Recent advances in the management of infants born <1000 g

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Received 25 February 2016
Revised 19 April 2016
Accepted 20 April 2016
Published Online First 10 May 2016

ABSTRACT

In this review, we survey some significant advances in the medical care of babies <1000 g and we highlight the development of care pathways that ensure optimal antenatal care, which is a prerequisite for good neonatal outcomes. We also suggest that the long overdue development of family integrated care will in the end prove at least as important as the recent medical advances.

INTRODUCTION

Neonatal medicine can now be regarded as a 'mature' specialty, meaning one in which the emphasis has moved from driving significant reductions in mortality to developing interventions aimed at reducing morbidities (infection, necrotising enterocolitis (NEC), retinopathy) and long-term morbidities (chronic lung disease, neurodevelopment), especially among the smallest babies weighing <1000 g at birth. Indeed the 10 years between EPICURE 1 and 2 revealed significant reduction in mortality (from 60% to 47%) for the most immature infants, but an ongoing almost unchanged morbidity burden.[1]

Babies born <1000 g (extremely low birth weight or ELBW) were first classified as such in the 10th revision of the WHO's International Classification of Diseases (ICD) in 1990. ICD-10 also gave primacy to birth weight over gestation when both were known, a prioritisation increasingly called into question in subsequent decades because babies <1000 g at birth constitute a heterogeneous mix of quite mature but growth restricted babies, together with very immature small babies, and with survival now achieved even at <500 g, these babies are quite different from those weighing nearer 1 kg. The term ELGAN (extremely low gestational age neonates) was coined by O''Shea *et al*[2] and corresponds to the ICD-10 definition 'extreme immaturity' of <28 weeks' gestation at birth. This term (ELGAN) is generally to be preferred and is increasingly widely used. In 2013, there were 3446 registered live births of <1000 g in England and Wales which constituted just under 0.5% of all births in that year. Of these, 27% died at <28 days, and 31% died before their first birthday. In contrast, there were 3068 live births at <28 weeks (4.4% of all live births) and 36% died in infancy.

Because ELBW babies who survive infancy have significant rates of neurodisability, it is important both to attempt, by public health interventions, to reduce rates of preterm delivery, and to offer the best care to the babies once they appear. For example, cerebral palsy rates in ELGAN babies are currently just under 10%,[3] but increased rates of autistic spectrum disorder are increasingly being recognised.[4] Some survivors have isolated special sensory deficits. A proportion has long-term consequences such as severe bronchopulmonary dysplasia or short gut syndrome from surgical resection for NEC.

In this review, we seek to highlight those recent advances in neonatal care that improve the outcome of ELBW babies, or have a high potential for doing so. However, we note that there are some areas in which there has been little or no advance. For example, other than avoiding the early use of corticosteroids in ELBW babies, positive indications for steroid use remain controversial, with no new evidence to guide practice, nor are we any further forward with the optimal management of the patent arterial duct. Important morbidities such as parenchymal damage to the brain have become uncommon, even in babies <1000 g. But there have been important developments in care networks and pathways, respiratory care, nutritional management, infection and retinopathy, so it is on these that we have concentrated.

ANTENATAL CARE AND THE ROLE OF NETWORKS AND PATHWAYS

Improvements in the outcome for infants born <1000 g cannot be achieved by neonatal care alone, because the quality of outcome depends as much on the pathway of care of the mother for whom preterm delivery seems imminent as on the subsequent neonatal management.[5] It is worth remembering that preterm delivery occurs either because babies are spontaneously born preterm or delivered preterm for maternal health reasons or delivered preterm for their own health. As such, management of the mother antenatally is about optimising the timing of interventions, centralising the place of delivery, maximising exposure to antenatal steroids and magnesium sulfate and using the most effective tocolytic drugs to allow steroid delivery optimal time to take effect, all of which are central to the recently published guidance from the National Institute for Health and Care Excellence (NICE, NG25). Recently, four trials of magnesium sulfate show benefit, with meta-analysis showing effect of risk reduction for cerebral palsy of 0.68 (95% CI 0.54 to 0.87) but it is still delivered suboptimally and variably from unit to unit.[6] Of these, some are now well embedded in clinical practice, and others should become so in the UK with the uptake of the NICE guidance. With increased survival of the most preterm of infants,[7] there has also been recent increased willingness to give antenatal steroids to those at the borders of viability

To cite: Berrington J, Ward Platt M. *Arch Dis Child* 2016;**101**:1053–1056.

(22–23 weeks gestation)[1] and acknowledgement in the literature that there is survival advantage to this even at 23 weeks gestation,[8] active resuscitation at <24 weeks is routinely offered in many places[9] and there is an increased presence in the medical literature of the parental perspectives of these situations.[10]

Neonatal care in many settings (including the UK) is now delivered through managed networks, with increasing centralisation of both resources and expertise for high-risk neonates and in some networks this increasingly extends to pregnancies, including centralised expert skills in fetal monitoring. Although local care provision brings benefits to families who have smaller distances to travel, there is increasing evidence that larger facilities which do most of the care for the smallest (<27 completed weeks) have better outcomes than those that do less, with mortality in high volume units being lower than in those with lower activity levels.[11]

DELIVERY ROOM MANAGEMENT

There is no obstetric consensus, and little robust evidence, to guide practice in relation to preferred mode of delivery for babies with a predicted weight <1000 g. However, there are now data to support efforts to ensure that these babies get as much placental blood as possible, either by delaying cord clamping or by cord milking. Of the two, milking is quicker, which may have advantage for the very preterm infant, and data suggest that in comparison to delayed clamping milking results in improved cardiac output and early haematological values, but long-term data, arguably the most important aspect of this potential delivery room intervention, are lacking, and there are concerns around the potential transfer of inflammatory cells.[12] Many clinicians feel the need to await more data, but doing neither is also of potential harm.

With regard to resuscitation, room air is now known to be preferable to oxygen for term infants, but this issue is less well studied in infants <1000 g, so initial use of 100% oxygen is not advised unless it is all that is available. It is unclear whether the use of electronic monitoring (mainly pulse oximetry) adds materially to clinical assessment during initial stabilisation among the smallest babies. Recent work has cast doubt on the ability of pulse oximeters to give an accurate representation of heart rate in the first few minutes after delivery,[13] and no one has attempted to assess the validity of the saturation readout in any babies, let alone those <1000 g, at this time. It is important that validation work is performed before the widespread introduction of oximeters to guide resuscitation, since inaccurate information on heart rate or saturation in the first 10 min after delivery has obvious potential for harmful clinical decision making.

In an effort to minimise rates of bronchopulmonary dysplasia, there has been a move to reduce rates of delivery room intubation by encouraging the use of very early nasal continuous positive airway pressure (nCPAP) even in the tiniest and least mature babies (23 and 24 weeks). In parallel, alternate methods of early surfactant delivery mechanisms have been developed: for example, 'InSurE' involves brief endotracheal intubation, surfactant administration and rapid extubation to nCPAP, while 'less invasive surfactant administration' (LISA) is tracheal intubation with a fine bore catheter purely to give surfactant, followed by nCPAP.[14 15] In a recent RCT, LISA was found to have a mortality advantage, but not a BPD advantage, in babies <26 weeks.[16] The evidence base for this approach is growing ever stronger.

Potential advances close to the point of implementation include the delivery of surfactant by nebuliser, and the creation of synthetic surfactants as effective as the existing animal-derived products.[17]

RESPIRATORY MANAGEMENT AFTER THE INITIAL PHASE

Arguably the most important advance for respiratory care in recent years has been the definition of appropriate oxygen saturation targets: we now know that targeting saturations >90% in babies born at <28 weeks gestation results in lower mortality, so this is now the standard of care.[18]

Advances in the practice of ventilation following delivery room care have also been seen. Ventilation that is volume targeted (or limited) seems to be associated with better respiratory outcomes than pressure-based strategies.[19] A more volume-orientated approach seems likely to become mainstream in the foreseeable future. Early oscillation for babies <1000 g was not adopted because the trials showed that there was no short-term advantage, but the longer term respiratory data from the UKOS study suggested that respiratory outcomes were improved at age 8 in those oscillated.[20] In contrast, there seems to be no place for the routine use of nitric oxide as part of early respiratory care to try to prevent bronchopulmonary dysplasia.

Whether the use of humidified air/oxygen through high flow nasal cannulas as an alternative to nCPAP delivered by flow driver devices will prove an advance in babies <1000 g remains speculative at present. Experience shows that this mode of therapy can provide a satisfactory alternative to nCPAP for many babies at some point in their NICU stay, and has been welcomed by nurses and parents because it makes other aspects of care of the baby much easier, potentially reduces nasal trauma and enhances direct parental skin-to-skin contact.

Many of the driver devices that are able to deliver nCPAP are also capable of delivering dual pressure (sometimes termed BIPAP and sometimes non-invasive IPPV) at operator determined rates, with obvious potential applications for those ELBW infants for whom a conventional flow driver is not quite enough to keep them off full mechanical ventilation. However, it seems important to ensure that infants can either entrain to a fixed rate of elevated pressure support or such support is synchronised with the baby's breaths. Asynchronous pressure may not actually constitute 'support' at all, and may well increase the work of breathing. It is quite common for physicians to give BIPAP a try, since it is easy to do, yet relatively little physiological science or pragmatic trial data are available to underpin this practice.

NUTRITION AND NEC

Concerns about the mortality from NEC, and an understanding of the long-term benefits of providing adequate early nutrition to ELBW babies, have resulted in an explosion of research into the best way to feed extremely small or preterm babies. Getting feeding right for the smallest babies underpins any further improvements in short-term and long-term outcomes. This review cannot do justice to all the work in this area, but it is worth considering a few of the recent advances.

Nutrition in ELBW infants is complex and comprises many individual decisions around macronutrients and micronutrients. This includes their sources and optimal quantities both enterally and parenterally, approaches to transitioning from parenteral to enteral feeds, supplementation and the potential use of immunomodulatory substances (probiotics, lactoferrin). In spite of this complexity, it is clear that feeding breast milk from the baby's own mother is best for even the tiniest infants, for key short-term (sepsis, NEC) and long-term (cognitive) outcomes. In addition, fortification of expressed breast milk (EBM)

appears to be safe and can compensate for most issues of borderline energy intake or nutrient insufficiency.[21]

The use of donor EBM is increasing worldwide but it is expensive and data supporting its use in ELBW infants is limited. A recent Dutch study, presented but not yet published, showed no effect on rates of NEC or sepsis when donor EBM was used rather than formula for the first 10 days, so further studies of donor EBM are clearly essential.

Recently, the main advances have been in our understanding of when to feed, and how much, also the importance and impact of very early provision of maternal colostrum. We now know that success in achieving lactation is possible even after very early birth if there is focused intervention including nurse education, maternal support and supervised expression.[22]

In many nutritional studies infants weighing <1000 g are poorly represented, so we have to be extremely cautious in extrapolating from trials conducted in larger and more mature babies. But many infants <1000 g were included in the ADEPT trial, which demonstrated that starting enteral feeds earlier reduced time on intravenous feeding, shortened length of stay and achieved better weight at discharge without adverse effects, even though growth restricted infants took much longer to establish full feeds, in line with clinical experience.[23] Faster rates (>24 mL/kg day and up to 40 mLs/kg/day) in ELBW babies seem to be associated with reduced sepsis without affecting rates of NEC,[24] and Lee *et al*[25] recently demonstrated the potential effectiveness of giving oropharyngeal colostrum (compared with placebo) in terms of a decrease in clinical sepsis, inhibited secretion of proinflammatory cytokines, and increase levels of circulating immune-protective factors, although only 48 infants were involved.

Optimising intravenous feeding for ELBW infants involves ensuring that the right contents are in the solution and that the practical issue of ensuring the requirements is delivered. The imposition of fluid restriction or the prescription of other infusions (eg, inotropes) can cause parenteral nutrition delivery to fall well below that prescribed. A new approach concentrates the solution into a smaller daily volume to mitigate this.[26] Finally, new lipid formulations based on fish oil and olive oil are now available. It is theoretically likely that these will reduce the liver damage associated with parenteral feeding, but solid evidence of benefit is still awaited.[27] The optimal use of micronutrient supplements such as iodine awaits the outcome of ongoing studies.

NEC is an important and increasing problem in ELBW infants who survive their early respiratory disease. Little recent progress has been made in understanding the aetiology but there is increasing recognition that it is multifactorial and represents the clinically recognised end point of different pathways including ischaemic, hypoxic and microbiomic elements. It follows that manipulations of the microbiome are a logical approach, and probiotics have been the subject of much exploration and controversy. The 2014 Cochrane review states that there is an overall benefit to preterm infants from receipt of probiotics both in reducing all-cause mortality and NEC, but in the subgroup of infants <1000 g (n=575) no reduction in all-cause mortality or severe NEC was seen.[28] This may be a genuine effect of gestation in these most immature infants, or relate to timing of milk/probiotic exposure as the most immature will receive milk later, or simply reflect that only small numbers of infants have been studied.

INFECTION

Late onset sepsis (LOS) remains a major hazard for ELBW babies. Contributing factors for LOS are the need for intravenous access for parenteral nutrition, the altered microbiome of the gut in infants exposed to modern-day NICU practices[29] and the relative immaturity of the neonatal immune system. Traditional approaches to reducing the incidence of LOS revolve around minimising breaches of the skin through interventions such as double lumen umbilical and central venous catheters, and reducing catheter-related blood stream infections through the use of 'line care bundles' like those in 'Matching Michigan'.[30]

Advances in reducing LOS include the deliberate administration of immune-modulating substances, such as lactoferrin. The data from the largest trial to date suggest benefit in reducing LOS,[31] but has yet to be reproduced, with two further much larger studies underway in Australia (LIFT) and the UK (ELFIN). Probiotics are efficacious in preventing NEC and the most recent evidence synthesis suggests a significant reduction in LOS.[32]

Studies in the last few years have demonstrated that fungal infection can virtually be eliminated. Fungal prophylaxis (orally or intravenously) seems to work best when targeted on those standing to benefit most: babies <1000 g, and those who have the most antibiotic and central venous catheter exposure.[33]

RETINOPATHY

Worldwide, there is an incipient epidemic of blindness from retinopathy. It is becoming clear that advances in neonatal care in many areas of poor or intermediate resource have outstripped the ability either to screen for this entirely preventable cause of blindness or to swiftly treat affected babies. In the richer countries, significant retinopathy is now largely confined to babies born <1000 g, though screening programmes include bigger and more mature babies too. The major advance has been that treatment options now include antivascular endothelial growth factor treatments like bevacizumab, which appeared superior to laser treatment for stage 3+ zone 1 disease.[34] It is not yet used very widely, and residual concerns remain about long-term effects, yet it has the potential both to advance retinopathy treatment in this country, and be a potential solution to the retinopathy epidemic globally. Other alternate prevention strategies are also being tested, including recombinant insulin like growth factor, which appears to show significant promise and is the focus of ongoing study (NCT01096784).

FAMILY INTEGRATED CARE

Programmes such as Newborn Individualised Developmental Care and Assessment Programme, which comprise individualised family-centred developmental care, with an emphasis on increasing involvement of parents in the care of their ELBW infant, and interactions between the infant and environment (including those artificial elements of NICU exposure) have long been known to be beneficial to both the infant and family.[35] Short-term infant physiological measures, longer term developmental outcomes and parental stress scores have all been shown to be improved by such approaches. But not all such interventions, when subjected to the rigour of adequately powered trials, have been shown to succeed in their intended purpose. It is those babies <1000 g who are likely to remain in a neonatal facility for 4, 5 or even 6 months, and their families, that have the most to gain or lose if we get their care right, or wrong. The emerging evidence of the psychological impact of having a baby in a neonatal facility for months should make us all think very hard about how we facilitate and support parental involvement.

In comparison to paediatrics, where it is now normal for parents to stay with their hospitalised children in single rooms with full facilities, neonatal practice has fallen far behind. Yet the importance and desirability of fully integrating families into the care of their babies is only just beginning to be appreciated. The recent POPPY report in the UK, the BLISS audits and the Baby Friendly Initiative (unicef) all highlight the fact that there is huge variation in the degree to which parents and families are placed at the heart of their baby's care.[36]

It is also clear that if the situation is to improve, radical alterations will need to be made to the way in which facilities are designed. Yet even without such changes, fundamentals such as staff attitudes to involving parents can be addressed: simple changes to nursing care and practice such as delivery of clustered cares, facilitating and encouraging 'skin to skin' and the use of breastfeeding or breast milk for procedural pain management can all improve baby and family experience at little or no cost. Two cluster randomised trials are currently investigating the family integrated care model.

CONCLUSION

In spite of all the medical advances in the care of the smallest babies that we have described, we predict that when the history of 21st century neonatal medicine is written, all the developments of the last 20 years will be mere footnotes to the radical transformation of the experience of neonatal care by the adoption of the family integrated model. The historians will seek to answer one simple question: Why did it take us all so long?

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

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