Low soluble FcRIII receptor demonstrates reduced neutrophil reserves in preterm neonates

EDITOR,—Studies of human neonate granulopoiesis have been hampered by the lack of a marker of overall neutrophil cell mass. Assumptions about neonate granulopoiesis have therefore largely been extrapolated from rat data. Direct measurement of total neutrophil cell mass (in terms of neutrophils per g body weight) in newborn rats has shown that they have about one quarter the neutrophil mass of adult animals and that their neutrophil mass increases by the time they are 4 weeks old.1 In addition, newborn rodents do not have the reserve pool of quiescent granulocyte progenitors, as found in adults, to recruit into production during sepsis. Circumstantial evidence for a similar immaturity of neutrophil production in human neonates comes from the low proportion of quiescent progenitors in cord blood2 and the frequent occurrence of postnatal neutropenia in preterm infants.3 More additional insight comes from a study of mid-trimester abortuses,4 which showed minimal numbers of neutrophils in haemopoietic tissue before 24 weeks gestation. Until now, direct quantification of total body neutrophil cell mass in human neonates between 24 weeks and term has remained elusive.

In 1992 we reported5 that preterm neonates born before 32 weeks gestation have very low plasma concentrations of the soluble FcRIII receptor (sFcRIII), sFcRIII is the plasma form of the neutrophil membrane receptor FcγRIII which, together with other membrane receptors, is responsible for binding opsonised particles and initiating phagocytosis. We observed that, between 24 and 32 weeks gestation, sFcRIII concentrations are about 15% of normal adult values (mean (SE) 15.3 (1.3)%), while sFcRIII concentrations in fetal samples collected between 19 and 23 weeks are even lower (mean (SE) 8.3 (1.4)%). Between 33 and 36 weeks in utero, sFcRIII increases rapidly so that both term and post term have concentrations similar to adults. In babies born before 32 weeks, sFcRIII concentrations gradually after birth to achieve adult concentrations by the fourth week of postnatal life. At the time, we interpreted these data to indicate reduced FcRIII production by individual cells and thus immaturity of neonate neutrophil function.

Since we published these data, further work has clarified the origins and significance of plasma sFcRIII. These studies have shown that sFcRIII is derived from apoptotic neutrophils, and its concentration in plasma reflects the total body neutrophil cell mass as well as the overall production of neutrophils in the bone marrow.6

This new understanding of sFcRIII alters the interpretation of our original observation. It is now apparent that our conclusion was partly incorrect: preterm human infants of less than 32 weeks gestation have reduced neutrophil production and a reduced total neutrophil cell mass at birth. Our data also show that neutrophil reserves remain low about three weeks after preterm birth. Term infants, by contrast, have neutrophil production and stores that are similar to those of adults.

The reduced neutrophil mass of preterm neonates explains the common occurrence of postnatal and sepsis induced neutropenia. The relevance of this finding to the high sep sis incidence associated with prematurity is emphasised by a recent study of patients with idiopathic neutropenia, which has shown that a low sFcRIII concentration is a more accurate predictor of infection risk than the peripheral blood neutrophil count.7 Furthermore, this new insight into neonatal immune development suggests that stimulation of neutrophil production by colony stimulating factors early in postnatal life could reduce the incidence and severity of sepsis in preterm neonates by accelerating expansion of their deficient neutrophil reserves.

ROBERT CARR
Department of Haematology, King’s College, St Thomas’ Hospital, London, UK

TOM W J HUIZINGA
Department of Rheumatology, University Hospital Leiden, Leiden, The Netherlands


Suxamethonium is safe in safe hands; mivacurium should also be considered

EDITOR,—We thank Whyte et al8 for detailing the premedication policies for intubation in United Kingdom neonatal units. There is a wide disparity in both the type and dosage of drugs. Whyte et al mention that, as a muscle relaxant, suxamethonium, has important safety benefits. It has a very rapid onset and offset of action, and therefore there is a “get out clause” for the difficult intubation or intubation by an inexperienced operator. However, other considerations need to be taken into account when suxamethonium is used.

Firstly, intravenous premedication is contraindicated in conditions known to be associated with difficult intubations, such as the Pierre Robin sequence. Further, suxamethonium is a depolarising muscle relaxant and therefore can cause sinus bradycardia. Atropine can be given in an attempt to avoid this.

Suxamethonium causes depolarisation at the neuromuscular junction, rarely leading to hyperkalaemic induced cardiac arrest.9 Undiagnosed myopathic conditions were found in a number of affected children, and paediatric licensing for this drug was therefore removed in the United States. However, no other very rapidly acting drug has been manufactured, and, because of its popularity, suxamethonium was reinstated. Before its use, a detailed family history for myopathic conditions must be taken. In our neonatal unit, we have started to use fentanyl, an opioid, with mivacurium as the muscle relaxant.10 The disadvantage of mivacurium is that it is only a rapidly acting muscle relaxant.11 Its major advantage is that it is non-depolarising muscle relaxant and therefore carries no risk of life threatening arrhythmias. The routine use of atropine is not necessary.

<table>
<thead>
<tr>
<th>Day no</th>
<th>Total fluids (ml/kg)</th>
<th>Urinary output (ml/kg)</th>
<th>Sodium input (mmol/d)</th>
<th>Serum sodium (mmol/l)</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>217</td>
<td>7</td>
<td>3</td>
<td>124</td>
<td>860</td>
</tr>
<tr>
<td>7</td>
<td>248</td>
<td>7</td>
<td>7</td>
<td>120</td>
<td>860</td>
</tr>
<tr>
<td>8</td>
<td>213</td>
<td>7</td>
<td>10</td>
<td>128</td>
<td>870</td>
</tr>
<tr>
<td>9</td>
<td>214</td>
<td>6.9</td>
<td>14</td>
<td>134</td>
<td>880</td>
</tr>
<tr>
<td>10</td>
<td>203</td>
<td>5.3</td>
<td>15</td>
<td>131</td>
<td>900</td>
</tr>
<tr>
<td>11</td>
<td>206</td>
<td>6.1</td>
<td>15</td>
<td>136</td>
<td>940 (PDA)</td>
</tr>
</tbody>
</table>

PDAs, patent ductus arteriosus.
We agree that a randomised trial needs to be undertaken to prove that predmedication has the desirable end point of reducing neonatal morbidity, particularly intraventricular haemorrhage.

ASRAH RASHID
Specialist Paediatric Registrar
Neonatal Unit
Birmingham Heartlands Hospital
Bordesley Green, Birmingham B9 5SS
email: Draze@inhone.net

MICHAEL WATKINSON
Consultant Neonatologist
Neonatal Unit
Birmingham Heartlands Hospital


Premedication for intubation in neonates

EDITOR,—We were very interested in the recent papers by Bhutada et al1 and Whyte et al2 on the use of predmedication for sedative intubation in neonates. It is now well accepted that term and preterm neonates tolerate awake intubation poorly, often exhibiting hypoxia, bradycardia, and systemic and intracranial hypertension during nasotracheal or orotracheal intubation.1,2 Analgesia and sedation are still used infrequently in nurseries for intubation and other ‘routine’, but invasive, therapeutic or diagnostic procedures. We recently performed a randomised, double blind, placebo controlled trial to assess whether sedation with midazolam in premature infants would improve physiologic stability and the success rate of endotracheal intubation. Eight premature infants underwent 16 intubation procedures after being randomly assigned to one of three groups: I (n = 3), the control group, received placebo only; II (n = 6) received atropine and placebo; and III (n = 7) received atropine and midazolam. Infants could be randomised again to a different group after completion of each intubation procedure. Heart rate, blood pressure, and oxyhaemoglobin saturation were recorded at 10 minute intervals for each infant. The study was terminated when data were reviewed early because of concerns over adverse events. The number of episodes of oxyhaemoglobin desaturation around the time of intubation was significantly greater in group III (86%) than in group I (0%; p = 0.01). Cardiopulmonary resuscitation was required in 29% of group III compared with 0% of group II (p = 0.16).

In our trial, premature infants who received midazolam were at increased risk of oxyhaemoglobin desaturation during tracheal intubation. There was also a trend toward an increased need for cardiopulmonary resuscitation in these infants. Although regrettably we could not find an association between improved survival and the development of severe ROP in infants less than 1251 g birth weight. Arch Dis Child Fetal Neonatal Ed 2000;82:F18–F41.

The inclusion of a relatively large number of extremely low birthweight infants is another strength of this study. In an attempt to define normal blood pressure values in a population that by definition is not a reliable parameter to assess cerebral blood flow, we could not find an association between improved survival and the development of severe ROP. ROP was defined as stage 3 in the five cities in England and Australia (table 1).

Unlike Vyas et al,4 we could not find an association between improved survival and the development of severe ROP. In six of the neonatal units in our study (two have been excluded from this analysis as they are children’s hospitals and have very few small premature infants), survival in infants of < 27 weeks gestation ranged from 51.3% to 68.8%. The percentage with severe ROP for the two units with the lowest and highest survival was 15 (3/20) and 24 (5/21) respectively, while the range of severe ROP in the six neonatal units was 15% (3/20) to 56% (9/25). In infants of 27–28 weeks gestation, survival ranged from 85.1% to 96.7% and the percentage with severe ROP for the two units with the lowest and highest survival was 7 (4/56) and 3 (2/58) respectively, while the range of severe ROP in this group of infants was 2% (1/50) to 7% (4/56) (unpublished observations). We have also shown that, despite an increase in survival of preterm infants following the introduction of surfactant, there was no significant impact on the incidence or severity of ROP.

Incidence of severe retinopathy of prematurity

EDITOR,—We were interested to read the article of Vyas et al5 on the incidence of severe retinopathy of prematurity (ROP) in 11 neonatal units in five cities in England in 1994. We have published similar data from eight neonatal units in five cities in England and Australia.6 11 We found an incidence of severe ROP in this group of infants (4/56) and 3 (2/58) respectively, while the two units with the lowest and highest survival was 15% (3/20) and 24 (5/21) respectively, while the range of severe ROP in the six neonatal units was 15% (3/20) to 56% (9/25). In infants of 27–28 weeks gestation, survival ranged from 85.1% to 96.7% and the percentage with severe ROP for the two units with the lowest and highest survival was 7 (4/56) and 3 (2/58) respectively, while the range of severe ROP in this group of infants was 2% (1/50) to 7% (4/56) (unpublished observations). We have also shown that, despite an increase in survival of preterm infants following the introduction of surfactant, there was no significant impact on the incidence or severity of ROP.

In infants of 29–31 weeks gestation, six of 27 (22%) infants had severe ROP. Three (2/58) required Cryo/Laser treatment.7 This infant was 30 weeks gestation with a birth weight of 1305 g. We therefore agree with Vyas et al that there should be no reduction in the upper limit of gestation or birth weight for screening for ROP.

Blood pressure standards for very low birthweight infants

EDITOR,—Based on careful invasive blood pressure measurements in a cohort of 61 very low birthweight (VLBW) infants requiring inotropic support for 24 hours of life, Lee et al8 report on blood pressure standards in this population. The quality of the blood pressure readings was assessed using continuous video recordings of the first wave forms. The inclusion of a relatively large number (n = 28) of extremely low birthweight infants is another strength of this study.

With the exclusion of infants who developed severe IVH, it became impossible to detect any association between blood pressure and IVH. Decreases in cerebral blood flow may play an important role in the pathogenesis of IVH, and, although blood pressure is not a reliable parameter to assess cerebral blood flow,9 at least two published studies10 have shown that the incidence of IVH was higher in infants with lower MAP. Perhaps the authors could indicate how many infants
with IVH grades III and IV were excluded and what blood pressures were recorded in these infants. For similar reasons, it remains uncertain whether the proposed blood pressure standards are applicable to very ill infants or infants who require isotropic support. It is conceivable that cerebral vascular resistance in sick preterm infants differs from that in the study patients, and consequently the application of the suggested blood pressure standards to sick preterm infants would result in different—and possibly inadequate—cerebral blood flows.

The data presented add to our knowledge on blood pressure in VLBW infants, but do not allow the conclusion that the suggested blood pressure standards are safe for all VLBW infants.

THOMAS M BERGER
Neonatal and Pediatric Intensive Care Unit
Kinderspital Luzern, CH-6000 Luzern 16
Switzerland


Drs Juin, Rajadurai, and Wee respond:

We would like to thank Dr Berger for his comments. Our objective was to define the normal range of blood pressures for very small infants and this would logically exclude those with IVH and those on inotropes, both of which could affect blood pressure.

We did not compare infants with and without IVH because that was not our aim. There may very well be a correlation between hypotension and IVH but studies looking at this association were not optimal because there is controversy as to what constitutes hypotension. We hope that our standards will provide norms for such studies. Blood pressure is the practical surrogate for cerebral blood flow because with present technology we cannot continuously monitor the latter by the bedside. Tyszczuk et al. determined that cerebral blood flow was independent of blood pressure in preterm infants, but again the selection of a mean arterial pressure of 30 mm Hg as the cut off is open to debate. We think that choosing such an arbitrary number was not appropriate and more such studies are needed with particular attention being paid to the very different normal blood pressures among preterm infants with various birth weights and gestational ages.

Patient triggered ventilation in neonatal respiratory distress syndrome

EDITOR,—Baumer reports the results of a large multicentre study comparing the effects of patient triggered ventilation (PTV) with conventional ventilation (IMV).1 There appears to be no benefit from PTV compared with IMV in death rate, development of chronic lung disease, pneumothorax rates, and cerebral ultrasound abnormality. In addition, because of an increased trend toward a higher pneumothorax rate, Baumer concludes that, at present, PTV delivered with either the SLE 2000 or the Dräger babylog 8000 cannot be recommended for infants of less than 28 weeks gestation with respiratory distress syndrome (RDS).

However, we are concerned that this may be a premature conclusion given the significant difference in PTV delivered by the two main ventilators used and the potential heterogeneity of clinical practice within the different centres involved, despite agreed ventilation protocols. Dimitriou et al. showed that neonates and infants trigger a significantly lower proportion of breaths using the SLE 2000, an airway pressure triggered ventilator that provides synchronised intermittent positive pressure ventilation (SIPPV). Attempts to optimise the trigger rate of the SLE 2000 ventilator by increasing pressure sensitivity often result in a high rate of false triggers discussed by Baumer. Therefore the PTV modes of the two ventilators are substantially different. This prompts us to ask whether the findings of this multicentre study are only applicable to PTV provided by the neonatal respiratory distress syndrome (ARCH DISEASES OF CHILDHOOD: FETAL AND NEONATAL EDITION)
PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

Table 1: Rate of pneumothorax in infants of less than 28 weeks gestation using two different makes of ventilator

<table>
<thead>
<tr>
<th></th>
<th>PTV mode</th>
<th>IMV mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dräger</td>
<td>19 (32%)</td>
<td>20 (33%)</td>
</tr>
<tr>
<td>SLE</td>
<td>134 (114)</td>
<td>114 (109)</td>
</tr>
<tr>
<td>Dräger with pneumothorax</td>
<td>19 (32%)</td>
<td>20 (33%)</td>
</tr>
<tr>
<td>SLE with pneumothorax</td>
<td>134 (114)</td>
<td>114 (109)</td>
</tr>
</tbody>
</table>

PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

The SLE 2000 in PTV mode in infants less than 28 weeks gestation, but not extend this caution to ventilating infants with the Dräger babylog 8000.

Given that none of these differences were statistically significant, no clear recommendation can be given. This is why the wording used in the publication was “it might be prudent to avoid...”.

As regards the number of infants departing from their assigned mode of ventilation, several points should be emphasised. The study protocol permitted changing the mode of ventilation at the discretion of the attending clinicians. This was inevitably interpreted differently by each clinical team. Departure from the assigned mode of ventilation was not an intended outcome, and it is evident that this occurred more commonly in the more immature infants and those that subsequently died. High rates of departure from the assigned mode cannot therefore readily be interpreted as evidence of failure of the assigned mode. Table 2 shows the numbers of infants of allgestations departing from the assigned mode of ventilation.

There was therefore a higher crude rate of departure from the assigned mode of ventilation in infants ventilated with the Dräger babylog 8000, with a similar proportion of infants leaving their assigned mode.

It would be difficult to interpret the pneumothorax rates for infants who were actually being ventilated with their assigned mode of ventilation. Some infants were switched to a different mode of ventilation after sustaining a pneumothorax. Most of the pneumothoraces occurred while infants were receiving their assigned mode of ventilation, and this included infants being trigger ventilated using the Dräger babylog 8000.

Burmester and Petros ask whether centres departing from their assigned mode of ventilation for infants randomised within three months had a pneumothorax rate of 5% compared with a rate of 13% for those randomised more than three months into the trial (odds ratio 0.30; 95% confidence intervals 0.12 to 0.74; p = 0.009). This was seen equally for both modes of ventilation.

In summary, there is no evidence from this study of any trend towards better outcomes with the Dräger babylog 8000 ventilator, although the small numbers enrolled make any conclusions less robust. There is evidence that suggests there may have been a short term reduction in pneumothorax rates from the educational package offered at the start of the study.

In conclusion, there was no convincing evidence of a beneficial effect of a policy of using PTV in preterm infants with RDS with the ventilators used. Regular attention to staff education on ventilator techniques is recommended.

I would like to use this opportunity to pay tribute to the two trial coordinators (Sue Ellis and Tom Mill), to the trial statistician (David Wright), and to the data monitoring committee (David Field and Diana Elbourne), whose details were inadvertently omitted from the final paper and without whom, together with the trial collaborators, the study would not have been possible.

Pyridoxine dependent epilepsy: a suggestive electroclinical pattern

Editor,—There are several problems with describing the electroclinical pattern in pyridoxine dependent seizures.1 One is defining the electroclinical features. Until now all published reports (including four of the five cases of Nabbout and colleagues) have described the electroencephalogram (EEG) in neonates who have received other anticonvulsants beforehand. It seems likely that these anticonvulsants could affect the EEG, as suggested by the infant with the most pronounced burst suppression pattern in the paper of Nabbout and colleagues. The other way of assessing the electroclinical pattern is on withdrawal, when we, like others, found that a continuous or intermittent high voltage slow wave pattern with or without spikes was typical.2 It would be very useful to know the EEG features of the patient who did not receive any other drugs before pyridoxine, as this would be the first description of the true electroclinical pattern in pyridoxine dependent seizures.

This study also concludes that the electroclinical pattern in neonatal units. Very few of the neonates reported in the literature or in the UK study had EEEGs before receiving pyridoxine. Presumably this reflects difficulties in obtaining EEGs out of hospital. One reason is that it is not routine practice in the neonatal unit, as well as the desire to treat without delay. As a result, for some neonatal units it may be difficult to detect a specific electroclinical pattern.

A second difficulty with the clinical features are not very specific. The neonatal presentation can be: as an acute encephalopa-thy, followed by later seizures; as seizures accompanied by encephalopathy (both of which introduce a wide differential diagnos-sis); as seizures alone; or, more unusually, as apparent acute abdominal obstruction or respiratory distress, usually accompanied by irritable behaviour, again followed by seizures. In some reports, seizures have been precipitated by sudden sounds or movements, although some of these could be an exaggerated startle response. Although these reports suggest that a variety of seizures, especially generalised tonic and generalised clonic, occurred in most of the cases, some only had one or two seizure types. In the UK study, five of the 20 definite and probable cases with an early onset were reported to have a single seizure type (unpublished data).

The third concern is that Nabbout and colleagues did not include later presenting cases (older than 28 days) in their report. These also appear to be pyridoxine dependent as judged by trials of withdrawal and occurrence in siblings. They accounted for three of the 23 definite and probable cases in the UK population study, although a further five had early seizures that responded to routine anticonvulsants and then remained seizure free for several weeks/months. In these, both the clinical and electrical features can differ from neonates. For example, the inter-ictal EEG can be normal, or show focal or generalised spikes or sharp waves with or without high voltage slow waves. These clinical features include recurrent episodes of status and less varied seizure types. Concentrating on a possible neonatal pattern risks overlooking such cases.

As Nabbout and colleagues emphasise, there needs to be a high index of suspicion. Clinically it is important that pyridoxine dependency should be considered in all early childhood seizures, because (a) it may be misleading and (b) early treatment does appear to be beneficial.

PETER BAXTER
Sheffield Childrens Hospital
Western Bank
Sheffield S10 2TH, UK


Parental visiting in neonatal units

Editor,—We read with interest the paper by Cuttini et al.1 Although policy on parental visiting is an easier issue to evaluate, parental participation in decision making, particularly in decisions with strong ethical overtones, is much more complex. It is difficult to evaluate with accuracy, and by its nature, much more controversial. The paper does not stress that data collected from each participating unit, through a structured questionnaire completed by the unit coordinator, represent policies—that is, the intention and stance of each unit towards the particular issue for evaluation. Data collected through questionnaires and interviews involving both unit staff and parents would have provided a better understanding of the actual practice of each participating unit.

No unit from Greece took part in the study by Cuttini et al,2 but Greece is briefly mentioned in the Discussion, using results from a previous study, which is only partly relevant to the study.
of 38 units from 11 European countries, it was shown that the nine units that imposed visiting restrictions were in France, Greece, Italy, and Portugal.

We would like to provide further information on visiting policy in Greek neonatal intensive care units (NICUs). There are 15, two of which are private; 12 are attached to maternity hospitals and the remaining three are in children’s hospitals and accept direct referrals. Of those without one (Agia Kyriakou Children’s Hospital), visiting restrictions are imposed. These allow parents only, and the usual practice is 30 minutes to one hour visiting time in the morning and afternoon (except mothers). The most common reasons given for imposing restrictions are increased danger of infection and a disruptive effect on the unit.

We conducted a survey, through questionnaire and interview, of parents with a baby who had been cared for in another NICU that imposed visiting restrictions before it was transferred to our NICU and/or parents who had had a previous baby in another NICU that imposed restrictions. The overwhelming majority (98.6%) said that they preferred our liberal policy on visiting. One mother of a preterm baby with bronchopulmonary dysplasia said that “if I had delivered at term I would be with my baby; if I had not delivered prematurely I would also be with my baby (in my womb); now that I have delivered prematurely why can’t I be with my baby?”

We conclude that in Greece there is a demand for unrestricted parental visiting, but most Greek NICUs do not meet this demand for reasons not based on medical or sociological evidence.

It is worth noting that, in Greece, infants beyond the neonatal period have been admitted to children’s wards with their mothers for many years.

H D DELLAGRAMMATICAS
NICOLLETTA IACOVIDOU
NICU, 2nd Department of Paediatrics,
University of Athens,
Agia Kyriakou Children’s Hospital,
115 27 Athens, Greece


Ureaplasma colonisation and chronic lung disease in neonates

EDITOR.—We read the article by Hannaford et al with interest. We would like to point out that in our recent retrospective analysis, our findings of the colonisation rate of genital mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis) in the respiratory tract of premature infants of 27% were similar to those in our recent retrospective analysis.

We are, however, intrigued by the implication of a “protective effect” of Ureaplasma urealyticum colonisation on respiratory distress syndrome (RDS) in this study. We postulate that the low grade inflammatory response and a higher rate of CLD. In the present study, the incidence of RDS in Uu colonised infants was lower—but their incidence of CLD at 36 weeks was higher. Were there other factors—for example, increased incidence of PDA, more IV fluid use, that predisposed these infants to develop CLD? Another issue is that in the multivariate analyses, Uu colonisation was a significant risk factor for CLD only in singleton infants, but the relationship did not hold true when all infants were analysed. Based on these observations, we wonder if the “protective effect” is real or a statistical aberration? More research needs to be done to study this “protective effect” of Uu colonisation on RDS before any conclusions can be drawn.

The treatment of Uu colonisation was not discussed in this paper. In our experience, erythromycin alone was not effective in clearing the organism from the respiratory tract. We found a short course of postnatal steroids alone or in combination with erythromycin more effective.2 We wonder if infants receiving postnatal steroids were confounders in the discrepancy between the incidence of RDS and CLD.

VINEET BHANDARI
Department of Paediatrics,
Albert Einstein Medical Center,
Philadelphia, PA 19141, USA

NAVEED HUSSAIN
Department of Paediatrics,
University of Connecticut Health Center,
Mailcode 2203, Farmington, CT 06030–2203, USA


CORRECTION

The authors of the paper “Risk adjusted and population based studies of the outcome for high risk infants in Scotland and Australia” Arch Dis Child Fetal Neonatal Ed 2000;82:118–123 have asked us to publish the following corrected version of table 6.

The authors apologise for the error.