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The Brain in pediatric critical care: unique aspects of assessment, monitoring, investigations, and follow-up

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Corresponding Author:	Kate L Brown Great Ormond Street Hospital NHS Trust London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Great Ormond Street Hospital NHS Trust
Corresponding Author's Secondary Institution:	
First Author:	Kate L Brown
First Author Secondary Information:	
Order of Authors:	Kate L Brown
	Shruti Agrawal
	Matthew P Kirschen
	Chani Traube
	Alexis Topjian
	Ronit Pressler
	Cecil D Hahn
	Barnaby R Scholefield
	Hari Krishnan Kanthimathinathan
	Aparna Hoskote
	Felice D'Arco
	Melania Bembea
	Joseph C. Manning
	Maayke Hunfeld
	Corinne Buysse
	Robert C Tasker
Order of Authors Secondary Information:	
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The Brain in pediatric critical care: unique aspects of assessment, monitoring, investigations, and follow-up

Kate L Brown[1,2], Shruti Agrawal[3], Matthew P Kirschen[4,5], Chani Traube[6], Alexis Topjian[4,5], Ronit Pressler[1,7,8], Cecil D Hahn[9,10], Barnaby R Scholefield[11,12], Hari Krishnan Kanthimathinathan[11,12], Aparna Hoskote [1,2], Felice D'Arco[1, 8], Melania Bembea[13], Joseph C. Manning[14,15], Maayke Hunfeld[16,17], Corinne Buysse[16], Robert C Tasker[18-19]

1. Biomedical Research Centre, Great Ormond Street Hospital for Children, London, UK
2. Institute of Cardiovascular, Science University College London, UK
3. Paediatric Intensive Care Unit Addenbrookes Hospital, Cambridge, UK
4. Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, USA
5. University of Pennsylvania Perelman School of Medicine, Philadelphia, USA
6. Department of Pediatrics, Division of Pediatric Critical Care Medicine, Weill Cornell Medical College, New York, USA
7. Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children, Great Ormond Street, London, UK
8. University College London Institute of Child Health, London, UK
9. Division of Neurology, The Hospital for Sick Children, Toronto, Canada
10. Department of Paediatrics, University of Toronto, Canada

11. Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
12. Paediatric Intensive Care Unit, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
13. Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
14. Nottingham Children's Hospital and Neonatology, Nottingham University Hospitals NHS Trust, UK
15. Centre for Children and Young People Health Research, School of Health Sciences, University of Nottingham, Nottingham, UK
16. Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
17. Department of Pediatric Neurology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
18. Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, MA
19. Selwyn College, Cambridge University, Cambridge, UK

COI Statement: RP is an investigator for studies with UCB and does consultancy work for Kephala, Ireland. She served as a Speaker and/or on Advisory Boards for Natus, GW, Esai, and UCB.

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Figure: The figure depicts the recently conceptualized 'Post-Intensive Care Syndrome in Pediatrics (PICS-p)

Abstract

As survival after pediatric intensive care unit (PICU) admission has improved over recent years, a key focus now is the reduction of morbidities and optimization of quality of life for survivors. Neurologic disorders and direct brain injuries are~~is~~ the reason for 11-16% of admissions to PICU. -In addition, many critically ill children are at heightened risk of brain injury and neurodevelopmental difficulties affecting later life, e.g., complex heart disease and premature birth. Hence, assessment, monitoring and protection of the brain, using fundamental principles of neurocritical care, are crucial to the practice of pediatric intensive care medicine. The assessment of brain function, necessary to direct appropriate care, is uniquely challenging amongst children admitted to the PICU. Challenges in assessment arise in children who are unstable, or pharmacologically sedated and muscle relaxed, or who have premorbid abnormality in development. Moreover, the heterogeneity of diseases and ages in PICU patients, means that high caliber evidence is harder to accrue than in adult practice, nonetheless, great progress has been made over recent years. In this 'state of the art' paper about critically ill children, we discuss 1) ~~at risk~~ patient types at risk of brain injury, 2) new standardized clinical assessment tools for age-appropriate, clinical evaluation of brain function, 3) latest evidence related to cranial imaging, non-invasive and invasive monitoring of the brain, 4) the concept of childhood 'post intensive are syndrome' and approaches for neurodevelopmental follow up. Better understanding of these concepts is vital for taking PICU survivorship to the next level.

Take home message

The practice of neurocritical care for children with injured or vulnerable brains entails clinical assessment, a range of monitoring methods within the PICU and the follow up of children's long-term neurodevelopment. TAlthough these activities involve inherent challenges related to the diversity of case-mix and age range. Nonetheless, tThe assessment of brain injury and brain function are vital both within PICU and later during follow-up, in order , overcoming such barriers is vital to take PICU survivorship to the next level.

Introduction

A key goal of care in the pediatric intensive care unit (PICU) is to achieve survival that ultimately leads to the fulfillment of neurodevelopmental potential. To protect the brains of critically ill children, as is necessary to achieve best possible outcomes, we need optimal evidence-based methods to assess it and to track neurodevelopmental function over the course of recovery. Such assessments are essential to guide treatment and care to protect the brain during the acute phase of illness, and then promote subsequent rehabilitation, as children return to normal life. The evolution of expertise in this field arose from diverse sources that span the age range. These include the experience from neonatal intensive care for hypoxic-ischemic encephalopathy (HIE) that translate to the vulnerable neonatal brain in related scenarios such as pediatric cardiac surgery[1, 2] and multisystem disorders special to the PICU such as metabolic encephalopathy[3]; lessons learned from adult stroke,[4] ~~post-~~cardiac arrest,[5] and neurotrauma care;[6]~~[2]~~ a~~s wel~~nd~~l as~~ from a range of bespoke studies set in the PICU that we reference specifically in the sections of this article. W~~In this narrative review, w~~e discuss unique aspects of assessment, monitoring, investigations, and follow-up of the brain in pediatric critical care, focusing~~. The review focusses~~ on 1) clinical groups in PICU with vulnerable brains, 2) bedside clinical assessment of neurological function, 3) non-invasive monitoring and imaging, invasive monitoring and, 4) the concept of post intensive care syndrome[7] and follow up entailing coordination with specialists, outside our specialty, to seek out best environmental enrichment and rehabilitation strategies that have the potential for improving the natural history post injury brain maturation.

Section 1: Vulnerable Brains in PICU

Brain assessment and its integration into pediatric critical care management is a cornerstone of care for children with primary neurological conditions or direct brain injury and the significant proportion of critically ill children at risk of secondary brain injuries. As an illustration of scale, we know that out of a total pediatric population in the UK of around 14 million, 11% of the 60,000 PICU admissions between 2017 to 2019, had a neurologic disorder, brain injury or nervous system morbidity.[8] In the *Prevalence of Acute critical Neurological disease in children: a Global Epidemiological Assessment (PANGEA)* point prevalence study, set in 109 hospitals predominantly in North America and Europe, 16.2% of children in the PICU were affected by an acute primary neurological condition, the most common being cardiac arrest and severe traumatic brain injury (sTBI).[9] An epidemiological study of PICU admissions in Australia and New Zealand found that amongst 103,367 admissions, 14.4% had a primary neurological diagnosis [10] (e.g., sTBI, neuro-infection or inflammation, status epilepticus, stroke and hypoxic ischemic brain injury[11]). In addition, a significant proportion of PICU admissions although not suffering from primary neurologic disease, are nonetheless at risk of secondary mechanisms of injury, such as the 2.8% with severe sepsis [3]. Last, there is the 20% risk of morbidity in the PICU population with cardiac disease or those seen after congenital heart surgery, with multiple interacting risk factors: abnormal *in utero* brain development [1]; underlying genetic abnormalities affecting cerebral structures [12]; cardiopulmonary bypass related acquired brain injury; and, inadequate peri-operative brain perfusion during post-operative low cardiac output states.[2]

Critically ill children with these complex multi-system conditions require a range of assessment and monitoring to guide the care, -including electroencephalographic (EEG) staging of encephalopathy, brain imaging tailored, use of invasive intracranial pressure (ICP) measurement, and meticulous attention to each organ system derangement. This strategy is seen in our current approach to multisystem problems in, for example: the infant with hyperammonemia and presumed metabolic disorder needing extracorporeal renal support;[3] the child with super refractory status epilepticus in a category of so-called febrile infection-related epilepsy syndrome undergoing anesthesia and immunomodulation for management;[13] and, the older patient seen after hematopoietic stem cell transplant with disseminated viral infection, coagulopathy, cardiac depression and acute-on-chronic lung injury.[14] The complexity and diversity of these clinical scenarios demonstrates why several approaches to brain assessment are required and integrated into the patients journey and care.

Section 2: Clinical assessment of neurological function in PICU

Clinical neuromonitoring is the process of serial neurologic examination in critically ill patients. Such assessment is invaluable in children with primary neurological conditions or direct brain injury, as well as those with neurological complications of systemic diseases. Available instruments used at the bedside are shown in Table 1 and described below.

Clinical evaluation of brain function in PICU

Clinical monitoring, whether intermittent or serial, [15, 16] has the potential to identify deficits representing new or evolving direct nervous system injury. In practice, however, the key to performing the neurologic examination is observation, as confrontational examinations can

be challenging, especially in children with developmental disabilities and those who are intubated and/or sedated. A common initial manifestation in children is encephalopathy (i.e., irritability, crying, sleepiness, or agitation), or seizures rather than focal deficits. Then, there is the problem of serial examinations by multiple assessors, such as physicians, nurses, therapists, and parents.[17] Here, in common with adult neurocritical care practice, there is the obvious need for a standardized screening tool to improve detection of clinically relevant neurologic changes, e.g., the Glasgow Coma Scale (GCS), Alert Voice Pain Unresponsive (AVPU), and Full Outline of UnResponsiveness (FOUR).[18, 19] Pediatric modifications of these scoring systems have been developed for children,[20-22] and even though scores such as the GCS are used in most PICUs, limitations impede the ability to reliably detect changes in a critically ill child's neurologic examination.[17, 18, 23]

The new *Serial Neurologic Assessment in Pediatrics* (SNAP) tool was developed to optimize screening neurologic assessments in children.[24] It was designed for contemporary PICU practice that includes children who are intubated, sedated, and/or have developmental disabilities. SNAP assesses mental status, cranial nerves, communication, and motor function. When used by PICU nurses, SNAP had substantial to near-perfect interrater reliability and is feasible to implement.[24] When standardized reporting of changes detected on a screening assessment is communicated to physician teams, it may lead to further diagnostics, earlier identification of neurologic injury, and management decisions directed at preventing or mitigating irreversible brain injury or death.

Delirium evaluation

In addition to identifying direct neurologic injury, it is also important to identify acute brain dysfunction that arises as a secondary complication of systemic disease. Delirium is a behavioral syndrome,[25] defined as an acute and fluctuating change in mental status, due to three possible (and synergistic) etiologies: underlying illness, treatment side effects, and/or as a reaction to the disruptive PICU environment. Delirium affects approximately one in four critically ill children, and is linked to poorer PICU outcomes [26, 27]. Without routine screening, delirium often goes undetected in its early stages[26]. Therefore, guidelines recommend routine delirium screening each shift as standard of care, throughout a child's PICU stay.[27, 28] The Cornell Assessment of Pediatric Delirium (CAPD), the most widely used pediatric tool, is an observational scale scored by bedside nurses. A score of nine or higher is consistent with the gold-standard psychiatric diagnosis of delirium.[29] A modified scoring algorithm has been developed for children with significant underlying developmental disabilities to improve delirium identification in this challenging population.[30] The CAPD has been validated in children of all ages and developmental stages, has excellent interrater reliability, and is available in more than a dozen languages. The Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) is used in children older than 5 years, and the accompanying preschool version (ps-CAM-ICU) for children under 5 years.[31] These are interactive screening tools that provide a point-in-time assessment for delirium. In addition, the Sophia Observation Withdrawal Symptoms Scale (SOS) has an extended pediatric delirium (PD) component (SOS-PD) that can be used to screen for delirium.[32] It consists of 18 items scored by the bedside nurse. Either the CAPD, p/psCAM-ICU, or SOS-PD can be used to screen for delirium, based on center preference for an observational versus interactive tool.

Table 1: Tools for Clinical Assessment of Brain Function in PICU

Assessment Tool	Domains included	Intended patients	Who administers	Practical issues
Pediatric modification of Glasgow Coma Scale (GCS)[21]	Global assessment of neurologic function • Eye response • Verbal Response • Motor Response	Scales for patients ≥2 and <2 years old	Nurse Advanced Nurse Practitioner Physician	• Administration is rapid • Widely used and understood across specialties (e.g., ED, ICU, trauma) • Institutional standardization is necessary • Limitations for patients who are intubated or sedated • Limitations for patients with developmental disabilities
Serial neurologic assessment in pediatrics (SNAP)[24]	Global assessment of neurologic function • Mental status • Cranial nerves • Communication • Motor function	Scales for patients ≥2 years old, <2 years and ≥6 months old, and <6 months old	Nurse Advanced Nurse Practitioner Physician	• New assessment tool • Limited validation studies. No validation outside of the pediatric ICU. • Longer duration and more complex to administer than GCS • Able to score children who are intubated, sedated, or have developmental disabilities
Cornell Assessment of Pediatric Delirium (CAPD)[29]	Assessment for delirium	All patients <18 years old	Nurse Advanced Nurse Practitioner Physician	• Observational tool • Administration is rapid • Validated in pediatric ICU setting • Able to score children who are intubated, sedated, or have developmental disabilities
Pediatric Confusion Assessment Method for the ICU (pCAM-ICU)[33] Preschool version of pCAM-ICU (Ps-CAM-ICU)[31]	Assessment for delirium	Ages >5-18 years Ages >6 mo-5 years	Nurse Advanced Nurse Practitioner Physician	• Interactive tool • Administration is rapid • Validated in pediatric ICU setting • Able to score children who are intubated and sedated. • Limitations for patients with developmental disabilities.
Pediatric delirium component (PD-scale)	Assessment for delirium	Ages >3 mo-18 years	Nurse	• Observational tool • Validated in pediatric ICU setting

of the Sophia Observation Withdrawal Symptoms scale (SOS-PD scale)[32]			Advanced Nurse Practitioner Physician	• Able to score children who are intubated and sedated. • Limitations for patients with developmental disabilities.

Section 3: Pediatric neurocritical care monitoring and clinical implications

Brain imaging in PICU

Neuroimaging offers valuable insights into characterisation, aetiology, response to therapy and prognostication of neurological disease in critically ill children but must always be interpreted within the context of the clinical history and findings. There are no evidence-based guidelines for neuroimaging in the PICU, and decision-making as to which scan is appropriate at specific timepoints in the patient journey is multi-disciplinary and guided by the patient's condition.

Portable cranial ultrasound (CUS) offers bedside diagnosis in critical unstable children, for example to rule out intracranial haemorrhage prior to initiation of extracorporeal membrane oxygenation (ECMO), but is inadequate for use in prognostication and is less sensitive than computed tomography (CT) and magnetic resonance imaging (MRI).[34] To increase yield, contrast enhanced ultrasound (microbubbles of ultrasound contrast) is a new technique for real-time perfusion in neonates,[35] [36] including after cardiac surgery.[37] Nonetheless CUS is used frequently as part of the bedside assessment of unstable neonates and infants with open anterior fontanelle following major events at any timepoint in their admission.

Early CT (≤24 hours) in children with suspected hypoxic, ischaemic or sTBI, helps exclude haemorrhage, may indicate severity of hypoxic ischaemic injury and with the use of CT angiography, and can resolve neck and intracranial arterial anatomy. The established indices in adults of early ischaemic changes of grey to white matter attenuation ratio (GWR), and the modified Alberta Stroke Program Early CT Score (mASPECTS), have shown initial utility for prognostication in children in the contexts of extracorporeal cardiopulmonary resuscitation and

other types of cardiac arrest.[38, 39] However the GWR should be interpreted in the context of serial clinical assessments and monitoring such as the results of the EEG.

In neonates, neurological injury may be subclinical or undetectable early on, and CUS may not detect subtle abnormalities, particularly in posterior cerebral lobes and cerebellum. Then, given that there is lower contrast resolution on CT, since neonates and infants have unmyelinated brains, MRI brain is considered the best imaging modality for characterisation and prognostication of brain injury in PICU. MRI diffusion weighted imaging (DWI) has an important role in the diagnosis of acute brain damage including arterial ischemic events during the acute phase, however diffusion changes start to disappear after 5 days (pseudo-normalization) and the timing of DWI changes may be influenced by the use of cooling.[40] With neonatal HIE, MR spectroscopy shows changes within the first 24 hours when even the DWI can be negative.[41] The optimal time for DWI is between 1 and 5 days, at which point the injury may be timed and characterized. Then, after day 5, chronic changes in T2 and T1 weighted images may be helpful in prognostication.

Non-invasive neuromonitoring in PICU

Non-invasive neuromonitoring is used broadly in PICUs: a recent US survey showed that all surveyed institutions had EEG monitoring capabilities, with 96% using continuous EEG, 87% using near infrared spectroscopy (NIRS) and 40% using transcranial Doppler (TCD), with other non-invasive monitoring capabilities (e.g., pupillometry, optic nerve sheath diameter [ONSD], bispectral index [BIS] monitor) used more sparingly.[42] The conclusion from the adult focussed International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care, that advanced analytical methods applied to multimodality monitoring of focal and global neurophysiologic cerebral alterations would enhance assessments compared to

clinical examinations only,[43] is currently being considered and adapted by PICU groups with age specific adjustments (Table 2).

Electro encephalography (EEG)

Seizures are the most common neurological emergency in critically ill neonates and children, and EEG is required for their accurate diagnosis. Due to growing awareness about the high prevalence of subclinical seizures among patients with acute encephalopathy, brain injury or clinical seizures, continuous EEG monitoring has become the standard of care for selected critically ill neonates and children in high-resource centres. Common indications for continuous EEG include hypoxic or traumatic brain injury, stroke, refractory seizures, meningoencephalitis, and unexplained encephalopathy (Table 2) [44, 45] Observational cohort studies in both neonates and children have demonstrated that higher seizure burden is associated with worse short- and long-term outcomes, even after adjusting for other factors such as brain injury aetiology and severity.[46, 47] Yet the question remains to what extent seizures independently cause secondary brain injury and worse outcomes. The potential deleterious effects of seizures likely depend on seizure aetiology (e.g.: acute stroke versus, epilepsy), seizure type (e.g.: focal versus. generalized) and other factors such as age and concomitant brain injury. Randomized controlled trials (RCT) in neonates of EEG-guided seizure treatment compared with treatment of clinical seizures alone demonstrated that EEG-guided therapy successfully reduced overall seizure burden; however, potentially related to poor sample size, RCTs failed to demonstrate a difference in outcome between the treatment groups[48], [49] Nonetheless, implementation of continuous EEG monitoring can improve the timeliness of seizure detection and seizure control, and that this in turn is associated with decreased use of anti-seizure medications both

in hospital and upon discharge, and less frequent progression to status epilepticus.[50, 51] Finally, in addition to providing insights on seizure burden, continuous EEG can provide valuable insights into prognosis through ongoing assessment of EEG background activity. Severe background suppression, or a burst suppression pattern, especially if invariant and prolonged, in the absence of confounding factors such as sedative medications portend a poor outcome.[52]

Near infrared spectroscopy (NIRS)

NIRS-based cerebral regional tissue oxygenation (rSO2) is used widely in children on ECMO and in children admitted to the PICU following cardiac surgery, in particular complex neonates who are at high-risk of brain injury, and is reported as standard of care in many high resource settings despite an absence of RCTs.[53] Management algorithms have been published, only for infants and children with congenital heart disease in the PICU, suggesting cerebral rSO2 thresholds (>20% decline from baseline cerebral rSO2, cerebral rSO2 <50% or <40%, left-to-right difference in cerebral rSO2 >10%) to trigger interventions intended to avert severe low cardiac output states, linked to secondary brain injury.[53] NIRS-based cerebrovascular autoregulation monitoring has been studied in children admitted to PICU following cardiac surgery,[54] sTBI,[55] and cardiac arrest.[56] Although it has been speculated that goal directed hemodynamic management that targets an optimal mean arterial pressure for preservation of autoregulation, using NIRS-based monitoring, could be linked to better neurodevelopmental outcome, this is as yet unproven.

Transcranial doppler (TCD)

TCD measures cerebral blood flow velocity in large cerebral vessels and is a useful tool in critically ill children with concern for pathophysiological changes in cerebrovascular hemodynamics.[57] In critically ill children with pathologies as varied as sTBI, arterial ischemic stroke, hydrocephalus, bacterial meningitis, or diabetic ketoacidosis, TCD has been utilized to noninvasively estimate ICP,[58] to serially monitor for presence and severity of vasospasm,[59] and to assess cerebrovascular autoregulation.[58] Other TCD applications in adult neurocritical care have either been extremely rarely used in the PICU or have not yet been reported (i.e., evaluation of arteriovenous malformations or of collateral pathways of intracranial blood flow, as adjunct to brain death evaluation, and in the assessment of cerebral microemboli, right-to-left shunts, ICP, hydrocephalus, hypoxic ischemic encephalopathy~~HIE~~, or dural venous sinus patency).[58] Pediatric-specific standards for technical performance, data interpretation, and data reporting standards have recently been published in an effort to ensure reproducibility between TCD operators and across institutions.[57]

Pupillometry

Automated pupillometry is gaining ground in clinical practice, primarily due to increased recognition of improved accuracy over manual assessment.[60] Normative data have been published for healthy paediatric volunteers,[61] but data in critically ill children are extremely limited. A recent single-centre prospective observational study conducted in 28 children admitted to the PICU with acute brain injury or encephalopathy requiring an ICP monitor showed that percent change in pupillary size, constriction velocity, dilation velocity, and Neurologic Pupil index (NPi) were lower when ICP was ≥20 mm Hg versus <20 mm Hg (among

1,171 concomitant automated pupillometry and ICP measurements).[62]~~[62]~~ Abnormal pupillary measurements were only associated with concurrent and not future ICP measurements.[62]~~[63]~~ Potential future uses of pupillometry may include the assessment and optimization of analgesic regimens for children in PICU[63] and prognostication, although this would be contingent on further research to understand the role of potential confounders.[64]

Table 2: Non-invasive Neuromonitoring Methods Currently Used or Under Investigation in Pediatric Neurocritical Care

Method (application in PICU)	**Intended Utility**	**Suggested thresholds**	**Disadvantages**
Electroencephalography (EEG represents standard of care in children clinically at risk of brain injury and seizures – *established*)[44]	Detection of seizures (electro-clinical and electrographic-only) Diagnosis of non-convulsive status Prognostication after hypoxic brain insult	High risk neonates and children (with hypoxic brain insult, stroke, infection, head trauma, inborn error of metabolism, clinically suspected seizures/epilepsy)	Limited availability in resource limited settings.
Near infrared spectroscopy (Guidelines are widely used in neonatal cardiac surgery - *established*, there is limited experience in other patient groups – *used less often, under investigation*)[53]	Regional cerebral tissue oxygenation	More than 20% decline from baseline rSO_2 <50% rSO_2 <40% Left-to-right difference in rSO_2 of >10%	Limited spatial resolution No evidence for outcome improvement
Transcranial Doppler (Consensus based guidelines exist for use in PICU although the evidence base is limited– *used less often, under investigation*)[57]	Cerebral blood flow velocity monitoring	Age dependent	Inter-operator variability
	Non-invasive intracranial monitoring		Poor accuracy for intracranial monitoring compared to invasive methods
Automated pupillometry (Occasionally used clinically, research tool, the evidence base is weak – *under investigation*)[65]	Assessment of pupillary size, asymmetry, constriction to light, latency, constriction and dilation velocity	Diameter <0.5 mm Asymmetry <0.5 mm %Pupillary light response 35%-40% Constriction velocity 1.5 mm/sec Dilation velocity 2.83 mm/sec Neurological pupillary index ≥3	Limited data on effects of sedatives and other medications on pupillary reactivity

Optic nerve sheath diameter (Occasionally used clinically, research tool, the evidence base is weak– *under investigation*)[66]	Non-invasive intracranial pressure measurement	Optic nerve sheath diameter >5 mm as indicator of intra cranial pressure >20 mmHg Age dependent	May be used to detect increased intracranial pressure shadowing artifact

Invasive monitoring

The latest international consensus guidance,[67] recommends invasive ICP monitoring in children with sTBI (usually in children with GCS<9 with trauma related abnormal CT scan) to allow titration of therapies in a tiered fashion. Insertion of intra-parenchymal catheter via a bolt is common due to ease of insertion, performance and use, though the catheters can also be placed elsewhere. Treatment pathways support keeping the ICP <20mmHg and achieving a minimum cerebral perfusion pressure (CPP) at least 40-50 mmHg.[67] This practice is supported by observational data from critically ill adults.[68] Observational data from children with sTBI indicates that prolonged and intense rises in ICP are adverse, with poor tolerance in young age groups, implying these require careful management.[69] Very young children with sTBI may be at heightened risk of impaired cerebrovascular pressure autoregulation, with potential to benefit from individualized treatment targets for management of cerebral perfusion pressure.[70] A prospective hybrid implementation and effectiveness study (PEGASUS) in pediatric sTBI indicated that adherence to cerebral perfusion pressure targets, avoidance of hypocarbia and adequate enteral nutrition were all linked to better hospital survival.[71] Intracranial hypertension is a major cause of morbidity and mortality in various non-traumatic encephalopathies that affect children (e.g. hypoxic ischaemic encephalopathy, stroke, sinus venous thrombosis, fulminant hepatic failure, diabetic ketoacidosis, meningo-encephalitis, brain tumours and idiopathic intracranial hypertension) and invasive monitoring can offer guidance for reducing secondary insults.[72] However, since such monitoring has limited links with outcome, invasive monitoring is used sparingly in these

conditions In the example of bacterial meningitis in PICU, risk stratification tools have shown the potential to identify where invasive monitoring benefits outweigh the risks through personalised treatment pathways.[73] There is insufficient evidence to recommend the use of partial pressure of brain tissue oxygen ($PbrO_2$) monitoring.[67] Though, if such monitoring is used, a minimum value of 10mmHg is supported.[67][54] Strategies to improve PbrO2 may include manipulation of CPP, haemoglobin, FiO_2, and CO_2. PbrO2 monitoring may also be used to monitor for evidence of cerebral ischaemia if hyperventilation is used as a treatment strategy for raised ICP. Cerebral autoregulation-based derivation of optimum CPP using correlation between ICP and blood pressure measurements, as well as cerebral microdialysis based analysis of lactate/pyruvate ratio, glucose, glutamate etc. are currently limited to research settings only.

Section 4: The brain following PICU discharge

Post Intensive Care Syndrome (PICS-p)

The figure depicts the recently conceptualized 'Post-Intensive Care Syndrome in Pediatrics (PICS-p)',[7] which describes how new or worsening morbidities in PICU survivors can align to physical, cognitive, emotional and social health domains. PICS-p recognizes that both the child's pre-existing health status, the management of their acute critical illness, and their stage of maturation and growth, may affect the severity and pervasiveness of acquired impairments beyond the PICU. Furthermore, the framework identifies the PICU survivors are part of a family unit, where family members such as caregivers and siblings may also be affected. For example, both children and caregivers may experience psychological responses such as post-traumatic

stress (PTS)[74] and psychological burdens may contribute to social and emotional recovery.[75]

Within the physical domain, outcomes of critical illness may be organ specific or more generalized including respiratory dysfunction, chronic pain, epilepsy, sleep disruption, fatigue, severe muscle weakness, reduced self-care and feeding disturbance[76]. Physical adverse outcome may be due to the underlying illness (e.g.: hearing loss after meningitis), due to PICU treatment (e.g.: subglottic stenosis after endotracheal intubation) or due to the combination of both. Clearly, brain injuries and neurological conditions may affect cognitive function and children's social and emotional development. The physical, cognitive, emotional, and social recovery which run simultaneously, starting at PICU discharge, and concluding in reaching a 'new normal', captured within the concept of health-related quality of life (QoL). A review of QoL following PICU admission concluded that worse scores related to pre-existing conditions, PICU interventions and events (e.g.: ECMO or cardiac arrest), social and environmental factors and parent mental health.[77] The concept of PICS-p helps us to contextualize ND outcomes after PICU admission by providing a framework that recognizes the complex and multifaceted nature of survivorship and frames short- and longer-term outcomes following childhood critical illness as holistic, dynamic, and inter-relational.

Neurodevelopmental (ND) follow-up programs and pathways

The provision of ND follow-up after PICU is better established in some regions, whereas elsewhere this is an emerging area of health care need that is yet to be developed. Although standards of care vary, there is little debate that children with confirmed brain injury (e.g.: sTBI, post-cardiac arrest, stroke, central nervous system infection, seizure disorders) require

structured follow up. In most high resource settings, ND follow up is also recommended for children who are at high risk of brain injury, even if this is not identified at the point of discharge, for example, ex-premature infants and children with complex congenital heart disease. When considering whether or not ND follow-up is required for specific children post PICU, the following risk features may be considered:

- *Pre-existing factors of the child and family:* e.g.: medical history of high risk conditions or co-morbidities, difficult socioeconomic status, and young age at the time of a critical event, which makes initial assessment less reliable.[78] [79]
- *Management during and characteristics of the PICU admission:* e.g.: high severity of illness, emergent nature of the admission, prolonged PICU stay, prolonged mechanical ventilation, specific treatments such as ECMO and presence of PICU-acquired delirium.[79] [80]
- *Recovery phase after PICU discharge:* e.g.: anxiety and stress levels of the child and parent, coping strategies within the family, readmissions to the hospital, rehabilitation needs of the child.[79]

Follow-up assessments should take place into early adulthood, given the importance of understanding and monitoring the impacts on long-term functioning, basic daily skills and education, and considering that children may grow into deficits. PICU follow-up needs to be a joint venture between the relevant practitioners and be delivered by the best available combination of professionals equipped to provide it, which varies based on local health care systems. This might include: PICU physicians, child development and neurology subspecialists, primary care providers, community pediatricians, nurses, physiotherapists, -psychologists and if applicable palliative care specialists, who ideally should follow standardized follow-up intervals

and use well validated instruments that have internationally normative data. Commonly used measures that cover most relevant domains and attributes are displayed in Table 3, noting their main limitations include: lack of precision (e.g. broad category descriptions); subjective scoring criteria and measurements methods; and failure to capture important functional problems, including sleep disruption, fatigue, and severe muscle weakness.[81] Of note all the measures listed have specific age appropriate versions and instructions for use.

There are major challenges in developing a ND follow-up program or facilitating a follow up pathway that is designed for use by a wide circle of linked health professionals outside the center where the PICU is located, for example the American Heart Association Guideline for the ND follow up of children with heart disease:[82]

Firstly, pediatric critical illness is extremely heterogeneous with respect to disease process and ages spanning widely different developmental stages. This means that a ND follow up program or pathway needs to be diverse, complex, flexible and multi-disciplinary, which can be difficult to achieve.

Secondly, if ND follow up data are to be used for future research, to improve consistency in reporting, outcomes should be based on a core outcome set (COS) to reduce heterogeneity and reporting bias, improve comparability and enable the pooling of data for meta-analyses. The recently developed PICU-COS emphasizes the domains of cognitive, emotional and physical function, overall health and QoL but has not yet established how these should be measured.[83] The methods and perceptions of these domains vary among health care professionals, caregivers and patients due to cultural aspects, beliefs and socio-economic

factors, hence the next phase of identifying preferred standardized methods to evaluate these will be crucial.

Thirdly, a PICU admission also impacts parents, and parental outcomes are of great interest during follow up, especially since outcomes such as executive functioning and QoL in young children are often assessed by parents. Due to the shared variance between parents and children, the reported child outcomes might be colored by the subjective well-being of the parent. This indicates the importance of screening for emotional and psychological sequelae of PICU admission in both the child and their parents and focusing on family centered interventions and care.[84]

Finally, ideally it would be possible to identify and intervene on potentially modifiable factors, from the timepoint of the child's admission in the PICU and onwards in their journey through ND follow up, with a goal of improving both immediate and long-term outcomes in critically ill children and their families. To achieve this necessitates a tight collaboration between research and clinical care through these stages in the patient's journey, which requires considerable investment of expertise, resources and time. Few countries have achieved this however, it is an ideal to aim at, whilst considering a range of service designs and the current technical developments in electronic health care records to get there.

Conclusions

Despite the inherent challenges involved in the assessment of brain function and the conduct of neurocritical care for children, this field will only gain greater emphasis over time. As pediatric critical care practitioners it is essential that we continue to use every available opportunity, including learning from adult studies and designing-conducting high-quality

pediatric studies in neurocritical care and entailing ND follow up. If we can rise to these challenges and prioritize learning about which PICU interventions are beneficial to brain health and/ or for optimizing later ND outcomes, we may see a step change in quality of life for survivors of childhood critical illness.

Table 3: Physical, Psychosocial, Neurocognitive and Quality of Life Outcomes after PICU Admission

Outcome or Parameter	Assessment in	By whom	When	How (example)
Physical outcomes				
Clinical neurological evaluation	Child	Nurse Advanced Nurse Practitioner Physician	Hospital discharge and follow up and at least 6 months later	• Neurological exam • (Pediatric cerebral performance category (PCPC) score)
Health status, functional status	Child	Nurse Advanced Nurse Practitioner Physician	Hospital discharge and follow up and at least 6 months later	• Physical exam • (Functional status scale (FSS))
Readmissions	Child	Parent/Physician	As applicable	
Motor development	Child	Physiotherapist	At least 6 months post discharge	• Motor function testing • (Bayley scales)
Perception/sensation	Child	Physician		
Psychosocial outcomes				
(Adaptive) Behaviour	Child	Self and/or parent	At least 6 months post discharge	• Questionnaire Scale • (Vineland adaptive behaviour scales (VABS))
Family burden	Parent	Parent	At least 6 months post discharge	• Questionnaire • (Peds QL Family impact module)
Emotions (regulation)	Child Parent	Self and parent Parent	At least 6 months post discharge	• Questionnaire • (Child behaviour checklist)
Coping	Child Parent	Self and parent Parent	At least 6 months post discharge	• Questionnaire • (Children's coping strategies checklist)
Social functioning	Child	Self	At least 6 months post discharge	• Questionnaire • (PROMIS peer relationships form)

Post-traumatic stress	Child Parent	Psychologist Self and parent Parent	At least 6 months post discharge and from age 7 years	• Questionnaire • (PTSD Checklist for DSM-5)
Neurocognitive outcomes				
General intelligence	Child	Psychologist	At least 6 months after discharge and age 2 years	• Intelligence assessment • (Bayley scales of infant development)
Attention	Child	Psychologist	At least 6 months after discharge and from age 6 years	• Neuropsychological assessment • (Developmental NEuroPSYchological Assessment (NEPSY))
Memory (visual/verbal)	Child	Psychologist	At least 6 months after discharge and from age 6 years	• Neuropsychological assessment • (Children's memory scales)
Visuo-motor integration	Child	Psychologist	At least 6 months after discharge and from age 2 years	• Neuropsychological assessment • (Beery test of Visuo-motor integration)
Executive functioning	Child	Psychologist Parent	At least 6 months after discharge and from age 2 years	• Neuropsychological assessment Questionnaire • (Behaviour rating of executive function)
Language development	Child	Psychologist	At least 6 months after discharge and from age 2 years	• Neuropsychological assessment • (Bayley and NEPSY)
Quality of life				
Physical functioning	Child and Parent	Self and parent	At least 6 months post discharge	• Questionnaire • (Pediatric quality of life inventory)
Emotional functioning	Child and Parent	Self and parent	At least 6 months post discharge	• Questionnaire • (Pediatric quality of life inventory)
Social functioning	Child and Parent	Self and parent	At least 6 months post discharge	• Questionnaire • (Pediatric quality of life inventory)

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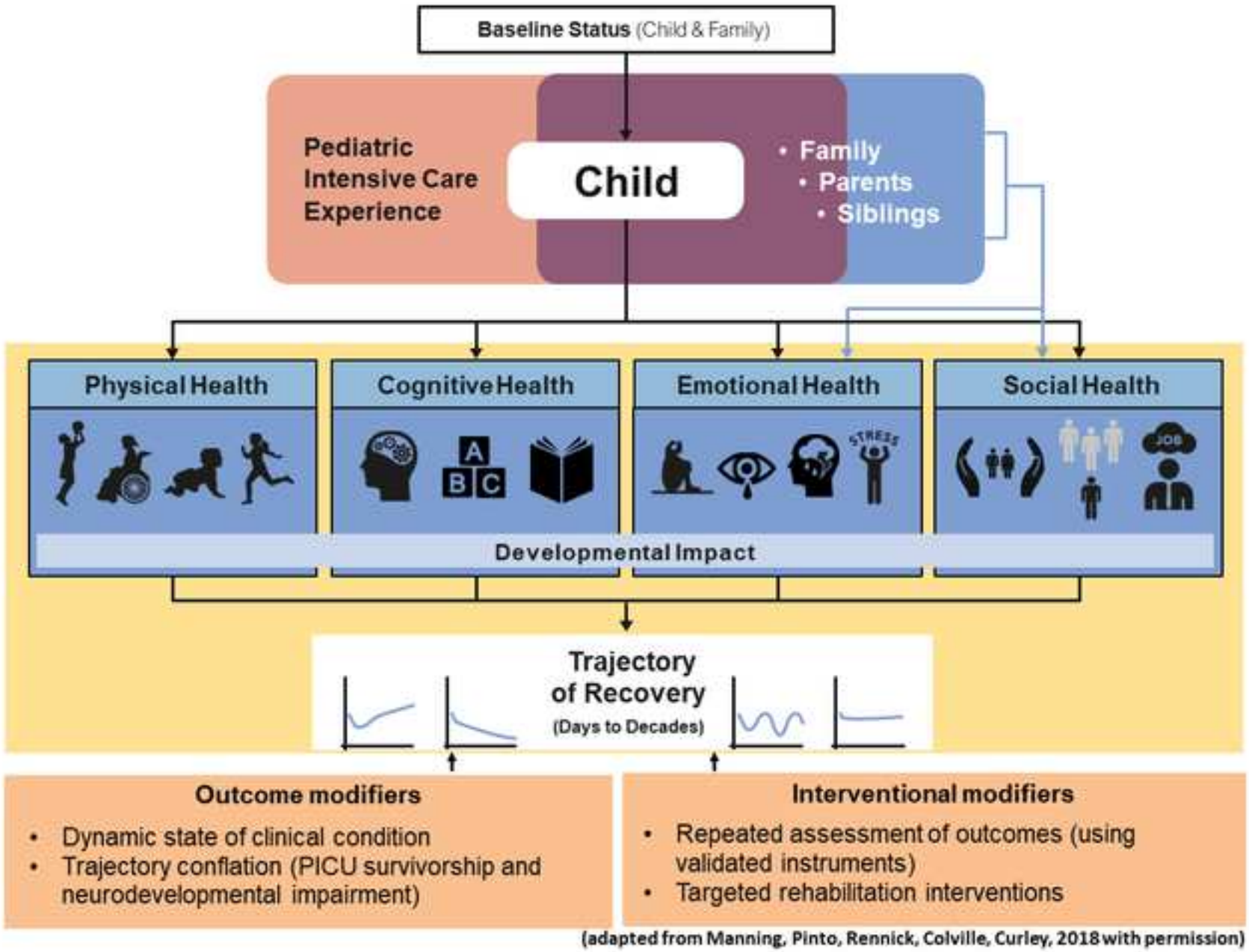
Figure



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AUTHORSHIP AND CONFLICT OF INTEREST STATEMENT

The undersigned authors declare that the **authorship roles** and **conflict of interest** statements reported in the manuscript are correct and true.

#	First name	Last name	email	Signature
1	Kate	Brown	katherine.brown@gosh.nhs.uk	kate brown
2	Robert	Tasker	robert.tasker@childrens.harvard.edu	robert tasker
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