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for neonatal and paediatric healthcare professionals

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CUROSURF® Endotracheopulmonary Instillation Suspension (Poractant alfa) **Please refer to Summary of Product Characteristics (SmPC) before prescribing PRESCRIBING INFORMATION. Presentation** Single dose vials of 1.5ml or 3.0ml containing either 120mg or 240mg of phospholipid fraction from porcine lung. **Indications** Treatment of Respiratory Distress Syndrome (RDS) or hyaline membrane disease in newborn babies with birthweight over 700g. Prophylactic use in premature infants between 24 and 31 weeks estimated gestational age at risk from RDS or with evidence of surfactant deficiency. **Dosage** (See SmPC for full details) ***Rescue treatment*** Recommended starting dose is 100-200mg/kg (1.25-2.5ml/kg) administered as a single dose as soon as possible after diagnosing RDS. Additional doses of 100mg/kg (1.25ml/kg) at about 12 hourly intervals may be given (maximum total dose of 300-400 mg/kg). ***Prophylaxis*** Single dose of 100-200mg/kg as soon as possible after birth (preferably within 15 minutes). Further doses of 100mg/kg can be given 6-12 hours after the first dose and then 12 hours later for persistent signs of RDS and ventilator-dependency (maximum total dose of 300-400mg/kg). **Administration** Warm vial to room temperature (e.g. by holding in the hand for a few minutes) and gently turn upside down a few times without shaking. Withdraw the suspension using a sterile needle and syringe (see SmPC for full details). A suitable catheter or tube should be used to instil CUROSURF into the lungs. Doses are administered either by: **1). Disconnecting the baby momentarily from the ventilator** Administer 1.25 to 2.5ml/kg of suspension, as a single bolus directly into the lower trachea via the endotracheal tube. Perform one minute of hand-bagging and then reconnect baby to the ventilator at original settings. Further doses (1.25ml/kg) can be administered in the same manner; **OR 2). Without disconnecting the baby from the ventilator** Administer 1.25 to 2.5ml/kg of the suspension, as a single bolus, directly into the lower trachea by passing a catheter through the suction port and into the endotracheal tube. Further doses (1.25ml/kg) can be administered in the same manner. After administration pulmonary compliance can improve rapidly, requiring prompt adjustment of ventilator settings. Rapid adjustments of the inspired oxygen concentration should be made to avoid hyperoxia. Continuous monitoring of transcutaneous PaO_2 or oxygen saturation is advisable; **OR 3). A third option** is to administer through an endotracheal tube in the delivery room before mechanical ventilation has been started – a bagging technique is used and extubation to CPAP is an option either in the delivery room or later after admission to neonatal unit (INtubation SURfactant Extubation – INSURE). **Contraindications** Hypersensitivity to active substance or excipients. **Warnings and Precautions** (See SmPC for full details). The baby's condition should be stabilised. Correction of acidosis, hypotension, anaemia, hypoglycaemia and hypothermia is recommended. Reflux, mucus plugging, bradycardia, hypotension, reduced oxygen saturation, signs of infection. Administration to preterm infants with severe hypotension has not been studied. **Undesirable effects** (See SmPC for full details) *Uncommon* sepsis, haemorrhage intracranial, pneumothorax. *Rare* bradycardia, hypotension, bronchopulmonary dysplasia, pulmonary haemorrhage, oxygen saturation decreased. *Not known* hyperoxia, cyanosis neonatal, apnoea, electroencephalogram abnormal, endotracheal intubation complication. **Pharmaceutical Precautions** Store in a refrigerator (2°C-8°C), protected from light. Unopened, unused vials that have been warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Do not warm to room temperature and return to refrigerated storage more than once. For single use only. Discard any unused portion left in the vial. Do not keep for later administration. **Legal category** POM **Basic NHS cost** Single dose vial 120mg/1.5ml - £281.64, Single dose vial 240mg/3ml - £547.40 **Marketing Authorisation Number** PL 08829/0137. Full prescribing information is available on request from the Marketing Authorisation Holder Chiesi Limited, Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY, United Kingdom. **Date of Preparation** August 2010.Curosurf is a Registered Trade Mark.

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Infant is an independent, peer-reviewed bimonthly journal for the multidisciplinary team that cares for sick or premature babies in their first year of life. The journal contains authoritative articles written by experts in their field, covering a wide range of subjects that reflects the varied roles of the professionals working in this area. Practically and clinically based, *Infant* supports neonatal and infant paediatric nursing and medical practice and develops professional education and health promotion skills. All opinions expressed in the articles published in *Infant* are those of the authors and not necessarily those of the publishers.

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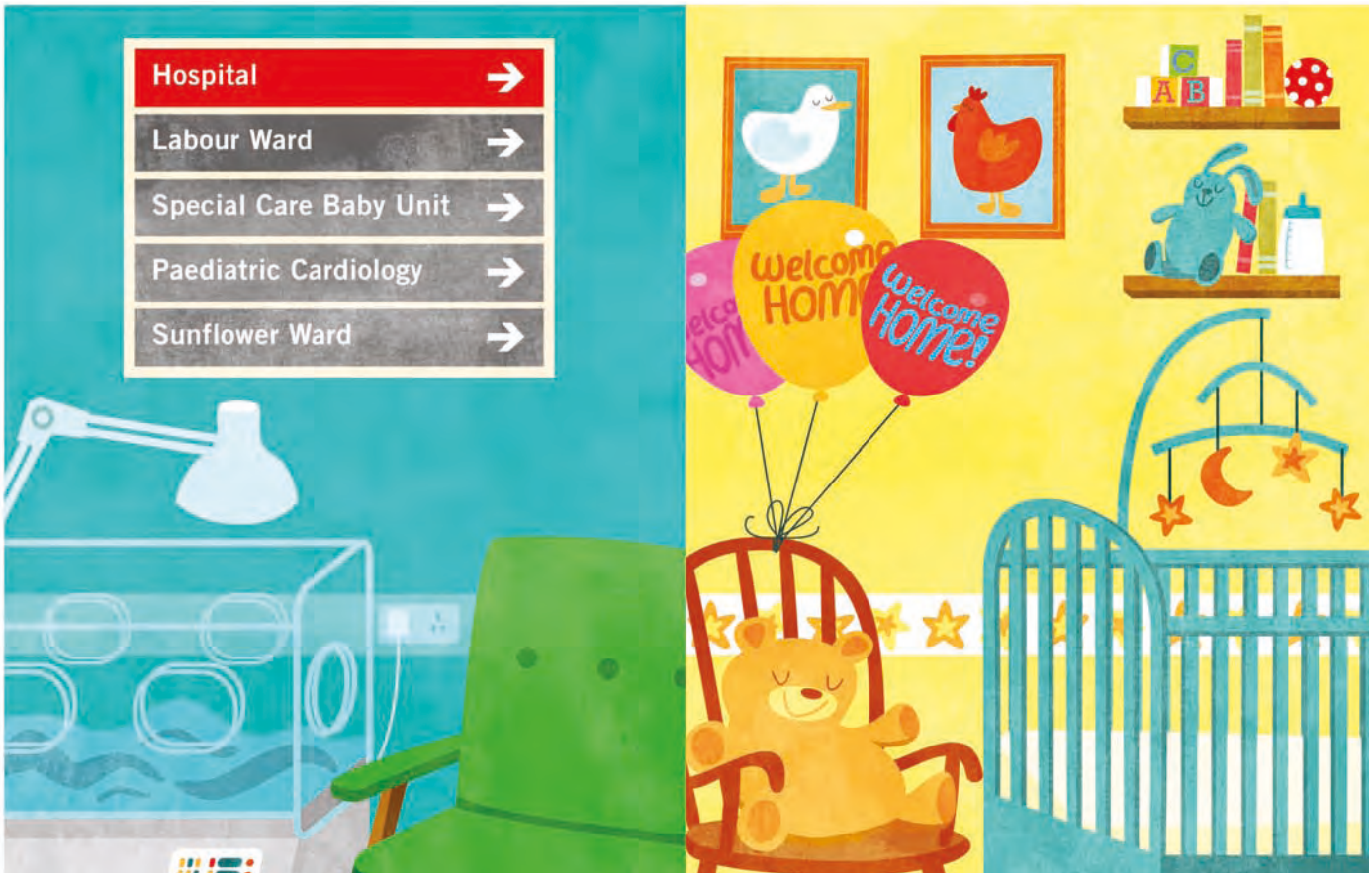

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Concerns with the NICE guideline on seeing and holding a dead baby

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Prior to the 1970s it was likely that following a miscarriage, stillbirth or neonatal death, parents would not be allowed to see or hold their baby and would be told to forget about the baby and get on with their lives. From the 1970s onward, arising out of the anguish of those who had not been allowed to do so and reflecting wider societal change, with feeling being expressed rather than repressed, the practice of offering bereaved parents the opportunity to see and hold their dead baby was introduced.

As a chaplain, I am frequently involved in naming and/or blessing ceremonies for babies where parents both see and will often hold their deceased baby. I was, therefore, somewhat surprised to discover that the NICE clinical guideline, Antenatal and Postnatal Mental Health[1], contains the recommendation that women should not be encouraged to hold stillborn infants. The guideline consists of four documents that contain a number of different, but related, statements and recommendations varying in detail. The most comprehensive comment comes in the full guideline on clinical management and service guidance[1] which states that:

> 'A matched case-control study found that women who had been encouraged to have continued contact with their dead baby, for example, holding the baby, had increased rates of depression, anxiety and post-traumatic stress disorder symptoms than women who had either not seen the baby at all or who had not held the baby. This study also found that having a funeral or keeping mementoes was not associated with increased rates in morbidity, although since many of these women also held their baby, this is not straightforward to interpret. However, the findings of this suggest that women should not be encouraged to hold their dead baby if they do not wish to[1].'

This leads to the recommendation, repeated in the service guidance, that:

> 'Mothers whose infants are stillborn or die soon after birth should not be routinely encouraged to see and hold the dead infant[1].'

Rather more bluntly, the quick reference guide starkly informs staff:

> 'Do not routinely encourage mothers of infants who are stillborn or die soon after birth to see and hold the dead infant[2].'

While not included in any of the documents downloadable from the NICE website, the website itself, following campaigning led by Sands, the stillbirth and neonatal death charity, contains the following clarification statement:

> 'This recommendation is not intended to suggest that women should not be given the choice of seeing and holding their baby but rather that they should not be routinely encouraged to take up this choice if they do not wish to.
>
> 'In line with patient-centred care it is expected that treatment and care should take into account the woman's individual needs and preferences. Sensitive support will be required in offering this choice or other choices such as seeing or holding the baby with other family members present. Current evidence suggests that seeing and holding the baby is not beneficial for everyone and if women do not wish to see or hold their baby they should not be encouraged to do so[3].'

Sands was particularly concerned, quite rightly, about the removal of choice from parents. However, I would also wish to raise a number of further issues with the recommendation and the research that lies behind it. Please note that, although the numbers are relatively small, I am not questioning the statistical validity of the research or the methodological approach. Instead I want to highlight the possibility of the research being interpreted from a different perspective.

The research quoted by the guideline states that, among other things, the level of contact a parent had with a stillborn infant correlated with increased adverse outcomes. From this, Hughes et al speculate that:

> 'Seeing and holding the dead infant further traumatises a woman who is already intensely distressed and physically exhausted[4].'

In speculating in such a way, Hughes et al make a logical fallacy by inferring causation from correlation. Today, some pregnancy tests can tell within 14 days of conception that a woman is pregnant. From an early gestation, through discussion of names and making physical preparations such as decorating rooms, many parents will have invested emotionally, spiritually and materially in their baby, forming strong bonds of attachment. Consequently loss, at any gestation, can be experienced as a devastating shock. Given this, is it not entirely possible that parents who wish to see and hold their baby choose to do so because they have already

formed a stronger bond with their baby than those who decide not to see their baby? From this perspective, seeing and holding a baby is a sign of greater trauma rather than a cause. In support of this, it is worth noting anthropological evidence that, in places with high infant mortality, children may not be given names or recognised as a 'person' until it is more certain they will survive[5].

Alongside that, it is important to point out that the research compares outcomes between those who did see their baby and those who chose not to see their baby, rather than comparing outcome between those who wished to, but were not allowed to see and hold their baby. If the bluntness of the quick reference guideline is followed, it is likely that parents would be discouraged from seeing their baby. Based on qualitative evidence, Kohner and Henley describe how parents who did not mark their baby's life and death in some way:

> 'Find they can neither grieve as they want to grieve, nor allow their grief to rest[6].'

Hughes et al state that there is limited quantitative evidence as to the effect this may have. However, they do note that one limited study suggested:

> 'That there was higher anxiety three years from stillbirth when the mother reported she was not allowed as much time with the dead child as she wished[4].'

My second concern with the recommendation lies with the implicit understanding of grief that underpins the research. Most models of grief and bereavement tacitly use a medical framework. Construed in this way, grief is seen as analogous to illness. A bereaved person has been struck down with something but, given time and the appropriate care, the expectation is they will recover and return to how they were before. Such a framework can be seen behind the research of Hughes et al and the NICE guideline. The problems with this medical framework, as the anthropologist Douglas Davies describes, is that it ignores:

> 'Deep facts of existence, whether existential experiences lying at the heart of life, or religious experiences at the centre of faith. Some experiences influence human life so much that people are never the same again. They simply become different people through what has happened to them. To speak of recovery is to talk about a kind of backward change, an undoing of what has been done, an un-living of part of life[7].'

Traditional understandings of grief suggest that the longer someone lived, the greater the loss felt when they died. In contrast to this understanding, researchers working with bereaved parents have argued that, despite the shortness of life, parental grief:

> 'May be more intense and longer lasting than grief resulting from other bereavements[8].'

Those who have suffered the death of a child talk about never fully recovering but continuing to live with the hurt. As part of this they describe how painful memories and sensations continue to arise on key dates such as anniversaries of the due date or the actual delivery day – a phenomenon given the term 'shadow grief'[9]. Perhaps, more pertinently, parents also talk about not wanting to recover when that would imply that they have forgotten about their child. We see an example of this in the words of Richard Olsen, the founder of the US National Stillbirth Society, when he writes:

> 'I don't want to be well adjusted. I don't want to be accepting. I don't want to be healed. When healing is to be freed of feeling[10].'

Accordingly, it could be argued that, far from indicating anything wrong, the fact that in the immediate years following the death of her baby a mother continues to be affected, is entirely normal and indeed, should be expected.

Neither in interviews I have carried out with bereaved parents (as part of a research project investigating chaplaincy support following neonatal death), nor in other similar research, did any parent make reference to feeling traumatised by seeing or holding their baby. Instead, the comments made portray the direct opposite. For example, one parent in my study described how, when seeing their dead baby:

> 'We just had this quiet moment and the chaplain blessed him, and they gave him his name and everything...it was just really quiet and peaceful.'

Likewise, another described how:

> 'It made me cope with it better knowing that…she was settled and I knew when the chaplain blessed her…I just felt like…she's alright, she's gone now.'

In conclusion, with the proviso that clearly no parent who does not wish to see or hold their baby should be made to do so, contra to the NICE guideline, I believe that bereaved parents should routinely be offered the opportunity to see and hold their baby.

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Using nasal high flow instead of nasal continuous positive airway pressure on the NICU

Most neonatal intensive care units use different types of nasal continuous positive airway pressure (nCPAP) to achieve non-invasive ventilation. The use of heated, humidified nasal cannulae to deliver nasal high flow (nHF) has gained support as an alternative to nCPAP, although there has been some conflicting evidence about how best to use it in a neonatal setting. This article will look at the safe and successful use of nHF as a direct substitute for nCPAP.

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Keywords

nasal high flow; neonatal; non-invasive ventilation; humidified, high flow cannulae

Key points

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1. Nasal high flow (nHF) is an effective replacement for nCPAP in neonates.
2. nHF is safe and well tolerated in neonatal practice.
3. Optimal weaning of nHF requires further understanding.
4. Users should appreciate the mechanics of nHF, especially optimising 'flush'.

The non-invasive ventilatory management of preterm babies has evolved over recent years. It is now normal practice in many neonatal intensive care units (NICUs) for very small preterm babies to be managed either with very short-term ventilation (a few hours) or without mechanical ventilation. Fewer babies are now routinely given prophylactic surfactant in the delivery room, with greater use of support/rescue policies[1,2]. Evidence has shown that this approach is safe and reduces the rates of bronchopulmonary dysplasia (BPD) and death[3,4]. Most NICUs use different types of nCPAP to achieve non-invasive ventilation. There have been comparisons between the various types of nCPAP, including fixed and variable flow nCPAP, bubble nCPAP, biphasic and synchronised biphasic nCPAP (BiPAP) and non-invasive positive pressure ventilation (NIPPV)[5]. The Extubate trial[6] is currently investigating if BiPAP offers greater extubation success than nCPAP in babies less than 30 weeks' gestation although a previous, but underpowered, study found no difference[7]. NIPPV is no better than nCPAP according to a recent study[8].

An alternative to nCPAP has emerged during the past decade. The use of heated, humidified nasal cannulae (HHNC) to deliver nasal high flow (nHF) has gained support, although there has been some conflicting evidence about how best to use it in the neonatal setting. A recent article in this journal described its use at Leeds General Infirmary as a step-down from nCPAP[9]. This is arguably an illogical way to apply nHF and this article will address this issue and how and why the fear of pneumothoraces has not been realised in practice. An update from the most recent literature will also be provided alongside a discussion of why some of the published literature, including the current Cochrane review, appears to be flawed. The NICU at St Peter's has gained extensive experience in using nHF and some practical hints on how to use it successfully and safely will be described (**FIGURE 1**).

Background

From 2005 to 2008 a culture of non-invasive ventilation of extremely preterm babies was developed in St Peter's NICU based on a policy of prophylactic surfactant for babies less than 27 weeks' gestation and rescue surfactant for others, as needed. Babies deemed stable and breathing spontaneously were extubated

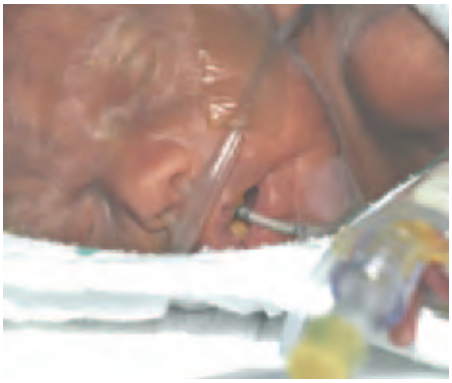

FIGURE 1 Safe and successful use of nHF on the NICU.

within a few hours of birth to BiPAP. They were sustained on BiPAP, which was then gradually weaned through a (fairly unscientific) combination of conversion to nCPAP, 'time off', nose-breaks with face mask and reduction in mean airway pressures. Despite emerging evidence that babies spent less overall time on nCPAP if they were weaned on pressure rather than 'time off'[10], there was still a real need to protect the nose from pressure effects caused by prongs and face masks.

Around this time, evidence for the efficacy of nHF in neonatal practice in the US was emerging. For example, in 2007 a large retrospective study demonstrated that the use of nHF compared with nCPAP appeared to be safe and resulted in fewer ventilator days, a reduction in BPD and a highly significant reduction in re-intubation after prophylactic surfactant and extubation[11]. A further study showed that nHF was as good as nCPAP in reducing the work of breathing and was well tolerated, with the potential to minimise nasal injury[12]. Evidence concerning distending pressure was mixed, however under circumstances where the prongs were correctly fitted, distending pressures were within normal limits. Regrettably, there were no UK clinical studies, despite nHF having been used in the neonatal population in the US for over five years. The next section will address the decision to use nHF instead of nCPAP/BiPAP at St Peter's.

nHF – differences and comparison to nCPAP

The NICU at St Peter's uses the Vapotherm™ Precision Flow© to deliver nHF. There are other different systems on the market which also deliver high flow, such as the Optiflow© by Fisher and Paykel Healthcare™. There are differences between the various high flow systems available that may be clinically important, but there has been very little direct comparison. One study demonstrated higher pressures in the Optiflow compared to the Vapotherm 2000i© system at flow rates <8L/min[13]. Another compared extubation success in 40 babies between 26 and 29 weeks' gestation between the 2000i and the Optiflow systems[14]. The failure rate of successful extubation by 72 hours for babies randomised to the 2000i was 9% and to Optiflow was 18%, which was not statistically significant due to the small size of the study. The HIPERSPACE trial compared nHF to nCPAP for post-extubation support in a multi-centre, randomised, non-inferiority trial[15]. It concluded that nHF is safe and non-inferior to nCPAP, with a trend to less re-intubation in the nHF group (p=0.12). The CHIPS trial presented similar results[16]. Another trial compared 432 babies over 28 weeks, showing that nHF was as safe and effective as nCPAP, with a significant reduction in nasal trauma[17].

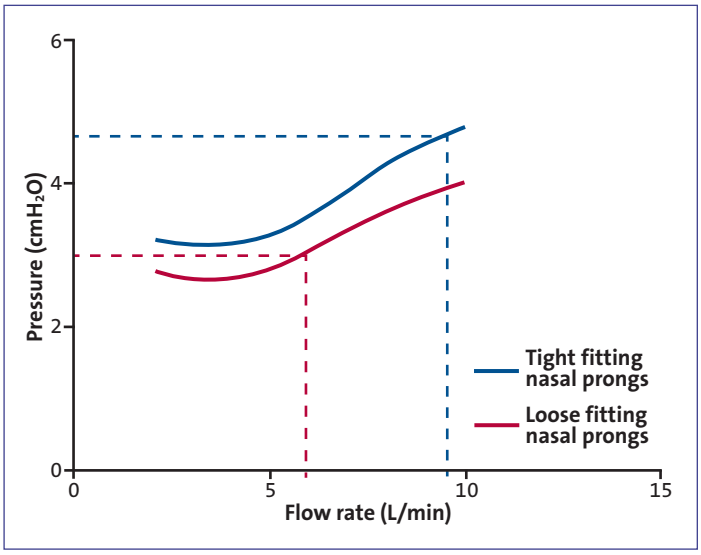

FIGURE 2 Adapted from Frizzola et al[19]. The graph shows increasing tracheal pressure in response to increasing flow rate using nasal prongs. At flow rates of 2-8L/min, the distending pressure varies between 2.5 and 4.2cmH_2O, even for tight fitting prongs. Where nasal prongs are applied correctly (ie loose fitting) the pressures are lower.

How does nHF work?

There are four key mechanisms that appear to underpin the efficacy of nHF when delivered through the Precision Flow system. This helps to explain the clinical experience of using nHF at St Peter's and the guidelines for starting, sustaining and weaning infants on nHF.

1. **Flush of the nasal passages and oropharynx.** In nHF, the respiratory 'dead space' in the upper airway is continuously replenished and exhaled gas instantly removed. This ensures that, for every breath taken by the infant, there is no re-breathing of expired gas. The higher the gas flow, the greater the flush, and there is evidence that low rates of nHF (<2L/min) are clinically ineffective and are unlikely to achieve adequate flush[18].
2. **Loose fitting nasal prongs.** This is one of the fundamental differences with nCPAP. nHF is an 'open' system, where prongs should not fit snugly in the nose and no attempts should be made to close the baby's mouth. By contrast, nCPAP is a 'closed' system where the mean airway pressure that is measured at the nose is achieved through the use of close-fitting and firmly applied prongs and, in some instances, mouth closing with pacifiers, chin straps or rolls.

   A study comparing the effects of tight and loose fitting prongs on blood gas levels of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) in an animal model of acute lung injury showed that oxygenation reached a maximum at a flow of about 6L/min, regardless of whether the prongs were loose or tight fitting[19]. Loose fitting prongs were much more effective at all flows at removing carbon dioxide. This effect has also been confirmed using computational flow dynamics (unpublished data, Vapotherm Inc), so that the larger the unoccluded nasal opening, the more effective the flush effect. This is seen clinically in larger babies where the prongs occupy less than 50% of the nares and carbon dioxide removal can be highly efficient, such that lower flows can achieve effective flush. Loose fitting prongs are also more comfortable for babies. Nasal inflammation or injury from the use of nHF is never seen at St Peter's NICU. This has abolished the need for 'comfort breaks' or 'time off' or any other of the routines developed when using nCPAP to try to prevent nasal injuries, which have been described as frequent[20]. Babies on nHF look comfortable, including term babies.
3. **Reduced work of breathing.** A number of studies have compared the work of breathing in infants on nHF or nCPAP and concluded that they appear to be similar, even at flow rates as low as 2L/min[12]. In addition, the delivery of

optimally heated and humidified (conditioned) inhaled gas appears to be important. There is substantial evidence that lung compliance and mucociliary function are rapidly and adversely affected by inhaled gas that is not humidified or heated, and nasal inspiratory resistance increases[21]. The lungs also expend metabolic work to heat and humidify inhaled gas with every breath. The aim should be to use gas delivered at core temperature with 100% humidification[22].

4. **Moderate upper airway pressures.** One of the concerns often raised is that high flow therapy can generate 'uncontrolled' or 'unmeasured' distending pressure. There is now experimental[19,23] and clinical evidence to show that upper airway pressures with nHF are similar to or lower than nCPAP (approximately 6cmH_2O)[12]. It is difficult to understand how significant pressure could build up in an open system. It has been shown that there is no increase in pressure at any flow rate, for any infant where loose fitting, small prongs are applied[24,25]. Even if the mouth is occluded, upper airway pressures are about 6cmH_2O[26].

Experimental data showed that tight fitting ('low leak') and loose fitting ('high leak') prongs gave only moderate distending pressures at flows up to 8L/min (**FIGURE 2**)[19].

At St Peter's the pneumothorax rate in 2006, when babies were extubated early to BiPAP, was compared with the rate during 2011, when babies were extubated to nHF. No babies in either year developed pneumothoraces while on either treatment, and pneumothorax is rare in non-ventilated babies of all gestations in St Peter's (<1%) and other units[17]. This reinforces the belief that nHF, used expertly, is safe. Clinical experience and evidence at St Peter's suggests that nHF does not give high or harmful levels of distending pressure.

Use of Precision Flow for nHF

The 'Vapotherm', as it is generally known in the NICU, is now the default for non-invasive ventilatory support for any baby at St. Peter's NICU, and has replaced nCPAP/BiPAP. nHF is not used as an additional step for weaning from nCPAP, as this appears to be an illogical use based on the available evidence and is likely to prolong the duration of respiratory support. Over the first few years of nHF use, there was a tendency to transfer babies who were failing to ventilate effectively on nHF onto synchronised BiPAP, in the hope that it would provide more aggressive back up to prevent re-ventilation. However, it was found that this was generally not effective – babies who had apnoeic episodes (usually due to a septic episode) could not be sustained on non-invasive ventilation of any type. It is now normal practice to just intubate and ventilate under these circumstances, as these episodes are usually transient. In fact, it has been observed that, despite rising activity rates, only 4.1% of babies were ventilated in 2010 (nHF era) compared to 8.5% of babies in 2006 (nCPAP era).

Anecdotally, it seemed that babies transferred into the unit who had been on nCPAP for a prolonged period were sometimes unable to manage on nHF. This could be because they may have chronically distended airways that cannot adapt to the lower pressures achieved on nHF.

Starting and sustaining babies on nHF

For preterm babies who have the largest ratio of dead space to lung volume, gas flows of 7-8L/min are routinely commenced. While this is above the level needed for optimal ventilation[19], it was recognised that the nares are often more than 50% occluded by the smallest prongs in the smallest babies and therefore using slightly higher flows enhances the efficiency of carbon dioxide removal.

Larger babies (>1.5kg) commence with flows of 6L/min but it may be necessary to reduce this within a few hours as hypocarbia can occur. The ventilatory effect with loose fitting prongs is so efficient that $PaCO_2$ levels less than 4kPa have been seen. The use of transcutaneous monitoring of carbon dioxide in the blood ($PaCO_2$) can be very useful in reducing the need for blood gas analyses and minimising 'over ventilation'.

Although successful extubation is hard to predict, it is expected most of the time at St Peter's. If a baby is stable a loading dose of caffeine is administered. Nasal prongs are applied prior to extubation; minimal handling and transcutaneous monitoring of carbon dioxide, are usual practice. Babies are always placed in the prone position, tilted upright. Initially the baby's breathing often appears 'jerky' and, in instances where the breathing pattern becomes smoother and more undulating, extubation is more likely to prove successful. Babies will often have frequent episodes of desaturation in the first few hours after extubation, but these episodes are usually transient and mostly self-limiting. Post-extubation blood gas analysis is not routinely performed unless there is concern.

Weaning

The purpose of weaning is to determine the minimum level of support that a baby requires. Once a baby is stable, weaning commences according to some principles learnt through experience.

- Babies should be weaned by a reduction in flow rate rather than oxygen level. However, when the fraction of inspired oxygen (FiO_2) is greater than 0.3, reducing the flow rate is questionable, especially in smaller babies.
- Even if they require some oxygen, stable babies should be weaned by a reduction in flow rate. As a guide, 30% oxygen is used in the unit.

	Duration of support (days)		
Gestational age at birth	**2006 (BiPAP/nCPAP era)**	**2010 (nHF era)**	**2011 (nHF era)**
24-27 weeks	31	22	18
28-30 weeks	10	16	10
>30 weeks	4	5	4

TABLE 1 Average duration of non-invasive support modality during different eras of modality use.

- In larger stable babies, weaning can take place at least every 24 hours – usually in decrements of 1L/min, as tolerated.
- In smaller stable babies, weaning is attempted every 24-48 hours, usually in decrements of 0.5L/min.
- Small babies (<900g) should be maintained on flow rates of 4-5L/min to minimise their work of breathing and promote stability and growth. This decision should be reviewed regularly.
- If a baby is stable, routine blood gas analysis following a change is unnecessary.
- Babies on air at flow rates of 2.5L/min can be discontinued from nHF.
- Babies who still require oxygen at flow rates of 2.5L/min can be weaned to 2L/min. nHF flow rates below 2L/min are not used on the unit – the baby is placed on 'low' flow nasal cannulae.
- Contrary to the manufacturer's recommendation, the gas temperature should not be lowered with flow rates below 4L/min. While a baby is in an incubator, the environmental temperature ensures that, even at lower flow rates, the risk of condensation and 'spitting' of water at the nares is very small. For some babies in open cots, this may be a problem and the temperature may need to be reduced to 36°C at lower flows. This varies from case-to-case and should be determined on an individual basis.
- If a baby becomes less stable after an attempt at weaning, the previous flow rate should be reinstated. If instability continues, the cause should be determined.
- There is no need to give a baby 'time off' from prongs as nasal trauma is not an issue for babies on nHF.
- Prongs and circuits should be changed in accordance with the manufacturer's guidelines.

There is still a need for research to establish best weaning practice for babies receiving nHF, which is likely to depend on the clinical situation. There is a 'flow gap' between the lowest 'high' flow and the highest 'low' flow, which may be important for a small number of babies. The move from highly humidified, to poorly humidified gas when changing to low flow, may also be important.

Length of time on non-invasive support

The time spent on nHF was compared against the time spent on BiPAP/nCPAP, by gestational age (**TABLE 1**). Not only is the average duration on nHF lower than historical controls on nCPAP, but also the maximum-recorded duration of support on nHF is lower than nCPAP for the equivalent gestational age. However, the validity of this data has limitations because of difficulties associated with retrieving historical data.

One concern was the apparent increase in 2010 of babies from 28-30 weeks' gestation who appeared to be spending more time on nHF. However, an emphasis on ensuring that weaning protocols were followed appeared to improve the trend in 2011. One theory for this is that the babies looked so comfortable on nHF that staff (and parents) were reluctant to remove it! The data provides some reassurance that babies are generally spending less time overall on nHF than they did on nCPAP.

Parent and staff satisfaction

Parents are routinely surveyed about their views on the care provided in the NICU. As far as nHF is concerned, most parents see no other type of non-invasive respiratory support and have no comparisons to make. However, only positive comments have been received about nHF from parents whose babies received nCPAP as a result of transfer from or to other units that do not use nHF. Parents report that they like seeing their baby's face and expressions, seeing them move their heads and appearing comfortable on nHF. The nursing and medical staff were surveyed a year after the move from nCPAP to nHF and the results strongly indicated a preference for nHF. The junior medical staff were particularly in favour of ease of access to the head for ultrasound and head circumference measurements. The nursing staff liked the comfort for the baby and ease of set-up and use.

Conclusions, opportunities and suggestions

Using nHF as a replacement for nCPAP in the author's NICU over the past four years has led to the conclusion that this is a better way to achieve non-invasive ventilation for babies requiring respiratory support, either from birth or after extubation. It is not necessary or logical to use nHF as a step-down, as it can be used as a direct replacement for nCPAP. It is disappointing that there was no opportunity to draw on UK-based research to inform a decision to start using nHF and it is equally disappointing that the current Cochrane review contains only one study using 'low' high flow (1.8L/min) to draw a negative comparative conclusion against nCPAP[15].

There are still opportunities for neonatologists to participate in comparative clinical trials; different nHF systems still need to be evaluated, and clinicians need to study the evidence, then choose and use the modality properly. High flow for neonatal use needs definition and the usefulness of lower flows needs evaluating. Categories of nHF (4-8L/min), medium flow (>2-4L/min) and low flow (≤2L/min) might be useful.

High-quality healthcare is defined as being safe, having a positive clinical outcome and good patient experience[27]. The use of nHF at St Peter's combined with emerging evidence, demonstrates that clinical outcome and safety of nHF are, at least, equivalent to nCPAP and that the patient, parent and carer experience is better. Based on current understanding and experience, the author believes it is reasonable to conclude that, compared to nCPAP, nHF is a better-quality mode of non-invasive respiratory support for babies.

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Reflections on a trip to Rukungiri, Uganda

FOCUS

BY Liz Crathern and Denise Evans

Before and after: the new and old (inset) nurseries at Nyakibale Hospital.

Easter 2012, Denise and I travelled to Rukungiri in southwest Uganda with a medical mission organised by the charity Mission Direct. This was our fifth year working together and eighth trip to Nyakibale Hospital and Karoli Lwanga School of Nursing in Rukungiri district. During our previous trips there we have:

- Embarked upon field trips in rural areas to gather a better understanding of local healthcare[1,2]
- Delivered a neonatal and child health module to pupil nurses[2]
- Designed and furnished a neonatal nursery in the midwifery unit at Nyakibale Hospital
- Trained staff in newborn life support (NLS) and fundamental neonatal nursing care to support the care of neonates admitted into the nursery[3].

Lack of skills in resuscitation is a major factor in the number of neonatal deaths in developing countries[4]. There have been improvements in survival of preterm and sick newborn babies at Nyakibale Hospital as a result of the NLS training and education, however, because of reliance on pupil nurses to deliver the majority of healthcare within the hospital, ongoing training and sustaining change is still an issue.

The Mission Direct medical team were an amazing bunch of practitioners. We reconnected with a GP with specialist skills in cardiac care who had accompanied us on a previous trip and also his wife, who brought valuable administration skills. Their son and his friend – both recently qualified doctors – were undertaking elective placements at Nyakibale Hospital. There was also a female GP with particular interest in sexual health and gynaecological problems. Another practitioner with specialist skills, a senior child physiotherapist for children with disabilities, joined the medical mission on this trip.

Our aims for the trip were to:

- Continue with NLS training in both the school and midwifery unit
- Connect with the nurse training school to gather a clearer understanding of how we could support their future education and training needs
- Deliver workshops on leadership and management
- Discern our long-term plans for the region.

Strengths of the trip

As the two-week trip unfolded, it became clear that Denise and I felt as though we were there to act as a catalyst for others to do their great work. Both GPs and the two new doctors were an incredible resource, running sexual health classes for the pupils at Rukungiri Modern Primary School and the Women's Institute training school for young women. They also conducted a health clinic at the school; the matron will keep the health records so that eventually, with every future medical team that goes to Rukungiri, a doctor will have checked all children at the school. It is a credit to the school governors, John and Alice, and all the people who support the school, that the children appeared well nourished. This is, in part, due to the success of their farming project which means that vegetables are grown for the children to eat alongside their main staple, a maize porridge called posha. Some children needed dental care, while others, including the matron, needed spectacles. Quite a few boys needed ringworm treatment and the matron was given advice on managing the boys with enuresis. One of the recently qualified doctors was interested in paediatrics so I discussed with him the need for daily health checks on neonates in the nursery and the importance of frequent medical rounds on the neonatal unit – he continued to be a good role model to the local doctors by caring for the sick and preterm neonates in the neonatal nursery during the rest of his elective.

The child physiotherapist and two 'in-country' team leaders organised a parent conference on managing a child with disability, while Denise talked with staff from rural clinics on how to manage an obstetric emergency. The physiotherapist spent most days quite literally out in the bush, supporting the work of the Chilli Children Trust. This project helps families with disabled children to grow chillies to raise funds for necessities such as school materials, wheelchairs, medication and transport to and from clinics. The physiotherapist brought hope to families with limited resources – those living in remote areas in mud huts – with advice and guidance on how to care for their disabled children. They felt blessed by her presence and her expertise. She identified a few children with cerebral palsy in need of equipment, such as specialist chairs, that could be made locally.

Sadly many of the children in the project suffered from brain damage due to complications at birth. Some of these

children were born at Nyakibale Hospital; a very sobering reminder of the need to educate and train midwifery staff on how to reduce the risks associated with neonatal asphyxia[4,5]. Denise and I witnessed the risks mothers put themselves and their fetus in, labouring at home as long as they can to avoid transport and hospital costs. This presents a very challenging situation for the midwives, who are always short of staff, as the women end up being admitted in a high risk situation[6,7]. The constant fear of maternal and/or neonatal death takes its toll on the midwifery staff and pupil nurses who can appear, through a 'western lens', to lack empathy with parents in this situation. In fact, in a resource-limited environment, they are overwhelmed with the enormity of their tasks, as we were at times.

What about Denise and I?

We achieved a lot in a short space of time. In two weeks, Denise and I taught 70 pupil midwives and staff midwives neonatal resuscitation, prevention of neonatal asphyxia and care of the newborn. Denise trained most of the pupils, and many of the trained staff, in the practical skills of NLS. I worked alongside the pupil nurses in the nursery, reinforcing the need for accurate recording of neonatal observations, thermoregulation and infection control (hand washing and environment). There is a newly built school of nursing with better teaching space and sporadic electricity that also has much better accommodation for the female students. We reconnected with the nursing school principal and made inroads into supporting tutors to engage more with learners and supervise clinical practice.

Aid – a team effort

Denise and I brought over 80kg of aid with us, including Teaching Aids at Low Cost (TALC) books for the hospital and nursing library. The team decided that, as the neonatal nursery was relatively self-sufficient, it would donate surplus funds, approximately £850, to the wider health needs of the local environment, as identified by the medical team:

- Transport and petrol for the paediatric physiotherapist to carry out home visits to disabled children
- Two locally-made special chairs for children with cerebral palsy
- Medical care and provision for one family and a child with disability to stay at the hospital
- Ringworm medication for the school children
- Medication for menstrual complications for the young women at Mother's Union
- A cerebral palsy parent education conference – including transport, food and learning materials
- Optical care and dental care for orphans at the school
- Teaching notes on NLS and preventing neonatal asphyxia for 70 midwifery pupil nurses.

NLS training with a midwife.

Future plans

We both feel that we have brought the neonatal nursery up to a standard that means it is fully functional and reasonably equipped. However, we would like to purchase two saturation monitors that can stay in the neonatal nursery. There are still problems with staff engaging fully with families; although that is a largely cultural issue, we can have some impact such as encouraging 'kangaroo care' (skin-to-skin contact).

We have been asked to do similar work in the north of the country, which presents a dilemma of what to do next. However, we feel we would like to return to this part of Uganda for one more year to consolidate 'training the trainers', particularly in NLS. Our aim is for a two-week elective in August 2013. Meetings with the hospital medical director have identified that management training needs to be a bigger part of our next visit – a taster training session went well. The school of nursing wants us to help by delivering the neonatal and child health module with assessment by exam. Ugandans love exams – a certificate of attendance and a good exam result will help students boost their curriculum vitae. We will continue with NLS training and I hope to acquire another resuscitation doll so that we can double-up and reduce the work for Denise; perhaps we might get a volunteer to come and help us.

On a practical level, we aim to work with Mission Direct to help raise funds to provide new mattresses with a protective mackintosh for the boys with enuresis. Each mattress should cost around £15-20. To have a mattress that is not sodden with urine will have a positive effect on the child's health and well-being.

Checking stock in the new nursery.

We would love to take other neonatal staff on our next medical trip – if anyone out there feels a yearning in this direction please do get in touch with us.

Email Liz or Denise at: lizcrathern@gmail.com, denise.evans@bthft.nhs.uk

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We are planning our next trip for August 2013. If you are able to donate please visit: https://mydonate.bt.com/fundraisers/lizcrathern1.

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Severe combined immunodeficiency in the newborn

Severe combined immunodeficiencies (SCIDs) are a group of rare diseases of T-lymphocyte or thymic failure, which comprise the most severe immunodeficiencies. Generally fatal by one year of age without treatment, they constitute a paediatric emergency and early diagnosis facilitates a better prognosis. This article will review the molecular mechanisms of SCID, clinical signs and symptoms, diagnostic investigations and review treatment modalities and outcomes, and discuss future developments.

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Keywords

severe combined immunodeficiency; newborn screening; haematopoietic stem cell transplantation; Omenn syndrome; materno-fetal engraftment

Key points

Maggina P., Gennery A.R. Severe combined immunodeficiency in the newborn. *Infant* 2013; 9(2): 52-55.

1. Severe combined immunodeficiency is a paediatric emergency – urgent referral should be made once the diagnosis is considered.
2. Persistent viral respiratory or enteral infections are hallmarks of disease.
3. A persistent low lymphocyte count should be investigated, particularly in the presence of a family history suggestive of immunodeficiency.
4. Newborn screening programmes to detect severe combined immunodeficiency before symptoms appear have been introduced in the USA and may soon be introduced in the UK.

T-and B-lymphocytes constitute the cellular components of adaptive immunity. Congenital absence of T-lymphocytes with associated panhypogammaglobulinaemia (low levels of all immunoglobulins) defines the group of disorders, which lead to the most profound immunodeficiency disorders, severe combined immunodeficiencies (SCIDs). While not common, with an incidence of around 1:50,000 in the UK, the disease is usually fatal by one year of age if not treated; successful treatment is often curative. A number of different genetic defects affecting development of T-lymphocytes or thymic development give rise to the immunological phenotype and clinical picture classified as SCID (**TABLE 1**)[1]. The definition of SCID, <500 CD3+ cells/μL, is based on the absolute number of T-lymphocytes present[2]. While newly discovered, rare defects permitting T-lymphocyte development but abrogating function are described, this article will discuss classical SCID conditions. The clinical presentation of severe, persistent viral infection, with a predisposition to protozoan infection is found, whatever the underlying molecular defect, although other specific associated anomalies may be seen in certain conditions.

History

Pregnancy and birth history may suggest possible congenital infection, intrauterine growth retardation or prematurity, all of which are associated with primary immunodeficiency. A family history of infective or unexplained infant death is important[3], particularly in consanguineous families or diagnosis of SCID in a distant family member. A history of affected male relatives suggests X-linked common gamma chain (CγC) deficiency, the most common form of SCID.

Presentation

In the newborn period, affected infants usually appear well. The hallmark presentation of an infant with SCID is persistent viral respiratory or gastrointestinal tract infection in the first few months of life. Persistent respiratory tract infection is common, with failure of viral clearance accompanying persistent bronchiolitic-like signs. *Pneumocystis jiroveci* pneumonitis develops insidiously over several weeks, leading to a gradual hypoxia and oxygen requirement. Co-infection with respiratory viruses is common[4]. Persistent diarrhoea, usually viral, with failure to thrive is an important presentation. Although most patients with SCID are initially well and grow normally, they usually fall away from their growth centile when infection occurs, because of intestinal villous atrophy, leading to malabsorption, which in severe cases results in malnutrition and wasting. For infants vaccinated with BCG, disseminated BCG infection, including skin lesions or hepatitis may be found. Materno-fetal-engraftment, due to transplacental passage of immuno-competent maternal T-lymphocytes can give rise to materno-fetal graft versus host disease (GvHD), with a skin rash and occasionally pneumonitis, hepatitis and bone marrow involvement[5]. Transfusion with non-irradiated blood products can give rise to transfusion related GvHD due to immunocompetent

Disorder	Disease	Phenotype	Inheritance
Cytokine signalling	CγC	T^-B^+	XL
	JAK3	T^-B^+	AR
	IL7Rα	T^-B^+	AR
Nucleotide biosynthesis salvage pathway defects	ADA deficiency	T^-B^-	AR
Defects affecting signalling through the T-lymphocyte antigen receptor	CD45	$T^{-/low}B^+$	AR
	CD3δ	$T^{-/low}B^+$	AR
	CD3ε	$T^{-/low}B^+$	AR
	CD3ζ	$T^{-/low}B^+$	AR
VDJ recombination defects	RAG1 and RAG2	T^-B^-	AR
	DCLRE1C (artemis)	T^-B^-	AR
	DNA-PKcs	T^-B^-	AR
	DNA ligase 4	$T^{low}B^{low}$	AR
	NHEJ1 (Cernunnos-XLF)	$T^{low}B^{low}$	AR
Mitochondrial defect	AK2 deficiency (reticular dysgenesis)	$T^-B^{+/-}$	AR
	RMRP (Cartilage hair hypoplasia)	T^-B^+	AR
Thymic defects	DiGeorge syndrome	T^-B^+	AD
	CHARGE syndrome	T^-B^+	AD
	FOXN1 (winged helix)	T^-B^+	AR
Other	Coronin-1A deficiency	T^-B^+	AR

TABLE 1 Classification of SCIDs.
Key: CγC = common gamma chain, JAK3 = Janus associated kinase 3, IL7R = interleukin 7 receptor, ADA = adenosine deaminase, RAG = recombinant activating gene, DCLRE1C = DNA cross-link repair 1C, DNA-PKcs = DNA protein kinase catalytic subunit, NHEJ1 = nonhomologous end-joining factor 1, AK2 = adenylate kinase 2, RMRP = RNA component of mitochondrial RNA processing endoribonuclease, CHARGE = coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, FOXN1 = forkhead box N1, XL = X-linked, AR = autosomal recessive, AD = autosomal dominant.

cells in the blood product.

Recalcitrant cutaneous candida infection can also manifest and, more rarely, serious invasive fungal or bacterial infection. Other rare presentations are listed in **TABLE 2**.

Examination

A newborn infant with SCID, who does not have infection, is likely to have a normal examination. A persistent napkin candidal rash or oral candidiasis may be a clinical finding. The absence of lymphoid tissue is an important sign, but detecting this is not easy, because lymph nodes and tonsils in normal infants are often very small. However, in Omenn syndrome evolving erythroderma is accompanied by large, rubbery lymphadenopathy, usually with hepatosplenomegaly. Alopecia is also prominent. An inflammatory, rather than infectious pneumonitis may also be present. Rarely, these features may be associated with other genetic causes of SCID[6]. A similar pneumonitis may also be found in ADA (adenosine deaminase)-deficient SCID.

Specific findings are encountered in particular genetic causes of SCID. Complete DiGeorge or CHARGE (Coloboma, Heart anomalies, choanal Atresia, Retardation of growth and development, and Genital and Ear anomalies) syndrome, with associated thymic aplasia may manifest other features of the syndrome, including characteristic facial features, cleft palate, cardiac defects, hypocalcaemia and tracheo-oesophageal or urogenital anomalies. Alopecia, nail dysplasia and skin abnormalities are characteristic in patients with *FOXN1* (forkhead box N1) mutations[7]. Disproportionate short stature may be seen in cartilage hair hypoplasia. Reticular dysgenesis leads to profound cytopenia including neutropenia and affected infants usually present in the first day or two of life with omphalitis or severe bacterial sepsis. Profound sensori-neural deafness is also a specific feature in these infants[8]. Microcephaly is a feature of DNA repair defects, which may present with SCID[9].

Radiological evaluation may be diagnostically useful. Cupping and flaring of the anterior costochondral junctions and metaphyseal cupping, and irregularity at the costovertebral junction may be seen on chest radiographs in ADA deficiency as well as a 'bone-in-bone' appearance of the vertebral bodies and squaring of the scapula tip[10]. Absence of a thymic shadow on anterior-posterior and lateral chest radiographs is consistent with a combined immune defect in infants and young children. However, atrophy may also occur in response to stress including infection and as such, this finding is not diagnostic. Classic signs of interstitial pneumonitis, including lung hyperinflation and interstitial shadowing, may be seen if infection is present.

Laboratory findings

Routine tests can be extremely helpful as an aid to diagnosing SCID. As most infants with SCID appear well, but full blood counts are performed commonly, the opportunity to make a diagnosis at this stage should not be missed. The most important laboratory finding is a persistent lymphopenia on a full blood count[11]. Other cytopenias including thrombocytopenia and neutropenia may be rarely present, particularly in reticular dysgenesis, or in some DNA repair disorders such as DNA ligase 4 deficiency. Eosinophilia is a feature of Omenn syndrome. A full blood count is the most common investigation requested, yet the absolute lymphocyte count is often overlooked. Lymphocyte counts are normally higher in infancy than in adulthood. An absolute lymphocyte count of less than 2.8×10^9/L is two standard deviations below the mean. When infants with infection have a count lower than this, especially if they are below six months of age and fail to thrive, it is likely that they have SCID. Although a normal lymphocyte count does not preclude a diagnosis of SCID, lymphopenia on two occasions, especially if there are also supportive clinical findings and/or a positive family history, should prompt detailed lymphocyte phenotyping. In Omenn syndrome, the lymphocyte count may be normal, or even above the normal range, due to proliferative expansion of a few

Common presentations	Rare presentations
Persistent or recurrent viral gastroenteritis	Bacterial septicaemia
Persistent or recurrent viral lower respiratory tract infection	Disseminated BCG infection
Pneumocystis jiroveci pneumonitis	Haemophagocytosis
Recurrent or recalcitrant candidiasis	Lymphoid malignancy
Fungal abscess	Autoimmune cytopenias
Recurrent bacterial lymphadenitis	Materno-fetal GvHD
Persistent cutaneous human papillomavirus warts	
Persistent molluscum contagiosum	
Failure to thrive	

TABLE 2 Disease-defining illness in SCID.

abnormal clones of T-lymphocytes.

Proportions of different lymphocytes and absolute numbers vary with age, and age-related normal ranges should be consulted[12]. Lymphocyte phenotyping by flow cytometry will demonstrate absence or very low numbers (<500 cells/μL) of CD3+ T lymphocyes and absent or low numbers of CD4+ and CD8+ lymphocytes. If T-lymphocytes are present, maternal engraftment should be excluded by molecular genetic analysis. Depending on the genetic defect, B-lymphocytes and natural killer (NK) cells may be present or absent. Conventionally, SCID is classified as T^-B^+ or T^-B^- SCID with further subdivision based on the presence or absence of NK cells. The presentation may not be classic, and the presence or absence of NK cells may be misleading. Therefore, a phenotype describing presence or absence of NK cells no longer forms a part of the current classification system (**TABLE 1**)[1]. The absence of recent thymic T-lymphocyte emigrants is highly suggestive of SCID and, if demonstrated, should prompt careful clinical and laboratory evaluation. Results are best interpreted in a laboratory that has experience of regularly processing these investigations and, if there is any doubt, specialist advice should be sought.

Immunoglobulin measurements will reveal very low or absent IgM, as well as absent IgA and IgG, although in young infants IgG is usually within the normal range due to transplacental transfer of maternal IgG. Vaccine antigen responses, if vaccines have been administered, will usually be absent. It is important that values are interpreted in the light of correct age-related reference values and care is taken in the interpretation of the IgG result, which may seem normal in neonates due to the presence of maternal IgG. The detailed analysis of lymphocyte phenotype, including assessing the presence of recent thymic emigrants is most useful in this situation, particularly in preterm infants, where measurement of immunoglobulins may be difficult to interpret, especially if the infant is born before the transplacental transfer of maternal IgG during the third trimester. The absence of IgM should always be noted and investigated. IgE is usually raised in Omenn syndrome.

Culturing lymphocytes *in vitro* for a defined time with an appropriate non-specific stimulus (eg phytohemagglutinin) and using the incorporation of radioactive or non-radioactive markers (eg tritiated thymidine or bromodeoxyuridine) into the DNA of dividing cells, acts as a surrogate measure of lymphocyte proliferation. An alternative method utilises the stable incorporation of an intracellular fluorescent dye (5-carboxyfluorescein diacetate succinimidyl ester) into cells to quantify cell division, because of the sequential decrease in fluorescent labelling in daughter cells. In patients with SCID, proliferation assays give a negative or markedly depressed result although there may be some background activity. Similarly, SCID patients in whom a genetic karyotype is requested, fail to proliferate because the assay normally examines chromosomes in lymphocytes stimulated into metaphase.

Identifying the molecular defect in specific patients with combined immunodeficiency or SCID is important for prognosis, treatment and genetic counselling. The genetic basis of most SCIDs is well defined. Usually, the genetic defect coding for the protein results in no protein expression, expression of low amounts, or expression of abnormally sized protein, and can be detected by western blotting and flow cytometry[13]. In the presence of an appropriate history or abnormal protein expression, genetic analysis may be undertaken.

Management

Liaison with and referral to a specialist centre should be made as soon as the diagnosis is suspected, and should not await the initiation or results of more specialist or detailed laboratory investigations. In the UK, two centres are nationally designated for the treatment of SCID and related disorders: Great Ormond Street Hospital, London and the Great North Children's Hospital, Newcastle upon Tyne. Patients with suspected SCID should be discussed with one of these centres, or with the local paediatric immunology team.

Newborns suspected of having a severe immunodeficiency disorder should be protected using isolation techniques, including limitation of the numbers of persons involved with care. Individuals with respiratory or gastrointestinal symptoms of infection should avoid contact. If the mother is cytomegalovirus (CMV) negative, breastfeeding should be encouraged – otherwise it should be discontinued to prevent neonatal CMV infection transmitted through the milk[14]. Wherever the child is managed, strict hand-washing procedures are paramount. Blood products, if required, should be CMV negative and irradiated to avoid the risk of transfusion GvHD. Prevention and treatment of infections is the mainstay of supportive care. Co-trimoxazole as prophylaxis against *Pneumocystis jiroveci* should be given on two or three days a week. If poor nutrition is present, such as associated with prematurity, weekly folinic acid supplements should be given to decrease the risk of bone marrow depression without compromising the antimicrobial efficacy. Antifungal prophylaxis with fluconazole should be instituted. Antiviral prophylaxis with aciclovir is recommended. Immunoglobulin replacement may be required, but only after diagnostic investigations have been performed, and only in consultation with a paediatric immunologist. In suspected cases, live vaccines, including BCG, must be avoided.

Currently, the standard curative treatment is haematopoietic stem cell transplantation (HSCT), using stem cells from bone marrow, or peripheral blood after granulocyte colony-stimulating factor (G-CSF) mobilisation from family donors.

Family or unrelated donor umbilical cord blood stem cells are increasingly used as an alternative source of stem cells. Best results are obtained using HLA-matched sibling donors[15], but these are available for only about 20% of patients. Since the early 1980s, techniques have been developed to facilitate HLA-mismatched parent-to-child (haploidentical) grafts, by removing mature T-lymphocytes that would otherwise cause fatal GvHD. New methods of manipulating different cell populations within the graft have improved; with better outcomes, all patients with SCID should undergo transplantation as quickly as possible[16]. In experienced centres, survival following transplantation approaches 90%, although the outcome depends on the underlying genetic condition, the type of donor available and the presence of infections[15]. For patients with ADA deficiency, the clinical status can be stabilised using infusions of glycosylated polyethylene glycol-ADA, until a suitable donor is identified[17].

In a few centres worldwide, clinical gene therapy trials for common gamma chain and ADA deficiency are in progress[18,19]. Using modified viral vectors, which contain a copy of the corrected gene, this method uses vector-transduced autologous haematopoietic stem cells to achieve correction of the immunodeficiency. Advantages include the ability to infuse cells without giving prior chemotherapy to create marrow space. Chemotherapy increases the risk of performing a transplant, particularly in the presence of infection. Additionally, patients with no well-matched donor can be safely treated, with HSCT or gene therapy as possible options. The initial trials demonstrated good immune reconstitution following treatment, but some patients developed leukaemia as a result of the viral vector inserting adjacent to an oncogene[20]. Newly developed vectors should reduce this risk, but close monitoring will be necessary.

For rare patients with complete DiGeorge or CHARGE syndrome, or FOXN1-deficient SCID, the primary defect is a failure of thymic development rather than an intrinsic defect in the haematopoietic stem cell. Haematopoietic stem cell transplantation in this situation leads to a high incidence of GvHD and mortality[21]. For selected patients who lack a matched family donor, thymic transplantation is an attractive alternative[22].

Future developments

The outcome of stem cell transplantation is superior for patients with SCID transplanted in the neonatal period when infection-free, than for older infants[23]. Screening programmes measuring molecular markers of T-lymphocyte production, absent in SCID, have been successfully developed from the Newborn Bloodspot Screening Programme in the USA[24]. Similar screening programmes are likely to be introduced in the UK over the next few years, but careful implementation with appropriate supporting infrastructure will be needed. Preterm infants pose a particular challenge in this respect, as false negative results are frequently observed and may introduce unnecessary familial anxiety while awaiting confirmatory tests[25]. However, given the much better results of transplanting asymptomatic patients, newborn screening is likely to significantly improve outcome of treatment. Indeed, this will be the first disease detected by newborn screening that can be cured, rather than simply have symptoms alleviated. The approach to transplantation may need to be modified, as the long-term effects of chemotherapy conditioning on immature and very young infants is not clear. Improved treatment regimens will need to parallel diagnostic advances to deliver the best outcomes for this group of patients.

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Bliss Chief Executive Andy Cole (right) presenting Dr Ian Laing with the Outstanding Neonatal Team of the Year award.

And the award goes to...

Edinburgh Royal Infirmary's neonatal unit won an award at the Mother & Baby magazine Big Heart Awards ceremony. The Big Heart Awards honour those who have either endured or who have helped families deal with extreme difficulties in pregnancy, birth or parenthood. The awards support the work of Bliss, the charity for babies born too soon, too small or too sick. From the many entries, Edinburgh Royal Infirmary's neonatal unit was selected as the winner of the 'Outstanding Neonatal Team of the Year' category, sponsored by the biopharmaceutical company AbbVie.

Meanwhile, at the Royal College of Midwives (RCM) Annual Awards, University of Nottingham midwifery lecturer Dr Jayne Marshall scooped the Johnson's Baby Award for Excellence in Midwifery Education for her innovative work developing midwifery practice through a work-based education programme. Other winners included Lorraine Bowen at Nottingham University Hospitals NHS Trust (Pampers Award for Excellence in Postnatal and Neonatal Care) and Sharon Hurst of Darent Valley Hospital (National Maternity Support Foundation Award Supporting Training and Rewarding Excellence in Bereavement Care).

Jayne Marshall receives her award from James Watson of Johnson's Baby, accompanied by the RCM's Chief Executive Cathy Warwick and broadcaster and journalist Natasha Kaplinsky.

Reducing the risk of stillbirth in older mothers

Induction of labour at an earlier stage of gestation (39-40 weeks) in older mothers (40+ years) may reduce the risk of stillbirth and neonatal complications. A Scientific Impact Paper from the Royal College of Obstetricians and Gynaecologists looked at a collection of studies exploring the rising age of mothers. The average maternal age in the UK has risen dramatically over the past two decades and studies have shown a link between advanced maternal age and increased risk of stillbirth and neonatal death.

The risk of stillbirth at 39-40 weeks gestation is doubled for women aged 40 years or over. Dr Mandish Dhanjal, Imperial College Healthcare NHS Trust and co-author of the paper, says: "While the mechanism for an excess risk of stillbirth in women of advanced maternal age is still fairly unknown, the findings collaborated in this paper provide a strong argument for an early induction of labour."

Sands, the stillbirth and neonatal death charity, welcomes the findings. Charlotte Bevan, Sands Advisor, says: "Sands has argued hard that every year hundreds of stillbirths are potentially avoidable with better, more targeted care. That is exactly what this paper shows: that the offer of induction to older women, which research has long shown are at greater risk of losing their baby just around the time when they are preparing for birth, could save babies' lives."

Diarrhoea bug – protecting babies

A new vaccination programme, planned for later this year, will see babies under four months vaccinated against rotavirus – a highly infectious bug that causes around 140,000 diarrhoea cases a year in children under five.

It is estimated that the Rotarix vaccine, manufactured by GSK, will halve the number of cases with 70% fewer hospital stays as a result. It will be given to infants orally in two separate doses, alongside other routine vaccines.

The programme is expected to cost around £25m a year but is expected to save the NHS around £20m per year through fewer stays in hospital, fewer GP and A&E visits and fewer calls to NHS Direct.

Tackling alcohol exposure before birth

A report from the FASD Trust proposes a new approach to identify alcohol exposure in the womb and enable those affected to access consistent support.

Fetal alcohol spectrum disorders (FASD) – an umbrella term for a range of conditions caused when a developing fetus is exposed to alcohol in the womb – are estimated to affect around 8,000 births per year. Guidelines for assessing and diagnosing FASD have been set at an international level, but there has been no established process, or care pathway, in the UK for recording information about FASD, referring people for support or agreement on the issues that need to be explored.

The FASD Trust report, entitled *'Consensus Statement Regarding the Recognition and Diagnosis of Fetal Alcohol Spectrum Disorders (FASD) Across the Lifespan in the UK: Development of Proposed UK Clinical Pathways'*, has been produced by a collaboration of nearly 70 medical experts from across the UK.

To see the report, visit the FASD Trust www.fasdtrust.co.uk

Increase in birth defects arising from multiple births

A study published in the *British Journal of Obstetrics and Gynaecology* suggests that the number of congenital anomalies arising from multiple births has almost doubled since the 1980s.

This study, led by the University of Ulster, found that the prevalence of congenital anomalies from multiple births increased from 5.9 (1984-1987) to 10.7 (2004-2007) per 10,000 births. Furthermore, the risk of birth defects was 27% higher in multiple than singleton births. The authors indicate that this increase may be related to assisted reproductive technologies, although this needs further research.

Multiple births with congenital anomalies were more than twice as likely to be stillbirths compared to singleton births and more than twice as likely to suffer early neonatal death.

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£25 million maternity unit makeover

More than 100 hospitals will secure funding to improve and upgrade their maternity units. Several older maternity hospitals will be refurbished and there will be funding for a large number of simple measures that improve choice for women and their experience of maternity care. Across the country, the improvements will include:

- almost 40 new birthing pools
- eight new midwife-led units
- more en suite facilities
- more family rooms that allow dads and families to stay overnight, supporting women while in labour or if their baby needs neonatal care
- better bereavement facilities

The funding comes from a £25 million government pot to improve maternity units nationwide. To receive a share of the money, local NHS Trusts and Foundation Trusts had to prove that their patients wanted the improvements. A panel, that included representatives from the Royal College of Midwives and Royal College of Obstetricians and Gynaecologists, judged the bids.

The Royal College of Midwives' Chief Executive Cathy Warwick says: "It is great to learn about the positive changes that this extra £25m will make to many units up and down the country."

Brothers Alex and Daniel.

Funding given to research rare disease

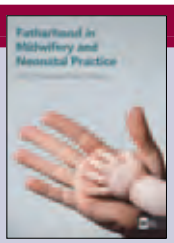
Action Medical Research has announced continued investment into vital research to help babies and children affected by rare and devastating diseases for which there is no cure.

Dr Emyr Lloyd-Evans of Cardiff University has been awarded funding by the charity to investigate two drugs that might benefit children with the rare metabolic condition, Smith-Lemli-Opitz syndrome (SLOS). Children with SLOS can have severe birth defects, neurological decline, life-threatening heart defects and autism spectrum disorders. There is no cure and no proven effective treatment.

Brothers Alex and Daniel have both been diagnosed with the condition. When Alex was born, his mum knew something wasn't right. "His spine was curved and I thought his head shape looked strange," she recalls. As a baby he barely slept: he vomited every two to three hours a night and didn't grow much during his first six months. When Daniel was born, he had similar problems and had a hole in his heart. At just one day old he needed heart surgery, followed by further operations at three months' and two years' old.

Book review

Fatherhood in Midwifery and Neonatal Practice



Kevin Hugill and Merryl Harvey
Quay Books, 2012
ISBN: 978-1-856424-301
£24.99, paperback

Traditionally, midwifery and neonatal research has been centred on the mother, creating an imbalance on available research-based evidence that pertains to the needs and experiences of fathers during childbirth and early years. However, in the past ten years this imbalance has begun to swing in favour of fatherhood research, particularly in the neonatal environment. This book is a timely addition to parenting literature at, and around, the time of birth. It is unique in that it introduces the pivotal role of fathers in parenting, beginning with the healthy pregnancy and well newborn infant through to fatherhood in a neonatal unit.

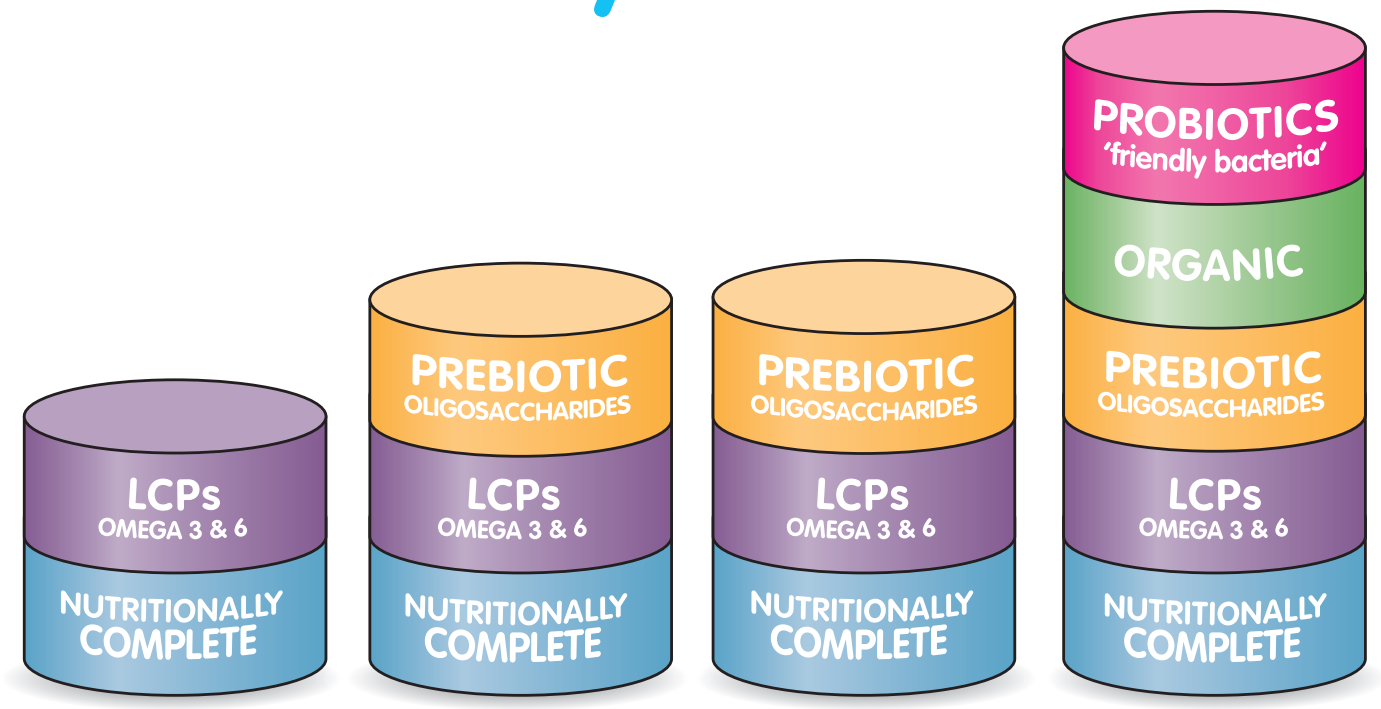
The back cover states that the book is an invaluable support for practitioners promoting the involvement of fathers during childbirth and early childhood. I would add that it is a very suitable addition to any university or NHS healthcare library that supports resources for medical, midwifery, health visiting, social work and neonatal training.

As a neonatal lecturer, I would certainly use this book as a valued teaching tool. The authors, both passionate researchers on the topic, have not sacrificed the need to present research evidence, theoretical perspectives and debates in support of their arguments and ideas. However, any 'dryness' that may seem apparent in some of the theoretical chapters is quickly dispelled by the inclusion of key points, case histories and reflective points that return the reader back to the rationale for the book – to inform, guide and challenge practice, beliefs and attitudes. The final reflective activity seeks to engage the reader with their personal biography of experiences of being fathered – a good place to start when engaging students in understanding parenting perspectives.

One caveat would be that the book is very much written from a UK perspective, particularly when drawing upon political agendas and other drivers. A comprehensive book of this type, if widened to include perspectives from Europe, Canada, USA, Australia and New Zealand for example, would be a welcome addition to international literature on the topic. Finally, it may be useful in future editions to include a perspective on fathers as part of a family system, with more discussion on the potential supportive role of grandparents when parenting a child with complex needs – this may encompass the reality of parenting in the 21st century and a return to multigenerational family living.

Liz Crathern
Neonatal Lecturer
University of Sheffield

Introducing…
the first infant formula with friendly bacteria*



Introducing the **first ever** formula in the UK to contain the probiotic culture L. fermentum hereditum,® or 'friendly bacteria', originally isolated from breastmilk.

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*Contains L. fermentum hereditum,® originally isolated from breastmilk

†Studies: Maldonado J et al. JPGN.Jan 2012. Vol 54. No.1, 55-61; Gil-Campos M et al. Pharmacol Res 2012;65(2):231

BREASTFEEDING IS BEST FOR BABIES

Important Notice: Breastfeeding is best for babies. Breastmilk provides babies with the best source of nourishment. Infant formula milks and follow on milks are intended to be used when babies cannot be breastfed. The decision to discontinue breastfeeding may be difficult to reverse and the introduction of partial bottle feeding may reduce breastmilk supply. The financial benefits of breastfeeding should be considered before bottle feeding is initiated. Failure to follow preparation instructions carefully may be harmful to a baby's health. Infant formula and follow on milks should be used only on the advice of a healthcare professional.

Neonatal nutrition research – what do we need to know?

Nutrition in fetal life and early infancy influences long-term health, making it particularly important that nutrition is optimised at these early stages. Research needs to address all aspects of nutritional support: what and how much babies need, how and when to provide it, how to nurture the gut to enable nutrition and growth and how to ensure that all high-risk babies receive the best evidence-based nutritional care.

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Keywords

preterm infant; nutrition; research; infrastructure; trial; feeding

Key points

Leaf A., Johnson M. Neonatal nutrition research – what do we need to know? *Infant* 2013; 9(2): 60-64.

1. Significant improvements in research infrastructure have made it easier to perform neonatal nutrition research.
2. There is a growing body of skilled professionals that are keen to develop clinical trials and recruit babies to multicentre trials.
3. Questions remain about what, when and how much to feed, as well as the use of probiotics and lactoferrin.
4. Clinical and academic networks must work with families to ensure that opportunities to advance clinical care through research are fully embraced.

Nutrition is fundamental to life. The recognition that nutrition and growth in fetal life and early infancy influences long-term health makes it particularly important that nutrition is optimised at these early stages. Preterm infants are challenged by immature gut and metabolic function, and balancing requirements with tolerance requires detailed knowledge and skill. Managing nutrition within the context of a busy NICU is not easy. Research needs to address all aspects of nutritional support: what and how much babies need, how and when to provide it, how to nurture the gut to enable nutrition and growth and how to ensure that all high-risk babies receive the best evidence-based nutritional care, both while in hospital and on discharge.

Research infrastructure

Recent years have seen significant changes to research infrastructure in the UK at national, regional and local levels, which have helped both improve capacity and create more coordinated and structured research networks. One such infrastructure change was the establishment of the National Institute for Health Research (NIHR) in 2006[1]. This is a large, multifaceted organisation funded by the Department of Health. Essentially the research arm of the NHS, it aims to support outstanding individuals, facilities and leading-edge research focused on the needs of patients and the public. In particular, it has increased the volume of applied health research, with an emphasis on the translation of basic science into clinical practice. The NIHR infrastructure consists of a national Clinical Research Network and local clinical research facilities, centres and units. The NIHR Clinical Research Network is made up of several different national research networks of which six are 'topic specific', including the Medicines for Children Research Network (MCRN). The specific aim of the MCRN is to: "Improve the coordination, speed and quality of randomised controlled trials (RCTs) and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment". In addition, the MCRN also coordinates the NIHR Paediatric (Non-Medicines) Specialty Group. Within the MCRN, a national Neonatal Network has been established to aid large-scale neonatal studies. In the context of neonatal nutrition research, this is important as nutritional studies are increasingly powered on substantive outcome measures, such as mortality, necrotising enterocolitis (NEC), late onset infection and neurodevelopment, which require large numbers of extremely preterm infants. Collaboration between networks to aid recruitment of, and large data collection on, large numbers of preterm infants is therefore essential for these studies.

The MCRN also comprises 15 different Clinical Studies Groups (CSGs), which cover specific research areas and aim to provide an overview of the current portfolio of studies, as well as providing opinions or advice to potential or upcoming studies. The MCRN Neonatal CSG, provides oversight of all current national neonatal portfolio studies, with access to information on study aims, current recruitment and recruitment targets. This is important, as having an overview of the national neonatal research portfolio allows the CSG to advise on areas

Trial name	Design	Patient group	Intervention	Primary outcome	Total study number	Current status	Funding source	Chief investigator	Clinical trials unit	MCRN status
ADEPT	RCT	<35 weeks, IUGR	Early vs late enteral feeds	Time to full enteral feeds	404	Published	AMR	Alison Leaf	NPEU	Adopted
PiPS	RCT	<31 weeks, <48h	Probiotic vs placebo	NEC (Bell Stage 2 or 3) and death, sepsis (>72 hours after birth) and death	Target 1,300	Recruiting	NIHR HTA	Kate Costeloe	NPEU	Adopted
NEON	RCT	<31 weeks, <12h	High or low dose AA, started within 24h; SMOF vs intralipid	Non-adipose body mass on MRI; intra-hepatocellular lipid content using MRS	160	Data analysis	EME	Sabita Uttaya	CTEU Royal Brompton & Harefield NHSFT	Adopted
SCAMP	RCT	<29 weeks, <1,200g, <72h	Standard concentrated vs maximal PN concentration	Rate of head growth at 28 days	150	Recruiting	Bliss	Colin Morgan	Liverpool Women's NHSFT	Adopted
ELFIN	RCT	<32 weeks	Prophylactic enteral supplementation with bovine lactoferrin vs placebo	Late-onset invasive infection	Target 2,200	Due to start April 2013	NIHR HTA	William McGuire	NPEU	Adopted on NIHR portfolio
SIFT	RCT	<32 weeks or <1,500g	Slow vs fast milk feeds increase	Survival without moderate or severe disability at two years	Target 2,500	Due to start March 2013	NIHR HTA	Jon Dorling	NPEU	Adopted on NIHR portfolio

TABLE 1 Summary of recent, current and imminent UK trials of nutrition and feeding in the UK.
Key: RCT = randomised controlled trial, IUGR = intrauterine growth restricted, AA = amino acid, SMOF = soybean oil, medium-chain triglycerides, olive oil and fish oil, PN = parenteral nutrition, NEC = necrotising enterocolitis, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, AMR = Action Medical Research, NIHR = National Institute of Health Research, HTA = Health Technology Assessment, EME = Efficacy and Mechanism Evaluation Programme, NPEU = National Perinatal Epidemiology Unit, MRCN = Medicines for Children Research Network, CTEU = Clinical Trials and Evaluation Unit, NHSFT = NHS Foundation Trust.

requiring more attention, or areas where certain study populations might become 'oversubscribed'. Again in the context of nutritional studies that can require large numbers, this oversight can help direct efforts accordingly or ensure trials are timed to start when others looking at a similar patient population are due to finish (**TABLE 1**).

In addition, there are 24 specialty groups within the NIHR Comprehensive Clinical Research Network, one of which is the Paediatric (Non-Medicines) Specialty Group. The remit of this group is to support a national portfolio of research studies in paediatrics, except those research studies that involve medicines. The Paediatrics (Non-Medicines) Specialty Group works very closely with the MCRN to ensure that there is a high quality research infrastructure in the NHS to support research involving neonates, infants, children and young people.

At a more local level, the NIHR also funds 11 Biomedical Research Centres (BRCs) and 20 Biomedical Research Units (BRUs). BRCs have substantial portfolios of research in one or several research areas, and promote innovation and translate research in biomedicine into NHS practice. BRUs have a similar remit but are focused on specific research areas with high disease burdens or clinical need. There are currently two BRUs (Bristol and Leicester) and one BRC (Southampton) that focus specifically on nutrition. The NIHR also funds (or co-funds) 18 Clinical Research Facilities for Experimental Medicine, which aim to speed up the translation of scientific advances to benefit patients.

At a more specialist level, there is also the Neonatal Nutrition Network (N3, www.nicunutrition.com), a national group of health professionals with an interest in improving the outcome of sick and preterm infants by optimising feeding and nutrition. This has informal links with the Royal College of Paediatrics and Child Health (RCPCH), the British Association of Perinatal Medicine (BAPM) and the British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) and is also associated with the Neonatal CSG of the MCRN. In addition, the National Perinatal Epidemiology Unit (NPEU, www.npeu.ox.ac.uk) undertakes a broad range of clinical research aimed at producing methodologically rigorous research evidence to improve the care provided to women and their families during pregnancy, childbirth, the newborn period and early childhood, as well as promoting the effective use of resources by perinatal health services. The NPEU's research is funded from a variety of

sources; the Department of Health Policy Research Programme (PRP) provides funding for an extensive and broad 'Programme of Work' covering a five-year period and the multicentre clinical trials are all grant funded, predominantly by NIHR funding streams.

What nutrients and how much?

An important first step in reviewing the direction of future neonatal nutrition research is to consider the objectives. A goal in the nutritional care of preterm infants is to try and maintain growth comparable to that which would be seen *in utero* at equivalent gestations[2]. This growth should be appropriate both quantitatively, with appropriate gains in weight, length and head circumference, and qualitatively, with infants achieving an appropriate body composition in terms of the proportions of fat and lean tissue. The quantity and quality of nutrition provided will therefore need to be correct in order to achieve this. Guidance exists regarding nutritional targets for extremely preterm infants; the requirements of term infants are well established[3,4]. However, there is little information regarding the nutritional needs of infants born in the 'moderate-to-late' preterm group (32-37 weeks) and there is a need to establish the nutritional needs and optimum feeding strategies for these infants. This is particularly pertinent given the growing body of evidence that these infants have suboptimal respiratory and neurodevelopmental outcomes, suggesting that the adverse outcomes associated with prematurity are on a spectrum from extreme preterm birth through to term[5-7].

While recommended nutritional targets exist for extremely preterm infants, there is good evidence that preterm infants as a group often fail to achieve these targets[8,9] and this has led to an interest in strategies to address shortfalls. These range from enhanced or concentrated parenteral nutrition (PN), through to clinical interventions aimed at standardising and optimising nutritional care. Current trials include the SCAMP study (Standardised, Concentrated, Additional Macronutrients, Parenteral nutrition)[10] and the NEON study (Nutritional Evaluation and Optimisation in Neonates) – an optimised amino acid and lipid regimen in PN[11] (**TABLE 1**). Such strategies offer promise, and improvements in nutritional care have meant that clinicians are now closer to consistently meeting nutritional targets and achieving optimum growth[12]. However, more work is required in order to establish efficacy and safety, as the use of higher amounts of nutrition to improve growth raises the issue of possible maximum safe limits for some nutrients, particularly protein[13]. Furthermore, the ability to get closer to recommended targets, combined with growing evidence regarding growth and later outcomes such as neurodevelopment[14,15] and the risk of cardiovascular disease[16,17], means there may be a need to begin to reconsider the validity of those original recommendations, which were essentially consensus opinion based on a review of scientific evidence available at the time.

FIGURE 1 The distribution of centres recruiting preterm infants for the Abnormal Doppler Enteral Prescription Trial (ADEPT).

Research outcome measures

There is increasing interest regarding the most appropriate outcome measures in nutrition research. Given that nutritional care aims to achieve body size and composition comparable to a full term infant, good measures of growth and body composition are vital. Weight, length and head circumference measurements should be part of routine care and provide readily available outcome data. However, in the context of research it is vital that these 'routine' measures are carried out in a standardised manner – protocols can help achieve this. The body composition of preterm infants at term equivalent age is currently different to infants born full term, so there is a need to consider body composition carefully[18]. This is more difficult to measure, and there is currently no 'gold standard' method for use in studies. Methods range from simple but relatively inaccurate techniques such as skinfold thickness or bioelectrical impedance, through to dual X-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and air displacement plethysmography (ADP), which have better validity but are more cumbersome and expensive[19]. More research is needed in this area in order to establish the most appropriate techniques, together with reference data sets.

In relation to this, a recent systematic review looking at PN in preterm infants highlighted variability in growth outcomes reported by neonatal nutritional studies, with disparate time points and choices of measurements[20]. Given that the preterm population is limited in size, it is vital that there is more consistency in the outcomes measured in neonatal studies that would facilitate prospective meta-analyses to answer important clinical questions. This could involve the COMET (Core Outcome Measures in Effectiveness Trials) initiative which works towards bringing together researchers interested in the development and application of agreed standardised sets of outcome measures[21].

While measures of growth and composition are clearly important, ultimately the main outcomes of interest will be those impacting on later life or associated with a significant healthcare burden. Several studies have shown a clear link between early nutrition and growth and neurodevelopmental outcomes at 18 months to two years of age, and such outcomes are clearly an important measure of the impact of any nutritional intervention in the neonatal period[14,15]. This presents a challenge, as more resources are needed for follow-up and the number of infants required to provide sufficient power to detect statistically significant and clinically important differences in neurodevelopmental outcomes are in the order of thousands. There is therefore a clear requirement to work within the networks described above in order to run successful multicentre nutritional trials in the preterm population. In addition, the need to follow-up such large numbers of infants in order to obtain these outcome measures requires a coordinated approach to ensure both completeness of follow-up and unnecessary repeat appointments.

When and how should we feed high-risk preterm infants?

Research questions such as when to start enteral feeds and how quickly to advance volumes might not seem exciting, however as these issues affect every preterm infant, even small differences can make a huge difference in terms of both clinical outcomes and use of resources.

When to start?

'ADEPT' – the Abnormal Doppler Enteral Prescription Trial (**TABLE 1**), was set up to answer a simple question: was it better to start enteral feeds early or late in preterm infants, born growth-restricted and with evidence of abnormal antenatal Doppler blood flow in the umbilical artery? The knowledge that these babies are at high-risk for NEC[22] had resulted in many neonatal units having policies to delay enteral feeding, however there was no good evidence to support this practice. Between 2006 and 2009, 404 infants of less than 35 weeks' gestation, were recruited in 53 hospitals in the UK and Ireland (**FIGURE 1**) and randomised to start enteral feeding on either day 2 or day 6 after birth. Increase of feeds was guided by an 'enteral prescription' which was included in the study protocol[23] and which allowed a slower rate of progression for the smallest and least mature infants, such that 'early feeding' babies would aim to achieve full feeds between day 10 and day 14 after birth and those in the 'late feeding' group between day 14 and day 18. The results showed that babies in the early feeding group achieved full enteral feeding significantly sooner than those in the late feeding group, with no difference in rates of NEC. Time to full feeds (sustained for 72 hours) and occurrence of any stage of NEC were the two primary outcomes. Other significant differences were a shorter duration of PN and high-dependency care, and a lower incidence of cholestasis in the early feeding group[24]. As well as providing useful answers to an important clinical question, ADEPT proved that there is enthusiasm and ability to conduct large and successful multicentre trials of neonatal feeding practice in the UK.

Systematic reviews with meta-analysis of combined data are a useful way in which to summarise best available evidence from clinical trials. The Cochrane Database of Systematic Reviews contains a number of reviews of relevance to preterm infant feeding and nutrition. Prior to ADEPT, 115 babies had been studied in three small RCTs of early (<4 days) compared to late (>4 days) introduction of feeding[25]. The conclusion was that there was no difference in weight gain or length of stay, and although no difference was seen in incidence of NEC, numbers were too small for this to be meaningful. This systematic review was updated in 2011, including early (and incomplete data) from ADEPT with the total number of cases increased to 600[26]. The conclusion states that there is no evidence that delaying feeds reduces the risk of NEC, however further data would be required to improve the precision of estimates on outcomes.

How fast to increase?

Another 'simple' question frequently asked is: how fast should feeds be increased? A systematic review of this subject was updated in 2011[27]. Four studies were included, with a total of 496 infants; 'slow' increase was defined as 15-20mL/kg/day and 'fast' as 30-35mL/kg/day. Meta-analysis showed that infants fed slowly took significantly longer to reach full enteral feeds and to regain birthweight, but there was no difference in rate of NEC (relative risk 0.91, 95% confidence interval 0.47-1.75) or all cause mortality (relative risk 1.43, 95% confidence interval 0.78-2.61). This is now going to be the topic of a large multicentre RCT – the Speed of Increasing Feeds Trial (SIFT)[28]. The trial aims to recruit 2,500 infants of less than 32 weeks' gestation and will be run by the NPEU Clinical Trials Unit (CTU). The primary outcome is survival without moderate or severe disability at 24 months of age corrected for prematurity (**TABLE 1**).

Trophic feeding

Another topic of interest, summarised in a systematic review, is trophic feeding or minimal enteral nutrition[29]. In this review there were nine trials, including 754 very low birthweight (VLBW) infants. Rather disappointingly, given the results of earlier physiological studies[30], there was no effect seen on feed tolerance or growth rates. Again no difference was seen in rates of NEC (relative risk 1.07, 95% confidence interval 0.67-1.70).

As can be seen from these systematic reviews, one reason that these simple questions are taken so seriously is because of the strong associations between enteral feeding and NEC. However, to date none of the trials and systematic reviews have shown a significant difference in NEC between intervention groups.

NEC remains one of the main challenges in establishing feeding/normal gut function in preterm infants. A thorough review of NEC[31] emphasised the importance of the intestinal microbiome, and the roles of inflammation and immune modulation in healthy adaptation of the immature gut. This is another area of exciting research in neonatal medicine, and two aspects are currently being addressed in the UK.

Optimising gut function

Probiotics

'Healthy bacteria' are crucial to normal intestinal function and it is well recognised that colonisation of the hospitalised preterm infant's gut is very different to the spectrum of organisms seen in a breastfed term infant. A systematic review and meta-analysis published in 2010[32], showed that administration of probiotic bacteria to preterm infants significantly reduced the rate of death and NEC with relative risks of 0.35 (95% confidence interval 0.23-0.55) and 0.42 (95% confidence interval 0.29-0.26) respectively. However detailed review of the included studies revealed that few VLBW and extremely preterm infants were included and few infants were receiving breast milk, thus interpretation and translation to contemporary UK neonatal populations is difficult. The Probiotics in Preterm babies Study (PiPS) hopes to address these limitations, as well as making detailed microbiological assessments of babies receiving probiotics (*Bifidobacterium breve* strain BBG) and population studies within participating centres. Again, NPEU CTU is running the trial and recruiting 1,300 babies of less than 31 weeks' gestation (**TABLE 1**).

Lactoferrin

Lactoferrin is a protein found in high concentration in colostrum and breast milk. It is an iron-binding glycoprotein and is an important component of the innate immune system. Intake is often low in preterm infants due to delay in establishing enteral feeding and there is evidence that supplementation may reduce the risk of infection, and along with the use of probiotics may also reduce the incidence of NEC[33]. A number of large-scale trials are being planned, including ELFIN in the UK (**TABLE 1**),

aiming to address the effect of enteral lactoferrin supplementation on these important outcomes in VLBW infants[34].

Strategies to implement change

Clinical trials and systematic reviews are important mechanisms for generating and summarising definitive evidence for effective clinical interventions. However, it is well recognised that adoption of evidence-based practice is often slow and incomplete. A further stream of research is now developing, with the aim of understanding how best to implement change and expedite best practice. As part of the Vermont Oxford Network Quality Improvement Collaborative (NIC/Q), Kuzma-O'Reilly and colleagues were the first to publish data showing improvements in nutritional care and outcomes through the application of 'potentially better practices'[35]. In Southampton, the sociological framework of 'normalisation process theory'[36,37] is currently used to assess and guide the process of introducing a complex nutritional intervention into the neonatal unit, as part of the Standardising Preterm Infant Nutrition study (SPIN).

Conclusion

In summary, neonatal nutrition research in the UK is in good shape. Recent years have seen a massive overhaul of research infrastructure, allowing improved communication, development of networks and access to training and financial support. There is a growing body of academic neonatologists keen to lead and develop clinical trials and a large number of neonatal doctors and nurses with skills, experience and commitment, willing to recruit babies to multicentre trials. Progress is being made, but there are still plenty of questions unanswered, and as survival of preterm infants improves, ever greater challenges arise of how best to meet the nutritional needs of these most vulnerable babies.

Clinical and academic networks are essential to optimise coordination and communication; however it is also vital to work in close partnership with parents. A greater number of trials will increase the likelihood of being approached to participate in one or more research study, and it is therefore essential that staff work closely with families to ensure that the opportunities to advance clinical care through research are fully understood and embraced by all.

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Managing complex ethical problems on the neonatal unit

Some neonatal patients, either due to the rarity of their condition or a combination of co-morbidity, can be very difficult to manage. When there are many or conflicting opinions, it can add to the difficulty of decision-making. The key ethical point is to determine what treatment choices lead to the best overall benefit ('best interests') to the infant. This article demonstrates a structured approach to managing complex problems on the neonatal unit. It also includes an example of an ethical framework, which can be used to help resolve difficult ethical problems.

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Keywords

ethics; decision-making; ethical framework; ethics committee

Key points

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1. A single spokesperson should represent the views of the MDT to work carefully with the family.
2. Ethical frameworks can improve the quality of decision-making and help develop teamwork.
3. It is important to identify what the infant's best interests are.
4. Difficult cases can be referred to a clinical ethics committee. External second opinions may be sought before pursuing mediation or legal review.

Although ethical dilemmas occur across all specialties, they are especially common in modern neonatal practice. Much has been said about the ethics of delivery room resuscitation, however most neonatal deaths now occur after intensive care is reoriented or following limitation or non-escalation of treatment orders. Due to a combination of factors including technological advances, improved service delivery and greater parental involvement, it seems that ethical dilemmas are even more challenging to resolve. There are a number of documents available to help professionals, including guidance for end-of-life care from the General Medical Council and protocols for better delivery of neonatal palliative care[1-4]. However, despite this, there are still a number of ethical problems that are more difficult to solve. Although judicial review has been sought in a number of headline cases, this is very much the last resort; such reviews are expensive and are extremely distressing for both professionals and parents. This article will look at some approaches to help the neonatal team cope with difficult ethical problems and for this, it is useful to consider some example case studies.

Case study examples

Amy

At birth, Amy has features consistent with Patau syndrome (trisomy 13) including a large cleft lip and palate and bilateral microphthalmia. Her cranial ultrasound shows an absent corpus callosum and her cardiac scan shows a large non-restrictive ventricular septal defect (VSD). She has a tracheoesophageal fistula – if she does not have surgery she will never be able to feed. One member of the team wonders whether surgery would be in her best interests but her parents are too distressed to make any decisions.

Thomas

Thomas was born at 23 weeks' gestation weighing 513g at birth. He has been ventilated for five months and has had four courses of postnatal steroids. He has had a patent ductus arteriosus (PDA) ligation, laser treatment for retinopathy of prematurity (ROP) and is growing well on high calorie milk given via continuous nasojejunal feeds. There was only a brief response to the last course of steroids and for the last two weeks he has had low oxygen saturations despite high pressure ventilation in 100% oxygen. His mother does not want to give up on him and refuses to discuss palliative care but his father is beginning to express that he does not want his son to continue to suffer. A number of nurses are concerned that he has very little interaction and responsiveness and think it is 'cruel' to carry on providing active intensive care.

Zach

Zach was born at 26 weeks' gestation. He had an absent left arm from mid-humerus, absent left leg from the lower femur and was missing all toes on the right foot – consistent with amniotic band syndrome. A cranial ultrasound showed an extensive haemorrhagic parenchymal infarction that could lead to hemiplegia. He develops fulminant gram negative sepsis and requires full cardiorespiratory support including high frequency

oscillatory ventilation and inotropes. Subsequently, he develops acute renal failure including hyperkalaemia that is unresponsive to treatments. The regional renal unit is unable to admit him because of his size and condition but have forwarded a peritoneal dialysis protocol and equipment. One of the consultants is prepared to start peritoneal dialysis but another thinks the treatment is 'futile'.

Step 1: Define and review the problem

In each neonatal unit the collective experience of all members of staff often exceeds several hundreds of years and it might be that once the problem is aired then the solution is very obvious. Often the problem is easier to resolve if the parents are fully informed of all the relative risks and benefits and are directly involved in the decision-making process. Some units have regular team meetings where difficult cases can be discussed. Alternatively arrangements can be made for a one-off meeting. As many neonatal units have consultants who work on a shift pattern, it is quite likely that a number of consultants will be directly involved in each case. It is advisable to designate a single clinician to act as spokesperson and be aware that parents' views and treatment choices are influenced by how information is presented[5].

One of the key elements of ethical decision-making is to define exactly what the problem is. In the case of Thomas, is the ethical problem one of making the right clinical decision or getting his parents to agree to a planned course of action? In the case of Zach, is the problem about pushing the boundaries of medical treatment or about managing conflicting opinions between individual consultants?

It can also be helpful in everyday management to use clear and unambiguous ethics language. Although it can be tempting to use general terms such as: "I think it is unethical to operate on Amy", it may be of more benefit to say: "I think complicated chest surgery is not in Amy's best interests as her lifespan is likely to be very limited". It is also important to realise the interpretation of ethical problems is also not always objective and even the concept of 'futility' means different things to different people – especially to parents who feel they can never give up hope.

Step 2: Arrange a multidisciplinary clinical review meeting

If the standard process for clinical problem solving on rounds fails to resolve the issue, it may be helpful to arrange a formal multidisciplinary review. By arranging a broader discussion of the problem, it firstly identifies that the problem itself is more difficult to resolve and secondly allows more people to be involved in the decision-making process. Particularly when there has been conflict of opinion, such a meeting allows all views to be aired and can help improve team working. Important features of such a meeting are detailed in **TABLE 1**. When there is uncertainty or confusion over conflicting opinions, it may be more appropriate to arrange a meeting without the parents.

UK practice has changed considerably over the last few decades, moving away from a paternalistic approach and placing a much greater emphasis on co-operation and parental involvement in end-of-life decision-making. Both staff and parents feel that improved dialogue helps to share the burden of decision in these difficult cases[6]. When treatment becomes increasingly unsuccessful it is even more important to help parents understand they have to make new choices[7]. Exceptional cases can haunt staff long after the case has ended and consequently there may be a need to provide a support mechanism for staff, eg a departmental counsellor.

- Ensure all relevant members of the multidisciplinary team (MDT) are present, or represented.
- Plan in advance – attendees should not have any other urgent duties or responsibilities.
- Choose an appropriate venue, especially if parents or their representatives are attending.
- Where appropriate and with permission from the parents, invite other family members, spiritual advisers, advocates, etc.
- Set aside adequate time – two hours may be necessary.
- Ensure all attendees are aware of the uncomfortable/distressing nature of the meeting.
- Delegate one team member as chairperson and another to take notes.
- The chairperson should present the clinical details and bring copies of investigations, etc.
- Use of an ethical framework may help structure the meeting, particularly in detailed cases.
- Ensure everybody has a chance to talk and recognise that some people find it difficult to talk openly in such circumstances.

TABLE 1 Important features of a multidisciplinary review.

Step 3: Use an ethical framework

There are various moral and ethical approaches to clinical care and conflict often arises when one particular ethical approach is used to contradict another. For example, a deontological approach (duty-based) would argue that clinicians have a duty to treat Amy and to respect the sanctity of her life. However, a consequentialist would argue that as she is likely to have a reduced life expectancy, all surgery (including for her cleft palate and VSD) would more likely cause her harm and be of little overall benefit – thus her quality of life is more important than her quantity. Moral philosophers may argue and counter-argue different ethical theories without ever reaching a firm conclusion. The clinician has to come up with a solution – like it or not!

One of the ethical frameworks more commonly used in adult practice is described as the Four Quadrant Approach[8]. A significant aspect of ethical discussion in adults, stems from ascertaining their capacity for decision-making and determining what their views were before their health deteriorated. Obviously for neonatal patients, the decision-making capacity and the right to self-determination are delegated (in most cases) to the parents. Several examples of neonatal ethical frameworks have been used in other European centres and have helped in the decision-making process and improved the quality of team working[9,10]; however they have limited applicability to practice within the UK.

For local use in Sheffield, a framework was devised (**TABLE 2**). This framework can be used to help resolve ethical dilemmas either on an individual basis or used as a focus within the setting of a MDT decision meeting. Some problems can be resolved relatively easily by a small number of

Section I: Background details	
Contextual details	**Time frame**
What were the relevant antenatal and fetal details – was there diagnostic certainty and what expectations of prognosis were given? What was the early clinical course? What information was given on effectiveness of treatments and clinical progress? What evidence is there that the baby is experiencing pain, suffering or distress? What measures are being taken to treat any pain, suffering or distress and how effective are they? What kind of interaction does the baby have with other people? Does the baby experience pleasure of any kind? Does the baby react to its surroundings? Does the baby exhibit any signs or efforts to survive?	When does the problem need to be resolved? Is there any possibility of delaying the discussion or decision? How long will the baby survive if life-sustaining treatment is continued? How long will the baby survive if life-sustaining treatment is withdrawn?
Stakeholder views	**Estimates on prognosis**
What do the parents think the most important clinical problems are? What do they understand about these problems? What support is being provided to the family? How are the parents coping with their child's condition? How do medical and nursing staff interpret the clinical problems? What current therapy and support is being provided? How easy is it to provide emergency care in terms of airway support, vascular access or other organ problems? Have other specialists been involved and what is their conclusion? What type of nursing care and specialist expertise is being provided? How does the baby behave during urgent procedures and care?	What diagnostic tests and information are available? What additional diagnostic tests could be considered? What is the range of opinion on prognosis and how is this uncertainty addressed? Is it likely that life-sustaining treatments will lead to the baby surviving independently? What plans are in place if current treatments do not work? What is the short-term prognosis? What is the long-term prognosis? How certain are these estimates of prognosis? Has the process of palliative care been appropriately considered as a treatment option?
Section II: Ethical issues	
Problem definition	**Dimensions of ethical problem**
What is the ethical problem – can the patient be cured, what burdens and challenges will the patient have to bear? Is the problem acute or chronic, permanent or reversible? What are the moral dimensions of this problem?	What are the goals of treatment? What is the probability of success? Do the benefits of current treatments outweigh the burdens? Do the benefits of alternative treatments outweigh the burdens? What are the ethical arguments for and against these? Are there any biases that might prejudice estimates of duration or quality of life? Is there any deprivation of moral rights to the patient? Are the relevant moral arguments valid?
Burdens and challenges to treatment	**Ethical decision-making**
What are the unwanted effects of current treatment? What degree of pain, suffering or discomfort will current treatments inflict on the baby? Will there be a need for repeated, painful and distressing medical interventions? What are the side-effects of future or alternative treatments? Are there any signs that the infant is suffering? What impact would the burdens have on the family? What are the prospects for a normal life? What physical or developmental impairments would the baby have if treatment succeeds?	What are the treatment choices? How much can the baby benefit from medical and nursing care and how can harm be avoided? What are the relevant arguments for and against these treatments? Which treatment choice leads to the best overall consequence for the patient? To what extent do the parents agree with these choices? If the parents do not agree with the conclusion, what further plan of action will be undertaken? Is there any evidence to suggest that parents lack capacity or legal validity for decision-making?

TABLE 2 A framework for ethical decision-making as used at Jessop Wing Neonatal Unit, Sheffield.

people, especially when there is no difference of opinion between staff and parents. However, for more complex issues it may be appropriate to broaden the discussion and include others, eg a dietitian, physiotherapist, psychologist, social worker, pastor or other religious representative. An assessment of an infant's responsiveness and developmental progress can be valuable as it helps to represent the identity of the baby and to reassure parents that their child's best interests are at the very core of the discussion.

Although most parents have very good relationships with the neonatal team, there are times when there are breakdowns in communication or misunderstandings of clinical problems. It is important to make clear that all those involved have a common understanding of the nature of the clinical problem. If parents are counselled in the middle of their pregnancy but do not deliver until later, they may still perceive that the clinical problems are unchanged. When they are updated and reassured after a few days of stability they may readjust their expectations, which may remain unrealistic in the face of additional information such as scan results.

Having defined the clinical problem it can be helpful to determine a time frame (Zach, for example, needs an urgent decision). In general, an urgent problem limits the number of people involved although it may still be possible to arrange an urgent second opinion or an ethics committee review. In general, the law protects clinicians when making urgent clinical decisions, providing they are doing so in the best interests of their patients. It is always helpful to ascertain the views of the parents and it may be useful to ask them to highlight these in order of importance. In Amy's case, her parents may simply need a little time to absorb the clinical information and a delay may help them reach a decision.

Even in the presence of diagnostic certainty, it can still be difficult to give a definite prognosis (as with Zach's intraventricular haemorrhage). If there are differences of opinion between staff about prognosis it is important to summarise these, especially as this contributes to communication difficulties between parents and team members.

One of the main issues is to determine what the overall benefit or best interests of treatment are to the patient. This is difficult as a parent will have their own view on their child's best interest based on their emotional and psychological status, personal health and belief system. It is very important that staff remain as objective and unbiased as possible. There have been numerous studies that have shown that intensive care doctors tend to underscore their patients' quality of life in determining intensive care decisions[11]. Although all may perceive that they have an infant's best interests at heart it can be difficult to decide precisely and objectively what these interests are. One of the key issues in determining best interests is to picture what life would be like for the baby and what burdens would need to be shouldered throughout their life. In adult practice, there is now a best interests checklist and external independent advocates can be appointed to determine these when a patient lacks capacity under the terms of the Mental Capacity Act[12]. When discussing these best interests, it is important to consider all views and if there is uncertainty among clinicians, it is even more important to take the views of the parents into overriding consideration. The notion that best interest may be death over continued survival is a very difficult concept – for both staff and parents.

Step 4: Arrange a formal second opinion

When there are a number of consultants involved, it is often assumed that a second opinion is not needed. However, a complex case or differences of opinion may warrant opinion from a consultant outside the specialty (eg a paediatric surgeon in Amy's case or a respiratory paediatrician for Thomas). It may be appropriate to ask the parents if they would prefer to see a particular doctor or one from a specific unit. The parents may also independently arrange for a second opinion, although they will have to inform the Trust to allow the clinical records to be inspected.

Step 5: Refer to the clinical ethics committee (CEC)

The main aims of a referral to a CEC are to:

- Clarify the facts of the case to ensure that all choices, goals and outcomes are understood
- Analyse the ethical dimensions and uncertainty
- Mediate conflicts of opinion
- Review opinions on best interests and overall benefit from a patient's perspective
- Re-establish relationships between the family and clinical team
- Help the healthcare team to decide on the right course of action.

There are over 80 CECs currently within the major acute healthcare Trusts in the UK[13]. Although some CECs are in specialist paediatric centres, many are hosted by mixed adult and paediatric Trusts; the lack of neonatal experience on the committee is no bar to referral. In general, neonatal or paediatric cases tend to be more acute and the patients are often sicker. They are also more likely to involve ethical issues relating to limitation of life-sustaining treatment and be emotionally more demanding. One of the key benefits of referral to a CEC is to focus specifically on the moral dimensions and also to help recognise the difficulty in resolving the matter. If a referral is made, it is helpful to inform the parents – some CECs have an open policy allowing family members to attend. Any discussion and conclusion from an ethical referral is advisory, not statutory, although most Trusts would consider the implications to be important from a clinical governance perspective.

Step 6: Arrange for an external review

As a final resort, before referral to the Trust legal department, it may be appropriate to ask for a formal second external opinion. Although such reviews are not very common, they can be upsetting for all staff involved. It may be that trust between family and staff has broken down and unless addressed, this may make the situation more difficult. The reviewer must have access to all notes and investigations and should also speak to staff and family members. There is no formal legal guidance on how this external review should be arranged and, in general, the NHS Litigation Authority supports this approach prior to organising either formal dispute mediation or legal action. It would be advisable to inform the Trust's senior management team and legal department if this course of action is necessary.

Conclusion

Dealing with complex cases can be challenging for all members of the team. It may help to have a structured approach, to use an ethical framework or to refer to an ethics committee if the problem cannot be solved by standard approaches. It is crucial to identify the 'what, who and how' of best interests. Referring to the legal system is very much a last resort and hopefully will not be necessary when there is shared decision-making and good communication.

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Contact: Tel: 0116 2502305
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symposium@medela.ch
www.medela-symposium.com

15 APRIL 13

When a Child Dies – Supporting Parents and Family Members

A Child Bereavement UK workshop to explore the impact of the death of a child.

Venue: Buckinghamshire
Cost: £99
Contact: Child Bereavement UK
Tel: 01494 568909
training@childbereavementuk.org
www.childbereavementuk.org

19 APRIL 13

Best Practice in Neonatal Bereavement Care

A one-day conference organised by the Neonatal Bereavement Team at Saint Mary's Hospital.

Venue: Manchester Royal Infirmary, Manchester
Cost: Nurses £30, Doctors £50
Contact: Tel: 01617 011903
peter.nield@cmft.nhs.uk

25 APRIL 13

Making Tomorrow's People

How Far Do We Go? Who is to Decide?
A clinical ethics symposium organised by Great Ormond Street Hospital for Children.

Venue: Institute of Child Health, London
Cost: Doctors £150, Nurses £100, Students £25
Contact: tessa.radcliffe@gosh.nhs.uk
www.ucl.ac.uk/ich/education-ich/events

25-26 APRIL 13

BMFMS 16th Annual Conference

The annual conference of the British Maternal and Fetal Medicine Society (BMFMS).

Venue: Convention Centre, Dublin
Cost: £240-470
Contact: Hampton Medical Conferences Ltd
Tel: +44 (0) 1920 88 5162
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www.bmfmsconference.ukevents.org

29 APRIL 13

The Neonatal Experience – Loss and Grief Without a Bereavement

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29-30 APRIL 13

Foundation Toolkit in Developmental Care

Organised by Inspiration Healthcare and Sheffield Teaching Hospitals, the course is relevant for all healthcare professionals working with preterm and newborn infants.

Venue: The Endcliffe Village, Sheffield
Cost: £200
Contact: sarah.wilson@sth.nhs.uk

9-10 MAY 13

Understanding Newborn Behaviour and Supporting Early Parent-Infant Relationships

Training courses organised by The Brazelton Centre

Newborn Behavioural Observations (NBO)

Venue: The Royal Society of Medicine, London
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Contact: info@brazelton.co.uk
Tel: 01223 314429
www.brazelton.co.uk

16-17 MAY 13

Neonatal and Paediatric Ventilation

This course combines lectures with practical workshop sessions.

Venue: Institute of Child Health, London
Cost: Nurses £329, Doctors £499
Contact: Tel: 0207 905 2699
info@ichevents.com
www.ucl.ac.uk/ich/education-ich/events

16-17 MAY 13

What Next? Dreams for the Future

The fifth Annual National Neonatal Conference for clinical matrons and their senior nursing team.

Venue: Tortworth Court, Four Pillars Hotel, Bristol

Contact: Sue Monk
Tel: 01173 236325
su.monk@nbt.nhs.uk

23 MAY 13

Developing a Nurturing Environment for Neonatal Care

A study day for those working in neonatal care. Topics include:

- Nutrition care pathway
- Supporting the preterm infant in establishing feeding
- Pseudomonas in the neonatal unit
- Building a developmental environment
- The neurodevelopment of the preterm infant

Venue: Hilton Bath City Hotel, Bath

Cost: £55 (£45 before 31 March 13)

Contact: kirstie.flood@nhs.net
www.ruh.nhs.uk/nicu

31 MAY 13

SNNG Annual Conference

Scottish Neonatal Nurses Group annual conference and exhibition. Topics include:

- Tissue viability
- Neonatal patient safety
- Use of high flow in transport
- Management of gender anomalies
- Role of the family nurse partnership
- Bliss nurses and support worker roles

Venue: Crowne Plaza Hotel, Glasgow

Cost: £75 (SNNG members £65)

Contact: Tel: 01412 012756
fiona.tait1@nhs.net
www.snng.org.uk

5-8 JUNE 13

Sixth Europaediatrics jointly held with the RCPCH Annual Conference

Date for the diary. For the first time ever, Europaediatrics, the biennial conference of the European Paediatric Association, will be held jointly with the RCPCH's Annual Conference.

Venue: Glasgow, Scotland

Cost: £339-£669

Contact: www.europaediatrics2013.org

6-8 JUNE 13

21st Annual Middlesbrough Neonatal Conference and Ventilatory Workshop

An important annual event attracting neonatologists, paediatricians and neonatal nurses. The conference starts with a one-day advanced ventilatory workshop followed by a two-day conference.

Venue: Durham University, Teesside

Cost: £180-£480

Contact: Tel: 01642 282534
nicky.robinson@stees.nhs.uk
www.neonatalconference.co.uk

12-15 JUNE 13

ESPNIC 24th Annual Meeting

The European Society of Paediatric and Neonatal Intensive Care (ESPNIC) meeting offers doctors and nurses the opportunity to hear presentations by internationally acclaimed experts and participate in a highly innovative scientific programme.

Venue: Rotterdam, Netherlands

Contact: Kenes International
Tel: +41 22 908 0488
espnic@kenes.com
http://espnic2013.kenes.com/

17 JUNE 13

Basic Ventilation Workshop

A practical study day for nurses and medical staff. Organised by CFS Events on behalf of Chiesi.

Venue: St Peter's Hospital, Chertsey, Surrey

Cost: £80

Contact: CFS Events Ltd
Tel: 0800 9177 405
wendy@cfsevents.co.uk
www.cfsevents.co.uk

19-21 JUNE 13

40th APA Annual Scientific Meeting

The Association of Paediatric Anaesthetists (APA) meeting consists of presentations and workshops. Topics include neuroanaesthesia, protecting the young brain and pain management. Early bird registration before 8 May 2013.

Venue: West Road Concert Hall, University of Cambridge

Contact: Tel: +44 (0)20 7631 8862
apaevents@aagbi.org
www.apagbi2013.co.uk

19-22 JUNE 13

11th World Congress of Perinatal Medicine

The conference addresses global challenges in maternal and child health: a call to improve outcome through pragmatic implementation of evidence-based care.

Venue: Moscow, Russia

Cost: €200-500

Contact: info@mcaevents.org
www.mcaevents.org/t/01/wcpm2013-1/index.aspx

1-2 JULY 13

Reason Conference

Annual conference for neonatal nurses and doctors. Platinum sponsors: Chiesi and Fisher & Paykel Healthcare.

Venue: University of Warwick, Coventry

Cost: Nurses £305, Doctors £415 (£20 discount before 18 May 2013)

Contact: CFS Events Ltd
Tel: 01438 751519
robyn@cfsevents.co.uk
www.cfsevents.co.uk

5-6 SEPTEMBER 13

Summer Conference on Neonatology

A conference for neonatal care professionals covering current aspects of neonatal care.

Venue: Palais des Papes Convention Center, Avignon, France

Contact: info@mcaevents.org
www.neonatalinprovence.org

5-8 SEPTEMBER 13

Eighth International Neonatal Nursing Conference

Organised by The Council of International Neonatal Nurses (COINN), the conference focuses on neonatal nursing and aims to translate latest findings into clinical practice.

Abstract submission closes 5 April 2013. Early bird registration by 7 June 2013.

Venue: Belfast, Northern Ireland

Contact: Kenes UK Ltd
Tel: +44 (0) 207 383 8037
coinn@kenes.com
www.kenes.com/uk
http://coinn2013.com/

12-13 SEPTEMBER 13

BAPM Annual General & Scientific Meeting 2013

Date for the diary.

Venue: Arena and Convention Centre (ACC), Liverpool

Contact: www.bapm.org/meetings

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The dose expressed as caffeine base is one-half the dose when expressed as caffeine citrate (20 mg caffeine citrate are equivalent to 10 mg caffeine base). In preterm infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10-20 mg/kg maximum may be given after 24 hrs. Higher maintenance doses of 10 mg/kg body weight could be considered in cases of insufficient response. Where clinically indicated, caffeine plasma levels should be monitored. The diagnosis of apnoea of prematurity may need to be reconsidered if patients do not respond adequately to a second loading dose or maintenance dose of 10 mg/kg/day. When given IV, caffeine citrate should be administered by controlled IV infusion. Caffeine citrate can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/ml (5%), or sodium chloride 9 mg/ml (0.9%) or calcium gluconate 100 mg/ml (10%) immediately after withdrawal from the ampoule. Caffeine citrate can be administered by intravenous infusion and by the oral route. The product must not be administered by intramuscular, subcutaneous, intrathecal or intraperitoneal injection. *Duration of treatment:* The optimal duration of treatment has not been established. Treatment is usually continued until the infant has reached a post-menstrual age of 37 weeks, by which time apnoea of prematurity usually resolves spontaneously. Caffeine citrate administration should be stopped when the patient has 5-7 days without a significant apnoeic attack. If the patient has recurrent apnoea, caffeine citrate administration can be restarted with either a maintenance dose or a half loading dose, depending upon the time interval from stopping caffeine citrate to recurrence of apnoea. Because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment. As there is a risk for recurrence of apnoeas after cessation of caffeine citrate treatment monitoring of the patient should be continued for approximately one week. **Contraindications** Hypersensitivity to active substance or excipients. **Special Warnings and Precautions** Other causes of apnoea should be ruled out or properly treated prior to initiation of treatment with caffeine citrate (see SmPC for full details). Baseline plasma concentrations should be measured in neonates born to mothers who consumed large quantities of caffeine prior to delivery or newborns previously treated with theophylline. Extreme caution in newborns with seizure disorder. Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume therefore caution should be exercised in newborns with known cardiovascular disease. Caution in newborns with impaired renal or hepatic function or suffering gastro-oesophageal reflux. Careful monitoring for development of necrotising enterocolitis. Caffeine citrate causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy. The diuresis and electrolyte loss induced by caffeine citrate may necessitate correction of fluid and electrolyte disturbances. **Interactions** Inter-conversion between caffeine and theophylline occurs in preterm neonates; these active substances should not be used concurrently. Caffeine has the potential to interact with active substances that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. However, caffeine metabolism in preterm neonates is limited due to their immature hepatic enzyme systems (see SmPC for full details). **Pregnancy and Lactation** Caffeine in animal studies, at high doses, was shown to be embryotoxic and teratogenic. These effects are not relevant with regard to short term administration in the preterm infant population. Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation. Breast-feeding mothers of neonates treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine (see SmPC for full details). **Undesirable effects** The known pharmacology and toxicology of caffeine and other methylxanthines predict the likely adverse reactions to caffeine citrate. Effects described include central nervous system (CNS) stimulation such as irritability, restlessness and jitteriness, and cardiac effects such as tachycardia, hypertension and increased stroke volume. These effects are dose related and may necessitate measurement of plasma levels and dose reduction. The adverse reactions described in short and long term published literature are: *Common*: infusion site phlebitis, infusion site inflammation; *Rare*: hypersensitivity reaction; *Not known*: sepsis, hypoglycaemia, hyperglycaemia, failure to thrive, feeding intolerance, irritability, jitteriness, restlessness, brain injury*, convulsion*, deafness* (*more frequent in placebo group), tachycardia, also associated with increased left ventricular output and increased stroke volume, regurgitation, increased gastric aspirate, necrotising enterocolitis (see SmPC for full details), urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine decreased. Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment. Transient falls in thyroxine (**T4**) have been recorded in infants at the start of therapy but these are not sustained with maintained therapy. **Pharmaceutical Precautions** None. After opening the ampoule, the product should be used immediately. For storage conditions of the diluted medicinal product see SmPC. **Special precautions for disposal and other handling** Aseptic technique must be strictly observed throughout handling of the medicinal product since no preservative is present. For single use only. Discard any unused portion left in the ampoule. Do not save unused portions for later administration. No special requirements for disposal. **Legal category** POM. **Packs and Prices** Basic NHS price of £172.50 per pack of 10 x 1 ml ampoules. **Marketing Authorisation Number** EU/1/09/528/002. Full prescribing information is available from the **Marketing Authorisation Holder** Chiesi Limited, Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY. **Date of Preparation** April 2012.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Chiesi Limited. (address as above) Tel: 0161 488 5555

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