Early Human Development 187 (2023) 105898

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

The critical role of technologies in neonatal care

Syed Taha, Rosalind B. Simpson, Don Sharkey *

Centre for Perinatal Research, School of Medicine, University of Nottingham, Nottingham NG7 2UH, United Kingdom

ARTICLE INFO

Keywords:
Neonatal
Technology
Newborn
Intensive care
Monitoring
Devices

ABSTRACT

Neonatal care has made significant advances in the last few decades. As a result, mortality and morbidity in high-risk infants, such as extremely preterm infants or those infants with birth-related brain injury, has reduced significantly. Many of these advances have been facilitated or delivered through development of medical technologies allowing clinical teams to be better supported with the care they deliver or provide new therapies and diagnostics to improve management.

The delivery of neonatal intensive care requires the provision of medical technologies that are easy to use, reliable, accurate and ideally developed for the unique needs of the newborn population. Many technologies have been developed and commercialised following adult trials without ever being studied in neonatal patients despite the unique characteristics of this population. Increasingly, funders and industry are recognising this major challenge which has resulted in initiatives to develop new ideas from concept through to clinical care.

This review explores some of the key medical technologies used in neonatal care and the evidence to support their adoption to improve outcomes. A number of devices have yet to realise their full potential and will require further development to optimise and find their ideal target population and clinical benefit. Examples of emerging technologies, which may soon become more widely used, are also discussed.

As neonatal care relies more on medical technologies, we need to be aware of the impact on care pathways, especially from a human factors approach, the associated costs and subsequent benefits to patients alongside the supporting evidence.

1. Introduction

All-cause neonatal mortality has steadily declined globally with latest estimates of 2.3 million neonatal deaths in 2021 and an annual mortality rate reduction of 2.4 % from 1991 to 2021; however, this decline is slower compared to mortality among children aged between 1 month and 4 years [1]. With improving survival there is often an increase in associated morbidity, particularly with the highest risk groups such as premature infants or those with hypoxic ischaemic encephalopathy (HIE).

In 2020, an estimated 13.4 million babies were born worldwide before 37 completed weeks of gestation, with prematurity-related complications being responsible for 900,000 deaths in 2019 [2]. Survival comes with its own set of challenges, and development of long-term complications is relatively common including bronchopulmonary dysplasia (BPD), brain injury and necrotising enterocolitis [3]. BPD has a global incidence of 17–75 % [4] and in the UK rates continue to increase with improving survival [5]. Preterm brain injury rates are significant but have remained unchanged over the past decade in the UK at 24 to 25/1000 live births [6]. Necrotising enterocolitis remains a significant cause of neonatal morbidity, with a current global pooled estimate of 7 % in very low birthweight infants [7].

In term and near-term infants, HIE is a leading cause of neonatal mortality and morbidity despite the introduction of therapeutic hypothermia. Recent UK data highlighted rates of moderate/severe HIE in infants ≥36 weeks gestation [8].

Whilst there have been advances across domains of neonatal care, medical technologies (MedTech) have allowed new therapies to be adopted to support care or explored in large clinical studies. The impact of MedTech in neonatal care cannot be underestimated; this review highlights some of those innovations and gives examples of where technologies have yet to deliver the benefits that earlier studies had suggested.

* Corresponding author.
E-mail address: don.sharkey@nottingham.ac.uk (D. Sharkey).

https://doi.org/10.1016/j.earlhumdev.2023.105898
Received 26 September 2023; Received in revised form 3 November 2023; Accepted 3 November 2023
Available online 4 November 2023

2. Development of neonatal technologies

High-risk infants invariably require medical care on neonatal intensive care units (NICUs) using a multitude of medical technologies. They require continuous care whilst connected to several monitoring devices, ranging from capillary oxygen saturations and ECG, to surface temperature and brain monitors. Many of these devices have been adapted from adult design and have not been specifically validated for use in newborn infants due to barriers presented by complex legal and regulatory frameworks [9]. A recent study highlighted that of 24 medical devices receiving pre-market regulatory approvals for use in children, 21 had never been studied in children [10]. Clinical trials evaluating US Food and Drug Administration (FDA)-regulated class 2 and class 3 medical devices in paediatric patients are often inadequate, with the majority being designed as single-centre (67 %), non-randomised (53 %) and open-label (72 %) studies [11]. Many (71 %) of these studies recruit less than one hundred participants, and 60 % include a primary outcome of efficacy only with no consideration of safety endpoints [11]. A summary of the medical device development pathway is presented in Fig. 1.

3. Newborn delivery room resuscitaires

As evidence has accumulated regarding the benefits of delayed cord clamping, including reduced in-hospital mortality [12], more consideration is being given to facilitating this process at birth during stabilisation or resuscitation. Numerous resuscitaire platforms have been developed to support delayed cord clamping including LifeStart, NOOMA, Inspire and Concord [13]. Only the LifeStart and Concord systems have been approved for use in Europe, but these platforms are not yet recommended for routine clinical use in infants requiring active resuscitation at birth. There are ongoing and planned trials to evaluate their usage.

4. Core bedside monitoring technologies

Monitoring core vital signs, such as heart rate, oxygen saturations and temperature, is an important component of neonatal intensive care (Table 1).

4.1. Heart rate

Electrocardiogram (ECG) monitoring has been in routine use within the NICU for decades for sick infants. In 2015, the International Liaison Committee on Resuscitation (ILCOR) made a recommendation on the basis of very-low-quality evidence that ECG can be used to provide a rapid and accurate estimation of heart rate in newborns requiring stabilisation or resuscitation at birth [14]. Systematic reviews have found ECG to be the most rapid, accurate, and reliable method of monitoring heart rate at birth when compared with methods such as auscultation, palpation, pulse oximetry (PO) and Doppler ultrasound [15–17].

PO is commonly used to measure heart rate and is superior to clinical assessment, although obtaining a rapid and reliable signal can be difficult due to multiple factors, including wet or vernix-coated newborn skin and during low perfusion states [18–21]. In comparison to ECG, PO takes longer to attach, provides a less reliable signal, takes longer to display an output and underestimates heart rate in the initial minutes of life [15–17].

Reflectance photoplethysmography (rPPG) is an optical measurement technique which uses a light source and photodetector at the skin

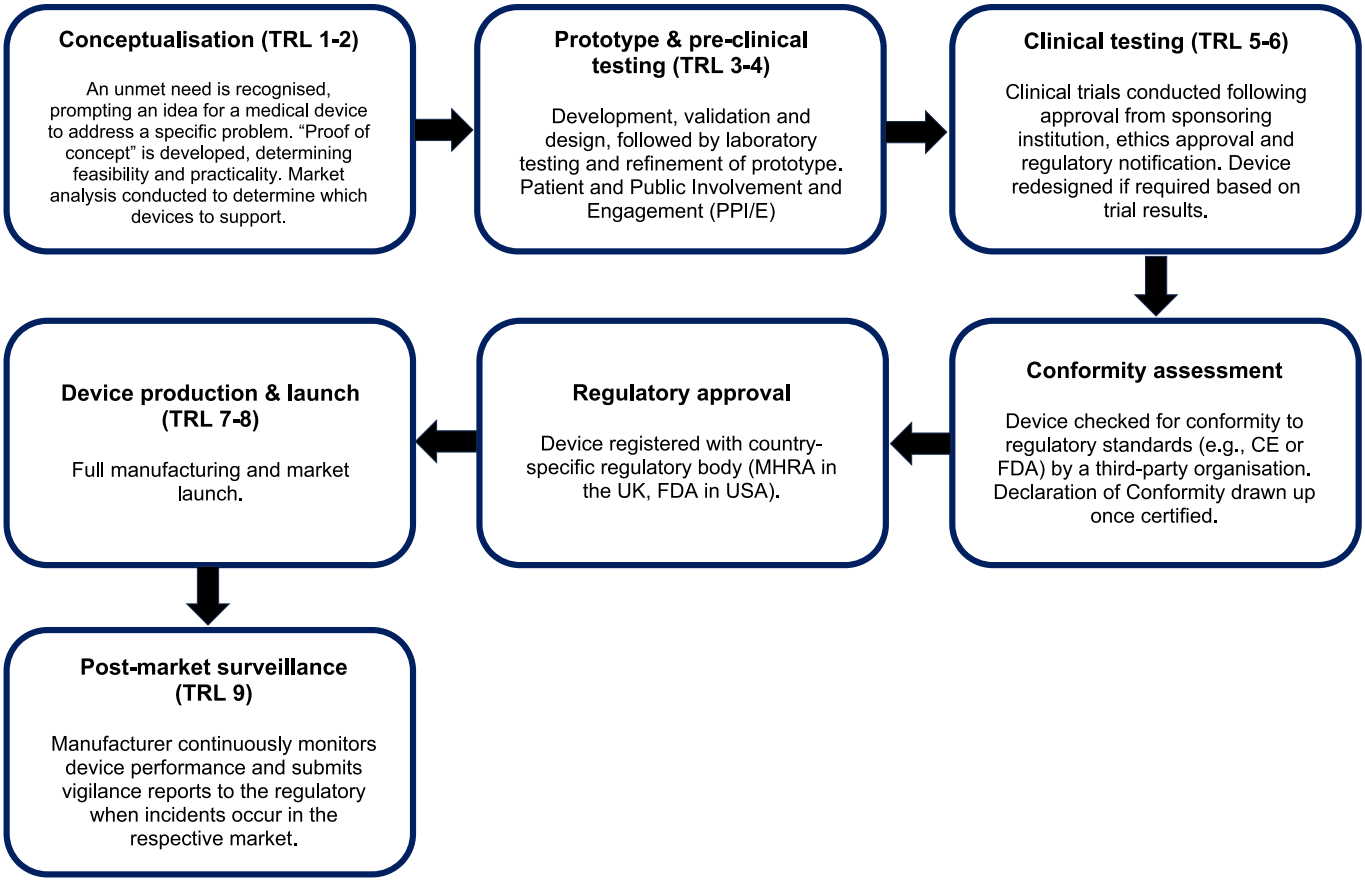

Fig. 1. Medical device development pathway. (Adapted from Guan et al [127]).

Table 1
A summary of important monitoring technology studies published since 2000.

Device/parameter	Study	Comparison	Gestation setting	Summary of results
Heart Rate (HR)	Murphy 2018 [99] (n = 100)	ECG vs PO	≥37 weeks DR	Time to first HR shorter for ECG vs PO (24 s vs 48 s)
	Murphy 2018 [100] (n = 92)	Auscultation vs ECG Auscultation vs PO	≥37 weeks DR	Time to determine HR using auscultation shorter than ECG (14 s vs 24 s) and PO (14 s vs 48 s) Auscultation underestimates HR compared to ECG
Pulse Oximetry (targeted oxygen saturations)	BOOST-II Collaborative Groups 2013 & 2016 [31,32] (n = 2448)	Lower (85–89 %) vs higher (91–95 %) target oxygen-saturation range	<28 weeks NICU (Recruitment stopped early when interim analysis showed increased rate of death at 36 weeks in lower-target group) <28 weeks NICU	Higher rate of death in lower-target group at 36 weeks and at discharge, increased rate of NEC, and reduced rate of ROP Increased risk of combined outcome of death or disability and of death alone at 2 years in lower-target group
	Schmidt 2013 [33] (n = 1201)	Lower (85–89 %) vs higher (91–95 %) target oxygen-saturation		No significant difference in rate of death or disability at 18 months
Respiratory function monitoring (RFM)	Schmolzer 2012 [47] (n = 49)	Visible vs masked RFM during neonatal mask resuscitation	<32 weeks DR	Reduced mask leak and lower rate of excessive tidal volumes
	Sarrato 2019 [49] (n = 106)	Visible vs masked RFM during neonatal non-invasive PPV	<32 weeks DR	Lower rate of excessive PIP values and tidal volumes
	Van Zanten 2021 [101] (n = 288)	Visible vs masked RFM during neonatal non-invasive PPV	<28 weeks DR	No effect on proportion of inflations within 4–8 mL/kg tidal volume range Reduced IVH and/or cystic PVL
Near Infrared Spectroscopy (NIRS)	Hyttel-Sorensen 2015 [102] (n = 166)	Cerebral NIRS with dedicated treatment guideline vs blinded NIRS with standard care	<28 weeks Unknown	Significantly reduced median burden of hypoxia and hyperoxia No significant difference in death or cerebral injury at term
	Hansen 2023 [56] (n = 1579)	Cerebral NIRS-guided treatment vs usual care	<28 weeks NICU	No significant difference in death or cerebral injury at 36 weeks
	Pichler 2023 [55] (n = 607)	Cerebral NIRS with dedicated treatment guideline vs standard care	<32 weeks DR	No significant difference in death or cerebral injury at term

DR = delivery room, ECG = electrocardiogram, IVH = intraventricular haemorrhage, NEC = necrotising enterocolitis, NICU = neonatal intensive care unit, PIP = positive inspiratory pressure, PO = pulse oximetry, PPV = positive pressure ventilation, PVL = periventricular leukomalacia, ROP = retinopathy of prematurity.

surface to measure variations in blood circulation volume in order to calculate heart rate. Video PPG (vPPG) is similar to rPPG, except that images are analysed using algorithms to measure heart rate. Observational and experimental studies have been performed in both term and preterm newborns, reporting a high correlation between rPPG/vPPG and ECG [15,17]. Movement artefacts can impact these technologies, although advanced extraction algorithms, higher resolution cameras and better sensor fixation can improve this.

Doppler ultrasound for heart rate assessment has been shown to correlate well with ECG measurements of heart rate and is faster compared to auscultation and palpation, with a suggestion that it may have greater utility than PO in the initial minutes of life [15,17]. However, it requires the user to maintain a good contact for a signal and is more bulky than more commonly used devices.

Other heart rate measurement technologies include piezoelectric and capacitive sensors, electrical velocimetry, digital stethoscopes and laser Doppler vibrometers. There are only a few small observational studies evaluating these devices with mixed success, identifying the need for further work prior to clinical implementation [15,17].

4.2. Peripheral oxygen saturations

Transmission mode PO devices have been used for indirect monitoring of peripheral blood oxygen saturation (SpO_2) since the 1980s, using a light emitter and photodetector at opposite ends of a thin body part to measure light transmission and calculate SpO_2 using proprietary calibration tables. PO was first recommended for use during newborn resuscitation within the 2010 ILCOR guidelines [22]. Additionally, PO screening for critical congenital heart defects in asymptomatic newborn babies has been found to be highly-specific and moderately-sensitive [23]. Early studies of PO devices in neonates in the 1980s had shown that they correlate with true arterial oxygen saturation (SaO_2) [24–26]. More recent studies with larger sample sizes have demonstrated that PO devices can underestimate SaO_2 values [27,28]. Other limitations of PO include reduced reliability in pigmented skin [29] and a possibility that SpO_2 is overestimated at lower oxygen saturations due to the presence of fetal haemoglobin [30], although it is possible to correct for this.

Transmission mode PO has been used in large randomised clinical trials (RCTs) targeting specific oxygen saturations in preterm infants, resulting in reductions in mortality and major morbidity in babies where targets are more consistently achieved [31–34]. However, during these studies researchers identified inaccuracies with the PO algorithm requiring correction [35], subsequently reporting better outcomes for preterm infants in the 91–95 % SpO_2 range [31].

Reflectance mode PO devices are less common than transmission mode and often aren't licensed for use in infants. They utilise a photodetector to measure light reflected back off body sites. Two small observational studies found good correlation between reflectance and transmission devices when measuring SpO_2 [36,37].

4.3. Temperature

Temperature is an important measure of neonatal care, especially for preterm infants in the first hour of life and subsequently in the NICU. Mercury-in-glass thermometers have traditionally been used in axillary and rectal positions to measure the 'gold standard' temperature, but their use is gradually declining with an increasing number of countries banning their use. Currently, digital thermometers placed in an axillary position are commonly used for measuring the temperature in neonates and several studies have found these to have good correlation with mercury-in-glass thermometers [38–40].

Electronic skin surface temperature probes are often used in an

intensive care setting to continuously measure both central and peripheral temperature. Whilst there is some evidence to show that these readings correlate well with axillary and rectal temperatures, their accuracy can be questionable due to factors such as ambient temperature, contact adequacy and peripheral perfusion status [41–43].

5. Supplementary bedside monitoring technologies

5.1. Respiratory function monitoring (Table 2)

There are now several respiratory function monitoring (RFM) devices available to support ventilation and guide tidal volume delivery. RFM has been shown to reduce mask leak [44–47], improve tidal volume and positive inspiratory pressure delivery [47–49], and is considered by clinicians to be a helpful tool when sufficient training is provided [50,51]. A recent systematic review and meta-analysis identified three RCTs including a total of 442 patients which compared RFM and clinical assessment versus clinical assessment alone [52]. There was no clinically significant difference in the primary outcome of percentage of inflations within a target tidal volume range of 4–8 mL/kg. Additionally, RFM has not demonstrated a difference in the need of surfactant administration or intubation in the first 72 h of life [49]. There was no impact on death before discharge from hospital, but a significant reduction in any brain injury and intraventricular haemorrhage in preterm infants was noted [52]. Better designed clinical trials are needed to establish any benefits of this technology.

Table 2
A summary of important respiratory technology studies published since 2000.

Device/parameter	Study	Comparison	Gestation setting	Summary of results
Volume-targeted ventilation (VTV)	D'Angio 2005 [103] (n = 212)	PRVC vs pressure-limited SIMV	24–32 weeks NICU	No significant difference in proportion of infants alive and extubated at 14 days or duration of mechanical ventilation
	Singh 2006 [104] (n = 109)	Volume-controlled vs time-cycled pressure-limited ventilation	24–31 weeks NICU	Significantly reduced time to reach alveolar-arterial oxygen gradient <100 mmHg or MAP of <8 cm H_2O in infants weighing 600-1000 g
	Liu 2011 [105] (n = 84)	SIPPV+VG vs HFOV vs IMV	27–35 weeks NICU	No significant difference in overall mortality, ventilation duration, BPD or brain injury Significantly shorter duration of mechanical ventilation in SIPPV+VG and HFOV vs IMV
Video laryngoscope (VL)	Moussa 2016 [106] (n = 213)	Intubation using VL vs DL (direct laryngoscopy)	NICU	Significantly higher success rate in VL group (75 % vs 63 %)
	Volz 2018 [107] (n = 101)	Intubation using VL vs DL	All gestations NICU	Significantly higher overall success rate in VL group (57 % vs 33 %), higher first attempt success rate (50 % vs 17 %)
Continuous positive airway pressure (CPAP) at birth	Morley 2008 [108] (n = 610)	Nasal CPAP vs intubation at birth	DR <29 weeks	No significant difference in rates of death or BPD at 36 weeks. Significantly fewer infants in the nasal CPAP group required oxygen or respiratory support at 28 days of age
	SUPPORT Study Group 2010 [109] (n = 1316)	CPAP at birth vs intubation and surfactant within 1 h of birth Early CPAP (within 30 min of birth) vs prophylactic surfactant	DR & NICU <28 weeks	No significant difference in rates of death or BPD at 36 weeks. CPAP group required intubation or postnatal steroids for BPD less frequently and required fewer days of mechanical ventilation No significant difference in need for mechanical ventilation in first 5 days of life, death and type of survival at 28 days of life and 36 weeks corrected age
	Sandri 2010 [110] (n = 208)	Initial bubble CPAP vs intubate-surfactant-extubate to CPAP (ISX) vs prophylactic surfactant with mechanical ventilation	DR <28 weeks	No significant difference in relative risk of BPD or death, mortality or other complications of prematurity. In CPAP group, 48 % were managed without intubation and ventilation, and 54 % without surfactant administration
	Dunn 2011 [111] (n = 648)		DR 26–29 + 6 weeks	
High-frequency oscillatory ventilation (HFOV)	Moriette 2001 [112] (n = 273)	HFOV vs SIMV	NICU 24–29 weeks	No difference in pulmonary outcome Twofold reduction in requirement for >1 dose of surfactant No difference in combined rate of death or BPD at 36 weeks Higher rate of survival without BPD Shorter duration of ventilation
	Johnson 2002 [113] (n = 797)	HFOV vs SIMV	NICU 23–28 weeks	No difference in rates of BPD, mortality at discharge, or neurodevelopmental outcome at 18–24 months
	Courtney 2002 [114] (n = 498)	HFOV vs IMV	NICU <28 weeks	No difference in combined rate of death or BPD at 36 weeks Reduced combined rate of death or BPD Shorter duration of mechanical ventilation
	Van Reempts 2003 [115] (n = 300)	HFOV vs IMV	<32 weeks	Reduced rate of surfactant requirement, ROP and moderate or severe neurological disability
	Schreiber 2003 [116] (n = 207)	HFOV vs SIMV	NICU <34 weeks	
	Sun 2014 [117] (n = 366)		NICU <32 weeks	

BPD = bronchopulmonary dysplasia, DR = delivery room, IMV = intermittent mandatory ventilation, NICU = neonatal intensive care unit, ROP = retinopathy of prematurity, SIMV = synchronised intermittent mandatory ventilation.

5.2. Near InfraRed spectroscopy (Table 2)

Near InfraRed Spectroscopy (NIRS) is used in the paediatric intensive care setting as a portable and non-invasive measure of oxygenation, particularly in post-operative cardiac patients [53,54]. NIRS use in neonatal care is currently limited and has traditionally been used as a research device. Two recent large multi-centre randomised controlled trials recruiting infants <32 weeks gestation comparing a cerebral NIRS monitoring protocol-driven management strategy soon after birth did not find any difference in death or brain injury compared to standard care [55,56]. A systematic review aiming to determine whether NIRS monitoring commenced before 6 h of age in infants with HIE could predict clinical outcomes found that there was very little standardised data present to draw any meaningful conclusions or to perform a meta-analysis [57]. Despite these challenges, on-going and planned studies in the neonatal population are aiming to establish any potential benefits of NIRS.

5.3. Amplitude integrated electroencephalography

Amplitude integrated electroencephalography (aEEG) is a crucial element of neonatal intensive care monitoring, aiding in the diagnosis of HIE and monitoring of seizure activity. It has been shown to correlate with later neurodevelopmental outcomes in both term and preterm infants [58–61]. Its utility in monitoring of seizures is less clear, as it has been shown to have relatively low and variable sensitivity with a lower seizure detection rate compared to conventional EEG [62,63]. Advances in EEG monitoring with seizure detection algorithms have demonstrated the possibility of automatic detection of clinical seizures, although further trials are needed to establish if this improves outcomes [64].

5.4. Transcutaneous CO_2 monitoring

Under stable haemodynamic conditions, capillary pCO_2 correlates well with arterial pCO_2 [65]. This principle underlies transcutaneous CO_2 ($TcPCO_2$) monitoring, which can be used as a method of continuous assessment of ventilation whilst minimising infant handling and blood sampling. A large retrospective cohort study including 5726 blood gas measurements and clinical outcomes for 123 ventilated neonates found a moderate agreement between $TcPCO_2$ and arterial PCO_2, and a reduction in blood gas monitoring frequency without affecting the duration of mechanical ventilation or clinical outcomes at discharge [66]. Newer devices appear more practical for use in the NICU and during neonatal transport, but well-designed studies exploring the impact on care have yet to be undertaken.

5.5. Continuous glucose monitoring

High-risk infants, particularly preterm and HIE infants are at risk of both hyper- and hypoglycaemia, and hence may benefit from continuous glucose monitoring (CGM).

CGM. Neonatal hypoglycaemia is associated with visual-motor impairment, executive dysfunction, and neurodevelopmental impairment in childhood [67], and hyperglycaemia in very preterm infants is associated with higher mortality, intraventricular haemorrhage (IVH) and retinopathy of prematurity (ROP) [68]. Studies in preterm and very-low-birthweight infants have shown that CGM can reduce the duration of hypoglycaemic and hyperglycaemic episodes and increase the time spent in an euglycaemic state [69–71], although they are costly, invasive and require calibration checks. These findings support the need for more well-designed prospective studies investigating the role of CGM in managing high-risk infants and if it can improve outcomes.

5.6. Point-of-care diagnostic imaging

There are many imaging modalities available at the cotside, but most require training and are subject to both intra- and inter-user variability and subsequent interpretation.

Cranial ultrasound is a frequently used, safe, inexpensive, and rapid method of assessing brain anatomy and injury, has been shown to have good neurodevelopmental prognostic value, and correlates well with MRI findings [72,73].

Functional echocardiography is a valuable tool for the management of the sick newborn infant. It allows for formal assessment of haemodynamic status, providing useful information in the context of conditions such as shock, hypotension, patent ductus arteriosus and persistent pulmonary hypertension of the newborn [74].

Lung ultrasound is a comparatively new imaging technique and can be used to aid in the diagnosis of several neonatal lung disorders, with the added benefit of decreasing radiation doses by reducing the need for chest radiographs. Systematic reviews have highlighted its utility in diagnosis of respiratory distress syndrome [75], pneumothorax [76], and evaluation of need for mechanical ventilation or surfactant [77]. Widespread adoption is yet to take place, however, and it is important that a standardised approach to training is taken to ensure uniformity in reporting.

6. Interventional technologies

6.1. Delivery room continuous positive airway pressure (Table 2)

Neonatal tracheal intubation is now less commonly performed, as practice has changed to less invasive methods of respiratory support [78]. There is a greater focus on providing initial effective mask ventilation in preterm infants, followed by consideration of early continuous positive airway pressure (CPAP) within the delivery room. In 2021, the Vermont Oxford Network reported that the rates of nasal CPAP during initial resuscitation increased from 35 % of infants in 2011 to 62 % of infants in 2019; this was based on an evaluation of 427,622 infants born at 22–29 weeks gestation from over 1400 hospitals in the Network [79].

A 2013 systematic review comparing nasal CPAP initiated at birth compared to intubation in preterm infants of <32 weeks identified four RCTs. Although there was no significant difference in mortality or BPD rates as separate outcomes, the composite outcome of mortality and BPD showed a significant benefit (RR 0.9, 95 % CI 0.83–0.98) and a number needed to treat of 25 [80].

6.2. Nasal high-flow therapy

A recent systematic review evaluated nasal high-flow therapy (nHF) for primary respiratory support in preterm infants [81]. Eleven studies compared nHF to CPAP: there was no difference in risk of death or BPD, and it is likely that nHF resulted in a need for escalation in ventilatory support within 72 h of trial entry. There was no increase in rate of mechanical ventilation, and a reduction in pneumothorax and nasal trauma. Four studies compared nHF to nasal intermittent positive pressure ventilation (NIPPV): there was no difference in risk of death or BPD, but there was a reduction in nasal trauma. Despite this lack of meaningful improvements in outcomes, the use of nHF has increased significantly in recent years [78].

6.3. Video laryngoscopy (Table 2)

Video laryngoscopy (VL) is becoming more frequently utilised within the neonatal setting, especially for difficult intubations and where Less Invasive Surfactant Administration (LISA) is required. A recent systematic review of eight RCTs comparing VL versus direct laryngoscopy (DL) found low-certainty evidence that VL may increase the success of intubation at first attempt and result in fewer intubation attempts, but may not reduce the time required for successful intubation [82]. There was also moderate-certainty evidence that VL results in less airway trauma. As experience with intubations declines with increasingly less

invasive methods of respiratory support being used, video laryngoscopy with real-time supervisor feedback could be useful as a training modality [83].

6.4. Volume-targeted ventilation (Table 2)

Volume-targeted ventilation (VTV) to reduce ventilator associated lung injury is currently recommended, especially for preterm infants. Use of VTV, compared to pressure-limited ventilation, reduces rates of BPD, pneumothoraces, hypocarbia, brain injury and duration of ventilation [84,85]. There remains significant variation in respiratory outcomes for preterm infants [5], and this may be related to the large number of ventilatory support devices in use. For example, in the UK, there are 21 different types of ventilators in use of which 19 have the ability to provide VTV (unpublished survey by authors).

6.5. Automated oxygen titration

Targeting specific SpO_2 in preterm infants reduces mortality and morbidity [31], but can be difficult to achieve as it requires manual adjustments of inspired oxygen which can be labour intensive [86]. To address this, numerous algorithms have been developed and integrated into ventilation devices to automate this process. Many studies have demonstrated better targeted saturation compliance using these automated systems, but these have yet to translate into meaningful clinical outcomes [87].

6.5.1. High frequency oscillatory ventilation (Table 2)

High frequency oscillatory ventilation (HFOV) has been studied in neonatal patients with the aim to reduce lung injury. A systematic review of elective HFOV versus conventional ventilation in preterm infants with respiratory distress syndrome concluded that there was no evidence of effect on mortality, IVH or neurodevelopment [88]. There was a significant reduction in BPD in survivors at term equivalent age, although this effect was inconsistent across studies. There was also a greater risk of pulmonary air leaks with using HFOV.

6.5.2. Therapeutic hypothermia (Table 3)

Since the first study employing therapeutic hypothermia (TH) in neonates with HIE was published in 2005 [89], several randomised controlled trials have been conducted to assess its efficacy in this population. A recent systematic review of RCTs in neonates with HIE undergoing TH versus standard care demonstrated a pooled neonatal mortality risk of 0.87 (95 % CI 0.75–1.00), risk of neurological disability at 18–24 months of 0.62 (95 % CI 0.52–0.75) and risk of cerebral palsy at 18–24 months of 0.63 (95 % CI 0.46–0.85) [90]. Observational population studies have demonstrated reductions in mortality for infants undergoing TH for HIE, decreasing from 17.5 % to 12.3 % between 2010 and 2016 [8]. However, this study also demonstrated increasing use of TH for more preterm infants and those with mild HIE outside of the evidence base. These populations are now being enrolled in multiple RCTs to explore any potential benefit (or harm).

Although the neurodevelopmental benefits of TH have been clearly demonstrated, the challenge to provide it consistently and in a timely manner within different settings persists. A recent UK-wide retrospective cohort study of infants ≥36 weeks gestation with moderate or severe HIE found that birth in a centre which provided passive TH (i.e., non-technological) was associated with suboptimal hypothermic treatment and reduced seizure-free survival compared to centres using active TH (i.e., technology delivered) [91]. In the UK, The British Association of Perinatal Medicine (BAPM)'s 2020 publication *Therapeutic Hypothermia for Neonatal Encephalopathy - a Framework for Practice* recommends that all neonatal units regardless of their designation should be able to commence active TH, although this must not delay transfer [92].

7. Artificial intelligence (AI)

With the vast amount of information generated by neonatal databases and monitoring devices, the potential for artificial intelligence to inform prediction models and provide targeted treatment is immense. Careful consideration of the role of AI in neonatal care is needed but the huge potential to advance and support treatments offers significant opportunities. Exploration of this field is beyond the scope of this review and readers are directed to a recent review of this topic [93].

8. The role of human factors in design and development

Human factors/ergonomics (HFE) involves the application of psychological and physiological principles to product engineering and design. It is seen as a crucial but often neglected component of device development. Cognitive ergonomics is one of the main areas of HFE research and may be the most relevant to medical professionals during the product design. It includes topics such as mental or cognitive workload, decision-making and skilled performance in the context of human-computer interactions. By applying a HFE approach to medical product development, additional user requirements can be identified which might otherwise remain hidden, as evidenced by a recent study which used this method to aid in the development of a neonatal device clinical interface [94].

Table 3
A summary of important cooling technology studies published since 2000.

Device/parameter	Study	Comparison	Gestation setting	Summary of results
Therapeutic hypothermia (TH) for moderate to severe HIE	Gluckman 2005 [89] (n = 218)	Head cooling for 72 h vs standard care	NICU ≥37 weeks	No difference in combined rate of death or severe disability at 18 months
	Shankaran 2005, 2012, 2012 [118–120] (n = 208)	Whole-body TH for 72 h vs standard care	NICU ≥35 weeks	Reduced risk of death or major sensorineural disability at 2 years and at 6–7 years Reduced brain injury on MRI
	Azzopardi 2009, 2014 [121,122]; Rutherford 2010 [123] (n = 325)	Whole-body TH for 72 h vs standard care	NICU ≥36 weeks	No difference in combined rate of death or severe disability at 18 months Reduced brain injury on MRI Improved neurocognitive outcomes at 6–7 years
	Jacobs 2011 [124], Cheong 2012 [125] (n = 221)	Whole-body TH for 72 h vs standard care	NICU ≥35 weeks	Reduced risk of death or major sensorineural disability at 2 years Reduced brain injury on MRI
	Thayyil 2022 [126] (n = 408)	Whole-body TH for 72 h vs standard care	NICU ≥36 weeks	No difference in rate of death or disability at 18 months Significantly increased rate of death

HIE = hypoxic-ischaemic encephalopathy, MRI = magnetic resonance imaging, NICU = neonatal intensive care unit.

9. Emerging neonatal technologies

Despite the challenges of developing new technologies for neonatal patients, there are some exciting developments in this field.

9.1. Genetic testing

Genetic testing has traditionally been utilised to diagnose rare conditions and inform their management on a long-term basis, and its usage on the NICU has been limited due to long wait times to diagnosis. With an increasing number of conditions being available for screening, shorter times to diagnosis, and the emergence of whole genome sequencing and point-of-care genetic testing, its application to the NICU population has become more relevant.

Whole genome sequencing and targeted neonatal gene panels can support rapid diagnosis, with turnaround times being as short as 4 days [95,96]. A point-of-care, swab-based genetic test device has recently been developed, which can detect the m.1555 A > G variant implicated in development of deafness in babies who are treated with gentamicin. It allows for results to be obtained in under 30 min, and alternative antibiotics can be given [97]. This technology could help prevent gentamicin-induced hearing impairment in those with the high-risk genetic variant.

9.2. Advanced multimodal brain monitoring

Neonatal brain monitoring devices under development could allow us to have a greater understanding of the newborn/developing brain, identifying biomarkers of brain injury, and the impact care pathways can have when aiming to reduce brain injury. Many of these developments focus on the use of optical pathways, such as NIRS devices, allowing the metabolic, tissue oxygenation and cerebral autoregulation of the brain to be monitored. These devices could provide vital information in the management of preterm infants and infants with HIE [98].

10. Conclusion

Neonatal medicine relies heavily on advances in medical technology to optimise care and improve survival. Unfortunately, many medical devices have not been developed specifically for this unique population, instead relying on clinical trials using devices designed for children and adults. Whilst there are promising technologies which have made it into the clinical arena, there are many which have not or remain as research-only technologies. We need to invest more resource and expertise to develop devices for the unique environment of the delivery room and NICU if we are to reduce the significant burden of mortality and life-long morbidities in this high-risk population.

CRediT authorship contribution statement

Syed Taha: Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Rosalind B. Simpson:** Investigation, Data curation. **Don Sharkey:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

DS is supported by the NIHR: National Institute for Health and Care Research (NIHR) Children and Young People MedTech Co-operative (CYP MedTech). DS has received funding for technology development from the Medical Research Council, NIHR and Action Medical Research, and is a non-executive director of SurePulse Medical who are developing monitoring solutions for neonatal care. ST is funded by the NIHR i4i funding programme on grant NIHR204171/2022. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or of the Department of Health.

References

[1] K.R. Paulson, A.M. Kamath, T. Alam, K. Bienhoff, G.G. Abady, J. Abbas, et al., Global, regional, and national progress towards sustainable development goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the global burden of disease study 2019, Lancet 398 (10303) (2021) 870–905.
[2] E.O. Ohuma, A.-B. Moller, E. Bradley, S. Chakwera, L. Hussain-Alkhateeb, A. Lewin, et al., National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis, Lancet 402 (10409) (2023) 1261–1271.
[3] R.M. Patel, Short- and long-term outcomes for extremely preterm infants, Am. J. Perinatol. 33 (3) (2016) 318–328.
[4] C. Siffel, K.D. Kistler, J.F.M. Lewis, S.P. Sarda, Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review, J. Matern. Fetal Neonatal Med. 34 (11) (2021) 1721–1731.
[5] K. Tng Chang, P. Caroline, A. Saleh, S. Lisa, S. Don, Respiratory management and outcomes in high-risk preterm infants with development of a population outcome dashboard, Thorax (2023). Published online first (thorax-2023-220174).
[6] C.O.K. Gale, S. Jawad, S. Uthaya, N. Modi, Brain injury occurring during or soon after birth: annual incidence and rates of brain injuries to monitor progress against the national maternity ambition 2018 and 2019 national data, Neonatal. Data Anal. Unit (2021). https://spiral.imperial.ac.uk/handle/10044/1/87336. accessed 4/11/2023.
[7] A. Alsaied, N. Islam, L. Thalib, Global incidence of necrotizing enterocolitis: a systematic review and meta-analysis, BMC Pediatr. 20 (1) (2020) 344.
[8] L. Shipley, C. Gale, D. Sharkey, Trends in the incidence and management of hypoxic-ischaemic encephalopathy in the therapeutic hypothermia era: a national population study, Arch. Dis. Child. Fetal Neonatal Ed. 106 (5) (2021) 529–534.
[9] C. Section On, S. Cardiac, On O. Section, Off-label use of medical devices in children, Pediatrics 139 (1) (2017).
[10] T.J. Hwang, A.S. Kesselheim, F.T. Bourgeois, Postmarketing trials and pediatric device approvals, Pediatrics 133 (5) (2014) e1197–e1202.
[11] S. Quazi, C. Narang, J.C. Espinoza, F.T. Bourgeois, Characteristics and results of pediatric medical device studies: 2017–2022, Pediatrics 152 (3) (2023).
[12] M. Fogarty, D.A. Osborn, L. Askie, A.L. Seidler, K. Hunter, K. Lui, et al., Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis, Am. J. Obstet. Gynecol. 218 (1) (2018) 1–18.
[13] A. Katheria, H.C. Lee, R. Knol, L. Irvine, S. Thomas, A review of different resuscitation platforms during delayed cord clamping, J. Perinatol. 41 (7) (2021) 1540–1548.
[14] J.M. Perlman, J. Wyllie, J. Kattwinkel, M.H. Wyckoff, K. Aziz, R. Guinsburg, et al., Part 7: neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations, Circulation 132 (16 Suppl 1) (2015) S204–S241.
[15] P.A. Johnson, P.Y. Cheung, T.F. Lee, M. O'Reilly, G.M. Schmolzer, Novel technologies for heart rate assessment during neonatal resuscitation at birth - a systematic review, Resuscitation 143 (2019) 196–207.
[16] E. Phillipos, A.L. Solevag, G. Pichler, K. Aziz, S. van Os, M. O'Reilly, et al., Heart rate assessment immediately after birth, Neonatology 109 (2) (2016) 130–138.
[17] O. Anton, R. Fernandez, E. Rendon-Morales, R. Aviles-Espinosa, H. Jordan, H. Rabe, Heart rate monitoring in newborn babies: a systematic review, Neonatology 116 (3) (2019) 199–210.
[18] R.J. Kopotic, W. Lindner, Assessing high-risk infants in the delivery room with pulse oximetry, Anesth. Analg. 94 (1 Suppl) (2002) S31–S36.
[19] J.T. House, R.R. Schultetus, N. Gravenstein, Continuous neonatal evaluation in the delivery room by pulse oximetry, J. Clin. Monit. 3 (2) (1987) 96–100.
[20] I. Dimich, P.P. Singh, A. Adell, M. Hendler, N. Sonnenklar, M. Jhaveri, Evaluation of oxygen saturation monitoring by pulse oximetry in neonates in the delivery system, Can. J. Anaesth. 38 (8) (1991) 985–988.
[21] P. Meier-Stauss, H.U. Bucher, R. Hurlimann, V. Konig, R. Huch, Pulse oximetry used for documenting oxygen saturation and right-to-left shunting immediately after birth, Eur. J. Pediatr. 149 (12) (1990) 851–855.
[22] C.C. Roehr, G. Hansmann, T. Hoehn, C. Buhrer, The 2010 Guidelines on Neonatal Resuscitation (AHA, ERC, ILCOR): similarities and differences—what progress has been made since 2005? Klin. Padiatr. 223 (5) (2011) 299–307.
[23] S. Thangaratinam, K. Brown, J. Zamora, K.S. Khan, A.K. Ewer, Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis, Lancet 379 (9835) (2012) 2459–2464.
[24] R. Ramanathan, M. Durand, C. Larrazabal, Pulse oximetry in very low birth weight infants with acute and chronic lung disease, Pediatrics 79 (4) (1987) 612–617.
[25] M.S. Jennis, J.L. Peabody, Pulse oximetry: an alternative method for the assessment of oxygenation in newborn infants, Pediatrics 79 (4) (1987) 524–528.
[26] M. Durand, R. Ramanathan, Pulse oximetry for continuous oxygen monitoring in sick newborn infants, J. Pediatr. 109 (6) (1986) 1052–1056.
[27] R.J. Rosychuk, A. Hudson-Mason, D. Eklund, T. Lacaze-Masmonteil, Discrepancies between arterial oxygen saturation and functional oxygen saturation measured with pulse oximetry in very preterm infants, Neonatology 101 (1) (2012) 14–19.
[28] D. Gerstmann, R. Berg, R. Haskell, C. Brower, K. Wood, B. Yoder, et al., Operational evaluation of pulse oximetry in NICU patients with arterial access, J. Perinatol. 23 (5) (2003) 378–383.
[29] C. Shi, M. Goodall, J. Dumville, J. Hill, G. Norman, O. Hamer, et al., The accuracy of pulse oximetry in measuring oxygen saturation by levels of skin pigmentation: a systematic review and meta-analysis, BMC Med. 20 (1) (2022) 267.

[30] E. Pritisanac, B. Urlesberger, B. Schwaberger, G. Pichler, Accuracy of pulse oximetry in the presence of fetal hemoglobin-a systematic review, Children (Basel) 8 (5) (2021).
[31] W. Tarnow-Mordi, B. Stenson, A. Kirby, E. Juszczak, M. Donoghoe, S. Deshpande, et al., Outcomes of two trials of oxygen-saturation targets in preterm infants, N. Engl. J. Med. 374 (8) (2016) 749–760.
[32] B.J. Stenson, W.O. Tarnow-Mordi, B.A. Darlow, J. Simes, E. Juszczak, L. Askie, et al., Oxygen saturation and outcomes in preterm infants, N. Engl. J. Med. 368 (22) (2013) 2094–2104.
[33] B. Schmidt, R.K. Whyte, E.V. Asztalos, D. Moddemann, C. Poets, Y. Rabi, et al., Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial, JAMA 309 (20) (2013) 2111–2120.
[34] L.M. Askie, D.J. Henderson-Smart, L. Irwig, J.M. Simpson, Oxygen-saturation targets and outcomes in extremely preterm infants, N. Engl. J. Med. 349 (10) (2003) 959–967.
[35] E.D. Johnston, B. Boyle, E. Juszczak, A. King, P. Brocklehurst, B.J. Stenson, Oxygen targeting in preterm infants using the Masimo SET radical pulse oximeter, Arch. Dis. Child. Fetal Neonatal Ed. 96 (6) (2011) F429–F433.
[36] K. Faisst, W. Hannon, J.S. Jørgensen, V. König, H.U. Bucher, A. Huch, et al., Reflectance pulse oximetry in neonates, Eur. J. Obstet. Gynecol. Reprod. Biol. 61 (2) (1995) 117–122.
[37] A. Kugelman, Y. Wasserman, F. Mor, L. Goldinov, Y. Geller, D. Bader, Reflectance pulse oximetry from core body in neonates and infants: comparison to arterial blood oxygen saturation and to transmission pulse oximetry, J. Perinatol. 24 (6) (2004) 366–371.
[38] R. Kitsommart, S. Phatthanasiriwetin, Accuracy and precision of digital thermometer in neonatal temperature measurement, Siriraj Med. J. 57 (5) (2005) 128–131.
[39] S. Uslu, H. Ozdemir, A. Bulbul, S. Comert, F. Bolat, E. Can, et al., A comparison of different methods of temperature measurements in sick newborns, J. Trop. Pediatr. 57 (6) (2011) 418–423.
[40] A. Sganga, R. Wallace, E. Kiehl, T. Irving, L. Witter, A comparison of four methods of normal newborn temperature measurement, MCN Am. J. Matern. Child Nurs. 25 (2) (2000) 76–79.
[41] R.D. van der Spek, R.A. van Lingen, D. van Zoeren-Grobben, Body temperature measurement in VLBW infants by continuous skin measurement is a good or even better alternative than continuous rectal measurement, Acta Paediatr. 98 (2) (2009) 282–285.
[42] D. Schafer, S. Boogaart, L. Johnson, C. Keezel, L. Ruperts, K.J. Vander Laan, Comparison of neonatal skin sensor temperatures with axillary temperature: does skin sensor placement really matter? Adv. Neonatal Care 14 (1) (2014) 52–60.
[43] B. Barekatain, A. Sadeghnia, M. Johari, M. Marofi, N. Tavakoli-Fard, M. Mehrkash, Which site is better for skin sensor temperature probe in newborns under open care system for prevention of hypo - hyperthermia, Int. J. Prev. Med. 13 (1) (2022) 132.
[44] B. Schwaberger, G.M. Schmolzer, C. Binder, W. Muller, B. Urlesberger, G. Pichler, Using respiratory function monitors affects mask leak during simulated neonatal resuscitation, Resuscitation 83 (Suppl. 1) (2012), e83.
[45] F.E. Wood, C.J. Morley, J.A. Dawson, P.G. Davis, A respiratory function monitor improves mask ventilation, Arch. Dis. Child. Fetal Neonatal Ed. 93 (5) (2008) f380–f381.
[46] E. O'Currain, M. Thio, J.A. Dawson, S.M. Donath, P.G. Davis, Respiratory monitors to teach newborn facemask ventilation: a randomised trial, Arch. Dis. Child. Fetal Neonatal Ed. 104 (6) (2019) F582–F586.
[47] G.M. Schmölzer, C.J. Morley, C. Wong, J.A. Dawson, C.O. Kamlin, S.M. Donath, et al., Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study, J. Pediatr. 160 (3) (2012) 377–381, e2.
[48] M. Kelm, S.K. Dold, J. Hartung, J. Breckwoldt, G. Schmalisch, C.C. Roehr, Manual neonatal ventilation training: a respiratory function monitor helps to reduce peak inspiratory pressures and tidal volumes during resuscitation, J. Perinat. Med. 40 (5) (2012) 583–586.
[49] G. Zeballos Sarrato, M. Sanchez Luna, S. Zeballos Sarrato, A. Perez Perez, I. Pescador Chamorro, J.M. Bellon Cano, New strategies of pulmonary protection of preterm infants in the delivery room with the respiratory function monitoring, Am. J. Perinatol. 36 (13) (2019) 1368–1376.
[50] A. Dalley, K. Hodgson, J. Dawson, M. Tracy, P. Davis, M. Thio, The NEOTRAIN study: introducing a novel respiratory function monitor for neonatal resuscitation training, J. Paediatr. Child Health 59 (Supplement 1) (2023) 70.
[51] K.L.A.M. Kuypers, H.A. van Zanten, V. Heesters, O. Kamlin, L. Springer, G. Lista, et al., Resuscitators' opinions on using a respiratory function monitor during neonatal resuscitation, Acta Paediatr. (Oslo, Norway : 1992) 112 (1) (2023) 63–68.
[52] S.M. de Medeiros, A. Mangat, G.R. Polglase, G.Z. Sarrato, P.G. Davis, G. M. Schmölzer, Respiratory function monitoring to improve the outcomes following neonatal resuscitation: a systematic review and meta-analysis, Arch. Dis. Child. Fetal Neonatal Ed. 107 (6) (2022) 589–596.
[53] K.L. Zaleski, B.D. Kussman, Near-infrared spectroscopy in pediatric congenital heart disease, J. Cardiothorac. Vasc. Anesth. 34 (2) (2020) 489–500.
[54] F. Desmond, S. Namachivayam, Does near-infrared spectroscopy play a role in paediatric intensive care? BJA Edu. 16 (8) (2015) 281–285.
[55] G. Pichler, K. Goeral, M. Hammerl, T. Perme, E.M. Dempsey, L. Springer, et al., Cerebral regional tissue oxygen saturation to guide oxygen delivery in preterm neonates during immediate transition after birth (COSGOD III): multicentre randomised phase 3 clinical trial, BMJ 380 (2023), e072313.
[56] M.L. Hansen, A. Pellicer, S. Hyttel-Sorensen, E. Ergenekon, T. Szczapa, C. Hagmann, et al., Cerebral oximetry monitoring in extremely preterm infants, N. Engl. J. Med. 388 (16) (2023) 1501–1511.
[57] A.A. Garvey, A.M. Pavel, D.M. Murray, G.B. Boylan, E.M. Dempsey, Does early cerebral near-infrared spectroscopy monitoring predict outcome in neonates with hypoxic Ischaemic encephalopathy? A systematic review of diagnostic test accuracy, Neonatology 119 (1) (2022) 1–9.
[58] E.P. Fogtmann, A.M. Plomgaard, G. Greisen, C. Gluud, Prognostic accuracy of electroencephalograms in preterm infants: a systematic review, Pediatrics 139 (2) (2017).
[59] F.M. Doandes, A.M. Manea, N. Lungu, T. Brandibur, D. Cioboata, O.C. Costescu, et al., The role of amplitude-integrated electroencephalography (aEEG) in monitoring infants with neonatal seizures and predicting their neurodevelopmental outcome, Children (Basel) 10 (5) (2023).
[60] M. Chandrasekaran, B. Chaban, P. Montaldo, S. Thayyil, Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuroprotection for hypoxic ischemic encephalopathy: a meta-analysis, J. Perinatol. 37 (6) (2017) 684–689.
[61] R.E. Spitzmiller, T. Phillips, J. Meinzen-Derr, S.B. Hoath, Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: a meta-analysis, J. Child Neurol. 22 (9) (2007) 1069–1078.
[62] A. Rakshasbhuvankar, S. Paul, L. Nagarajan, S. Ghosh, S. Rao, Amplitude-integrated EEG for detection of neonatal seizures: a systematic review, Seizure 33 (2015) 90–98.
[63] R. Falsaperla, B. Scalia, F. Giaccone, A. Suppiej, A. Pulvirenti, J. Mailo, et al., aEEG vs cEEG's sensivity for seizure detection in the setting of neonatal intensive care units: a systematic review and meta-analysis, Acta Paediatr. 111 (5) (2022) 916–926.
[64] A.M. Pavel, J.M. Rennie, L.S. de Vries, M. Blennow, A. Foran, D.K. Shah, et al., A machine-learning algorithm for neonatal seizure recognition: a multicentre, randomised, controlled trial, Lancet Child Adolesc. Health 4 (10) (2020) 740–749.
[65] R.J. Johns, W.J. Lindsay, R.H. Shepard, A system for monitoring pulmonary ventilation, Biomed. Sci. Instrum. 5 (1969) 119–121.
[66] S. Mukhopadhyay, R. Maurer, K.M. Puopolo, Neonatal transcutaneous carbon dioxide monitoring—effect on clinical management and outcomes, Respir. Care 61 (1) (2016) 90–97.
[67] R. Shah, J. Harding, J. Brown, C. McKinlay, Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis, Neonatology 115 (2) (2019) 116–126.
[68] C.P. Rath, M. Shivamallappa, S. Muthusamy, S.C. Rao, S. Patole, Outcomes of very preterm infants with neonatal hyperglycaemia: a systematic review and meta-analysis, Arch. Dis. Child. Fetal Neonatal Ed. 107 (3) (2022) 269–280.
[69] F. Uettwiller, A. Chemin, E. Bonnemaison, G. Favrais, E. Saliba, F. Labarthe, Real-time continuous glucose monitoring reduces the duration of hypoglycemia episodes: a randomized trial in very low birth weight neonates, PLoS One 10 (1) (2015), e0116255.
[70] A. Galderisi, A. Facchinetti, G.M. Steil, P. Ortiz-Rubio, F. Cavallin, W. V. Tamborlane, et al., Continuous glucose monitoring in very preterm infants: a randomized controlled trial, Pediatrics 140 (4) (2017).
[71] K. Beardsall, L. Thomson, C. Guy, I. Iglesias-Platas, M.M. van Weissenbruch, S. Bond, et al., Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial, Lancet Child Adolesc. Health. 5 (4) (2021) 265–273.
[72] K.J. Rademaker, C.S.P.M. Uiterwaal, F.J.A. Beek, Icv Haastert, A.F. Lieftink, F. Groenendaal, et al., Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm, Arch. Dis. Child. Fetal Neonatal Ed. 90 (6) (2005) F489–F493.
[73] S. Delin, K. Bošnjak Nađ, S. Martinec, D. Čokolić Petrović, A. Šimić Klarić, Bošnjak V. Mejaški, Prognostic value of cranial ultrasonography in comparison with magnetic resonance imaging in children with cerebral palsy: a population-based study, Acta Clin. Croat. 59 (2) (2020) 260–269.
[74] E. Nestaas, Neonatologist performed echocardiography for evaluating the newborn infant, Front. Pediatr. 10 (2022), 853205.
[75] H. Ma, W. Yan, J. Liu, Diagnostic value of lung ultrasound for neonatal respiratory distress syndrome: a meta-analysis and systematic review, Med. Ultrason. 22 (3) (2020) 325–333.
[76] Q. Fei, Y. Lin, T.M. Yuan, Lung ultrasound, a better choice for neonatal pneumothorax: a systematic review and meta-analysis, Ultrasound Med. Biol. 47 (3) (2021) 359–369.
[77] A. Razak, M. Faden, Neonatal lung ultrasonography to evaluate need for surfactant or mechanical ventilation: a systematic review and meta-analysis, Arch. Dis. Child. Fetal Neonatal Ed. 105 (2) (2020) 164–171.
[78] L. Sand, L. Szatkowski, T.C. Kwok, D. Sharkey, D.A. Todd, H. Budge, et al., Observational cohort study of changing trends in non-invasive ventilation in very preterm infants and associations with clinical outcomes, Arch. Dis. Child. Fetal Neonatal Ed. 107 (2) (2022) 150–155.
[79] Network VO, Delivery Room CPAP Increased 27% From 2011 to 2019 2021, 23/09/. Available from: https://public.vtoxford.org/nicu-by-the-numbers/delivery-room-cpap-increased-27-from-2011-to-2019/, 2023.
[80] G.M. Schmölzer, M. Kumar, G. Pichler, K. Aziz, M. O'Reilly, P.Y. Cheung, Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis, BMJ 347 (2013), f5980.

[81] D. Wilkinson, C. Andersen, C.P. O'Donnell, A.G. De Paoli, B.J. Manley, High flow nasal cannula for respiratory support in preterm infants, Cochrane Database Syst. Rev. 2 (2) (2016), Cd006405.
[82] K. Lingappan, J.L. Arnold, C.J. Fernandes, M. Pammi, Videolaryngoscopy versus direct laryngoscopy for tracheal intubation in neonates, Cochrane Database Syst. Rev. 6 (6) (2018), Cd009975.
[83] J. MacKinnon, C. McCoy, Use of video laryngoscopy versus direct laryngoscopy as a teaching tool for neonatal intubation: a systematic review, Can. J. Respir. Ther. 59 (2023) 111–116.
[84] W. Peng, H. Zhu, H. Shi, E. Liu, Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis, Arch. Dis. Child. Fetal Neonatal Ed. 99 (2) (2014) F158–F165.
[85] C. Klingenberg, K.I. Wheeler, N. McCallion, C.J. Morley, P.G. Davis, Volume-targeted versus pressure-limited ventilation in neonates, Cochrane Database Syst. Rev. 10 (10) (2017), Cd003666.
[86] A.C. van der Eijk, J. Dankelman, S. Schutte, H.J. Simonsz, B.J. Smit, An observational study to quantify manual adjustments of the inspired oxygen fraction in extremely low birth weight infants, Acta Paediatr. 101 (3) (2012) e97–104.
[87] V. Nair, P. Loganathan, M.K. Lal, T. Bachman, Automated oxygen delivery in neonatal intensive care, Front. Pediatr. 10 (2022), 915312.
[88] F. Cools, M. Offringa, L.M. Askie, Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants, Cochrane Database Syst. Rev. (3) (2015), Cd000104.
[89] P.D. Gluckman, J.S. Wyatt, D. Azzopardi, R. Ballard, A.D. Edwards, D.M. Ferriero, et al., Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial, Lancet 365 (9460) (2005) 663–670.
[90] J.L. Mathew, N. Kaur, J.M. Dsouza, Therapeutic hypothermia in neonatal hypoxic encephalopathy: a systematic review and meta-analysis, J. Glob. Health 12 (2022) 04030.
[91] L. Shipley, A. Mistry, D. Sharkey, Outcomes of neonatal hypoxic-ischaemic encephalopathy in centres with and without active therapeutic hypothermia: a nationwide propensity score-matched analysis, Arch. Dis. Child. Fetal Neonatal Ed. 107 (1) (2022) 6–12.
[92] Medicine BAfP, Therapeutic Hypothermia for Neonatal Encephalopathy - A Framework for Practice, 2020.
[93] T.C. Kwok, C. Henry, S. Saffaran, M. Meeus, D. Bates, D. Van Laere, et al., Application and potential of artificial intelligence in neonatal medicine, Semin. Fetal Neonatal Med. 27 (5) (2022), 101346.
[94] L. Pickup, A. Lang, L. Shipley, C. Henry, J. Carpenter, D. McCartney, et al., Development of a clinical Interface for a novel newborn resuscitation device: human factors approach to understanding cognitive user requirements, JMIR Hum. Factors 6 (2) (2019), e12055.
[95] A.M. D'Gama, M.C. Del Rosario, M.A. Bresnahan, T.W. Yu, M.H. Wojcik, P. B. Agrawal, Integrating rapid exome sequencing into NICU clinical care after a pilot research study, NPJ Genom. Med. 7 (1) (2022) 51.
[96] J.L. Maron, S. Kingsmore, B.D. Gelb, J. Vockley, K. Wigby, J. Bragg, et al., Rapid whole-genomic sequencing and a targeted neonatal gene panel in infants with a suspected genetic disorder, JAMA 330 (2) (2023) 161–169.
[97] J.H. McDermott, A. Mahaveer, R.A. James, N. Booth, M. Turner, K.E. Harvey, et al., Rapid point-of-care genotyping to avoid aminoglycoside-induced ototoxicity in neonatal intensive care, JAMA Pediatr. 176 (5) (2022) 486–492.
[98] K. Harvey-Jones, F. Lange, I. Tachtsidis, N.J. Robertson, S. Mitra, Role of optical neuromonitoring in neonatal encephalopathy-current state and recent advances, Front. Pediatr. 9 (2021), 653676.
[99] M.C. Murphy, L.D. Angelis, L.K. McCarthy, C.P.F. O'Donnell, Randomised study comparing heart rate measurement in newly born infants using a monitor incorporating electrocardiogram and pulse oximeter versus pulse oximeter alone, Arch. Dis. Child. Fetal Neonatal Ed. 104 (5) (2019) F547–F550.
[100] M.C. Murphy, L.D. Angelis, L.K. McCarthy, C.P.F. O'Donnell, Comparison of infant heart rate assessment by auscultation, ECG and oximetry in the delivery room, Arch. Dis. Child. Fetal Neonatal Ed. 103 (5) (2018). F490-F2.
[101] H.A. van Zanten, K. Kuypers, E.W. van Zwet, J.J. van Vonderen, C.O.F. Kamlin, L. Springer, et al., A multi-centre randomised controlled trial of respiratory function monitoring during stabilisation of very preterm infants at birth, Resuscitation 167 (2021) 317–325.
[102] S. Hyttel-Sorensen, A. Pellicer, T. Alderliesten, T. Austin, F. van Bel, M. Benders, et al., Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial, BMJ 350 (2015), g7635.
[103] C.T. D'Angio, P.R. Chess, S.J. Kovacs, R.A. Sinkin, D.L. Phelps, J.W. Kendig, et al., Pressure-regulated volume control ventilation vs synchronized intermittent mandatory ventilation for very low-birth-weight infants: a randomized controlled trial, Arch. Pediatr. Adolesc. Med. 159 (9) (2005) 868–875.
[104] J. Singh, S.K. Sinha, P. Clarke, S. Byrne, S.M. Donn, Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? J. Pediatr. 149 (3) (2006) 308–313.
[105] C.Q. Liu, Z. Cui, Y.F. Xia, L. Ma, L.L. Fan, Randomized controlled study of targeted tidal volume ventilation for treatment of severe neonatal respiratory distress syndrome, Zhongguo Dang Dai Er Ke Za Zhi 13 (9) (2011) 696–699.
[106] A. Moussa, Y. Luangxay, S. Tremblay, J. Lavoie, G. Aube, E. Savoie, et al., Videolaryngoscope for teaching neonatal endotracheal intubation: a randomized controlled trial, Pediatrics 137 (3) (2016), e20152156.
[107] S.C. Volz, T.P. Stevens, R. Dadiz, A randomized controlled trial: does coaching using video during direct laryngoscopy improve residents' success in neonatal intubations? J. Perinatol. 38 (2018) 1074–1080.
[108] C.J. Morley, P.G. Davis, L.W. Doyle, L.P. Brion, J.M. Hascoet, J.B. Carlin, Nasal CPAP or intubation at birth for very preterm infants, N. Engl. J. Med. 358 (7) (2008) 700–708.
[109] N.N. Finer, W.A. Carlo, M.C. Walsh, W. Rich, M.G. Gantz, A.R. Laptook, et al., Early CPAP versus surfactant in extremely preterm infants, N. Engl. J. Med. 362 (21) (2010) 1970–1979.
[110] F. Sandri, R. Plavka, G. Ancora, U. Simeoni, Z. Stranak, S. Martinelli, et al., Prophylactic or early selective surfactant combined with nCPAP in very preterm infants, Pediatrics 125 (6) (2010) e1402–e1409.
[111] M.S. Dunn, J. Kaempf, A. de Klerk, R. de Klerk, M. Reilly, D. Howard, et al., Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates, Pediatrics 128 (5) (2011) e1069–e1076.
[112] G. Moriette, J. Paris-Llado, H. Walti, B. Escande, J.F. Magny, G. Cambonie, et al., Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome, Pediatrics 107 (2) (2001) 363–372.
[113] A.H. Johnson, J.L. Peacock, A. Greenough, N. Marlow, E.S. Limb, L. Marston, et al., High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity, N. Engl. J. Med. 347 (9) (2002) 633–642.
[114] S.E. Courtney, D.J. Durand, J.M. Asselin, M.L. Hudak, J.L. Aschner, C. T. Shoemaker, High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants, N. Engl. J. Med. 347 (9) (2002) 643–652.
[115] P. Van Reempts, C. Borstlap, S. Laroche, J.C. Van der Auwera, Early use of high frequency ventilation in the premature neonate, Eur. J. Pediatr. 162 (4) (2003) 219–226.
[116] M.D. Schreiber, K. Gin-Mestan, J.D. Marks, D. Huo, G. Lee, P. Srisuparp, Inhaled nitric oxide in premature infants with the respiratory distress syndrome, N. Engl. J. Med. 349 (22) (2003) 2099–2107.
[117] H. Sun, R. Cheng, W. Kang, H. Xiong, C. Zhou, Y. Zhang, et al., High-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation plus pressure support in preterm infants with severe respiratory distress syndrome, Respir. Care 59 (2) (2014) 159–169.
[118] S. Shankaran, P.D. Barnes, S.R. Hintz, A.R. Laptook, K.M. Zaterka-Baxter, S. A. McDonald, et al., Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy, Arch. Dis. Child. Fetal Neonatal Ed. 97 (6) (2012) F398–F404.
[119] S. Shankaran, A. Pappas, S.A. McDonald, B.R. Vohr, S.R. Hintz, K. Yolton, et al., Childhood outcomes after hypothermia for neonatal encephalopathy, N. Engl. J. Med. 366 (22) (2012) 2085–2092.
[120] S. Shankaran, A.R. Laptook, R.A. Ehrenkranz, J.E. Tyson, S.A. McDonald, E. F. Donovan, et al., Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy, N. Engl. J. Med. 353 (15) (2005) 1574–1584.
[121] D. Azzopardi, B. Strohm, N. Marlow, P. Brocklehurst, A. Deierl, O. Eddama, et al., Effects of hypothermia for perinatal asphyxia on childhood outcomes, N. Engl. J. Med. 371 (2) (2014) 140–149.
[122] D.V. Azzopardi, B. Strohm, A.D. Edwards, L. Dyet, H.L. Halliday, E. Juszczak, et al., Moderate hypothermia to treat perinatal asphyxial encephalopathy, N. Engl. J. Med. 361 (14) (2009) 1349–1358.
[123] M. Rutherford, L.A. Ramenghi, A.D. Edwards, P. Brocklehurst, H. Halliday, M. Levene, et al., Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial, Lancet Neurol. 9 (1) (2010) 39–45.
[124] S.E. Jacobs, C.J. Morley, T.E. Inder, M.J. Stewart, K.R. Smith, P.J. McNamara, et al., Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial, Arch. Pediatr. Adolesc. Med. 165 (8) (2011) 692–700.
[125] J.L. Cheong, L. Coleman, R.W. Hunt, K.J. Lee, L.W. Doyle, T.E. Inder, et al., Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy: substudy of a randomized trial, Arch. Pediatr. Adolesc. Med. 166 (7) (2012) 634–640.
[126] S. Thayyil, S. Pant, P. Montaldo, D. Shukla, V. Oliveira, P. Ivain, et al., Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh, Lancet Glob. Health 9 (9) (2021) e1273-e85.
[127] A. Guan, P. Hamilton, Y. Wang, M. Gorbet, Z. Li, K.S. Phillips, Medical devices on chips, Nat. Biomed. Eng. 1 (3) (2017) 0045.