



REVIEW ARTICLE

The development of neonatal neurointensive care

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Brain injury remains one of the major unsolved problems in neonatal care, with survivors at high risk of lifelong neurodisability. It is unlikely that a single intervention can ameliorate neonatal brain injury, given the complex interaction between pathological processes, developmental trajectory, genetic susceptibility, and environmental influences. However, a coordinated, interdisciplinary approach to understand the root cause enables early detection, and diagnosis with enhanced clinical care offering the best chance of improving outcomes and facilitate new lines of neuroprotective treatments. Adult neurointensive care has existed as a speciality in its own right for over 20 years; however, it is only recently that large prospective studies have demonstrated the benefit of this model of care. The 'Neuro-intensive Care Nursery' model originated at the University of California San Francisco in 2008, and since then a growing number of units worldwide have adopted this approach. As well as providing consistent coordinated care for infants from a multidisciplinary team, it provides opportunities for specialist education and training in neonatal neurology, neuromonitoring, neuroimaging and nursing. This review outlines the origins of brain-oriented care of the neonate and the development of the Neuro-NICU (neonatal intensive care unit) and discusses some of the challenges and opportunities in expanding this model of care.

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INTRODUCTION

Brain injury can affect both preterm and term infants; the most common disorders are neonatal encephalopathy (NE) and perinatal arterial ischaemic stroke (PAIS) in term infants and the consequences of germinal matrix-intraventricular haemorrhage (GMH-IVH) and white matter injury (WMI) in extremely low birthweight preterm infants. Metabolic and rare genetic disorders can also present with seizures and encephalopathy in the neonatal period. All these vulnerable infants are at significant risk to develop cerebral palsy, epilepsy and other forms of neurological disability.¹ These outcomes place an enormous physical, psychological and financial burden on individuals, families and society; for example, costs of preterm birth to the public sector in the United Kingdom is estimated at over £2.9 billion/year;² the additional lifetime cost of looking after a child with cerebral palsy in the United States can be over one million dollars.³

The past 40 years have seen a dramatic improvement in the survival of extremely preterm and critically ill neonates; however, the incidence of cerebral palsy and other neurodevelopmental problems remains high.^{4,5} The global scale of perinatal brain injury cannot be underestimated: in 2015 an estimated 690,000 infants died from intrapartum-related events, and just over 1 million infants died from complications of prematurity.⁶ Therapeutic hypothermia represents the first neuroprotective therapy for infants with NE, yet even with hypothermia, over half treated infants are at risk for moderate–severe cerebral palsy or death.⁷ No single intervention can ameliorate neonatal brain injury, given the multiple pathologies, complex interaction between pathological processes, developmental trajectory, genetic susceptibility and environmental influences. But a coordinated, high-expertise approach to enable early detection and diagnosis and with enhanced clinical care could offer the best chance of improving outcomes as well as facilitate new lines of neuroprotective

research. It is this philosophy that has motivated clinicians in developing the neonatal neurocritical care (NNCC) model of service delivery, which over the past 10 years has gained considerable traction in North America and is being increasingly adopted across the world.

This article examines the evidence from adult medicine that a dedicated neurointensive care approach can improve outcomes, reviews the development of neonatal neurointensive care and addresses what some of the challenges and benefits of this model of care might be.

ADULT NEUROINTENSIVE CARE: WHAT CAN WE LEARN?

'Neurocritical care is devoted to the comprehensive care of critically ill patients with neurological or neurosurgical disease. Care of such patients requires an understanding of the physiology and pathophysiology common to brain diseases in general, as well as the skills and knowledge to treat a range of specific conditions. Given the exquisite vulnerability of the injured brain to physiological insults, optimal care of such patients demands meticulous attention to maintenance of systemic and cerebral physiological targets while ensuring appropriate protection of extra-cranial organs.'⁸

This is the definition of adult neurocritical care given by the UK Intensive Care Society, but could equally be applied to a definition of neonatal neurocritical care. Adult neurocritical care has been recognised as a subspecialty in its own right for almost 20 years. Its origins can be traced back to specialist critical care units developing within neuroscience centres focusing on patients with traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH); today large dedicated neurocritical care units care for patients with a wide range of neurological and neurosurgical conditions. A key question with the emergence of a new subspecialty is whether

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it improves outcomes? In this respect, improvement science has lagged behind other areas of clinical research with most of the evidence coming from single centre studies using retrospective data and historical controls; only a few multicentre prospectively controlled studies have been carried out. Most of the evidence relates to TBI. Data from the Trauma Audit and Research Network showed that outcome for patients managed in a general hospital were worse than those cared in a neuroscience centre (2.15-fold increase (95% confidence interval (CI):1.77–2.60) in the odds of death adjusted for case mix).⁹ A large multicentre observational study, Risk Adjustment In Neurocritical care (RAIN) confirmed better outcomes in neuroscience centres.¹⁰ Similar improved outcomes have been reported in patients with intra-cerebral haemorrhage and SAH.^{11,12}

As well as the methodological limitations outline above, another issue is that the outcome data is primarily mortality and short-term outcome, with little in the way of long-term neurological outcome studies. If we accept that specialist neurocritical care units improve outcomes, a perhaps more important question is why? Given the complexity of the specialty and heterogeneity of the patients, there is no simple answer. However, a number of factors, highlighted by Tweedie, include specific experience and increased caseload of multidisciplinary teams, brain centred care and specialist neuromonitoring, rapid neurosurgical access and early input of physiotherapy and neurorehabilitation, and a less nihilistic attitude and more conservative approach to the end of life.¹³

Outside the neurocritical care unit, the development of specialised stroke units has revolutionised the management of adult stroke.¹⁴ A Cochrane review in 2013, analysing 28 trials enrolling 5855 patients concluded that stroke patients who received organised inpatient care in a stroke unit were more likely to be alive, independent, and living at home 1 year after the stroke. As with neurocritical care, the focus of the stroke unit is to provide consistent specialised care by a multidisciplinary team. While a major advance was the alteplase trial in 1995, which demonstrated improved outcome with hyperacute thrombolysis (within 3 h of treatment), it is the provision of this therapy within the context of a dedicated stroke unit which appears to maximise benefit.¹⁵ The authors of the Cochrane review acknowledge that their analysis does not explain how these units may improve outcome, but speculate that this could be due to, among other things, greater staff expertise, better diagnostic procedures, better nursing care and more effective rehabilitation procedures. As with many causes of brain injury, rapid and timely intervention is crucial as highlighted by the development of mobile stroke units for prehospital thrombolysis.¹⁶ In adults, children and neonates timely intervention prior to admission to specialised units is important to prevent lifelong brain injury.

BRAIN INJURY IN THE NEWBORN

Gestational age remains the most important factor determining the aetiology and consequences of brain injury. In the term infant, NE resulting from a perinatal hypoxic-ischaemia insult is the leading cause of acquired brain injury and neurodisability, with an incidence ranging from 1 to 12 per 1000 live births depending on the precise definition and resource setting.¹⁷ In many respects this condition most closely resembles adult TBI in that it follows an acute insult, early management is time critical and the goal is to prevent secondary injury by meticulous attention to cerebral and systemic physiology. PAIS is perhaps an under-recognised cause of acquired brain injury: with an incidence of around 2.5 per 1000 live births, it is the second most common cause of neonatal seizures and the most common cause of childhood hemiplegia.¹⁸ Preterm brain injury is complex and multifactorial. With improvements in intensive care, the incidence of GMH-IVH has fallen in infants >26 weeks; however, with increased survival, the

prevalence remains high.¹⁹ The spectrum of injury to the periventricular white matter has shifted from the destructive lesions of periventricular leukomalacia to a more subtle reactive WML.²⁰ In the preterm infant, brain injury is not always the primary event, but the consequence of preterm birth and associated comorbidities has a profound impact on brain development. In a large meta-analysis looking at the cognitive outcomes of preterm infants born since 1990, Twilhaar et al.²¹ reported that bronchopulmonary dysplasia was the most significant factor for long-term cognitive outcome. This is why no single intervention is likely to ameliorate preterm brain injury, yet approaches to minimise the impact of prematurity on the infant may be beneficial. A number of childhood neurological conditions also present in the neonatal period, where early recognition and diagnosis could have a significant impact on the disease progression. The most famous condition being phenylketonuria, where universal screening has dramatically altered the prognosis of this condition;²² there is emerging evidence that some epileptic encephalopathies, if diagnosed early, may benefit from specific anti-epileptic medication with altered outcome.²³

STRATEGIES TO PROTECT THE NEWBORN BRAIN

With improvements in overall survival of newborn infants on intensive care, it was natural that attention would shift to intact survival with good neurodevelopmental outcome. Many groups around the world recognised this, but it is certainly worth mentioning that the NICU (neonatal intensive care unit) at the University College London under the leadership of the late Professor Osmund Reynolds. Not only did he recognise the importance of long-term neurodevelopmental follow-up (the 1979 cohort of infants from UCL are still being studied)²⁴ but also the value of the then emerging technologies of cranial ultrasound (CUS) and later magnetic resonance imaging and spectroscopy to understand the pathophysiology of cerebral injury.^{25,26} Work by the Reynolds group and others in the 1990s led to the concept of a delayed, or secondary energy failure following hypoxia–ischaemia.²⁷ This directly led to the experimental studies and subsequent clinical trials of therapeutic hypothermia.²⁸ Despite equivocal data on the benefit of therapeutic hypothermia following TBI and cardiac arrest in adults and children,²⁹ cooling neonates following perinatal asphyxia has shown to be particularly efficacious: the meta-analysis of over 11 clinical trials involving 1505 infants showed therapeutic hypothermia significantly reduced death or disability at 18 months (relative risk 0.75, 95% CI 0.68–0.83 vs. standard care); the number needed to treat for one newborn baby to be alive and free of disability is 7.⁷ In 2010 the International Liaison Committee on Resuscitation published guidelines stating:

Newly born infants born at or near-term with evolving moderate to severe hypoxic–ischemic encephalopathy should be offered therapeutic hypothermia...Cooling should be initiated and conducted under clearly defined protocols with treatment in neonatal intensive care facilities and with the capability for multidisciplinary care.³⁰

There is often a delay in translating clinical research into the standard of care; this did not seem to be the case though in the UK where therapeutic hypothermia was widely adopted, mainly a result of many NICU's participating in the largest randomised controlled trial for therapeutic hypothermia, the TOfal BodyY hypothermia trial (TOBY) study (ISRCTN8954757).³¹ Following completion of that trial, the UK TOBY Cooling Register was set up to provide guidance to clinicians considering the introduction of this therapy, audit the uptake and conduct of therapeutic hypothermia in the United Kingdom and to undertake surveillance

for adverse effects related to cooling. Reporting the results from 4.5 years of data from the register was published in 2012, providing a unique insight into the uptake of a new therapy in the United Kingdom.³² During this period, a total of 2069 infants were registered, which equates to 1–2/1000 live births/year. However, without contemporaneous epidemiological data on the incidence of NE, it remains unclear whether all infants who may benefit from this treatment actually receive it.

The UK experience also benefited from an established regional neonatal network provision of care and neonatal transport infrastructure. For example, in the East of England, the Acute Neonatal Transfer Team began transferring infants for therapeutic hypothermia in October 2009; in the first 18 months, the time taken to achieve target temperature had reduced significantly (regression coefficient –12.8; 95% CI 19.2 to –6.5, $p = 0.0002$). To address the issue of infants arriving at the cooling centre outside the target temperature range, a servo-controlled cooling mattress was installed on the transport incubator, which resulted both in a significant improvement in thermal control and also a reduction in stabilization time.³³ The practice of active cooling on transport has subsequently been adopted by most transport teams in the United Kingdom.

DEVELOPMENT OF THE NEURO-NICU

The multidisciplinary approach to the care of the newborn infant with brain injury is not new, with many units working closely with paediatric neurologists, neurosurgeons and other professionals. However, the advent of therapeutic hypothermia represented a step change requiring a coordinated approach to the identification and management of patients with NE. The University of California San Francisco (UCSF) were one of the first units in the United States to set up what they called a neonatal neurointensive care nursery (NICN).³⁴ Over the past decade, this approach has gained considerable traction, particularly in North America with a number of units reporting their experience of setting up similar models of care.^{35,36} The goal of the NICN is to utilize the advances in neuromonitoring, imaging with new treatments, which would ultimately improve neurodevelopmental outcomes in newborns at risk of neurological disability. Three key patient groups emerged as potentially benefitting from this management approach: (i) term infants with NE and seizures, (ii) extremely preterm infants and (iii) infants with congenital or rare neurological conditions presenting in the neonatal period. Four key themes have also emerged in the development of this and other NNCC services and are discussed below: (i) co-management of infants, (ii) standardized protocols and care bundles, (iii) increased utilization of neuromonitoring and (iv) development of training programmes.

Co-management of infants

Central to the Neuro-NICU is the co-management of infants at risk of neurological injury with neonatologists, paediatric neurologists, neurophysiology/epileptologists, neuroradiologists, neurosurgeons and specialist nurses. Historically, neonatal neurology was always seen as the purview of the neonatologist, with paediatric neurologists being called upon later on in the management of complex neurological infants. The major step change was the involvement of the paediatric neurologist from the point of admission or initial diagnosis. This gave a broader perspective to both neonatologist and neurologist in the investigation and management of these infants as well as providing continuity of care for families while in the NICU and through to follow-up following discharge.³⁷

Standardized protocols

The process of standardization is a common practice in many industries and has repeatedly been shown to improve outcomes within healthcare settings.^{38,39} As part of an integrated care

pathway or care bundle, treatment protocols enable consistency of care, reduces variability and mitigates against error. The NNCC special interest group (NNCC-SIG), set up in 2016, has a number of protocols from different US centres available to download (www.sites.google.com/view/nccsig/home). It should be noted though that apart from protocols for therapeutic hypothermia, none has been rigorously validated in multicenter studies with meaningful outcomes, which is important to demonstrate improvement. Nevertheless, increased open access and sharing of protocols is an important first step in this process.

Neuromonitoring and neuroimaging

The use of CUS and amplitude-integrated electroencephalography (aEEG) has been universal among large NICU's for many years. Interestingly, the use of aEEG was first described in the late 1960s for long-term monitoring of adults on intensive care during status epilepticus or following cardiac arrest.⁴⁰ The first use of aEEG from neonates was published in the early 1980s and early studies revealed the presence of subclinical seizures in infants with NE.^{41,42} It was not until the CoolCap and TOBY trials for therapeutic hypothermia, which coincided with the digitization of instrumentation, that its use to monitor infants with NE and seizures became more commonplace.^{31,43} aEEG has also shown to be of value in infants with congenital heart disease and inborn errors of metabolism.^{44,45} The use of aEEG in preterm infants is increasing both to assess brain maturation and also identify seizures, which are increasingly recognized in this group.^{46,47}

Despite its ease of use, aEEG remains a long-term trend monitor and lacks the temporal or spatial resolution to a full montage video EEG (vEEG). However, despite the concept of the Neuro-NICU being around for over 10 years now, the use of prolonged continuous vEEG is not universal, with only between 35 and 67% of NICU's reporting their usage.³⁷ This is despite the recommendations from the American Clinical Neurophysiological Society, and may represent the challenges around prolonged monitoring and reporting of full montage EEGs.⁴⁸

Continuous monitoring of cerebral oxygenation using near-infrared spectroscopy (NIRS) is appealing as it is the nearest clinicians have to a measurement of cerebral perfusion at the bedside. While NIRS has been used extensively as a research tool for many years, it has been slow to translate into clinical practice.⁴⁹ There are a number of patient groups at risk of brain injury who may benefit from NIRS monitoring, including preterm infants (especially at risk of IVH or with a large patent ductus arteriosus), encephalopathic infants and infants with congenital heart disease. Potential reasons for the lack of universal uptake include concerns around 'normal' values, variation between instruments, need for treatment guidelines for when thresholds are reached and whether monitoring improves outcomes. The SafeBoosC consortium made up of NICUs across Europe undertook a phase II randomized controlled trial comparing standard treatment against continuous NIRS monitoring with an evidence-based guideline and demonstrated in the treatment group a significant reduction in the burden of hypoxia.⁵⁰ A larger phase III trial is currently underway to see if NIRS monitoring reduces mortality and brain injury as assessed on CUS (NCT03770741).

Following the introduction of CUS on the NICU in the 1980s, early studies showed the prognostic value of both imaging and assessment of post-asphyxial hyperaemia in term infants with NE and seizures.^{51,52} Later studies, however, have shown a more limited role of CUS in predicting outcome.⁵³ Today, the use of MRI both from a diagnostic and prognostic perspective is almost universal in these infants.⁵⁴ The value of MR spectroscopy in predicting outcome was highlighted in the study by Lally et al.,⁵⁵ which reported that thalamic proton spectroscopy 4–14 days after birth was more predictive of 2-year outcome than both conventional MRI, aEEG and neurological examination. While CUS scanning in preterm infants is almost universal in the early

neonatal period and is particularly valuable for diagnosing GMH-IVH and following up infants with post haemorrhagic ventricular dilatation, CUS is less sensitive at diagnosing non-cystic white matter lesions. The prognostic value of CUS has been extensively investigated, while there are some studies which have shown that CUS at TEA improves prognostication;⁵⁶ there are also studies which demonstrate abnormal developmental outcomes despite normal CUS at TEA and others which demonstrate normal outcomes with abnormal CUS.^{57,58} The practice of MRI scanning preterm infants at term equivalent age (TEA) is not universal and data on its value is conflicting. Woodward et al.⁵⁹ reported that MRI at TEA predicts cognitive delay, motor delay, cerebral palsy and neurosensory impairment at 2 years. More recently the ePRIME study in the United Kingdom reported that although MRI predicted adverse motor outcomes slightly better than CUS, both were insensitive at predicting cognitive outcome at 20 months.⁶⁰ However, WMI is often associated with behavioural abnormalities, which may not become apparent at a later age; in this respect, Iwata et al.⁶¹ found that, in a cohort of very preterm infants, abnormal white matter appearance on term MRI was associated with cognitive impairment at 9 years of age. Finally, it should be noted that the predictive value of MRI scans is highly dependent on the quality of the images, neuroradiology expertise and also associated clinical co-morbidities.

Development of training programmes

Recognized early by the UCSF team was the requirement to engage the nursing staff.⁶¹ The aim was to train a cohort of nurses in what were seen as the 'core competencies' of neonatal neurocritical care. This included an understanding of the common neurological conditions encountered in the NICU with an emphasis on clinical presentation, investigations, treatment protocols and use of aEEG/EEG and NIRS monitoring. Once a critical number of Neuro-NICU nurses had been trained, there would be at least two available on each shift to take a lead for these patients. A growing number of online and in-person training programmes, including certified courses, are now available.

More recently, it has been proposed to develop formal training for medical staff in neonatal neurocritical care. While certification in Critical Care Neurology has been available since the early 2000s, Smyser et al.⁶² argue that there is a strong case for a similar programme in fetal and neonatal neurology, pointing out that many trainees currently undergo personal 'bespoke' training mainly in centres with strong neonatal neurology research credentials.

DOES THE NEURO-NICU IMPROVE OUTCOMES?

The development of the Neuro-NICU has many similarities with the origin of adult neurocritical care and other evolving specialties. Various models of care have been put forward with similar aims and objectives. Like adult neurocritical care, the challenge is to demonstrate that this model of care improves outcomes. To date, data are limited to single centre studies with only short-term outcomes reported. Perhaps, not surprisingly, the presence of a neonatal neurologist led to an increase in the number of consultations, visits per patients and types of patient seen.⁶³ The use of vEEG has been shown to significantly increase the seizure detection rate: an important finding considering the limitations on making a diagnosis on clinical grounds alone.⁶⁴ The use of vEEG has also been shown to result in a modest decrease in the use of anticonvulsants and reduced use of anticonvulsant medication at discharge.⁶⁵ It is unclear why this may be the case, but the authors speculate that it may be due to increased confidence in decision making (including stopping anticonvulsants) with vEEG.

The use of care bundles has been most widely used in the context of sepsis.⁶⁶ Within the Neuro-NICU preventing

hospital-acquired infection is highly relevant given the relationship between sepsis, necrotizing enterocolitis and neurodevelopmental outcome in the preterm infant.⁶⁷ More recently, the use of care bundles to prevent or minimize the complications of IVH have been reported with promising results. Chiriboga et al.⁶⁸ reported an impressive and sustained reduction of IVH from 24 to 9.7% through the implementation of a multidisciplinary quality improvement initiative, which included focusing on delivery unit management (delayed cord clamping, optimizing cardiopulmonary resuscitation and improved thermoregulation), as well as a bundle of care on the NICU focusing primarily on minimal handling over the first 72 h of life.

In 2006, following the completion of the TOBY trial, the largest RCT for therapeutic hypothermias, a national register was set up to collect data from all participating units in the United Kingdom as therapeutic hypothermia became the standard of care for infants with HIE.³² This register proved to be a valuable resource to monitor the uptake of this therapy, report rare adverse events and document 'drift' in inclusion criteria. Although a number of national and international registers exist, the most well known being the Vermont-Oxford Network, none are specifically focused on the Neuro-NICU. The creation of the NNCC-SIG is a welcome development in bringing the community together, but it is important that lessons from adult neurocritical care are learnt and national and international data repositories are created to formally evaluate the benefits from the Neuro-NICU model.

As an example that neonatal neurocritical care extends beyond dedicated 'NeuroNICU's, the PRevention of Cerebral palsy in PreTerm labour (PReCePT) project in the United Kingdom is an initiative to ensure all mothers in threatened preterm labour are given antenatal magnesium sulfate to prevent cerebral palsy in preterm infants, regardless of where they are born.⁶⁹ The initial package of training and support materials was developed in the South West of England and has now been rolled out across all maternity units in England. The UK benefits from an integrated clinical research network, which enables both rapid roll out and nationwide evaluation.

DEVELOPMENTS IN NEONATAL NEUROPROTECTION

New therapies for HIE

Therapeutic hypothermia for HIE was one of the main drivers in the development of the first NICU at UCSF; while cooling represents one of the most significant developments in neonatal care in recent years, nearly half of infants who receive it will still have an abnormal outcome.⁶ The search for adjunct therapies has moved from preclinical to clinical studies. Although the early promise of Xenon as a neuroprotectant did not appear to translate into clinical benefit, other drugs including erythropoietin and allopurinol are subject to ongoing clinical trials and the results are awaited with interest.⁷⁰⁻⁷² The debate as to whether infants with mild HIE may benefit from therapeutic hypothermia is ongoing.⁷³ The COoling in Mild EncephalopaThy (COMET) trial is a phase II trial investigating the feasibility and optimal duration of cooling infants with mild encephalopathy (NCT03409770). The challenge in this patient cohort remains the ability to identify early infants who may benefit from therapeutic hypothermia and assess meaningful outcomes in a timely manner.

Precision medicine in the NICU

A number of rare congenital neurological disorders present in the neonatal period, sometimes with subtle manifestations which can be easily missed. With the advent of rapid whole-exome and -genome sequencing (WGS), it is possible that many conditions can be diagnosed early on enabling more timely management, including in some instances early treatment, for example, in the case of neonatal seizures caused by KCNQ2 mutation, which can be responsive to carbamazepine therapy.²³

Several groups have reported preliminary findings using rapid WGS in targeted cohorts on the NICU;^{74,75} the largest of these studies from Cambridge, UK, enrolled a total of 195 families undertaking predominantly trio analysis from both the NICU and Paediatric Intensive Care Unit.⁷⁶ In the neonatal cohort, 113 families were recruited (representing 47% of those approached and ~10% total admissions to the NICU) and the resulting diagnostic rate was 13%. Of interest, the phenotypic description of the infant was a poor predictor of the gene identified. The diagnosis affected clinical management in 83% of the neonatal cases, including modification of treatment and care pathways and/or informing palliative care decisions. Of note, the study was integrated into the clinical NHS pipeline, with meaningful results being turned around within 2–3 weeks.

As the Neuro-NICU develops, it is likely rapid WGS will become a requisite investigation tool for a large number of patients, but in turn will also raise important ethical questions.⁷⁷

Multiparameter 'intelligent' monitoring

Critical care medicine has always been a data-rich environment, with real-time monitoring of many physiological parameters and frequent investigations. However, it is only recently with the advent of computer algorithms driving the 'big data' revolution that the power of these data can potentially be harnessed in the NICU. The purpose of this approach is multifactorial, including deriving new physiological parameters and indices in real time (e.g. cerebral autoregulation),⁷⁸ aiding clinical diagnosis (e.g. seizures),⁷⁹ reducing false-positive alarms⁸⁰ and predicting early patient deterioration (e.g. sepsis).⁸¹

Biological systems are inherently complex and interrelated at different levels. However, there is a tendency in the management of the critically ill patient to treat data as discrete, linear and stationary and the inherent complexity within the whole biological system is often overlooked. For example, using a non-linear approach, Sortica da Costa et al.⁸² investigated the complexity of biological signals in preterm infants in the first 24 h of age using multi-scale entropy and found that reduced complexity of brain oxygenation signals was predicative of mortality and brain injury.

Bioinformatics and artificial intelligence are rapidly developing fields, but their translation into clinical practice within the Neuro-NICU will require close collaboration between clinicians, engineers, computer scientists, and bioinformaticians and large-scale multicenter studies to validate the different methodologies.

Global challenges in developing neonatal neurocritical care

The global burden of perinatal brain injury cannot be underestimated: approximately a quarter of all newborn deaths result from NE, with 96% occurring in low- and middle-income countries (LMICs), equating to 690,000 deaths/year. In 2010 an estimated 14.9 million infants were born preterm with 60% born in south Asia and sub-Saharan Africa.⁸³ While therapeutic hypothermia has become standard of care for NE in the developed world, it is perhaps surprising, given the simplicity of the treatment that it has not been universally adopted in LMICs. A meta-analysis of therapeutic hypothermia in LMICs has shown a reduction in neonatal mortality from seven randomized controlled trials enrolling a total 567 infants, although the reduction was not statistically significant.⁸⁴ The data are difficult to interpret due to inconsistent inclusion and exclusion criteria and poor follow-up. The studies were heavily biased towards India, with only one RCT in Africa and none in Central and South America or countries of the former Soviet Union.

Despite inconsistency in evidence across different resource settings, there has been a gradual, if inconsistent, uptake of therapeutic hypothermia (TH) across the world. A recent survey from Brazil of 1092 professionals representing 92% of Brazilian states and federal districts found that therapeutic

hypothermia was being provided in 62% of units.⁸⁵ Of interest, the survey went on to show that 20% did not use any neurological score or amplitude-integrated electroencephalogram (aEEG) to assess encephalopathy; specific training for encephalopathy assessment was only provided to 19% of professionals and only 31% reported having a well-established follow-up programme for these infants.

The potential dangers of translating practice to different resource settings was highlighted by the ACT trial on the use administration of antenatal corticosteroids to mothers in threatened preterm labour. While this has clearly been shown to reduce neonatal mortality and neurodisability in high-income countries, this large cluster randomized trial across multiple LMICs showed an increase in mortality.⁸⁶ Therefore, any translation of practices in the NeuroNICU model needs to be carefully assessed within different populations tailored to the needs, pathology and resources of each environment.

The neonatal environment and the developing brain

With its initial focus on survival, the NICU has traditionally been modelled on conventional intensive care units. Indeed, in the early years, parents were actively discouraged from visiting their babies. The importance of family centred care was championed in the 1970s by Als⁸⁷ who created the Newborn Individualized Developmental Care and Assessment Program (NIDCAP).⁸⁷ While the evidence base for NIDCAP specifically in improving neurodevelopmental outcome is limited, parents have increasingly been encouraged to take a far more active role in the care of their baby right from admission to the NICU.^{88,89}

The harshness of the NICU is in stark contrast to the warm, dark protective in utero environment. The preterm infant is exposed to numerous painful procedures, which may directly impact on brain development.⁹⁰ The effect of the environment, such as noxious noise or excessive light, may alter short-term physiological stability and in the longer term, impede growth and development.⁹¹ However, the evidence base for the effects of noise reduction and cycled light on neurodevelopmental outcome remains limited.^{92,93} Sleep-wake cycling develops in the third trimester and impaired quality and quantity of sleep on the developing brain may have a significant effect on the developing brain.⁹⁴

In designing the NICU, the debate between single rooms vs. open wards remains ongoing; the evidence from a recent systematic review and meta-analysis by van Veenendaal et al.⁹⁵ reported a reduction in the incidence of sepsis and increase in breastfeeding rates in single family rooms, but no effect on neurodevelopmental outcome.

CONCLUSIONS

Neonatal intensive care has been one of the remarkable success stories in modern medicine, with dramatic improvement in survival of the smallest and sickest infants over the past 50 years. Learning from the experience of adult neurocritical care, the development of the Neuro-NICU offers real promise that the gap between survival and improved neurodevelopmental outcome can be closed. However, this requires significant investment of time, manpower and equipment, and so it is essential that prospective data is collected from large cohorts, to determine whether this development equates with improvement in outcome.

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AUTHOR CONTRIBUTIONS

I can confirm that I, T.A., am the sole author of this paper, having conceived of the idea for the manuscript, undertaken the relevant literature search into the subject and written the manuscript.

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