Review Article

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Neurocritical care of high-risk infants during inter-hospital transport AQ1 AQ2 AQ3

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Abstract

The centralisation of neonatal intensive care in recent years has improved mortality, particularly of extremely preterm infants, but similar improvements in morbidity, such as neurodevelopmental impairment, have not been seen. Integral to the success of centralisation are specialised neonatal transport teams who provide intensive care prior to and during retrieval of high-risk neonates when in-utero transfer has not been possible. Neonatal retrieval aims to stabilise the clinical condition and then transfer the neonate during a high-risk period for patient. Transport introduces the hazards of noise and vibration; acceleration and deceleration forces; additional handling and temperature fluctuations. The transport team must stabilise the infant fully prior to transport as when on the move they are limited by space and movement to effectively attend to clinical deterioration. Inborn infants have better neurodevelopmental outcome compared with the outborn and aetiology of this seems to be multifactorial with the impact of transport itself during critical illness, remaining unclear. To improve the neurological outcomes for transported infants, it seems imperative to integrate the advancing intensive care neuromonitoring tools into the transport milieu. This review examines current inter-hospital transport neuromonitoring and how new modalities might be applied to the neurocritical care delivered by specialist transport teams.

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Keywords

brain; neonatal transport; neurocritical care; neuromonitoring

Abbreviation

CBF	Cerebral blood flow
CFM	Cerebral function monitor
CPU	Clinician performed ultrasound
CUSS	Cranial ultrasound
EC	Electrical cardiometry
HIE	Hypoxic ischaemic encephalopathy
IUT	In-utero transfers
IVH	Intraventricular haemorrhage
MBP	Mean blood pressure
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
NTG	National Transport Group, UK
TH	Therapeutic hypothermia
WBV	Whole-body vibration

Key notes

- Advances in neurocritical care in the transport setting could improve outcomes for high-risk preterm and encephalopathic infants.
- Neonatal neurocritical care during inter-hospital transfer is challenging and adaptation of the neuromonitoring technologies may be required.
- Significant knowledge gaps exist regarding how to best deliver optimal neurocritical care in transport and how this could translate into better outcomes for high-risk newborns.

1. **INTRODUCTION** AQ7

In-utero transfer (IUT) remains the safest way to transport the high-risk foetus to a perinatal centre.[1] IUT is not always possible leading to the need for postnatal transfer. Adoption of coordinated strategies, aimed at centralisation of high-risk births and transport of these infants to perinatal centres, improves mortality.[1, 2] Severe neurological morbidities remain higher in outborn preterm neonates transferred in early life compared with inborn (Table 1).[2, 3]There are likely to be many factors influencing this including maternal risks and antenatal management, early newborn management[4, 5] and potentially the transport pathway itself, which occurs at a time of greatest instability and risk (Figure 1).

Table 1 Summary of major published studies comparing inborn and outborn neonatal neurological morbidities

Country	Year	Infants (n)	Population	Major neurological morbidity in transferred infants
USA [4]	1992-1995	329	BW: 500-1200 g L1 to L3 transfer	Severe IVH: Inborn 9% vs Outborn 23%
UK [5]	1995	804	GA: 20-25 wk	Severe IVH: aOR 2.61 (95% CI: 1.20-5.71)
USA[57]	1997-2004	67 596	BW: <1000 g	Severe IVH: aOR 1.36 (95% CI: 1.12-1.66)
			BW: 1000-1400 g	Severe IVH: aOR 1.60 (95% CI: 1.18-2.18)

USA[37]	2005-2010	758	BW <1500 g	Severe IVH: aOR 1.14 (95% CI: 1.69-1.80)
UK[58]	2006	1781	GA: 22-26 wk	Severe CrUSS abnormality: aOR 1.17 (0.74-1.85)
Canada[59]	2009-2011	2951	GA: <29 wk	Severe IVH: Inborn 14% vs Outborn 24%, *P* < .01 Mortality or Severe NDI at 18-21 mo: aOR 1.68 (95% CI: 1.25-2.24)
Australia[3]	2010-2011	796	GA: 22 to 27 wk	Severe IVH: aOR 0.85 (0.19-3.70)
South Africa[60]	2013	1032	BW: <1500 g	Severe IVH: Inborn 4% vs Outborn 14%, *P* < .001
UK[61]	2007-2016	1047	GA:<32 wk	Severe IVH: aOR 1.69 (95% CI: 1.04-2.76)

Abbreviations: aOR, adjusted odds ratio; BW, Birth weight; CI, confidence interval; CrUSS, Cranial Ultrasound; GA, Gestational age; IVH, Intraventricular haemorrhage; L1, level 1 neonatal unit; L3, level 3 neonatal unit; NDI, Neurodevelopmental impairment.

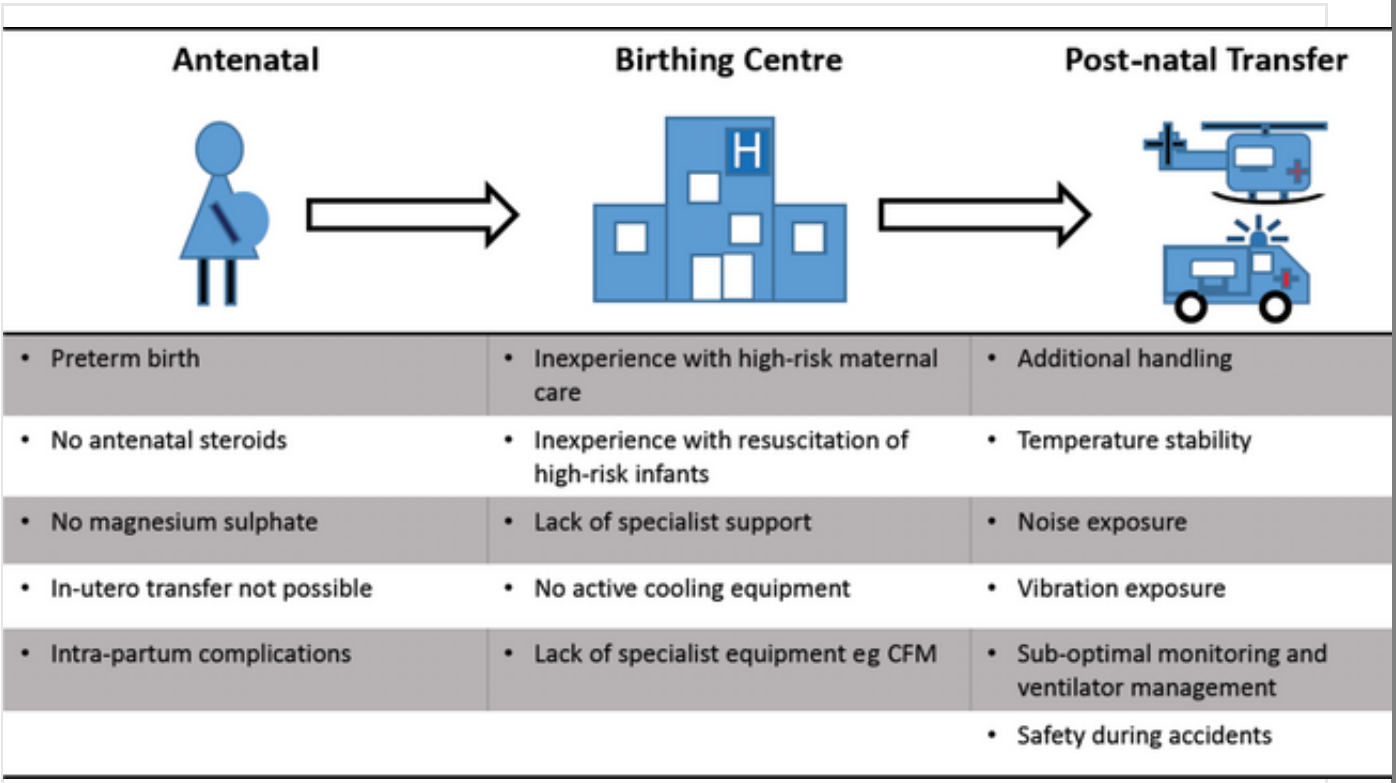

Fig. 1 Factors which could impact on the neurological outcome for outborn high-risk infants requiring transfer for neonatal intensive care

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A significant number of high-risk newborns, including preterm and infants with hypoxic-ischaemic encephalopathy (HIE) requiring therapeutic hypothermia (TH), are transferred by specialised transport teams.[6] These infants are already at risk of neurological problems including intraventricular haemorrhage (IVH) and seizures that can lead to abnormal neurodevelopmental outcome. The underlying risks of infants' gestation and/or pathology are compounded by the transport environment with exposure to noise, whole-body vibration (WBV), accelerative and decelerative forces and variable thermal environment.[7, 8, 9]

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In the UK, the Neonatal Transport Group (NTG, ukntg.net) collates transport activity annually from all the commissioned neonatal transport services. Table 2 provides an overview of the number of preterm and encephalopathic infants transferred for intensive care in the first 3 days of life. These data are for 6 months in each year, the annual total is likely to be approximately double. The UK, Australia, North America and Europe all have adopted the model of centralised neonatal care and therefore likely that a similar proportion of high-risk neonates require transfer.

Table 2 Number of infants transferred for therapeutic hypothermia or born <32 wk gestation and transferred within 72 h of life in the UK

Yeara	Infants with HIE transferred for Therapeutic hypothermia	Infants 23^{+0}-26^{+6} gestation	Infants 27^{+0}-31^{+6} gestation
2012	247	-	-
2013	288	-	-
2014	249	228	398
2015	274	212	482
2016	288	226	468
2017	245	200	462
2018	255	228	409

Note

-, data not collected

[a]Data are for 6 mo (1st Jan-30th June) for the given year (UK Neonatal Transport Group, unpublished data).

Neuromonitoring during neonatal transport currently lags behind that in the neonatal intensive care unit (NICU). Standard evaluation for neurological status is rudimentary and variance of vital signs can be difficult to gauge in the transport environment. If we are to improve inter-hospital transfer care, we need suitable clinical and research tools to support relevant outcome measures.

Various neuromonitoring modalities could be considered but they need to be proven to add value to the space confined transport setting. They need to be portable and provide actionable, reliable and reproducible information. This is challenging as vibration in the moving vehicle affects the equipment and acquisition of physiological data.[10] Practical issues, such as weight and electrical supply are essential to address.

Despite these challenges, a systematic neurological assessment and neuromonitoring of sick infants during retrieval is achievable to identify neurological deterioration and to minimise or prevent secondary cerebral insults. This review explores various aspects of neurocritical care along with key environmental exposures during inter-hospital transport.

2. **NEUROCRITICAL CARE FOR HIE**

Dedicated transport services that are appropriately trained, equipped and capable of rapid mobilisation and targeted stabilisation are key to achieve optimal care of high-risk infants during transport.[11]

Optimisation of ventilation is a key tenant for neuroprotection. Carbon dioxide (CO_2) level in the blood influences cerebral blood flow (CBF) so CO_2 should be monitored and controlled for transported infants as it is on the NICU. Both hypocarbia and hypercarbia should be avoided. Data from the UK NTG suggest that hypocarbia may be more prevalent than hypercarbia in transported infants. In 2018, UK NTG data (Jan-Jun) from neonatal transport teams had a rate of 6% of ventilated transfers with a CO_2 below 4 kPa on completion of transfer. These national data encompass hypocarbia rates for individual transport services ranging from 3% to 14%. Over the same period the rate of hypercarbia with acidosis (pCO_2 > 7 kPa, pH < 7.2) in ventilated infants was 5% (range 1%-12%). Monitoring can be achieved directly with point-of-care blood gas analysis and transcutaneous measurement of CO_2. Advances in ventilators used for transport may reduce the prevalence of CO_2 abnormalities, but this remains to be systematically demonstrated. Whilst end-tidal CO_2 monitoring has utility in monitoring airway patency it has not been demonstrated to be a useful guide to CO_2 level or trend in ventilated newborns.[12]

2.1. **Neurological assessment**

Neurological assessment facilitates identification of the infant with neurological injuries who requires further investigations, specialist input, or commencement of a specific treatment such as TH. There are significant challenges in the early identification of newborns as well as barriers in achieving neuroprotective core temperatures prior to 6 hours of age.[13]

The majority of newborns enrolled in the TH randomised control trials were outborn[14] and often had more severe HIE.[15] For outborn infants to be in TH target range by 6 hours of life, there are a number of key steps, not all in the control of the transport service or tertiary centre. Timely identification requires early referral following careful assessment of the perinatal events and a structured neurological assessment after birth with Sarnat staging[16] or a Thompson score[17] by referring units. Neurological assessment can be difficult as the clinical condition is evolving during the first hours of life and can be obscured if sedation is commenced. There is a need for discussion with the tertiary centre about candidacy for TH or other treatments, followed by a referral for transport and timely dispatch of the team especially in territories with large distances between centres and no local facilities to commence controlled active cooling.

Often the documentation of neurological assessment by referring and transport team is incomplete even when standard neurological assessment forms are used.[18] This can have clinical, resource and medico-legal implications.

2.2. **Amplitude integrated electroencephalography**

An assessment with amplitude-integrated electroencephalography (aEEG), using a Cerebral Function Monitor (CFM), can provide information about the global electrical activity of the brain. CFM is predominantly used in neonatal encephalopathy to identify electrical seizures, although it also has a role in the assessment of preterm infants and muscle relaxed sick neonates who cannot have neurological status monitored clinically.[19]

Cerebral Function Monitor can also support recognition of neonates who will benefit from TH. The combination of CFM and neurologic examination shortly after birth enhances the ability to identify high-risk infants and limits the number of infants who would be falsely identified compared with either evaluation alone.[20] The development of portable devices has allowed the use of CFM by transport teams during stabilisation at the referring units that do not have access to the equipment. Whilst this aids the diagnosis of the infant, it should not delay timely TH. Use of CFM in referral centres may support the assessment of the moribund newborn with severe HIE. This may inform counselling of parents regarding direction of care in referral centre when there is minimal electrical activity in a normothermic sick infant. The use of CFM during transport requires further assessment. It is unlikely that reliable data can be obtained that will inform changes to patient management during the journey due to vibration artefact.

2.3. **Therapeutic hypothermia**

Earlier initiation of TH provides greater neuroprotection.[21] Initiating cooling <3 hours of age has significantly better psychomotor developmental index scores at 18-20 months (88, 95% CI: 82-93) compared with being cooled later at >3 hours (78, 95% CI: 71-85; $P = .033$].[22] Therefore, initiation of TH at the birth hospital and during transport is necessary given the limited therapeutic window, travel distances and often late referral.[23]

Passive cooling with rectal temperature monitoring has been used as an effective method

whilst awaiting transfer to tertiary care.[24] The availability of servo-controlled cooling equipment for transport has allowed commencement of active cooling at the referring unit.[25, 26] Actively cooled infants achieve the target temperature significantly sooner and maintain stability better than those passively cooled.[26] Implementation of portable, servo-controlled, active cooling equipment in the transport services is highly recommended. Core (rectal) temperature monitoring is the best available therapeutic proxy for brain temperature measurement and is mandatory to prevent hypothermia below the target range during TH.[27]

The effective implementation of TH during neonatal retrievals is a key performance indicator for transport teams[28] and also for the referring units. This allows evaluation of the process and efficacy of the screening criteria and to identify any unintended consequences. UK NTG data demonstrate that the majority of infants are transferred with active TH (Table 3), although 17%-21% do not achieve target temperature by 6 hours of age.

Table 3 Infants transferred for therapeutic hypothermia (TH) from 1st January to 30th June each year in the UK (UK NTG, unpublished data)

	2016	2017	2018
Transfers for TH, n	288	245	255
Transferred on active cooling, n (%)	277 (96)	229 (93)	250 (98)
Infant temperature data available, n (%)	216 (75)	191(78)	230 (90)
Temp 33-34°C at 6 h, n (%)	180 (83)	154 (81)	182 (79)

The improved time to achieving TH target temperature when servo-controlled active cooling is used instead of passive cooling techniques suggests that for outborn infants there is a case for the more widespread deployment of servo-controlled active cooling equipment in referring units. This would also reduce reliance on transport services which may be committed to other time critical transfers.

Development and implementation of regional guidelines and clinical pathways, with close collaboration between hospitals, neonatal networks and the transport team, and family integrated neonatal neuroprotection service is essential to ensure infants with HIE are managed effectively throughout the care pathway. Training and education and availability of CFM in the referral units can also aid in management and timely referral of these cases.

3. **PAIN ASSESSMENT**

During transport, infants of all gestations show increased levels of discomfort above non-transport levels([29]) Despite recommendations[30, 31] neonatal pain continues to be inadequately assessed and managed. Painful stimuli have both short and long-term

adverse neurodevelopmental effects especially in very preterm infants.[32] Currently, there are no validated pain assessment scales for use in the transport setting but some have been described.[33, 34] The adverse effects of pain warrant accurate pain assessment and control measures during transport including nesting and consideration of appropriate sedation.

4. **NEUROCRITICAL CARE MODALITIES**

4.1. **Cranial ultrasound**

Cranial ultrasound (CUSS) is an essential neuroimaging tool in the care of high-risk infants. A study looking at the feasibility and utility of performing CUSS pre- and post-transport has provided information in preterm babies (<31 weeks) requiring transport in the first hours of life.[35, 36] In this study (n = 44), there was no evidence of evolving severe IVH post transfer. The mode of transport (road, rotary and fixed wing) did not contribute to further deterioration in the CUSS findings. This is despite significant vibration forces in the different modes of transport particularly the rotary wing and road vehicles. With only approximately 10% of infants in this population developing severe IVH there is a need for larger studies to further this information.

There is continued need to examine babies pre and post transport to further establish the safest mode of transport. More subtle neurovascular injury may occur, as seen in chronic vibration models, so long-term follow-up data would be useful. The outborn preterm babies have vulnerabilities relating to antenatal care, steroid and $MgSO_4$ coverage that puts them at increased risk of IVH and not just the transport process.[37, 36]

Being cognisant of the CUSS findings prior to transport allows for more informed treatment and counselling during stabilisation and retrieval. Evidence of more severe grades of IVH, allows for more informed counselling of parents in preparation for adverse outcomes, including severe disability and death. In a recent review of 1472 preterm infants (23-28 weeks), those with severe grade III-IV IVH (n = 93) had higher rates of developmental delay (17.5%), cerebral palsy (30%), deafness (8.6%), and blindness (2.2%).[38] Notably in this study, those with no and mild (grade I-II) IVH still had significant risk of moderate/severe neurosensory impairment (12.1% and 22.0% respectively) and cerebral palsy (6.5% and 10.4% respectively) suggesting brain injury may not be readily identified with CUSS alone.

4.2. **Haemodynamic monitoring**

There is a pathophysiologic association between preterm cerebral injury and MBP <30 mm Hg and CBF fluctuations, during first few postnatal days.[39] CBF can be measured by near-infrared spectroscopy (NIRS) but this has not yet been available in transport.[40, 41] Current practices for monitoring the haemodynamic status of critically ill infants during transport to tertiary care are poorly validated. These include arterial blood pressure monitoring, urine output and capillary refill time.

Electrical cardiometry (EC) is a form of impedance cardiometry, a continuous non-invasive method for calculating cardiac output by measuring changes in electrical conductivity within the thorax.[42] It is non-invasive and simple to use although requires specialised

equipment. Boet et al[43] has shown its feasibility and reliability and demonstrated that EC measurement is not affected by movement and vibration related to transport. This is a promising modality to enhance hemodynamic monitoring and with further development may be able to be assessed in the transport setting to reveal its impact on clinical outcomes.([44])

Clinician performed ultrasound (CPU- cardiac) has now been validated in the transport setting as has assessment of stroke volume in critically ill neonates.[36, 43] Use of ultrasound for haemodynamic assessment during transport may provide an opportunity for earlier and targeted circulatory support, ensure appropriate triage to the correct tertiary care facility (congenital heart disease) and prevent iatrogenic injury through untargeted haemodynamic management.[44] CPU of the lung, abdomen and for line placement also adds to the utility of ultrasound in transport. Importantly the addition of CPU to the transport did not lead to prolonged stabilisation times.[45]

The use of ultrasound for haemodynamic assessment to target therapy and for surveillance of brain injury is a valuable tool for neonatal retrieval teams, particularly for extreme preterm infants, surgical transfers and those with HIE. This can be facilitated by the training of the dedicated neonatal retrieval teams and the inclusion of a portable ultrasound device in the transport equipment.

4.3. **Cerebral near-infrared spectroscopy**

Cerebral oximetry records regional saturation of the brain using near infrared spectroscopy (NIRS) and provides a non-invasive method to continuously monitor brain oxygen imbalance and is a tool for measuring CBF.[46] The use of NIRS in the neonatal population is growing as evidence of its utility in the delivery room, the NICU and during surgery is emerging.[47] Cerebral oximetry lacks quantitative precision and so it is used as a trend monitor in critically ill neonates and its utility in neonatal transport is currently under investigation by some of the authors (DS/LS/AL). An example of an ambulance transfer (Figure 2) of a preterm infant demonstrates the potential of the technique with a marked drop in cerebral saturations once the ambulance journey is underway. Such fluctuations have been described in infants who then develop significant IVH.[48] More studies are needed to explore these observations and establish if reducing the environmental stressors of inter-hospital transfer, such as noise and vibration, can have an impact on these and decrease the incidence of neurological injury and long-term impairment.

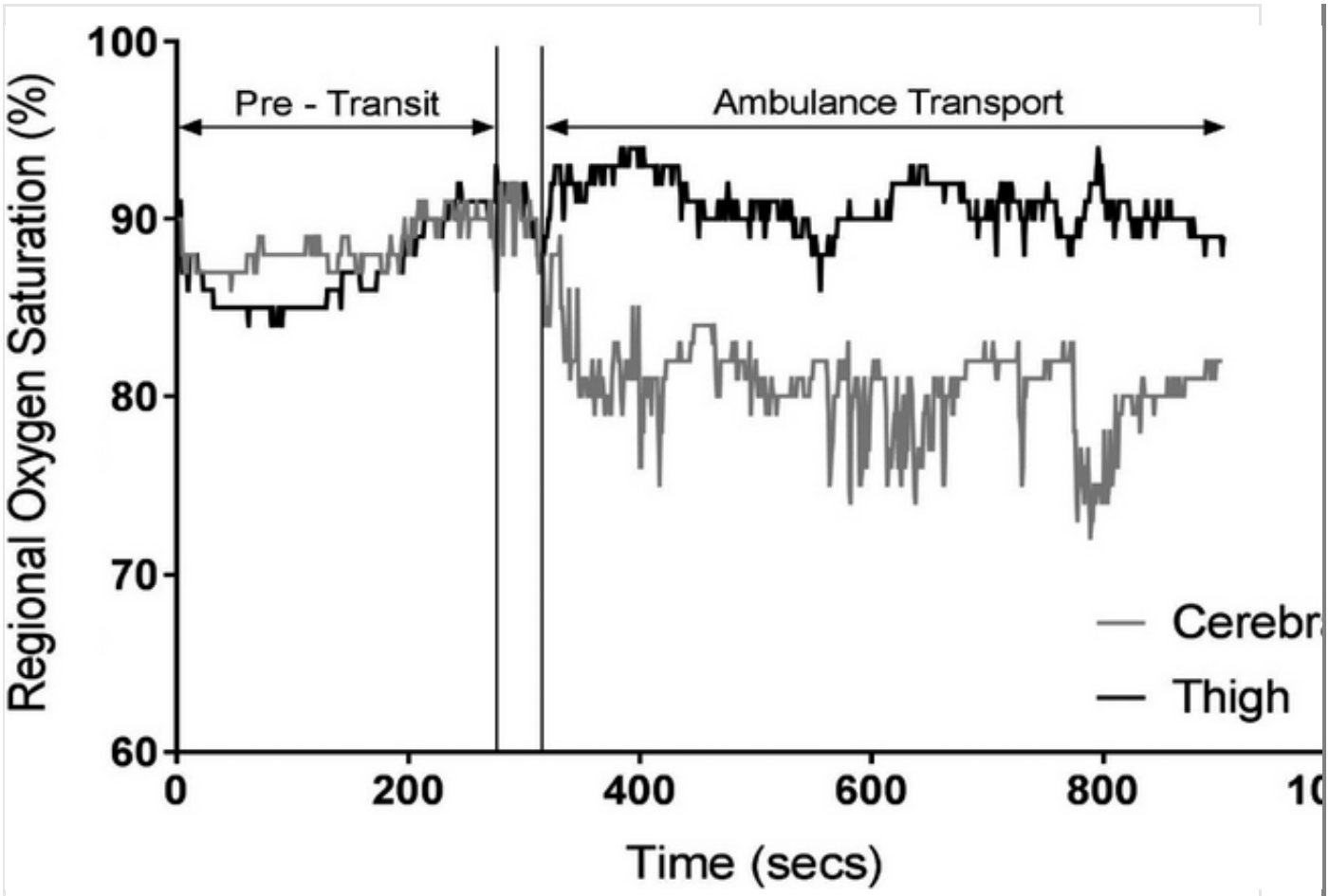

Fig. 2 Dual NIRS on a 28/40 preterm infant undergoing ambulance transfer on day 1 of life. The infant was cardiovascularly stable, ventilated in air and maintained oxygen saturations of >93% throughout. First 15 min of transfer with (a) pre-transfer phase with similar cerebral and quadricep muscle saturations, (b) during transfer cerebral saturations drop from mean 90% to 75% but quadriceps remain unchanged

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KEY ENVIRONMENTAL EXPOSURES DURING INTER-HOSPITAL TRANSPORT

Inter-hospital transfer of high-risk infants exposes them to additional risks. These vary from additional handling and exposure to fluctuating environmental temperature, through to more extreme risks such as rapid acceleration/deceleration forces. Noise and vibration are constant exposures which can impact on infant wellbeing.

5.1. **Noise exposure**

The American Academy of Pediatrics recommends noise levels on the NICU are kept <45 dB.[49] Sick premature infants, when exposed to excessive noise in the NICU are

known to develop cardiorespiratory instability, which could potentially impact on neurodevelopmental outcome.[50] In stable infants, loud noises 10-15 dB above background levels lead to changes in cerebral oxygenation.[51] Preterm infants transported between centres are exposed to prolonged periods of excessive noise with ground ambulance transfer often >70 dB and air transport >80 dB.[7] Efforts to reduce noise exposure are limited and well-designed trials are needed to establish the impact on clinically important outcomes.[52] Tackling the higher levels of noise in the transport setting is more challenging and efforts to design neonatal transport systems that attenuate noise exposure are in development. Commercially available ear defenders (MiniMuffs) claim to reduce noise only by up to 7 dB.[53] Greater noise attenuation will increase comfort and minimise cardiovascular instability, potentially improving outcomes for high-risk preterm infants.

5.2. **Vibration exposure**

During neonatal transport, WBV often exceeds the recommended level deemed safe for adults with the head of the infant appearing to be at greatest risk.[8] Excessive exposure in adults can cause ill effects including musculoskeletal and neurovascular injury.[54] However, the long-term effects of WBV in infants is currently unknown. Vibration and linear acceleration experienced during the transfer process may lead to fluctuations in CBF and be the key mechanism for IVH in preterm infants[9] and although causation is challenging to demonstrate it is supported by animal models.[55] Attempts to reduce WBV exposure with the use of different mattresses, including gel materials, have not demonstrated effective attenuation of WBV, especially in infants at high risk of IVH.[8, 56] Innovations are needed to significantly reduce WBV during neonatal transport which can then be studied in appropriately powered clinical trials.

6. **CONCLUSION**

For high-risk infants, inter-hospital transfer is common and increases their chance of survival. However, many studies have demonstrated worse neurological outcomes for outborn infants. Neuromonitoring is rapidly developing in the NICU setting and extension into the transport setting is challenging with both practical and environmental issues. Neurocritical care, and the technology required to deliver it, requires innovation in the transport setting to ensure that outborn babies receive care that is equitable to the NICU. Advancements in this domain should also consider the role of family-integrated care in these pathways and if this could further enhance outcomes for babies and families. The aim of the retrieval team is to ensure a safe, comfortable transfer to close the gap between the neurological outcomes of inborn and outborn high-risk infants.

CONFLICT OF INTEREST

None.

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