

PostScript

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Amiodarone and breast feeding

An infant was born at 33+2 weeks gestation by caesarean section after an in utero diagnosis of fetal ascites and tachycardia. The mother had received treatment during pregnancy with flecainide, amiodarone, and propranolol. The amiodarone was prescribed initially at 200 mg three times a day and was reduced to twice a day after 11 days.

The mother was keen to breast feed the baby. In previous reports of amiodarone and breast feeding, amiodarone treatment was for a maternal indication and hence continued post partum.^{1,2} In this case, the amiodarone treatment stopped at delivery. However, because of the long terminal half life of amiodarone (about 50 days³), it could take several months for the level to fall. As one of the adverse effects of amiodarone is thyroid toxicity, the baby's thyroid function was assessed and found to be normal. A decision was made to allow the mother to breast feed, and the baby was closely monitored.

Breast milk was sent for analysis to determine the amiodarone level on days 5, 11, 18, and 25. It had increased on day 11 (2.1 mg/l) compared with day 5 (0.6 mg/l). This may be due to changes in composition of the milk. We do not know at what time of day the milk was expressed or whether the sample was taken at the beginning or the end of the feed. The fat content of the milk was likely to be greater after 11 days than after 5 days, which may affect the distribution of amiodarone. McKenna *et al*⁴ described changes in amiodarone concentration in breast milk

throughout the day. By 25 days, amiodarone was undetectable. Throughout this period the baby remained well and thyroid function was normal.

Although we would not recommend that breast feeding is necessarily safe for all babies exposed to amiodarone, this case illustrates that, in some circumstances, with close monitoring, breast feeding can be initiated.

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Reducing antibiotic use on the neonatal unit by improving communication of blood culture results: a completed audit cycle

It is common clinical practice to discontinue antibiotic treatment of asymptomatic babies if the blood cultures are negative at 48 hours.¹⁻³ However, if blood culture results are only available during the normal working day, then antibiotic treatment of some babies may continue into the next working day. In our neonatal unit, blood culture results were routinely received from the microbiology laboratory via fax as a list every morning. Extra positive results would be telephoned through, if they became available, during the normal working day. Results could also be checked by the clinical staff telephoning the laboratory during "office hours". This gave the potential for inadvertent prolongation of antibiotic courses for up to a day. In a previous study, McDonald *et al*⁴ found this to be a common occurrence. It is of concern because unnecessary antibiotic use may contribute to antibiotic pressure within the neonatal unit and may encourage the selection of drug resistant organisms.

We performed two audits into this problem within our neonatal unit. Our audit standard

on each occasion was that antibiotics should be stopped at 48 hours, if blood cultures were negative, unless a decision to continue was clearly documented in the case notes. Babies with negative blood cultures were identified from the microbiology database. Each episode was classified into one of four groups: (a) antibiotics not started; (b) antibiotics stopped within 48 hours; (c) antibiotics given for more than 48 hours deliberately; (d) antibiotics given for more than 48 hours unintentionally. The results are summarised in table 1.

The first audit was conducted on 451 babies with negative blood cultures between January 1997 and December 1998. We were able to collect complete data from case notes and drug charts for 376 (83.4%) of these blood cultures. We found that the audit standard was not met in 144/376 (38.3%). The median (range) duration of antibiotic treatment for each baby was 60 (16.9-332) hours.

The blood culture analyser in use in our laboratory (BacT/Alert Microbial Detection System; Organon Teknika Corporation, Durham, North Carolina, USA) tests for bacterial growth every 10 minutes and communicates the blood culture status (positive or negative) to a computer. After our initial audit, we established a computer link between the blood culture analyser and the neonatal unit. This allows the clinical staff to check the status of any blood culture in the analyser in real time, 24 hours a day.

The second audit was performed on babies with negative blood cultures between May 2000 and August 2000. Two hundred negative blood cultures were identified. Complete data were available for 179/200 (89.5%). The audit standard was not met in only 20/179 (11.2%); $p < 0.001$ compared with the first audit. The median (range) duration of treatment was reduced to 48 (1-182) hours ($p < 0.0001$). There was an overall reduction of two doses of antibiotic per baby (from a mean of 8.8 to 6.8 doses per baby).

Overall, we estimated that we gave 21 684 doses of antibiotics on the neonatal unit between January 1997 and December 1998. If the computer system had been in operation during this period, we estimate that we could have reduced this by 16.2% to 18 169. We think that this magnitude of reduction in antibiotic pressure on the neonatal unit is worth achieving.

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Table 1 Reduction in unintentional antibiotic use over 48 hours after introduction of real time availability of blood culture status by a computer link between the blood culture machine and our neonatal unit

Results	No antibiotics started	Antibiotics stopped after <48 h	Antibiotics continued for >48 h deliberately	Antibiotics continued >48 h unintentionally
First audit	25 (6.6%)	132 (35.1%)	75 (19.9%)	144 (38.3%)
Second audit	15 (8.4%)	117 (65.4%)	27 (15.1%)	20 (11.2%)

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Swaddling and heat loss

The letter of Hawkes *et al*¹ raises the important issues of swaddling and temperature on admission to the neonatal unit. Besch *et al*² carried out a limited comparison of different swaddling materials and found a transparent plastic bag together with radiant heat to be effective in preventing heat loss in infants over 2 kg. Following a report in the literature,³ we have begun wrapping all preterm infants < 1000 g in a thin plastic wrap. The wrap is preheated on a radiant warmer and the infant is immediately placed (undried) on the plastic sheet, which is folded over to completely (but loosely) enclose the torso and extremities from the neck down. The infant is left in the wrap until transported to the neonatal unit and the temperature has stabilised in a humidified environment. The median temperature of the 19 < 1000 g infants admitted since wrapping was commenced was 36.7°C on arrival to the nursery compared with 35.5°C for the previous 86 unwrapped infants ($p = 0.002$; using Mann-Whitney U test). There were no significant differences in birth weight, gestational age or Apgar scores between the groups.

Although our experience is in smaller preterm infants (who are more prone to hypothermia), our results are in keeping with those of Vohra *et al*, who studied infants < 32 weeks.³ We now plan to wrap all preterm infants < 1500 g.

The plastic wrap is likely to be more effective than towels because of reduction in evaporative heat loss and because it allows observation of the infant. However, the plastic wrap is unlikely to significantly reduce radiant heat loss, so an additional heat source is essential for preterm infants. Some form of head swaddling is also important and needs further study. Aluminum foil may reduce evaporative, convective, and radiant heat loss but does not allow observation or radiant warming.

It appears there are many aspects of swaddling that require further investigation.

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Preventing hypothermia at birth in preterm babies: at a cost of overheating some?

In the Epicure study, the odds ratio of death before discharge for babies whose temperature on admission to the neonatal unit was > 35°C was 0.58 (95% confidence interval (CI) 0.39 to 0.85) compared with those with lower temperatures.¹ In 2001, we therefore introduced a policy of wrapping neonates < 30 weeks gestation in polythene bags at birth without first drying them. Temperatures on admission to the neonatal unit after the introduction of this policy were compared with those of historical controls of < 30 weeks gestation admitted unwrapped between 1996 and 2000. The admission temperatures were analysed by stepwise multiple regression against being “bagged” or not, time to admission to the unit, birth weight, gestation, mode of delivery, month of delivery, and maternal temperature. Significant coefficients of variation existed between admission temperature and:

- being bagged +0.35°C (0.09 to 0.62) (coefficient, 95% CI);
- time to admission –0.02°C (–0.01 to –0.03) per minute;
- birth weight +0.07°C (0.02 to 0.1) per 100 g;
- gestation +0.0007°C (0.0002 to 0.001) °C per week.

Thus “bagging” increased admission temperatures by 0.35°C, which is rather less than the rise of 1.9°C in babies < 28 weeks gestation reported in a previous study.²

Table 1 shows that, in the comparable groups, this rise of 0.35°C resulted in a significant reduction in incidence of hypothermia (< 35.5°C) in “bagged” babies. However, significantly more of them (12%) were hyperthermic (> 37°C), a phenomenon previously reported but not discussed.² The risks of hyperthermia are less well defined than those of hypothermia, but it may increase the risk of neurological damage, particularly after ischaemia.³ The technique of wrapping babies in polythene bags would seem to benefit very preterm babies, although we may yet have to learn to use it appropriately.

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Technique for insertion of percutaneous central venous catheters in the newborn period

The use of percutaneous central venous catheters is of proven value for the provision of parenteral nutrition and intravenous drug treatment in neonates. They have become an integral part of the management of very low birthweight infants in most intensive care units.

At the Royal Children’s Hospital in Melbourne we used a silastic catheter, which has an external diameter of 0.6 mm and comes in a variety of different lengths (Epicutaneo-cava catheter manufactured by Vygon; lengths 15, 30, and 50 cm; ref nos 2184.015, 2184.00, and 2184.005; cost AU\$59.10). It is packaged with a metal 19 GA butterfly needle for use in insertion of the line.

This technique has some drawbacks.

- (1) The 19 GA needle is difficult to put directly into neonatal veins because of its large size.
- (2) It can be difficult to appreciate “flash back” of blood into the metal needle.
- (3) It is not possible to “flush” the needle to ensure correct positioning of the line as well as patency of the vessel.
- (4) It is not feasible to place femoral venous lines using this method.

We therefore use a method whereby the vein, using the Seldinger technique, is ultimately cannulated with a 20 GA catheter through which the silastic line can be inserted.

- (1) The procedure should be carried out under optimal conditions using an aseptic technique. If the infant is already ventilated, we advocate the use of a muscle relaxant as well as adequate sedation. This is especially advisable for insertion of femoral venous lines.

- (2) The vein is initially cannulated with a 24 GA (external diameter 0.7 mm) cannula. The sites most often used are the great saphenous vein at the ankle or knee joint, the femoral vein, the basilic or cephalic veins in the antecubital fossa, or, occasionally, the superficial temporal vein. A transilluminator or “cold light” inserted into the finger of a sterile glove can be of use in locating deep veins as well as protecting the sterile field.

- (3) A guidewire is then inserted through the cannula into the vein. We use a “duoflex spring wire guide”: diameter 0.45 mm, length 25 cm (duoflex spring wire guide manufactured by Arrow; product no AW-04018; cost

Table 1 Incidence of hypothermia and hyperthermia in control babies and babies wrapped in polythene bags (study group)

	Control group	Study group	Difference (95% CI)
Number	230	48	–
Gestation (weeks)	27.5 (23–29)	28 (23–29)	–
Weight (g)	1020 (400–1900)	1027 (500–1700)	–
Number <35.5°C	96 (42)	12 (25)	–17 (–2 to –29)
Number >37.0°C	1 (0.4)	6 (12.5)	12 (5 to 24)

Values are either median (range) or number (%). CI, Confidence interval.

AU\$13.00; Insyte intravenous catheter manufactured by Becton Dickinson catheter; GA 24, 22, and 20; cost AU\$2.00). This has the advantage of having a soft tip at both ends of the wire and being a snug fit to the smallest catheter. Care must be taken not to advance the wire if any resistance is met.

(4) A small nick is made in the skin at the site of wire to facilitate the insertion of the larger intravenous cannulae.

(5) A 20 GA (external diameter 1.1 mm) cannula is then threaded over the wire into the vein (a 22 GA (external diameter 0.8 mm) can be used to dilate the vein before the larger cannula is inserted). This can be flushed with saline to ensure patency of the vein.

(6) The silastic catheter can then be fed up the vein through the 20 GA cannula with a pair of toothless forceps. Occasionally the silastic line coils up in the hub of the cannula. This can be overcome by cutting the cannula flush to the hub and reinserting the silastic line.

(7) The silastic catheter is placed to the required length and the other cannula is withdrawn.

(8) The silastic catheter should be placed outside the cardiac outline in accordance with new guidelines.¹⁻³ The position is always confirmed radiologically either by plain radiograph or, if necessary, by injection of radio-opaque dye. We have seen neonates with pericardial tamponade associated with malpositioned catheters, which has been well documented in the literature.¹⁻³

We have found this method to be extremely reliable in the insertion of percutaneous venous catheters.

The use of the guidewire incurs additional costs (see above). In our experience these are partially offset by an improved success rate using the above method. We do not open the silastic catheter until the 20 GA is in place within the vein. This means that a line is not wasted if the vein cannot be cannulated.

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Umbilical granulomas: a randomised controlled trial

The Archimedes section has previously contained a brief section on the treatment of umbilical granulomas.¹ We have now conducted a randomised controlled trial of the management of umbilical granulomas. The trial compared silver nitrate cauterisation with the use of alcoholic wipes at each nappy change (conservative management). The impetus for this work was a series of three burns to the anterior abdominal wall after silver nitrate cauterisation, seen in a single London hospital over a two year period.

The trial aimed to show equivalence between the two treatment modalities. On the basis of equal efficacy, we intended to change practice to conservative management. More than 40 infants were referred, but a large number of parents chose conservative management rather than randomisation. Difficulty in recruitment meant there were inadequate numbers to show statistical significance within the limited time span available.

The salient results were that two of three granulomas resolved over a three week period without cauterisation. Those infants whose granulomas did not resolve went on to treatment with cauterisation following a protocol that involved drying the area both before and after silver nitrate application, surrounding the umbilicus with white soft paraffin, and leaving the area exposed for 10 minutes after application. This resulted in resolution in all remaining cases without harm due to delay in treatment.

On the basis of this work, we suggest a change in current practice to initial conservative management followed by cauterisation only when conservative treatment fails.

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Progressive ventricular dilatation (PVD) over the past 22 years

We read with interest the article of Murphy *et al*,¹ and it prompted us to review our own experience with progressive ventricular dilatation (PVD) over the past 22 years at the

Maine Medical Center (MMC). Since 1980, we have used a single approach to management of PVD. As noted in previous publications, we have considered the need for intervention to be rapid head growth defined as an increase in occipitofrontal circumference of 2 cm a week or more rather than relying on imaging.^{2,3} As this degree of head growth suggests increased intracranial pressure,⁴ we have intervened by directly draining ventricular fluid through a 21 gauge angiocath placed through the right coronal suture into the right lateral ventricle. This catheter is connected to a ventriculostomy drainage system, and drainage is continued for seven days if possible. The catheter is then removed and the decrease in head circumference and ventricular size recorded. The infant is watched for return of rapid head growth, and an angiocath is reinserted as needed. This procedure is repeated until the infant reaches about 2 kg in weight, and if rapid head growth continues, a permanent ventriculoperitoneal shunt is placed.⁵ We do not use pharmacological treatment or repeat lumbar puncture to treat PVD.

As pointed out by Murphy *et al*, PVD sufficient to require intervention occurs almost exclusively in infants with grade 3 or 4 intraventricular haemorrhage (IVH). As expected, the very low birthweight infants with high grade IVH have a high mortality. Table 1 shows a comparison between the outcomes for grade 3-4 IVH at MMC during the 1980s and over the past five years (1997-2001 inclusive), and the data of Murphy *et al* grouped in the same way. As noted, there is little difference over time or between studies. Overall mortality for grade 3-4 IVH was 33% (26/79) for Murphy *et al*, 33% (31/94) for MMC in the 1980s, and 31% (9/29) for MMC in 1997-2001. Until grade 3-4 IVH can be eliminated, posthaemorrhagic hydrocephalus will continue to occur with high morbidity and mortality.

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Table 1 Comparison between the outcomes for grade 3-4 intraventricular haemorrhage (IVH) in the three studies

	Murphy <i>et al</i> ¹	MMC 1980s ³	MMC 1997-2001
Grade 3-4 IVH (% of all <1500 g)	79 (7%)	94 (6%)	29 (6%)
Death <14 days	18/79 (23%)	29/94 (30%)**	8/29 (28%)**
PVD requiring treatment	34/61 (56%)	24/65 (37%)	11/21 (52%)
VP shunt/late death (% of PVD treatment)	18/8 (26/34=76%)	12/3 (15/24=63%)	6/1 (7/11=63%)

*Rate for all infants <35 weeks.

**Rate for all deaths <30 days.

MMC, Maine Medical Center; PVD, progressive ventricular dilatation; VP, ventriculoperitoneal.

Do we need to assess the thyroid function in the infants of mothers with Hashimoto's thyroiditis?

We read with interest the recent comprehensive review of neonatal thyroid disorders, which gave evidence-based answers to many important questions. The author recommended that all babies born to mothers with Hashimoto's thyroiditis should be reviewed at 10 days to 2 weeks and a thyroid function test taken because infants may develop transient hypothyroidism or, very rarely, hyperthyroidism.¹

As paediatricians, in a hospital with a paediatric endocrine caseload similar to some tertiary centres and a subregional neonatal intensive care unit with local deliveries of 6000 per annum, we think that the potential benefits of this practice are difficult to justify. We do understand that such practice will help in identifying babies who may develop transient congenital hypothyroidism caused by maternal thyrotropin receptor blocking antibodies. However, the incidence of this form of hypothyroidism has been estimated to be 1 in 180 000 normal infants (~2 % of congenital hypothyroidism) and the majority of them will have raised thyroid stimulation hormone levels that can be detected by the current neonatal screening.² Based on a simple calculation, in a unit of our size only one baby will be detected every 30 years. We feel that there would be major disadvantages if we are to adopt the author's recommendation. Firstly, an extra hospital visit for babies and parents; secondly the need to bleed many healthy infants; and finally the potential for confusion and unnecessary anxiety. Until objective evidence emerges about the significance of subtle thyroid dysfunction in early life we feel that the current screening programme should not be extended.

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CORRECTIONS

In the CD Review (*Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F164) reviewed by C Wren, please note that the affiliation of the authors is published incorrectly. This should have read Royal Prince Alfred Hospital, Sydney. Also, the web address in the final paragraph is incomplete. The correct address is: <http://www.cs.nsw.gov.au/rpa/neonatal/default.htm>. The errors are much regretted.

The authors would like to acknowledge and apologise for an error in our article Socioeconomic status and preterm birth: New Zealand trends, 1980 to 1999. ED Craig, JMD Thomp-

son, EA Mitchell (*Arch Dis Child Fetal Neonatal Ed* 2002;**86**:F142-6).

Paragraph four in the Results section should read "Figure 2 summarises changes in preterm birth rates by Deprivation Index decile between 1980 and 1999. During this period rates rose from 5.2% to 5.9% among those living in the most deprived areas (a 13.5% increase), from 4.0 to 5.5% amongst those living in average areas (a 37.5% increase) and from 3.1% to 5.4% amongst those living in the least deprived areas (a 74.2% increase). Thus while in 1980 a marked social gradient in preterm birth existed, by 1999 this had diminished markedly." Table 2 and table 3 are amended. These errors do not significantly change the reported trends in preterm birth or the interpretation of the findings previously published.

Table 2 Multivariate odds ratios for preterm birth by gestational age category and Deprivation Index decile; New Zealand singleton live births 1980, 1990, and 1999

Year	NZDep Index Decile	Gestational age category			
		All preterm (n=51 711) OR*	20-27 weeks (n=2697) OR**	28-33 weeks (n=12 703) OR*	34-36 weeks (n=36 311) OR*
1980	1	1.00	1.00	1.00	1.00
1980	5	1.15	1.08	1.16	1.15
1980	10	1.36	1.18	1.39	1.36
1990	1	1.30	1.31	1.21	1.33
1990	5	1.44	1.45	1.34	1.47
1990	10	1.63	1.66	1.52	1.67
1999	1	1.64	1.67	1.44	1.72
1999	5	1.76	1.91	1.53	1.84
1999	10	1.93	2.25	1.64	2.02

Multivariate analysis adjusted for gender, maternal age, parity, birth year, decile and birth year*decile, year*age, year*parity, decile*age, decile*parity.

*Odds ratios (OR) with reference category Deprivation Index decile 1, 1980.

**Odds ratios for the 20-27 week category did not reach statistical significance.

Table 3 The "social gradient in preterm birth"; risk of preterm birth amongst decile 10 women compared to decile 1 women (same year), New Zealand singleton live births 1980, 1990, and 1999

Year	Gestational age category			
	All preterm (n=51 711) OR*	20-27 weeks (n=2697) OR**	28-33 weeks (n=12 703) OR*	34-36 weeks (n=36 311) OR*
1980	1.36	1.18	1.39	1.36
1990	1.26	1.27	1.25	1.26
1999	1.17	1.35	1.14	1.17

Multivariate analysis adjusted for gender, maternal age, parity, birth year, decile and birth year*decile, year*age, year*parity, decile*age, decile*parity.

*Odds ratios (OR) for preterm birth amongst decile 10 women compared to those in decile 1 for each particular year reflects the social gradient for that year.

**Odds ratios for the 20-27 week category did not reach statistical significance.

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The editors will decide, as before, whether to also publish it in a future paper issue.

Late anaemia in Rh haemolytic disease

As it is clearly stated in the review by Gottstein and Cooke,¹ we consider it unethical to withhold or delay high dose intravenous immunoglobulin (IVIG) treatment in infants with haemolytic disease of the newborn. Since the study we did in 1995,² we have treated 129 patients with Coomb's positive haemolytic disease of the newborn, with the same method and had to resort to exchange transfusions only in three cases. On the other hand, late anaemia is a frequent problem in these cases, necessitating multiple blood transfusions, with well known complications.

The authors suggest that multiple doses of IVIG may reduce late anaemia. However, our observation in a limited number of cases is that, even multiple doses of IVIG are ineffective in preventing late anaemia. In an earlier unpublished study, we had shown that the erythropoietin levels were low in these infants. Therefore, we had conducted a double blind, randomised pilot study to investigate the effects of recombinant erythropoietin (rHEPO) in these patients.³ In this study, rHEPO was administered at a dose of 200 units/kg, subcutaneously, three times a week, starting at the 14th day of life and lasting for six weeks. This protocol reduced the number of erythrocyte transfusions significantly. With the impetus of this pilot study, we have used the same protocol for the subsequent 103 patients and the mean number of transfusions in this group was 1.5, with the majority of patients (55%) not needing any transfusions at all. There were no complications, including changes in neutrophil or platelet counts, and haemorrhagic or infectious complications. The administration of rHEPO to patients with haemolytic disease of the newborn, who had received IVIG early in life, not only decreases the infants' exposure to multiple blood donors, but also diminishes the need for hospitalisation and hence the cost that is involved. Therefore, rHEPO treatment is a suitable alternative to erythrocyte transfusions in these infants.

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Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn

We read with interest the recent review of Gottstein and Cooke.¹ Their systematic review of trials reporting treatment of infants with proven Rh and/or ABO haemolytic disease of the newborn (HDN) treated with high dose intravenous immunoglobulin (HDIVIG) and phototherapy, with phototherapy alone demonstrated that significantly fewer infants required exchange transfusion in the HDIVIG group. The authors point out that anti-D is the commonest red cell antibody responsible for HDN. We have recently treated two children both of whom developed evidence of immune haemolysis due to anti-D antibodies acquired from IVIG.

The first patient, a 4 month old infant with Kawasaki's disease, was treated with intravenous immunoglobulin (2g/kg) with immediate control of fever and irritability. Ten days later her disease became clinically active again and she was therefore given a second dose of IVIG (2g/kg from a different batch), which is a recognised therapeutic option.² Her clinical condition again improved rapidly. A blood count two days after the second dose of IVIG showed that her haemoglobin had fallen suddenly by 2g/dl to 6.4g/dl, the blood film showed spherocytes and the direct antiglobulin test was positive, evidence of immune haemolysis. Samples that were collected prior to the second dose of IVIG confirmed her blood group to be AB Rh D positive with a negative direct antiglobulin test. Anti-D antibodies were now detected in the patient's serum; these were not present in her mother whose antibody screen was negative and whose blood group was A Rhesus D positive. The manufacturer of the IVIG investigated the batches used and reported that the IVIG used for the second dose contained anti-D. The second patient, a 12 year old boy with systemic juvenile idiopathic arthritis received a fifth dose of IVIG from the same batch. He was screened for evidence of haemolysis and his antiglobulin test was positive 14 days after treatment. He remained asymptomatic with no fall in haemoglobin.

IVIG is a pooled blood product not a drug; each batch is made from a pool of plasma collected from several thousand donors. Passive transfer of potentially significant red cell antibodies is a recognised hazard, reported in the company literature but only as a serological phenomenon, not as a clinical warning.

The first case is a reminder that such complications may have serious clinical consequences. We would agree with the comment of Gottstein and Cooke that the use of IVIG is not without potential risks, including haemolysis. IVIG is not universally effective in autoimmune haemolysis in older children and adults where steroids are the first choice.

Indications for the use of IVIG must be clear and evidence based, and as with all pooled blood products, including albumin solutions, the individual batch numbers must be recorded in the case notes, so that adverse events can be appropriately and fully investigated.

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High dose intravenous immunoglobulin in haemolytic disease of neonates

It was encouraging to read article of Gottstein *et al.*,¹ on the use of high dose intravenous immunoglobulin (HDIVIG) in cases of haemolytic disease of newborns (HDN) with their conclusion showing the effectiveness of HDIVIG. I have the following observations to make with respect to implications on practice and future research.

Firstly, all the references mentioned were between three and ten years old.²⁻⁶ These trials did not take into consideration the irradiance of the phototherapy used, although they did observe the number of exchange transfusions performed. Presently, a combination of blue and white fluorescent light double surface phototherapy, with effective higher irradiances of 20-40 uW/cm²/nm, can practically eliminate the need for exchange transfusion, even in severe cases of HDN. Irradiance of phototherapy can be increased further by decreasing the distance between the phototherapy unit and the patient, especially with an undersurface phototherapy unit, keeping thermal and nursing issues under consideration.

Secondly, the authors did not address enterohepatic recirculation of bilirubin from the gut. Inexpensive measures can decrease the back entry of bilirubin from gut, like early enteral feeds, oral administration of agar agar, isbagol husk and so forth, and further reduce serum bilirubin levels. Further randomised controlled trials are required before administration of HDIVIG becomes routine in HDN. These trials should compare use of current effective phototherapy combinations with the

highest possible irradiance, agents that decrease enterohepatic recirculation of bilirubin with or without HDIVIG, and the need for exchange transfusion in HDN. They should also address cost effectiveness and safety, considering the cost of HDIVIG in the developing world.

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Authors' reply

We are grateful to our colleagues for their interest and responses to our paper.¹ In response to Dr Ovaly's comments we agree that late anaemia can be a problem in babies who receive intravenous immunoglobulin (IVIG), as is also demonstrated in our systematic review. Even when infants have received exchange transfusions (XTs) top up red cell transfusions may be required. In a recent local audit of XTs, 35% of babies received top up red cell transfusions after one or more exchange transfusions. During a five year period from 1998–2002, 27 babies with Rhesus, Kell, or ABO incompatibility had 28 XTs. Gestation ranged from 28 to 40 completed weeks. Of 26 infants for whom follow up data was available, nine (35%) had received top up red cell transfusions.

We read with interest Dr Ovaly and colleagues paper describing a double blind randomised controlled trial of subcutaneous recombinant human erythropoietin (rHEPO) and its use in this situation.²

We await with interest the outcome of a Cochrane meta-analysis of this therapy in newborn infants (currently at the protocol stage).

We reviewed our computer database for a three year period from December 1999 to December 2002 to postulate what impact IVIG might have on our population of babies with haemolytic disease of the newborn. Two hundred and five babies had a positive direct Coombs test (DCT) result. Of these infants, 12 received XTs. There is a degree of under ascertainment with this database as there were four additional babies who required an XT during this time period. However, we make the assumption that the proportions of those missed requiring XTs is similar to the proportions of DCT positive babies who were missed from the database. Eighty five babies had moderate or strongly positive DCT. Of these 11 received an XT, giving an XT rate in this group

of 13%. After IVIG the relative risk of requiring an XT is 0.28,¹ thus with IVIG the XT rate would be reduced to 3.6%, decreasing the number of XTs to three and therefore preventing eight. If IVIG were administered to all babies with moderate or strongly positive DCT, in our population the number needed to treat would be 10.6 to prevent one XT. The degree of positivity of the DCT is an objective validated assessment of the strength of antigen/antibody reaction, determined by the degree of agglutination in the laboratory.³ During the three year period of this database there was only one infant who had only a weakly positive DCT and required an XT.

We were interested to read Dr Cleary and colleagues case reports. We recognise that IVIG is not specific for a particular type of haemolysis and that it is a pooled blood product. We therefore agree that all the usual procedures regarding documentation of batch number and so on are followed as for any other blood product. IVIG has been used previously even in preterm and low birthweight infants⁴ and is currently being used in the INIS Trial.⁵ As with any drug or blood product we will need to remain vigilant for the occurrence of any adverse events.

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Discharging twins separately from neonatal units

We recently had a debate in our unit about whether or not it was better for a well twin to remain with its sibling in hospital until the latter was fit to be discharged. Our current practice is to keep the well twin in the special care baby unit until its twin is fit for discharge. The group who favoured separate discharge cited reduced risk of nosocomial infection, decreased costs, cot availability, and the possibility of settling into a routine with one twin at home as supportive factors for their argument. Those against separate discharge cited impaired bonding, breast feeding difficulties, and transport issues as their reasons.

We took the discussion to the RCPCH and NICU-net email discussion groups and found no clear consensus. Our American colleagues routinely send multiples home separately and cite health insurance companies as a major factor in this decision. They find little problem with this arrangement. European opinion was split between the two camps. British doctors seemed to be in favour of asking the parents' opinion, so we identified 10 sets of twins from the last three years who could have been sent home separately. We then sent their parents a

questionnaire exploring their opinions; five (50%) were returned.

Most parents agreed that their twins were ready for discharge at different times and said that they would have preferred separate discharge. However, they believed that they had been given this option and had not taken it. They realise that this would have caused problems with visiting, feeding, and bonding with the remaining twin even although they all had their own transport. They did not think that having one twin home first would have helped them to adjust and settle into a routine. Their preferred option would have been to have roomed in with the well twin while the other twin stayed on the special care baby unit.

Our current practice is that we have an informed discussion with the parents when this situation arises. As one email respondent (a doctor and father of twins) wrote "Bringing up twins is full of decisions about when to pair them and when to split them up."

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Role of serum peak levels of vancomycin in neonatal intensive care units

We would like to comment on the article by Tan *et al.*¹ The purpose of measuring serum levels of a drug is either to monitor the toxicity of the drug or the therapeutic concentration for a particular condition. Emergence of infections with β -lactam-resistant *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Enterococcus* sp, has led to the frequent use of vancomycin in neonates. Vancomycin has historically had a reputation for toxicity. Many of its original adverse reactions, including ototoxicity and nephrotoxicity, were probably due to impurities in the formulation.² Now that a more purified form is available, these adverse reactions are uncommon. However, concomitant administration with aminoglycosides or other nephrotoxins may increase the risk of toxicity.³ Effective drug therapy is measured by response, not by achievement of a particular circulating drug concentration. Because the association between vancomycin peak concentrations and toxicity is poor, some have recommended measuring trough concentration only⁴ as this study is clearly documenting, but others have suggested not measuring any concentrations in the majority of children with normal renal function.⁵ However, in critically ill premature neonates with poor glomerular filtration rate, prematurity, and compromised cardiovascular function, it remains prudent to measure both peak and trough concentrations in those with poor or changing renal function. Caution must be exercised when other nephrotoxic or ototoxic drugs such as aminoglycosides are administered concurrently.⁶ In this study, the authors did not mention the concomitant use of aminoglycoside.

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Methaemoglobinaemia with concurrent blood isolation of *Saccharomyces* and *Candida*

Saccharomyces boulardii is closely related to *Saccharomyces cerevisiae* and is used as biotherapeutic agent,¹ although some reports suggest pathogenicity.² We present a case of neonatal fungaemia with concurrent methaemoglobinaemia, occurring after a brief period of treatment with *S. boulardii*. A male infant was born at 30 weeks of gestational age by caesarean section because of intrauterine growth restriction and maternal hypertension. The baby was well apart from persistent gastrointestinal symptoms that hampered feeding and forced parenteral support. During the third week of life, administration of *S. boulardii* (Codex DNB; half a capsule a day, equivalent to 2.5×10^9 organisms) was started in an attempt to prevent bacterial overgrowth. After four days of treatment, the baby developed symptoms suggesting sepsis and an unexplained methaemoglobinaemia (methaemoglobin concentration = 16%). Codex was stopped and empirical antibiotic coverage, including liposomal amphotericin B, was started. Blood cultures showed growth of *Candida albicans*, but the central venous catheter tip was negative. Methaemoglobin levels halved in two days (7%), but remained constant during the following two weeks of antifungal treatment. Blood cultures at that point showed growth of *S. cerevisiae*, which is susceptible to amphotericin B, in the absence

of any clinical finding; again, the catheter tip was sterile. Methaemoglobin concentration was still abnormal (6.2%). Liposomal amphotericin B treatment was prolonged for a further six days and then discontinued. At this time, methaemoglobin levels were near normal (3%), and blood cultures were negative. The gastrointestinal symptoms resolved with age and full gastrointestinal function was achieved.

Recovery of *Saccharomyces* two weeks after administration had been stopped suggests persistence in the gut. It is tempting to think that the methaemoglobinaemia was caused by the continued presence of the yeasts, perhaps through excessive host production of nitric oxide. Several studies have shown that nitric oxide plays a pivotal role in the interaction between yeasts and the phagocytic system,³ and it is well known that this radical readily oxidises haemoglobin. It is also reasonable to link late bloodstream invasion by *Saccharomyces* to previous enteric mucosal damage caused by a *Candida* infection, which was itself probably gut related. The recovery of *S. cerevisiae* in place of *S. boulardii* has been reported by others,⁴ and can be explained by the similarities between the two. It is ironic that the intervention used to prevent sepsis from enteric overgrowth not only did not succeed but was itself a cause of the problem that it was intended to prevent.

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Wafting does work

We were interested to see the article “Oxygen administration in infants”,¹ and eLetter responses. The original article and eLetters were unsure of the efficacy of “non-contact” oxygen delivery or “wafting” as it is more commonly known. Our study “The efficacy of noncontact oxygen delivery methods”,² demonstrated how effective wafting oxygen can be. We found that an area of 34cm by 37cm obtained a concentration of >30% when oxygen is delivered by face mask at 10 l/minute. Although this is not a substitution for the more reliable methods of administration as detailed by Drs Frey and Shann, in the short term it can be used with confidence.

We caution against holding a self inflating resuscitation bag over an infant’s airway (without manipulation of the bag itself), as it delivers a negligible amount of oxygen. It is much more efficient to use the oxygen tubing without any attachments.

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CORRECTION

We wish to apologise for an error that occurred in a letter by Daniels *et al* (*Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F257). The first line of the third paragraph should have read: The salient results were that two thirds of granulomas resolved over a three week period without cauterisation.



Progressive ventricular dilatation (PVD) over the past 22 years

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Arch Dis Child Fetal Neonatal Ed 2003 88: F257

doi: 10.1136/fn.88.3.F257-a

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