry (IITR, Mariani *et al*, 1994), the North American Immune Tolerance Registry (NAITR, DiMichele *et al*, 1999, 2001) and the German Immune Tolerance Registry (GITR, Lenk, 1999). There are no controlled comparisons of the regimens currently used for ITI and no agreement on the optimal regimen to be used.

Factors influencing the outcome of immune tolerance induction

The most important predictor of successful ITI is the inhibitor titre at the start of ITI, which affects both the likelihood of success and the time taken to achieve tolerance. An inhibitor titre of < 10 Bethesda units (BU)/ml at the time of initiation of ITI significantly correlated with successful outcome in both the NAITR and the IITR ($P = 0{\cdot}004$ and $0{\cdot}001$ respectively) (Mariani *et al*, 1994; DiMichele *et al*, 1999, 2001; Lenk, 1999). The success rate

Table I. Commonly used immune tolerance protocols.

Protocol	Therapeutic regimen
Bonn	Phase 1: VIIIC 100 IU/kg b.d.
(Brackmann, 1996)	Phase 2: Tail-off over 3 months when VIIIC half-life normal
Van Creveld	Neutralizing dose: 25 IU/kg b.d. for 1–2 weeks
(Mauser-Bunschoten *et al*, 1995)	Tolerizing dose 25 IU/kg every 2nd day until tolerant
Malmo	Neutralizing CI of VIIIC to maintain 0·3 IU/ml VIIIC level for 10–14 d
(Nilsson *et al*, 1988)	Cyclophosphamide 12–15 mg/kg i.v. (d 1,2)
	Cyclophosphamide 2–3 mg/kg orally (d 3–10)
	i.v. IgG 2·5–5 g on d 1, 0·4g/kg/d on d 4–5 + protein A adsorption if the inhibitor titre is > 10 BU/ml before the start of treatment

and time to success for patients starting ITI with an inhibitor titre of < 10 BU/ml was 85% and 11 months compared with 43% and 15 months for patients with inhibitors of > 10 BU. Most other studies show a similar relationship between the starting inhibitor titre, the outcome and the time taken to achieve tolerance (Kreuz *et al*, 1995; Mauser-Bunschoten *et al*, 1995).

A low peak historical inhibitor titre prior to ITI has been said to predict successful ITI, but this variable was far less strongly related to outcome than the inhibitor titre at the start of ITI in the IITR or NAITR (Mariani *et al*, 1994; DiMichele *et al*, 1999). Very high starting inhibitor titres of > 500 BU/ml are associated with resistance and a poor response to ITI (level IIb, Mariani *et al*, 1994; Kreuz *et al*, 1995; Mauser-Bunschoten *et al*, 1995; DiMichele *et al*, 1999).

Although it is widely believed that ITI should start as soon as possible after the inhibitor is detected, there is no firm scientific basis for this approach. A short interval between inhibitor detection and the initiation of ITI predicted a successful outcome in some studies (Mariani *et al*, 1994; Kreuz *et al*, 1995), but not others (Mauser-Bunschoten *et al*, 1995; DiMichele *et al*, 1999, 2001). The chance of achieving successful ITI should be enhanced by deliberately deferring the initiation of ITI until the inhibitor titre has declined below 10 BU/ml and preferably below 5 BU/ml, as the success of ITI relates significantly to the starting inhibitor, but not to the peak historical inhibitor titre. Series in which ITI was deferred either deliberately or by circumstance until the inhibitor titre was < 10 BU/ml have been notably successful (Mauser-Bunschoten *et al*, 1995; Smith *et al*, 1999; Rocino *et al* 2000). These authors report similar success-rates of 88–100%, despite using widely varying factor VIII dose rates.

The influence of the dose of factor VIII used is disputed. The IITR suggested that larger doses are significantly more effective, particularly in patients with inhibitor titres of > 10 BU/ml (Mariani *et al*, 1994). In contrast, neither the NAITR nor the GITR were able to demonstrate such a dose relationship (DiMichele *et al*, 1999, 2001; Lenk, 1999). Furthermore, the low-dose regime has been reported to achieve a success rate of 88% amongst a cohort in whom the inhibitor titre had declined to < 10 BU/ml before the initiation of ITI (Kreutz *et al*, 1995; Mauser-Bunschoten *et al*, 1995; Brackmann, 1996; Lenk, 1999).

Tolerance may be induced more easily in younger patients whose inhibitors are not long established (Mariani *et al*, 1994; Kreuz *et al*, 1995; Mauser-Bunschoten *et al*, 1995), although this is disputed by DiMichele *et al* (1999, 2001).

There are no convincing data to suggest that any particular type or brand of factor VIII concentrate is more or less effective for ITI. Although Kreuz has suggested that patients may be more readily tolerized using intermediate-purity factor VIII concentrate, this data is inconclusive and is based on uncontrolled observations in six patients (Kreuz *et al*, 1996). Others have demonstrated similar success using high-purity or recombinant factor VIII concentrates (Smith *et al*, 1999; Rocino *et al* 2000).

Many low-level inhibitors will disappear spontaneously without ITI, although troublesome inhibitors may also present with a low titre. It would be reasonable therefore for inhibitors presenting with a titre of 2 BU/ml or less to be monitored weekly for evidence of an increase in titre and to defer initiation of ITI.

Procedure of immune tolerance induction

Tolerance is achieved by the regular administration of factor VIII or IX over a period of a few months to two or more years. Widely differing doses of factor VIII have been used, varying from 50 IU/kg three times a week to 300 IU/kg/d. Intermediate doses of 50 or 100 IU/kg/d are also widely used with success. The regimens in common use are summarized in Table I. Regimens that combine intensive factor VIII/IX replacement with concomitant immunosuppression have also been described and are outlined in the table (Nilsson *et al*, 1988). The best described of these is the Malmo regimen, in which high-dose factor VIII or IX replacement is combined with cyclophosphamide, high-dose immunoglobulin and protein A immuno-adsorption (Nilsson *et al*, 1988; Berntorp & Nilsson, 1996). This regimen is not in wide use as immuno-adsorption is difficult in small children and clinicians are also reluctant to use cyclophosphamide in this group.

The optimum approach to immune-tolerance induction has not been agreed. Although high-dose regimens may achieve tolerance more rapidly, it is not clear whether their overall success rate is superior to that obtained using a low-dose regimen. Low-dose regimens may be administered more readily than high-dose regimens without the use of

central lines and may also be more acceptable for the patient and parents.

Intensive factor VIII or IX replacement therapy for ITI may require central venous access and the immediate availability of bypass therapy such as FEIBA or Autoplex (Baxter) or recombinant VIIa (rVIIa, Novoseven, Novo Nordisk, Denmark). Interruption of ITI and intercurrent infection should be avoided during the course of ITI, as they may adversely influence both success and the time taken to achieve tolerance (Kreuz *et al*, 1995; Brackmann, 1996; Lenk, 1999).

During immune tolerance therapy, the inhibitor should be quantified at regular intervals until free inhibitor is no longer detectable using the Bethesda assay. Factor VIII recovery should be estimated at intervals until normal ($\geq$ 66%). When recovery is normal, the factor VIII half-life should be determined at intervals until it is also normal ($\geq$ 6 h). Tolerance is generally taken as restoration of normal factor VIII recovery and half-life.

In North America, ITI is discontinued and factor VIII prophylaxis started as soon as tolerance has been demonstrated (DiMichele *et al*, 1999). In Europe, it is more usual to continue ITI for several months after tolerance is established and then to tail the factor VIII dose down over 3 months before starting normal prophylaxis (Mariani *et al*, 1994; Kreuz *et al*, 1995; Brackmann, 1996; Lenk, 1999). This tailing-off procedure is not of proven value, given that the rate of relapse is very low regardless of whether the patient's factor VIII dose is tailed off or stopped abruptly.

ITI in haemophilia B

There are few published reports of immune-tolerance induction in haemophilia B as factor IX inhibitors are rare. All the regimens previously described have been used for haemophilia B with some success using doses of factor IX similar to the doses of factor VIII used for ITI of factor VIII inhibitors (Nilsson *et al*, 1988; DiMichele *et al*, 1999). Considerations peculiar to ITI in haemophilia B include the risk of treatment-related thrombosis, transfusion reactions, the nephrotic syndrome and a comparatively poor overall response rate to ITI.

Immune tolerance should be attempted using high purity factor IX concentrates or recombinant factor IX to avoid the thrombogenicity associated with high doses of prothrombin complex concentrates (PCCs). Some patients with a history of allergic reactions have received ITI with factor IX, but most continued to require premedication with anti-histamines and steroids (Warrier, 1998;Warrier *et al*, 1998). An association between allergic reactions to factor IX and nephrotic syndrome has also been reported in patients treated with large doses of factor IX for ITI. The nephrotic syndrome arose after a median of 9 months ITI (range 8–36 months) (Ewenstein *et al*, 1997; Warrier, 1998; Warrier *et al*, 1998). These patients did not respond to steroids, but some improved following a dose reduction or discontinuation of ITI (Warrier, 1998; Warrier *et al*, 1998). The relative risks and benefits of ITI should be carefully considered in patients with factor IX inhibitors and a history of reactions in view of the relatively low success rate reported and the high risk of the nephrotic syndrome.

Recommendations

Immune tolerance induction is recommended for patients with congenital haemophilia A or B 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).

ITI should be conducted under the supervision of a Haemophilia Comprehensive Care Centre as defined by NHS Management Executive Health Service Guidelines (HSG) 30 (1993) (grade C recommendation based on level IV evidence).

Immune tolerance induction is demanding for both patients and parents, and documented informed consent should be obtained from the parents or guardian before starting (grade C recommendation based on level IV evidence).

The haemophilia centre conducting the ITI should have immediate availability of factor VIII/IX bypass therapy (Feiba, Autoplex or recombinant factor VIIa) and facilities for the placement of central venous catheters for IV access (grade B recommendation based on level IIb evidence).

It is recommended that, prior to the initiation of ITI, bleeding should be managed on demand with bypass therapy, preferably using recombinant factor VIIa (Novoseven) to avoid an anamnestic rise in inhibitor titre. ITI should be deferred until the inhibitor titre has fallen below 10 BU/ml (and preferably below 5 BU/ml).

It is recommended that all patients undergoing ITI be entered into comparative clinical trials of ITI for which they are eligible, 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).

Current UKHCDO policy is that immune tolerance in children under the age of 16 years should be conducted using recombinant factor VIII or IX, where available, in accordance with the Health Service Circulars (HSC)1998/033 (1998), HSC1999/006 (1999) and current UKHCDO therapeutic Guidelines (UKHCDO, 1997) (grade B recommendation based on level 1B evidence).

Interruption of ITI should be avoided (grade C recommendation based on level IV evidence).

During immune tolerance, the inhibitor titre should be estimated monthly until free inhibitor is no longer detectable. Recovery should then be determined monthly until normal and then half-life determined every 3 months until tolerance is confirmed. Tolerance is defined as the restoration of normal factor VIII recovery and half-life (grade C recommendation based on level IV evidence).

Once tolerance has been achieved it is recommended that factor VIII or IX prophylaxis start immediately, without further ITI or tailing-off of the factor VIII/IX dose (grade B recommendation based on level III evidence).

PRODUCTS AVAILABLE FOR THE TREATMENT OF BLEEDING IN PATIENTS WITH INHIBITORS TO FACTOR VIII OR IX

A number of haemostatic agents are available for the treatment of bleeding in patients with congenital haemophilia A and inhibitors.

Human factor VIII

Patients with low-titre inhibitors of < 2 BU/ml will respond well to increased doses of human factor VIII. It is common clinical experience that inhibitors of up to 5 BU/ml may be overcome by large doses of human factor VIII, although other products may be more effective. When the inhibitor titre is in excess of 5 BU/ml, human factor VIII is probably ineffective.

Porcine factor VIII (Hyate:C, Speywood, UK)

Porcine FVIII may not cross-react with the patient's antibody to human FVIII. A retrospective survey of 154 patients found a median inhibitor cross-reactivity to porcine FVIII of 15%. Twenty-seven per cent of these patients had no reactivity at all to this product in the Bethesda assay (Hay *et al*, 1996b). Efficacy has been reported in up to 90% of bleeds (Gatti & Mannucci, 1984; Kernoff *et al*, 1984; Brettler *et al*, 1989). Anamnesis may follow the use of porcine FVIII less frequently than human FVIII, occurring after 25–35% of infusions (Gatti & Manucci, 1984; Kernoff *et al*, 1984; Brettler *et al*, 1989). Specific anti-porcine FVIII inhibitors may also arise following treatment, preventing regular replacement therapy in about a third of patients who have a brisk specific anamnestic response.

A post-infusion fall in platelet count is common after treatment, but is usually transient and clinically insignificant (Kernoff *et al*, 1984; Brettler *et al*, 1989; Hay *et al*, 1996b). Intensive replacement therapy may sometimes be associated with a progressive fall in platelet count. This has been attributed to agglutination by porcine von Willebrand factor (Altieri *et al*, 1986). It has been suggested that platelet activation with this product may provide an additional mechanism for haemostasis, accounting for the clinical observation that patients with very high inhibitors may still respond to porcine factor VIII in the absence of a measurable factor VIII increment (Chang *et al*, 1998). Transfusion reactions follow 3–5% of infusions, but are usually minor or moderate in degree and follow the administration of large doses (Kernoff *et al*, 1984; Brettler *et al*, 1989; Hay *et al*, 1996b). Occasional patients have reactions with every infusion and may not be treated regularly with this product (Hay *et al*, 1996b). The risk of reactions and the effect on platelet count are reduced by the administration of porcine factor VIII by continuous infusion, a mode of administration that should also have pharmacokinetic advantages (Bona *et al*, 1993; unpublished observations). Although porcine FVIII is not virally attenuated, most porcine viruses are not zoonotic and have not been shown to transmit viral infection to man.

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

Prothrombin complex concentrates contain varying amounts of the vitamin K-dependent factors II, VII, IX and X. It is not clear how they promote haemostasis, but it is presumed to be as a result of small amounts of activated factors VIIa, IXa and Xa. PCCs are effective in approximately 50% of haemarthroses (Lusher *et al*, 1980). aPCCs [factor VIII inhibitor bypassing activity (FEIBA) and Autoplex] have undergone a deliberate controlled activation during manufacture and so contain higher levels of activated factors. FEIBA was found to be more effective than PCCs in a controlled comparison, with response rates of 64% and 52% respectively (Sjamsoedin *et al*, 1981). In a further randomized, controlled trial, Autoplex was found to be no better than a PCC (Lusher *et al*, 1983). 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% (three out of four) and 95% (13 out of 14) have also been reported in two prospective studies (Hilgartner & Knatterud, 1983; Shapiro *et al*, 1998).

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 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. Isolated episodes of myocardial infarction and disseminated intravascular coagulation (DIC) have been reported in patients lacking these clinical risk factors treated with very large doses of PCCs or aPCCs.

The recommended dose of FEIBA is 50–100 u/kg and, because of the thrombotic risk, a maximum daily dose of 200 u/kg is recommended. Concurrent anti-fibrinolytic therapy carries a theoretical risk of increased thrombogenicity and is generally avoided. Efficacy is judged clinically, there being no readily available laboratory correlates with efficacy or thrombogenicity.

FEIBA contains significant concentrations of factor VIII and may induce an anamnestic response in at least 31% of patients, particularly after intensive replacement therapy with this product (Negrier *et al*, 1997). Although the efficacy of PCCs and aPCCs is independent of the inhibitor titre, such an anamnestic response may compromise any future response to large doses of factor VIII.

Recombinant factor VIIa (rVIIa)

It is assumed that rVIIa is localized to the site of injury by the presence of tissue factor where it initiates haemostasis. Clinical experience with rVIIa has recently been reviewed (Lusher *et al*, 1998a). This review reported rVIIa to be effective in 81% (17 out of 21) of major and 86% (49 out of 57) of minor surgical procedures, and 92% of dental procedures (Lusher *et al*, 1998a). It has been evaluated in 518 serious bleeding episodes and found to be effective in 62% of muscle, 80% of ear, nose and throat (ENT), 88% of central nervous system (CNS), 76% of joint and 75% of retroperitoneal bleeds. Recently, one to three bolus doses of 90 μg/kg given every 3 h as a home treatment for haemarthrosis and mild bleeding episodes has been described (Key, 1998; Santagostino *et al*, 1999). Key (1998) reported this to be effective in 92% of cases 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 79% of mild or moderate bleeding episodes responded to a single infusion in 40% of cases and with two infusions in a further 40%, with a partial response in a further 11% of cases after a

Table II. Suggested therapeutic options for the treatment of bleeding episodes in patients with Haemophilia A and inhibitors (for details see text).

	Minor haemorrhage	Major haemorrhage
Low responder	VIII	VIII
	Porcine VIII*	Porcine VIII*
	FEIBA	FEIBA
	RVIIa	RVIIa
High responder with titre < 5 BU/ml	Porcine VIII*	VIII
	FEIBA	Porcine VIII*
	RVIIa	FEIBA
		RVIIa
High responder with titre > 5 BU/ml	Porcine VIII*	Porcine VIII*
	FEIBA	FEIBA
	RVIIa	RVIIa
		Plasmapheresis or protein A adsorption

*Porcine VIII should only be considered if anti-porcine titre is < 15 BU/ml and should only be used for minor haemorrhage in high responders if they are known not to have an anamnestic response to this product. For definition of low and high responders, see text.

median of 1·5 doses per episode. This study also showed a greater success rate for treatments initiated early.

If given by bolus injection in doses of 70–90 μg/kg, the short half-life of rVIIa requires 2–4 h administration. Although a standard dose of 90 μg/kg has tended to be used, a recent randomized dose comparison has shown that, for haemarthroses and muscle haemorrhage, 35 μg/kg had similar efficacy to 70 μg/kg (Lusher *et al*, 1998b). Larger doses may be required for serious bleeding or surgery, as a randomized study of 29 patients with factor VIII and IX inhibitors suggested that 90 μg/kg was more efficacious than 35 μg/kg (Shapiro *et al*, 1998). This makes treatment very expensive if it has to be given over a prolonged period. Administration of rVIIa by continuous infusion (CI) would seem logical, but the published data are difficult to interpret. Some reports describe the use of rVIIa alone and some report the use of CI of rVIIa with concomitant fibrin glue and tranexamic acid (Schulman *et al*, 1996a; Mauser-Bunschoten *et al*, 1998). Fibrin glue and tranexamic acid may add to the efficacy of rVIIa, permitting a reduction in dose without loss of haemostasis. A variety of dose-rates of CI have been reported, but two trials using doses of 50 μg/kg/h are ongoing. The optimum dose of rVIIa by CI has not been established and further studies are needed before CI can be recommended. Monitoring of factor VII levels has been suggested (Hedner, 1996), but is not of proven value.

rVIIa has not been conclusively associated with prothrombotic problems, but continued vigilance is required. Anti-fibrinolytic agents may be given concurrently and may increase efficacy. rVIIa is relatively free from side-effects and does not cause an anamnestic increase in inhibitor titre.

TREATMENT OF BLEEDING IN CONGENITAL HAEMOPHILIA A AND FACTOR VIII INHIBITORS

Management of bleeding

The management of an acute bleed depends on the severity of the bleed, the inhibitor levels to human and porcine factor VIII, and whether the patient is a low or a high responder to factor VIII. Low responders have inhibitor levels of < 5 BU/ml and, on further exposure to factor VIII, do not develop an anamnestic response. High responders have inhibitor levels > 5 BU/ml and even if their levels have decreased to < 5 BU/ml over time they will rise above this level again on re-exposure to factor VIII. The choice of 5 BU/ml as the cut-off is arbitrary, but clinical experience suggests that above this level further FVIII dosage escalation is usually fruitless. Table II suggests therapeutic options for different categories of patient and bleed. When selecting the most appropriate treatment option, probable efficacy, the risk of anamnesis and product safety, including viral safety, should all be considered.

Minor haemorrhage

In low responders, higher than normal doses of factor VIII may be effective and the response to this treatment can easily be monitored with factor VIII assays. In high responders, human factor VIII should be avoided for minor bleeding episodes as the expected anamnestic response may preclude the use of factor VIII for subsequent serious bleeding. Some high responders who do not exhibit significant cross-reactivity with porcine factor VIII have little anamnestic response following treatment with this product and may be treated with porcine factor VIII for minor bleeds (Hay *et al*, 1996b).

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 randomized, controlled trial. rVIIa will be preferred in those who have been treated exclusively with recombinant factor VIII and have never used pooled blood products. It will also be preferred in those high responders with a low initial titre who are known to develop an anamnestic response when exposed to FEIBA.

Major haemorrhage

Very large doses of factor VIII sufficient to overcome the antibody may be considered in patients with an initial antibody titre of < 5 BU/ml. Porcine factor VIII may be given in preference to human factor VIII if the inhibitor levels indicate that it will probably be more successful. The response to therapy must be monitored using factor VIII assays. If the initial antibody titre is > 5 BU/ml, human factor VIII will probably not be effective without removal of antibody by plasmapheresis or protein A adsorption. If the antibody titre to porcine factor VIII is < 15 BU/ml, then it may be given as an alternative to human factor VIII. If the anti-porcine antibody titre is above this level, porcine FVIII will probably be less effective, although responses to large doses of porcine factor VIII have been reported, even in the presence of very high titre inhibitors (Lozier *et al*, 1993). If the patient fails to respond to rVIIa, FEIBA may be used or antibody removal using plasmapheresis or Protein-A adsorption, followed by high-dose human or porcine factor VIII (Lozier *et al*, 1993; Gordon *et al*, 1994). Continuous infusion of human or porcine factor VIII may offer particular pharmacokinetic advantages over bolus administration in this group of patients (Gordon *et al*, 1994; Rubinger *et al*, 1997).

If inhibitor levels are such that satisfactory levels could not or cannot be achieved with human or porcine factor VIII, we recommend the use of rVIIa for major bleeding. If the patient fails to respond to rVIIa, the choice is between FEIBA or antibody removal with plasmapheresis or protein adsorption, followed by high-dose factor VIII (human or porcine).

Surgery

Surgery in haemophiliacs with inhibitors is a high-risk procedure and should not be undertaken lightly. Elective procedures need strong justification as no product can guarantee sustained haemostasis. Haemostasis must be adequate perioperatively and for a period of days post-operatively, to facilitate wound healing.

If the antibody titre is low, human or porcine factor VIII may be considered (see section on major bleeding). Such treatment is easily monitored and, if satisfactory factor VIII levels can be maintained, efficacy should be assured. Porcine factor VIII has been reported to give excellent, good or fair haemostasis in 91% of cases (Lozier *et al*, 1993). An anamnestic response may render human or porcine factor VIII ineffective in high responders after as little as 3–4 d, but usually longer (Negrier *et al*, 1997).

The main alternatives are FEIBA or rVIIa. There is relatively little published data on the use of FEIBA for surgery (see above). There has been no controlled comparison of FEIBA and rVIIa for surgery and both have a significant failure rate. In view of the risk of venous thromboembolism with prolonged use of large doses of FEIBA in this setting we recommend rVIIa as the first-line treatment in patients in whom a satisfactory factor VIII level cannot be achieved.

Recommendations

The management of an acute bleed depends on a clinical assessment of severity, knowledge of the inhibitor level to human and porcine factor VIII and, if titres are low, whether the patient is a high or low responder.

Minor haemorrhage. These cases may be managed with porcine FVIII or larger than normal doses of human 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. This may be treated with human or porcine factor VIII if inhibitor titres are low enough to allow satisfactory plasma levels to be achieved (Grade B level III). Otherwise, rVIIa is recommended (Grade C, level IV). If this fails, FEIBA or human/porcine FVIII given with concomitant antibody removal using plasmapheresis or protein A adsorption may be considered.

Surgery. Human or porcine factor VIII can be used if satisfactory plasma levels can be achieved (Grade B level III). Otherwise, rVIIa is the first line treatment (Grade C, level IV). If rVIIa fails, FEIBA or human/porcine FVIII given with concomitant antibody removal using plasmapheresis or protein A adsorption may be considered.

INHIBITORS IN HAEMOPHILIA B

Management of the bleeding episode

The options for treatment are high doses of factor IX concentrate to neutralize the inhibitor or rFVIIa, PCCs or aPCCs to bypass the inhibitor. Treatment options for patients who have had reactions to factor IX are very limited. rVIIa is the only haemostatic agent specifically licensed for use in the treatment of factor IX inhibitors.

Patients without anaphylactic reactions

Patient with low titre inhibitors (< 5 BU) may respond to factor IX. The decision to use this option will depend on the severity of the bleed and the past history of the anamnestic response. rVIIa, aPCCs and PCCs have also been used for patients with factor IX inhibitors, in doses similar to those used for patients with factor VIII inhibitors.

Although FEIBA has been used successfully, published data are limited (Giddings *et al*, 1983; Hilgartner & Knatterud, 1983; Negrier *et al*, 1997; Wilde & Linin, 1998). The risk of anaphylaxis and anamnesis should be considered when choosing to treat patients with factor IX inhibitors with PCCs or aPCCs. rVIIa may be considered the treatment of choice for the management of bleeding episodes. rVIIa has been used successfully to treat haemarthroses, muscle bleeding (Bech, 1996; Key *et al*, 1998; Laurian *et al*, 1997), including ileopsoas bleeds (Lusher, 1996), and central nervous system bleeds (Rice & Savidge, 1996).

Patients with a history of allergic reactions

Some patients with haemophilia B and inhibitors suffer allergic reactions following administration of factor IX, especially those with major gene deletions (Ewenstein *et al*, 1997). The reactions vary from urticaria, cough, bronchospasm, syncope, hypotension, emesis, angio-oedema, rash and restlessness to acute anaphylaxis. The reactions present at the same time as the inhibitor after a median of 11 exposure days and follow infusion of both high- and low-purity factor IX concentrate.

The nephrotic syndrome has also been associated with reactions and intensive factor IX therapy for ITI (see above). As reactions usually recur, rVIIa is the treatment of choice for this group of patients (Warrier *et al*, 1998). There are a number of reports of a good haemostatic effect with this agent in this context and no reported adverse events (Soulieres *et al*, 1996; Warrier, 1998; Warrier *et al*, 1998). If rFVIIa is unavailable and treatment is urgent, then factor IX-containing products may be used with caution. Pre-medication with anti-histamines and steroids may be used. Facilities for resuscitation should be immediately available and the patient and their family should be informed of the relative risks of the treatment.

Recommendation

Recombinant VIIa is the treatment of choice for bleeding in patients with high-responding factor IX inhibitors or reactions (grade B recommendation based on level III data).

Surgery

Experience of surgery in patients with inhibitors to factor IX is limited. rVIIa may be used in doses recommended for factor VIII inhibitors (Goudemand *et al*, 1996; DiMichele, 1997, Ingerslev *et al*, 1996). Post-operative haemostatic failure of rFVIIa has been reported (Shapiro *et al*, 1998; de Goede-Bolder *et al* 1998).

ACQUIRED HAEMOPHILIA

Acquired haemophilia is caused by auto-immune depletion of factor VIII. This leads to a severe bleeding diathesis, often of sudden onset. The incidence of acquired haemophilia has been reported to be between one and four per million of population (Margolius *et al*, 1961; Lottenberg *et al*, 1987). Acquired haemophilia has an equal sex distribution, presenting most commonly in the elderly at a median age of 60–67 years (Green & Lechner, 1981; Lottenburg *et al*, 1987; Morrison *et al*, 1993). Although acquired haemophilia is commonly associated with rheumatoid arthritis, systemic lupus erythamatosus (SLE) and other autoimmune diseases, pregnancy, malignancy and drug therapy, about half the patients have no such clinical association (Green & Lechner, 1981; Soriano *et al*, 1987; Struillou *et al*, 1993).

The clinical features of acquired haemophilia 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 bleeding has been reported in up to 87% of cases. Mortality from haemorrhage has been reported in 7·9% to 22% of cases (Green & Lechner, 1981; Morrison *et al*, 1993; Hay *et al*, 1997). Most haemorrhagic deaths occur within the first few weeks after presentation.

Treatment of acquired haemophilia

Elimination of the inhibitor is attempted using immunosuppression, which is initiated as soon as the diagnosis has been established. Where successful, this restores haemostasis to normal. Severe bleeding in acquired haemophilia should be treated aggressively as there is a significant mortality from haemorrhage in this condition. There are differences in the choice of haemostatic options between congenital and acquired haemophilia, which are described below. The side-effects of these agents are described in a previous section.

Immunosuppressive treatment

Prednisolone 1 mg/kg/d results in the abolition of the inhibitor in approximately 30% of patients (Green & Lechner, 1981; Spero *et al*, 1981; Green *et al*, 1993). Sixty to seventy per cent of patients respond to a combination of prednisolone and oral cyclophosphamide at 50–100 mg/d (Green & Lechner, 1981; Green *et al*, 1993). Although this combination has been the mainstay of treatment for many years, other combinations of prednisolone with azathioprin or with cyclophosphamide and vincristine have been shown to be effective (Green & Lechner, 1981; Lian *et al*, 1989). Alkylating agents may cause infertility, so prednisolone alone or combined with azathioprin and/or high-dose immunoglobulin may be preferred for patients with acquired haemophilia associated with pregnancy. Although most patients respond to immunosuppression within three to six weeks, some respond slowly over months.

High-dose immunoglobulin. Approximately 30% of patients with acquired haemophilia have been reported to respond partially or completely to high-dose immunoglobulin 2 g/kg given over 2–5 d. The response cannot be predicted reliably (Sultan *et al*, 1984; Green & Kwaan, 1987; Struillou *et al*, 1993; Schwartz *et al*, 1995). High-dose immunoglobulin should probably be considered a second-line therapy.

Cyclosporin A. A number of inhibitors have been successfully abolished using cyclosporin A in doses of 10–15 mg/kg/d to give normal therapeutic serum levels of 150–350 ng/ml, but there is limited experience of this approach (Hart *et al*, 1988; Pfliegler *et al*, 1989; Schulman *et al*, 1996b). Cyclosporin has usually been used alone, or in combination with prednisolone, as a salvage therapy for patients who have failed to respond to conventional first- or second-line treatment. Where successful, cyclosporin has been discontinued after a year or more without recurrence of the inhibitor.

Recommendation

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).

Treatment should be initiated with prednisolone 1 mg/kg/d combined with cyclophosphamide 50–100 mg/d orally, or larger doses as an i.v. pulse. It may be preferred, in women of reproductive age, to initiate therapy with prednisolone ± azathioprine (grade B recommendation based on level IIb evidence). If there is no response within 2–4 weeks, second-line therapies may be considered. These include high-dose immmunoglobulin, multiple immunosuppressive and cyclosporin A (grade C recommendation based on level IV evidence).

Treatment of bleeding in acquired haemophilia

Factor VIII concentrate and desmopressin (DDAVP). 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 neutralized 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 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 & Kane, 1993). The effect of DDAVP may be very transient and it has no place in the management of patients with a very low factor VIII level.

Porcine factor VIII. A median inhibitor titre of 1·9 BU/ml has been reported for porcine FVIII in acquired haemophilia (Morrison *et al*, 1993; Hay *et al*, 1996b). The response to porcine FVIII has been shown to be good or excellent in 78% of bleeds (Morrison *et al*, 1993). The pharmacokinetics of porcine factor VIII are unpredictable in this group and close laboratory monitoring is therefore recommended. Good responses have also been observed in patients with high levels of anti-porcine inhibitor activity. It is probably justifiable to persist with porcine factor VIII replacement if reasonable factor VIII increments are achieved and the patient continues to obtain a good clinical response, even if the anti-porcine inhibitor level is high. This product may usefully be administered by continuous infusion (Bona *et al*, 1993; Rubinger *et al*, 1997). Anamnesis has been reported to follow 4% of single-treatment episodes (Morrison *et al*, 1993).

Prothrombin complex concentrate. Prothrombin complex concentrates are widely used for the treatment of non-life-threatening bleeding episodes in acquired haemophilia. The efficacy and side-effect profile appear to be similar in congenital and acquired haemophilia.

Recombinant VIIa. Hay *et al* (1997) reported the treatment of 74 bleeding episodes in 38 patients with rVIIa. 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% of 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.

Recommendations

The management of patients with acquired haemophilia should be supervised by Haemophilia Comprehensive Care Centres as defined by HSG 93(30) (1993) (grade C recommendation based upon level IV evidence).

Severe bleeding should be treated without delay, using the product most suitable for achieving haemostasis. Both porcine factor VIII and rVIIa are useful as first-line haemostatic therapy, although PCCs may also be considered, particularly for minor bleeding (grade B recommendation based on level IIb 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.

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

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

Levels of evidence.

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized studies
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
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