Late anaemia in Rh haemolytic disease

As it is clearly stated in the review by Gottstein and Cooke, 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, we have treated 129 patients with Coombs’ 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 In an earlier unpublished study, we had shown that the erythropoietin levels were low in these infants.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. 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 transfusion.

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. 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 not 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 batch 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 not an exchange 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.
highest possible irradiance, agents that de-
crease enterohepatic recirculation of bilirubin with or without HDIVIG, and the need for
exchange transfusion in HDN. They should also
address cost effectiveness and safety, con-
sidering the cost of HDIVIG in the develop-
ing world.

G Gupta
Armed forces Medical College, Pune, India;
guptas@yahoo.net

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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 have received intravenous immunoglobulin
(IVIG), as is also demonstrated in our system-
atic review. Even when infants have received exchange transfusions (XTs) top up red cell
transfusions may be required. In a recent local
audit of XT, 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 Rhessus, Kell,
or ABO incompatibility had 28 XT. Gestation ranged from 26 to 40 completed weeks. Of 26
infants for whom follow up data was avail-
able, nine (35%) had received top up red
cell transfusions.

We read with interest Dr Ovaly and colleagues paper describing a double blind
dominated trial of subcutaneous recombinant human erythropoietin (HFEPO)
and its use in this situation.1

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
time 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 hun-
dred and five babies had a positive direct
Combs test (DCT) result. Of these infants, 12
received XT. There is a degree of under as-
certainment 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 XT is similar to the propor-
tions 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, thus with IVIG the XT
rate would be reduced to 3.6%, decreasing the
number of XT to three and therefore prevent-
ing 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.8
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 are 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 prod-
uct. We therefore agree that all the usual pro-
cedures regarding documentation of batch
number and so on are followed as for any
other blood product. IVIG has been used pre-
nviously even in preterm and low birthweight
infants9 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 occur-
rence of any adverse events.

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

We would like to comment on the article by
Tan et al.10 The purpose of measuring serum
levels of a drug is either to monitor the toxic-
ity of the drug or to determine the right concen-
tration for a particular condition. Emergence of
infections with β-lactam-resistant Staphylococ-
cus epidermidis, Staphylococcus aureus, and Ente-
roccus sp. has led to the frequent use of van-
comycin in neonates. Vancomycin has historically had a reputation for toxicity. Many of its original adverse reactions, includ-
ing ototoxicity and nephrotoxicity, were prob-
ably due to impurities in the formulation.11 Now
that a more purified form is available, these
adverse reactions are uncommon. However,
concomitant administration with aminogly-
cosides or other nephrotoxins may increase
the risk of toxicity.12 Effective drug therapy is
monitored 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 concen-
tration only as this study is clearly
documenting, but others have suggested not
measuring any concentrations in the majority
of children with normal renal function.13
However, in critically ill premature neonates
with poor glomerular filtration rate, prematu-
ritry, and compromised cardiovascular func-
tion, 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 adminis-
tered concurrently. In this study, the authors
did not mention the concomitant use of
aminoglycoside.

S Jain
Southern Illinois University School of Medicine,
Springfield Illinois, USA; jainsunil@hotmail.com

References
regimen for vancomycin not needing serum

www.archdischild.com

Methaemoglobinaemia with concurrent blood isolation of Saccharomyces and Candida

Saccharomyces boulardii is closely related to Saccharomyces cerevisiae and is used as biotherapeutic agent, although some reports suggest pathogenicity. We present a case of neonatal fungaemia with concurrent methaemoglobinemia, 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 x 10^5 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, 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, 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.

M S Lungarotti, D Mezzetti, M Radicioni
Policlìnica Monteluce, Via Brunamonti, Perugia, PG 06100, Italy; dm2@unipg.it

References

Wafting does work

We were interested to see the article "Oxygen administration in infants", and letter responses. The original article and letters 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” 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.

P Davies
NETS, Sydney, Australia; daviespatrick@hotmail.com

D Cheng
Department of Oncology, Great Ormond Street Hospital, London, UK

A Fox
Department of Paediatric Allergy, St Mary’s Hospital, London, UK

L Lee
Neonatal Intensive Care Unit, Rosie Maternity Hospital, Cambridge, UK

References

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 cautery.