

## Annotations

# Anti-D prophylaxis in 1997: The Edinburgh Consensus Statement

Over 200 delegates from hospitals and blood transfusion units around the world attended a consensus conference on anti-D prophylaxis in Edinburgh on 7 and 8 April 1997. The conference was convened jointly by the Royal College of Physicians of Edinburgh and the Royal College of Obstetricians and Gynaecologists. The aims were to reach a consensus on: the current management of rhesus D (RhD) negative women in pregnancy and the future management of such women

The consensus process was fairly rigorous. It was mediated through a panel of independent healthcare and lay professionals. The available evidence in the form of written, oral, and poster presentations were reviewed and opposing views were presented by an advocate and an adversary, each with a seconder. A draft consensus statement, prepared by the panel, was debated by the delegates and the resulting second draft statement with amendments was adopted by the conference. The final consensus statement is now in the public domain.<sup>1</sup>

### Current status of rhesus disease and anti-D prophylaxis in the UK

Perinatal deaths in the UK due to RhD alloimmunisation have fallen a 100-fold since the introduction in 1969 of a policy to administer anti-D immunoglobulin (Ig) to RhD negative women after sensitising events in pregnancy and the birth of RhD positive infants.<sup>2</sup> There is no dispute that this represents a dramatic success in preventive medicine. However, rhesus disease has not been eradicated. In the 1990s pregnancy, loss, and death in the first week after delivery due to RhD alloimmunisation is about 50 a year in the UK (position papers presented at the conference).

Opinion was divided at the conference over the acceptability of this level of loss. On the one hand should further efforts be directed to reduce a mortality that is already less than 10 in 100000 pregnancies? Yet the contrary view was also presented—namely, that no loss is

acceptable if there are known means of prevention. About one to two in every 100 RhD negative women at risk become sensitised.<sup>2</sup> There are two main reasons for this<sup>3-8</sup>: failure of application of current guidelines (see below) and sensitisation by undetected “silent” fetomaternal haemorrhage (FMH) especially in the last 12 weeks of pregnancy.

### Current guidelines on anti-D prophylaxis: effectiveness and scope for improvement

The current guidelines were produced by the UK National Blood Transfusion Service IgG Working Party in 1991<sup>9</sup> and are summarised in table 1. There was general agreement that the failure of full application of these guidelines was a matter of great concern. Compliance failure rates of over 30% have been reported in some studies of anti-D administration for potentially sensitising events in pregnancy.<sup>3-4</sup> Of particular concern was the failure to give prophylaxis in RhD negative women with bleeding in early pregnancy, especially when such cases presented to accident and emergency departments rather than to general practitioners or antenatal clinics.<sup>5</sup>

The dose of anti-D used routinely to prevent sensitisation differences between countries is illustrated in table 2.

The consensus panel recommended that the UK guidelines of 1991<sup>9</sup> should at present remain the reference standard for good clinical practice and that there should be no change to the dose principle of 500 IU for up to 4 ml of transfused fetal red blood cells. Studies of rhesus sensitised infants have variably reported apparent therapeutic failure of anti-D for potential sensitising events during pregnancy of between 18 and 66% (position papers presented at the conference). Clearly, the use of a higher dose of 1500 IU might prevent some of these cases. It is impossible to estimate accurately the size of this effect and its cost implications, but it was unfortunate that there was not more extensive debate on this issue at the conference. It must be acknowledged, however, that even if the higher (1500 IU) dose were to be used it would not protect those women who have a postnatal FMH of over 12 ml (estimated at over 200 women annually in the UK).

The 1991 guidelines are currently being revised by representation of the British Blood Transfusion Society's Special Interest Group on Haemolytic Disease of the Newborn and of the Royal College of Obstetricians and Gynaecologists. There are three main areas where these guidelines might differ from current recommendations—namely, routine antenatal anti-D prophylaxis, first trimester prophylaxis, and inadvertent transfusion of RhD positive blood to a RhD negative woman.

Apart from failures to administer anti-D IgG following sensitising events during pregnancy, the panel also expressed concern over the high incidence of failures to estimate the size of FMH by Kleihauer or alternative tests. In one study of sensitising events after 20 weeks this test was performed in only 10% of cases (position papers presented at the conference).

Table 1 Dosage of anti-D Ig for RhD negative women<sup>9</sup>

Potential sensitising event during pregnancy*	Anti-D 1g dose
Prior to 20 weeks' gestation	250 iu
Later than 20 weeks' gestation	500 iu <sup>1</sup>
Post-delivery of Rh D positive infant	500iu <sup>1</sup>

\*eg abdominal trauma, abortion, amniocentesis, antepartum haemorrhage, chorionic villus sampling, ectopic pregnancy, external cephalic version, termination of pregnancy.

<sup>1</sup>A Kleihauer test should be undertaken, as a larger dose may be required.

Table 2 Routine prophylactic dose of anti-D

Organisation/country	Standard postpartum dose (iu)	Reference
UK NBTS guidelines 1991	500	9
Early US trials	1500	10
Early MRC trials	1000	11
Later MRC trials	500	12
WHO report guidelines	1000-1500	13
EC CPMD guidelines	1000-1500	14

### Routine antenatal anti-D prophylaxis

Over 90% of spontaneous (absence of overt sensitising event) FMH during pregnancy occurs in the last trimester (position papers presented at the conference). There is good evidence from many trials that antenatal prophylaxis significantly reduces the incidence of sensitisation by a factor of between 2 and 16 fold.<sup>6-8 13-18</sup> The lower improvement rates were in those trials which used either single dose regimens or low dose anti-D (250 IU) in double dose regimens. In the light of this very strong evidence the panel proposed that because all RhD negative pregnant women are at risk from hidden bleeds, they should be given anti-D IgG prophylactically.

The critical question is, what is the cost effectiveness of this strategy? Estimates of the costs of current antenatal interventions in the UK in the absence of routine antenatal prophylaxis were presented at the conference (table 3). There are also the costs of neonatal care after delivery. Apart from the financial costs there are the costs incurred in terms of complications from such medical interventions. For example, approximate fetal loss rates are 5% for intrauterine transfusion, 1.5% for fetal blood sampling, and 0.3–0.5% for late amniocentesis. Determining cost effectiveness is very difficult as the figures will be influenced by factors such as the population studied, dose regimens, and outcome measures.

A review of the published cost effectiveness data was presented at the conference. The general conclusions from this review were: routine antenatal prophylaxis for all RhD negative pregnant women will increase costs. Cost effectiveness is influenced by the dose(s) of anti-D used, and programmes restricted to women who have not had a baby before are more cost effective and in certain theoretical models may result in a net cost saving.

In summary, the panel felt that the paucity of recent cost effectiveness studies made it difficult to draw definitive and accurate conclusions about the benefits of extending the current policy to include routine antenatal prophylaxis. The cost of offering routine antenatal prophylaxis will depend on the dose and frequency regimen used. Current evidence suggests that antenatal prophylaxis has the potential over time to save more resources if restricted to pregnant women without a living child, although this will involve a modest degree of preliminary investment to increase the supply of anti-D IgG.

Increasing the programme to include all RhD negative pregnant women will have a considerable net cost. It must be acknowledged, however, that the approximate range of possible costs presented at the conference per life year saved still compared favourably with the costs of other interventions in the NHS. Furthermore, the panel felt that, while the greatest cost benefits of routine prophylaxis had been theoretically calculated for childless mothers, it could not be ethically or economically justified to limit the policy to that group of women.

The most effective dosage and schedule of prophylaxis has to be determined. The two main options are: 500 IU

anti-D at 28 and 34 weeks or a higher dose (1250 IU) of anti-D early in the third trimester

It is anticipated that UK blood transfusion centres will be able to meet the requirements for supply of polyclonal anti-D at least for a programme in primigravidae. In the long term, however, it is reasonable to expect that the supply will be sufficient to protect all RhD negative women routinely. Until a safe monoclonal product is available the principal source of donors will have to be sensitised men and women. No serious adverse reactions have been reported in women receiving intramuscular anti-D IgG, but it is important that the viral and other safety issues raised by changes in product manufacture are kept under rigorous review. Furthermore, in introducing antenatal prophylaxis the panel suggests that health authorities should first check on compliance with current guidelines. If initially there is insufficient anti-D IgG for all women at risk, primigravidae should be given priority. Early consultation with professionals in primary care will be essential.

### Current status of monoclonal Anti-D

The authors of the 1991 guidelines for anti-D prophylaxis hoped that an effective monoclonal anti-D would soon be available to supplement polyclonal anti-D, and that there would be sufficient quantities to allow antenatal prophylaxis to be started. In 1997 it seems that monoclonal preparations, of which supply would be theoretically limitless, could, in principle, replace polyclonal anti-D, yet only phase 1 trials are at present complete on monoclonal preparations. It is not yet certain if these preparations will be safe and efficacious, reliable or affordable. There may be advantages from an intravenous preparation that can also be given intramuscularly. It is also uncertain how long it will be before monoclonal products are available in sufficient quantity, and whether they will be acceptable to regulators. The process of introducing monoclonal products and possibly phasing out polyclonal anti-D will need to be agreed nationally, and will require a comparative trial. Polyclonal products should not be phased out until the monoclonal supply has been shown to be secure.

### Other issues considered

The first was whether anti-D should be used for the treatment of immune mediated thrombocytopenia. The panel accepted that anti-D IgG may have a place in the treatment of RhD positive patients who have not had their spleens removed, especially children with chronic immune thrombocytopenia, and that in these patients it may have a similar role to high dose intravenous immunoglobulin. However, with current UK practice it is only likely to be used in a small number of patients. In the UK an imported anti-D IgG preparation is available for use in immune mediated thrombocytopenia on a named patient basis.

The second issue related to the ethical considerations of using immunised volunteers to provide anti-D. The conference concluded that the donor should be able to make a full and free informed choice before consenting to the immunisation procedure. Voluntary consent to this procedure must be genuine and explanation geared to capacity to understand and act on what is required. A comprehensive information leaflet should be made available for prospective donors. There will probably continue to be a need for immunised donors well into the 21st century, and until the safety, efficacy, and quality of monoclonal anti-D is established to the standard of European regulatory requirements. The question of compensation for non-negligent harm is vexed but clearly some effective and transparent arrangement to compensate volunteers is desirable.

Table 3 Costs of antenatal interventions: a survey of 10 UK units in 1995 (total patients=268)

	Numbers	Approximate cost (£)	
		Cost per procedure	Total costs
Amniocenteses	197	£2–400*	£39400–78800
Fetal blood sampling (FBS)	115	£3–500	£34500–57500
Intrauterine transfusion (IUT)	224	£5–800	£112000–179200
		Approximate total	£185900–315500

\*Including laboratory work. Data presented by Professor M J Whittle (Birmingham)

## Conclusions

The conference considered present and future issues relating to the management of RhD negative pregnant women in a thorough, balanced, and fair way. Some cynics have criticised the conclusions of the conference panel because the blood products industry were co-sponsors and inevitably this would have been expected to have led to a recommendation to increase the use of anti-D. This is unfair criticism. The evidence of scientific effectiveness of routine anti-D prophylaxis is very robust and on that conclusion alone, the practice must be recommended.

The important question providers of health care will have to answer is: is the present hidden or spontaneous RhD sensitisation rate acceptable? If the answer to that is "no" then offering routine anti-D prophylaxis to RhD negative pregnant women in the third trimester may be cost effective in the long term. The dose which seems to be preferred is 500 IU anti-D at 28 and 34 weeks.

Finally, and as a more immediate priority, all professionals involved in pregnancy care should improve the implementation of the 1991 guidelines. Specifically, there needs to be a tightening up of the practice of the administration of anti-D to RhD negative women and the use of Kleihauer testing at the time of sensitising events in pregnancy. This advice is especially relevant to those working in accident and emergency departments and in primary care.

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## Pump up the volume? The routine early use of colloid in very preterm infants

Rarely does a very low birthweight infant escape at least 10 ml/kg of colloid in the first few hours of life. Most units do not give volume routinely on admission, in the same way that most units don't prescribe routine antibiotics, yet almost every very preterm baby gets both, as routinely as vitamin K or a photograph for the mother. In the case of antibiotics there is usually some feature of the history or examination that can be invoked to suggest a risk of infection, even if the mother had an elective caesarean section. In the case of colloid there is always a slight metabolic acidosis, or a lowish temperature on arrival from labour ward, or a casual tweak of the big toe by a passing consultant which, of course, provides conclusive proof of hypovolaemia.

A few hours later the baby is warmer and pinker, peripheral perfusion is improved (the ritual toe tweak evokes a satisfied hmm rather than a tut-tut), the base deficit is less, so the colloid must have worked. But is this necessarily cause and effect? These improvements may well have occurred without specific treatment.

The clinical instinct to improve peripheral perfusion and blood pressure fairly quickly after birth is not purely cosmetic in very preterm infants who are at major risk of both haemorrhagic and ischaemic cerebral lesions. Both intraventricular haemorrhage (IVH) and periventricular leucomalacia have been attributed to hypotension and cerebral hypoperfusion,<sup>1</sup> but does routine volume expansion prevent these complications of prematurity?

In 1985 Beverley *et al*<sup>2</sup> randomised 80 infants who were <1500 g birthweight or <32 weeks of gestation, or both, to

a regimen of 10 ml/kg fresh frozen plasma (FFP) on admission and again 24 hours later, or to a control group who were to be given "small volumes" of purified protein fraction only if they became hypotensive. The authors excluded seven of these neonates from their analysis, two in the treatment arm who had an IVH or died before treatment with FFP, and five controls who required FFP on clinical grounds for severe hypotension or coagulopathy. Including these cases and analysing by intention to treat, there were seven deaths and five severe IVHs (grades III or IV according to Papile's classification)<sup>3</sup> in the treatment group. There were eight deaths and 10 severe IVHs in the control group. These differences were not significant. The authors' analysis included minor degrees of IVH and suggested a benefit of routine volume expansion. This was attributed to the haemodynamic effects of the FFP rather than any effect on impaired coagulation status, because clotting studies were similar in the two groups at 48 hours.

In 1996 the Northern Neonatal Nursing Initiative Trial Group reported a much larger multicentre randomised controlled trial of infants of under 32 weeks of gestation.<sup>4</sup> They compared a control group with a group given FFP routinely, and also a group who were volume loaded with a gel based colloid, to assess the independent effect of colloid infusion without any beneficial effect on coagulation status. Fairly aggressive volume loading was used. Each of the treatment groups received 20 ml/kg over 15 minutes in the first few hours of life and another 10 ml/kg the following day. Because cerebral ultrasound scanning may fail to detect clinically significant ischaemic lesions and is

therefore an inadequate proxy for long term outcome, they chose survival without major disability at 2 years as their endpoint. It is a huge credit to those who organised and carried out this trial that they managed to recruit 776 babies from 21 hospitals in the Northern Region, and achieved 100% follow up. The result was clearcut. Neither the number of deaths, nor the number of survivors with major disability, differed between the two treatment groups and the controls. Not surprisingly, infants in the control group were more likely than those in the two treatment groups (20% *vs* 8%) to need colloid infusions to correct anaemia or hypotension during the first 48 hours.

Any true difference between the outcomes for higher risk babies in these groups might have been diluted by the inclusion of relatively large preterms in the 30–32 weeks gestational age range (who might be expected to benefit less from early colloid) and the exclusion of 61/834 babies (who might be expected to benefit more from routine volume expansion) on the grounds of severe illness or extreme prematurity. It is also possible, if unlikely, that a slower or smaller colloid infusion may have shown a net benefit, but the rapid rate of infusion of a large bolus of colloid in this study led to sudden increases in venous pressure in some babies leading to cardiac or cerebral sequelae. Despite these minor reservations about applicability to the extremely preterm infant, this very large trial used a more clinically valid endpoint than the smaller Beverley study, and the assessments were carried out blind to initial treatment allocation. Routine colloid infusion in the first hours of life in all preterm infants of <32 weeks of gestation is therefore of no value, which leaves clinicians in the difficult position of needing to make clinical decisions.

Such a decision seems straightforward in the slightly grey, hypothermic, ventilated 24 week gestational age infant just admitted from the labour ward. The entire arm goes white when you lift it to insert an intravenous cannula, the base deficit is 13 mmol/l, and colloid is probably appropriate even before arterial access is achieved and blood pressure measured. The results of the controlled trial do not help in this situation, as such cases would have been excluded or lost in the analysis among the much larger numbers of 31 week gestational age infants. The decision is even easier in the well perfused, vigorous 31 week old gestational age baby with minimal respiratory disease in whom arterial access is deemed unduly invasive. Most neonatologists are unlikely to give colloid to such a baby (unless constrained by a trial protocol) and now the evidence supports that gut reaction. We can now cite the results of a large trial in our arguments with senior house officers and specialist registrars who tend to be very aggressive in their use of volume and have a very low threshold for “treating” mild metabolic acidosis.

Unfortunately, the current evidence does not help in the less clearcut cases, and we are limited in our means of assessing which preterm infants do need colloid. Capillary refill times correlate poorly with hypovolaemia in adults.<sup>5</sup> They have been evaluated in older children in whom peripheral temperature is an important confounder.<sup>6</sup> Recent work has established a normal range in neonates in different thermal environments in a neonatal unit, and has suggested that the chest or forehead are preferable sites to assess capillary refill.<sup>7</sup> However, there are no data testing the accuracy of capillary refill time for the detection of hypovolaemia in the recently born who often have very marked vasomotor instability. Of course I can hmm, and tut-tut, and toe tweak with the best of them (and in future I shall tweak the forehead), because we have little else to judge objectively. Measurement of urine output is obviously unhelpful as a means of assessing circulating volume in the first few hours of life. Central venous pressure

(CVP) measurements are rarely used, but are easily available in those babies in whom an umbilical venous catheter is sited and passes into the right atrium. Skinner *et al*<sup>8</sup> published some normative data from 13 babies with respiratory disease, eight of whom were preterm, but there is very little published on the use of CVP monitoring in “medical” neonatal patients. Skinner *et al* concluded that CVP monitoring was useful for detecting trends, and in some circumstances individual measurements of CVP could help in clinical decision making. For instance, in ventilated neonates a CVP of 0 mm Hg was likely to be associated with other signs of hypovolaemia. It is important to realise the effect of intrathoracic pressure and respiratory status on the CVP, and that negative values do not necessarily represent hypovolaemia in the spontaneously breathing baby.<sup>8</sup>

Lyon *et al*<sup>9</sup> studied central–peripheral temperature differences in infants with birthweights of < 1000 g and concluded that in the first few days of life thermoregulation is immature, so central and peripheral temperatures are similar. Both are directly affected by external temperature, so the baby is effectively poikilothermic. Central–peripheral temperature gaps of > 2°C became more frequent after three days of life when babies became more competent at vasoconstriction, but even then were more likely to represent thermal stress than hypovolaemia. Continuous monitoring showed that a clinically significant temperature gap was associated with other indicators of hypovolaemia for only 11% of the time, so dual temperature monitoring is not going to inform decisions about colloid infusions on day 1. Actual measurements of circulating plasma volume have been made in neonates using dye dilution techniques<sup>10–11</sup> but these are very much research procedures. It is probably more important in any case to look at the functional effect of a reduced circulating volume. Electrodes for continuous monitoring of tissue pH have been available for many years<sup>12</sup> without having any impact on neonatal practice, perhaps because it is assumed that the additional information from an invasive electrode adds little to intermittent arterial pH measurements.

Venous oxygen tensions or saturations may be better than arterial values as a guide to tissue oxygen delivery, and measurements made from right atrial samples taken from an umbilical venous catheter have been suggested as a reasonable proxy for the pulmonary artery samples used in adult intensive care.<sup>13</sup> Non-invasive measurements of peripheral venous oxygen saturation<sup>14</sup> or cerebral venous oxygenation<sup>15–17</sup> are possible using near infra-red spectroscopy, but the complexity of the current methodology precludes routine application.

Blood pressure can be measured directly and accurately, but hypotension represents a decompensation we should be aiming to avoid rather than treat. Of course, even the definition of hypotension and the appropriate treatment are still in doubt. The appropriate level of mean blood pressure for intervention in very preterm infants remains controversial. Should treatment with colloid be the mainstay of treatment of “hypotension”? It often seems to work, but evidence suggests that early “hypotension” is not usually due to hypovolaemia.<sup>10</sup> Should we therefore resort to inotropes at an earlier stage, as suggested by Gill and Weindling?<sup>18</sup> Dopamine seems to be an effective agent for increasing the blood pressure, but may peripherally vasoconstrict without increasing ventricular output,<sup>19</sup> and may exacerbate pulmonary vasoconstriction.<sup>19–20</sup> Dobutamine may have theoretical advantages, but seems to be a less effective pressor.<sup>19</sup>

The trial in the Northern Region was nearly as good as it could be, and it may lead to some moderation and common sense in the use of blood products such as FFP,

cryoprecipitate, and human serum albumin (HAS). Times have changed since SHOs were selected at interview on the basis of their blood group and used as walking whole blood donors every time they suggested a baby needed colloid. The routine use of FFP in the absence of confirmed coagulopathy is now discouraged, and both the Beverley<sup>2</sup> and the Northern Neonatal Network trial<sup>4</sup> support that approach. HAS is still used frequently, and it is a blood product even if it comes in a cardboard box. There is certainly a case for further evaluation of synthetic alternatives to colloid treatment in neonates; one such is crystalloid. However counterintuitive it might seem, recent evidence from a small randomised trial by King W So *et al*<sup>21</sup> shows that physiological saline is no less effective than albumin for the treatment of early hypotension in preterm infants and is associated with less fluid retention.

It should be easier to sort out what fluid to use for volume expansion than to decide to whom to give it and when. Toes will continue to be tweaked until there are simple objective techniques to assess hypovolaemia in preterm neonates.

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