Critical Care Neurology (H Hinson, Section Editor)

Postintensive Care Syndrome in Pediatric Critical Care Survivors: Therapeutic Options to Improve Outcomes After Acquired Brain Injury

Cydni N. Williams, MD[1,2,*]
Mary E. Hartman, MD, MPH[3]
Kristin P. Guilliams, MD, MSCI[3,4]
Rejean M. Guerriero, DO[4]
Juan A. Piantino, MD[1,5]
Christopher C. Bosworth, PhD[6]
Skyler S. Leonard, MEd, MA[7]
Kathryn Bradbury, PhD[7]
Amanda Wagner, PhD[7]
Trevor A. Hall, PsyD, ABPdN[1,7]

Address
[*,1]Pediatric Critical Care and Neurotrauma Recovery Program, Oregon Health and Science University, 707 SW Gaines St., CDRC-P, Portland, OR, 97239, USA
Email: willicyd@ohsu.edu
[2]Department of Pediatrics, Division of Pediatric Critical Care, Oregon Health and Science University, Portland, OR, USA
[3]Department of Pediatrics, Division of Critical Care Medicine, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, USA
[4]Department of Neurology, Division of Pediatric and Developmental Neurology, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, USA
[5]Department of Pediatrics, Division of Pediatric Neurology, Oregon Health and Science University, Portland, OR, USA
[6]Department of Psychology, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, USA
[7]Department of Pediatrics, Division of Pediatric Psychology, Oregon Health and Science University, Portland, OR, USA

This article is part of the Topical Collection on *Critical Care Neurology*

Abstract

Purpose of review Children surviving the pediatric intensive care unit (PICU) with neuro-logic illness or injury have long-term morbidities in physical, cognitive, emotional, and social functioning termed postintensive care syndrome (PICS). In this article, we review acute and longitudinal management strategies available to combat PICS in children with acquired brain injury.

Recent findings Few intervention studies in this vulnerable population target PICS mor-bidities. Small studies show promise for both inpatient- and outpatient-initiated thera-pies, mainly focusing on a single domain of PICS and evaluating heterogeneous popula-tions. While evaluating the effects of interventions on longitudinal PICS outcomes is in its infancy, longitudinal clinical programs targeting PICS are increasing. A multidisciplinary team with inpatient and outpatient presence is necessary to deliver the holistic integrated care required to address all domains of PICS in patients and families.

Summary While PICS is increasingly recognized as a chronic problem in PICU survivors with acquired brain injury, few interventions have targeted PICS morbidities. Research is needed to improve physical, cognitive, emotional, and social outcomes in survivors and their families.

Introduction

Neurologic injury and disease accounts for > 20% of intensive care unit (ICU) admissions in children and includes traumatic brain injury (TBI), stroke, cardiac arrest (CA), and infectious and inflamma-tory diseases [1–3]. Each year, tens of thousands of children receive specialized pediatric neurocritical care (PNCC) to treat the primary insult and mini-mize secondary neuronal injury in an effort to improve outcomes. Many interventions have little evidence base relying on adult data or small obser-vational studies [1]. Even with specialized care and available therapies, PNCC patients have the highest rates of death and long-term morbidity in pediatric critical care [2, 3•, 4•].

Impairments in physical, cognitive, emotional, and social function, termed postintensive care syndrome (PICS), affect these children years after discharge and similarly affect family members (PICS-F) [5•, 6•, 7, 8•]. PICS is increasingly recognized, though few thera-peutic interventions have been studied specifically targeting this important entity. In this article, we review therapeutic treatment options with a focus on PICS outcomes in PNCC patients (Tables 1 and 2). In addi-tion to therapies administered during hospitalization, we review treatment options for PICS delivered longitu-dinally by multidisciplinary providers that include pedi-atric critical care, pediatric neurology, and pediatric neu-ropsychology [9•, 10•]. We also highlight gaps in knowledge related to interventions for PICS and the need for future research to improve outcomes through prevention and treatment among these vulnerable chil-dren and families.

Inpatient treatment

Much of the inpatient care provided to PNCC patients relies on data extrapo-lated from adult populations or observational studies [1, 11••]. To date, large intervention trials among PNCC patients have failed to show benefit or suffered from lack of recruitment [12, 13••, 14, 15]. Despite challenges, these large studies created infrastructure to study acute interventions in PNCC populations,

Table 1. Highlighted studies evaluating inpatient-initiated treatments for the prevention or treatment of postintensive care syndrome

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
Esses et al. 2019	Pilot randomized trial	62 caregivers of PICU patients and 19 nurses	Each caregiver randomly received 1 of 3 educational strategies: brochures, scripted conversation, or a 3-min video; nurses were asked how the intervention affected work flow	PRISM framework for effectiveness of the education, the effect of each educational intervention, and costs	All strategies had notable improvement in understanding of PICS, with no single strategy being superior; nurses reported that all 3 interventions minimally disrupted workflow	Small sample; unsure of duration of the duration effect of each of the 3 strategies
Rennick et al. 2018	Pilot randomized controlled trial	20 subjects aged 2–14 years who are admitted to the PICU; n = 10 intervention and control group	PICU soothing consisted of (1) parental comforting (touch and reading), followed by (2) a quiet period with music via soft headbands, administered once daily throughout hospitalization	Participation rates, observation, measurement completion rates, semistructured interviews, telephone calls; psychological well-being was assessed using measures of distress, sleep, and child and parent anxiety in the PICU, on the wards, and 3 months of post discharge	70% of parents responded positively to comforting and 100% to music; intervention data suggested lower child and parent anxiety after transfer from PICU to the ward	Nonblinded, small sample; relatively high study refusal rate
Moler et al. 2017	Randomized controlled trial	329 subjects aged 0–18 years after in-hospital cardiac arrest requiring chest	Targeted temperature management, either therapeutic hypothermia (target	VABS-II	No significant difference between the groups in the primary outcome of survival with a	Trial stopped early because of an assessment of futility; long time from the return of circulation to the

Table 1. (Continued)

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
		compressions ≥2 min	temperature, 33 °C) or therapeutic normothermia (target temperature, 36.8 °C)		favorable neurobehavioral outcome at 12 months (VABS ≥70)	achievement of a temperature within the target temperature range; no pretrial phase-in; did not use only high-enrolling sites
Moler et al. 2015	Randomized controlled trial	295 subjects aged 0–18 years after out-of-hospital cardiac arrest requiring chest compressions for ≥2 min	Targeted temperature management, either therapeutic hypothermia (33 °C) or therapeutic normothermia (target temperature, 36.8 °C)	VABS-II	No significant difference between the groups in the primary outcome of survival with a favorable neurobehavioral outcome at 12 months (VABS ≥70)	Caregiver/research staff awareness of treatment assignment; no pretrial phase-in; did not use only high-enrolling sites
Adelson et al. 2013	Randomized controlled trial	77 subjects aged 0–17 years with nonpenetrating brain injury (GCS 3–8) and motor GCS < 6 after resuscitation	Targeted temperature management: hypothermia (32–33 °C) for 48–72 h versus normothermia	Mortality at 3 months, global function at 3 months with the Glasgow Outcome Scale	No difference in mortality or global function	Terminated early for futility; small sample; variability of pathology seen on imaging despite similar GCS score
Linton et al. 2008	Pilot study	35 questionnaires to gather transfer information to develop brochure and 21 questionnaires about the brochure from families of children who had	Discharge information brochure from PICU to the ward	12-question questionnaire with 5-point Likert scale	95% of parents believed the brochure was easy to read, understand, and helpful in improving their understanding of what to expect on the ward	No validated measure of stress or anxiety; low response rate; English speaking only

Table 1. (Continued)

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
		spent 1–28 days in the PICU				
Melnyk et al. 2004	Randomized controlled trial	174 mothers and their 2- to 7-year old children who were admitted to the PICU	3-phase educational-behavioral intervention program (COPE program) delivered: (1) 6–16 h after PICU admission, (2) 2–16 h after transfer to the ward, (3) 2–3 days after discharge from hospital	1-, 3-, 6-, and 12-month follow-up: maternal anxiety, negative mood state, depression, maternal beliefs, parental stress, parent participation in their children's care, child adjustment assessed with BASC	Mothers who received the COPE intervention experienced less stress, improved maternal functional and emotional coping outcomes, and participated more in their child's care; children had significantly fewer withdrawal symptoms, fewer negative behavioral symptoms and externalizing behaviors at 12 months; mothers reported children had less hyperactivity and greater adaptability	High rate of attrition through 12 months; questionnaire-based assessments; English speaking only

Acronyms for Table (alphabetical order): *BASC* behavioral assessment system for children, *COPE* creating opportunities for parent empowerment, *GCS* Glasgow Coma Score, *PICU* pediatric intensive care unit, *PRISM* practical, robust implementation and sustainability model, *VABS-II* Vineland Adaptive Behavior Scales, second edition

Table 2. Highlighted studies evaluating outpatient-initiated treatments for postintensive care syndrome

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
Treble-Barna et al. 2016	Open-label controlled pilot trial	13 subjects with complicated mild-to-severe TBI (average 5 years of postinjury) and 11 healthy comparison subjects aged 9–15 years	AIM program cognitive intervention	TEAch subtests, D-KEFs, BRIEF, GAS	Children with TBI demonstrated significant improvement post intervention on a neuropsychological measure of sustained attention; reported expected or more-than-expected personalized goal attainment	Small sample; high attrition rate; lack of long-term follow-up
Samuel et al. 2015	Randomized controlled trial	209 parents of 145 children consecutively admitted to the PICU	High-risk parents ($n = 78$) randomized to follow-up clinic appointment 2 months after discharge versus control	Parents were assessed for risk of developing posttraumatic stress disorder at discharge with the Posttraumatic Adjustment Scale; Impact of Event Scale-Revised and Hospital Anxiety and Depression Scale were completed at 6 months	There was no significant differences between the intervention and control groups, but there was a small positive impact on symptoms of anxiety and depression in a group prospectively identified as at risk of poorer psychological outcome	Only 37% of parents randomized to clinic appointment intervention completed the appointment; follow-up data for only 75% overall
Wade et al. 2015	Randomized controlled trial	132 subjects aged 12–17 years with TBI	6-, 12-, and 18-month assessment after CAPS intervention or Internet resource only control	Children and Functional Assessment Scale; IFIRS	Significant improvement in overall rates of impairment and school/work functioning with CAPS when compared with control	Potential for selection bias and confounders of therapist interactions
Als et al. 2015	Pilot randomized controlled trial	31 parents of children aged 4–16 years admitted to the PICU	Psychoeducational tool within 7 days of discharge, supported by a telephone call within 14 days of receiving the tool	Number of feasibility criteria successfully met (linked to the intervention and the study design)	Parents who received intervention reported lower posttraumatic stress symptoms in themselves and fewer emotional and behavioral difficulties in their children	Small sample, single-center study

Table 2. (Continued)

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
Catroppa et al. 2015	Pilot observational study	10 subjects aged 8–13 years with ABI	18-week intervention program, preintervention, immediate, and 6-month postintervention assessments	Attention and memory, assessed by Amat-c using both neuropsychological and ecologically sensitive measures	Improvement of postintervention (immediate and 6-month) attention and memory, with generalization to everyday life	Small sample; lack of control group; assessors and parents were not blind to intervention
Ho et al. 2011	Prospective observational study	15 subjects aged 11–17 years with mild, moderate, or severe ABI 1–12 years since injury (9 TBI; 3 had strokes, 2 near drowning accidents, and 1 infection)	6-week treatment protocol using diaries and self-instruction training	Attention and memory, assessed by TEAch subtests	Although memory was the primary outcome targeted by treatment, attention scores improved significantly after the training (selective/focuses attention and attentional control)	Self-selected cohort; not randomized; small sample; limited cognitive testing
Colville et al. 2010	Exploratory randomized controlled trial	154 families of children admitted to the PICU (82 intervention; 72 control)	Follow-up clinic appointment 2 months after discharge versus control	Parent's baseline stress assessed using Parental Stressor Scale: PICU; posttraumatic stress, anxiety, and depression were assessed at 5 months using Impact of Event Scale and the Hospital Anxiety and Depression Scale	No significant differences were found between the intervention and control groups as a whole; parents with higher baseline stress reported lower rates of posttraumatic stress and depression at 5 months if they had been offered an appointment than if they had not	Only 18/82 families chose to attend the follow-up clinic appointment; outcome data were provided by 55/82 parents in intervention group and 50/72 in control group screening measures were used to establish psychopathology rather than full diagnostic interviews
Wade et al. 2008	Pilot observational trial	9 subjects aged 11–18 years with TBI (2 severe and 7 moderate) less than 24 months prior; either TOPS with or without audio	TOPS intervention; 10 core sessions and up to 4 supplemental sessions	Adolescent and family psychosocial functioning	Significant improvements in parent-reported adolescent internalizing behaviors, self-reported adolescent depressive symptoms, parental depression, and	Small sample; lack of control group; self-reported measures

Table 2. (Continued)

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
					parent-adolescent conflict; providing audio may enhance some outcomes	
King et al. 2007	Randomized controlled trial	11 school-aged children with sickle cell disease and memory deficits	2-year education rehabilitation program, including tutoring with (intervention group) or without memory training (control)	Neuropsychological evaluation prior to intervention; at 1st test session, WASI; all sessions included CVLT-C, Digit Span subtest, Wechsler Individual Achievement Tests-Second Edition	Children with memory deficits receiving educational rehabilitation may improve with general tutoring alone; some students may have greater improvement after receiving general tutoring and targeted memory strategies	Small sample
Wade et al. 2006	Randomized controlled trial	32 subjects aged 5–16 years with moderate-to-severe TBI	7 sessions of problem solving/skill-building intervention over 6-month period (FPS) or control	Child Behavior Checklist, Brief Symptom Inventory, Conflict Behavior Questionnaire	FPS group reported significantly greater improvements in their children in internalizing symptoms, anxiety, depression, and withdrawal	Small and heterogeneous sample; structure of intervention
Hooft et al. 2005	Randomized controlled trial	38 subjects aged 9–16 years with ABI	17-week cognitive program for 30 min per day with a teacher or parent	Attention and memory, assessed by neuropsychological tests at end of program	Significant improvements of the treatment group in the majority of neuropsychological tests of sustained and selective attention as well as in memory performance	Small sample; no long-term effects tested

Table 2. (Continued)

First author/year	Study design	Population	Intervention	Primary outcomes	Study conclusions	Study limitations
Braga et al. 2005	Randomized controlled trial	87 subjects aged 5–12 years with chronic impairment after TBI	1 year of intensive services either family-supported (intervention) or clinician-delivered (control)	Physical outcome with Sarah scales and cognitive outcome with WISC-III	Family-supported intervention sample efficiently acquired the skills needed to deliver physical and cognitive interventions within the context of everyday routines of the child's life at home and showed significant improvements on outcome measures compared with control group	Multiple interpretations of interventions; relatively small sample size
Yerys et al. 2003	Pilot observational study	6 children with sickle cell disease-related infarcts	8 weekly 1-h sessions; 3/6 children received additional memory training	Sessions 1 (preintervention) and 8 (postintervention), children completed learning and memory assessments (numbers of subtest from CMS, CVLT-C)	Children who received additional memory training appeared to improve more than that of children receiving only tutoring	Small sample; limited testing period

Acronyms for Table (alphabetical order): *ABI* acquired brain injury, *AIM* attention improvement and management, *Amat-c* Amsterdam Memory and Attention Training for Children, *BRIEF* Behavior Rating Inventory of Executive Function, *CAPS* counselor-assisted problem solving, *CVLT-C* California Verbal Learning Test–Children's Version, *CMS* Children's Memory Scale, *D-KEFS* Delis-Kaplan Executive Function System, *FPS* family-centered problem solving intervention, *FPST* family problem solving therapy, *GAS* Goal Attainment Scale, *GCS* Glasgow Coma Score, *IFIRS* Iowa Family Interaction Rating Scale, *IRC* Internet resource comparison, *MVC* motor vehicle collision, *PICS* postintensive care syndrome, *PICU* pediatric intensive care unit, *SES* socioeconomic status, *TBI* traumatic brain injury, *TEAch* Test for Everyday Attention for Children, *TOPS* teen online problem solving intervention, *WASI =* Wechsler Abbreviated Scale of Intelligence, *WISC-III* Weschler Intelligence Scale for Children, third edition

provided meaningful secondary analyses highlighting the high prevalence of PICS outcomes in children with acquired brain injury, and informed consensus guidelines [11••, 16, 17•, 18•, 19•, 20•, 21•, 22••]. While a review of therapeutic strategies in all PNCC populations is beyond the scope of this review, we highlight existing PNCC intervention trials and potential therapeutic targets to impact PICS outcomes in the acute phase.

Likely the best data on interventions in PNCC populations comes from trials of targeted temperature management (TTM). Hyperthermia after brain injury increases neuronal injury and excitotoxicity, and fever is associated with worse outcomes [23]. Hypothermia is effective at lowering intracranial pressure (ICP) when refractory to medical therapy [11••, 24•]. However, multiple randomized trials evaluating therapeutic hypothermia with TTM in pediatric TBI and CA populations failed to show benefit for mortality or gross functional outcome improvements compared with normothermia 1 year after discharge [12, 13••, 14, 25, 26]. TTM with active normothermia is considered standard of care by many PNCC providers for comatose patients with brain injury, but improvements in PICS outcomes have not been documented.

Another promising trial in PNCC, the Thrombolysis in Pediatric Stroke study, closed early due to poor enrollment from delays in pediatric stroke diagnosis [15]. Thus, there remain no randomized clinical trials for acute stroke treatment in children. Pediatric stroke patients may still be offered thrombolysis or mechanical thrombectomy based on adult data. Since the advent of multiple successful thrombectomy trials in adults [27], particularly those extending the therapeutic window to 16 or 24 h [28, 29], there has been increasing enthusiasm and case series on the use of thrombectomy in children [30–33]. Studies report low complication rates and improved physical and cognitive outcomes, but these results may be limited by publication bias [30–33].

Seizures lead to secondary brain injury and complicate admissions in 10–40% of critically ill children, particularly PNCC patients. Patients with status epilepticus due to a range of etiologies have a higher mortality and worse PEDIATRIC CEREBRAL PERFORMANCE CATEGORY [34–36]. Higher seizure burden is also associated with a significant neurological decline during critical care hospitalization and worse neurobehavioral outcomes after discharge [37, 38]. However, the intensity of treatment of seizures with sedating medications like benzodiazepines may be associated with unintended sequelae, such as prolonged ICU stays and intubation, which are risk factors for delirium in the acute setting and ultimately PICS [39•, 40•]. There are few studies that address the impact of seizures, seizure burden, or seizure treatment on PICS, but seizures offer a potentially modifiable target for intervention studies.

ICU liberation

Implementation of the ABCDEF bundle improves outcomes in adult critical care [41, 42]. The bundle geared toward assessing and treating pain, early extubation, minimizing oversedation, identifying and treating delirium, early mobility, and family engagement may mitigate PICS and PICS-F [41–43]. Many institutions have implemented protocols in critically ill children addressing some or all of these components, but it is unclear if similar benefits on outcomes can be achieved in pediatrics [44–46, 47••, 48, 49].

Early and intensive rehabilitation can improve outcomes in critical care patients, stroke, and TBI, but the exact timing and regimens that will provide optimal outcomes in PNCC survivors remain unknown [42–44, 46•, 49, 50]. Early mobilization in critically ill patients has potential to reduce delirium, decrease length of mechanical ventilation, and decrease length of stay, but the longitudinal benefits of early mobilization related to PICS in children are unknown [44, 46•, 47••, 48, 51]. Research on mobilization therapies implemented in the pediatric ICU, especially among PNCC patients, is in its infancy and may offer one route to improving PICS morbidities. Fink et al. showed early protocolized mobilization was well tolerated and feasible in PNCC [47••].

PNCC patients are at risk for delirium, which is associated with worse outcomes including death, functional outcome, quality of life, and psychosocial morbidity in adult critical care populations [39•, 40•]. Studies in children show increased mortality, length of stay, and mechanical ventilation duration [40•]. Relationships between delirium and long-term PICS outcomes have not been studied well in children, but delusional memories are associated with increased risk of posttraumatic stress [52]. Environmental strategies to reduce delirium are considered first line and include attention to light, noise, and sleep. Weaning from sedatives and narcotics, early mobilization, and early extubation are additional strategies to reduce delirium [44, 53•]. While pharmacologic interventions such as dexmedetomidine and atypical antipsychotics are used, these therapies are not approved for delirium in children, and the safety profile in the PNCC population is unknown [39•].

Sedatives, anesthetics, and analgesics commonly used in the pediatric ICU are linked to delirium and worse cognitive outcomes in children [54•]. Many of these medications are shown to induce neuronal apoptosis and likely have detrimental effects on the developing brain in addition to increasing risk of delusional memories and delirium [52, 55, 56]. While these medications are necessary for the acute care of many critically ill children, clinicians should be mindful of potentially harmful effects, minimize overall exposure as able, and ensure patients and families are aware of the need for longitudinal monitoring of cognition and development.

Outpatient treatment

Outpatient management of PNCC survivors requires multiprofessional care and attention to the unique differences in screening and treatment for different ages and developmental stages. PNCC survivors and families suffer chronic morbidities in all domains of PICS that require systematic screening, identification, and management [9•]. Similar to inpatient management strategies, little evidence base exists to guide care in regard to outpatient prevention and treatment of PICS and PICS-F.

Physical sequelae treatment

PNCC patients are at higher risk for ongoing functional impairments compared with other critical care survivors [4•]. Physical impairments may include headaches, pain, sleep disturbances, fatigue, weakness, or spasticity limiting independence and leading to impaired quality of life [6•, 57•]. Referrals to

occupational, physical, and speech therapies as well as discharge to rehabilitation services are common in PNCC [3•, 9•].

Headache and chronic pain are reported in over 20% of all PNCC survivors [9•]. Headache is best studied in the pediatric TBI population, showing a prevalence >40% and persistence for years after injury [58, 59]. No evidenced-based headache interventions exist [60], and treatment is often multifaceted combining pharmaceutical intervention, diet and lifestyle modifications, and behavioral therapies to concurrently address comorbidities like sleep disturbance, anxiety, or depression [60]. Opioids should be avoided. Acetaminophen, ibuprofen, and nonsteroidal antiinflammatory medications can be used in the acute period, but chronic overuse should be avoided due to risk of adverse effects including rebound headaches. Triptans can be used for migrainous headaches. Amitriptyline, gabapentin, and topiramate are alternatives for headache prevention when other measures fail. Other sources of chronic pain in the PNCC population are less studied, but both headache and general pain are associated with cognitive and psychosocial sequelae in children similar to PICS suggesting pain management is an important research gap in PNCC patients [61, 62].

Sleep disturbances and fatigue are reported in over half of PNCC survivors [9•]. Sleep disturbances are known to be common and pervasive in TBI literature, but few studies focus on injuries more severe than concussion such as those in PNCC patients [63]. Insomnia, daytime somnolence, and fatigue are the most commonly reported phenotypes, all showing associations with worse cognitive, behavioral, psychosocial, and quality of life outcomes [64–69]. There are no evidenced-based therapies for the management of sleep disturbances in PNCC patients [65, 70–72]. Clinicians are left to extrapolate treatment options from adult literature or studies in children with chronic conditions such as epilepsy or neurodevelopmental disorders [70, 72–75]. It is vital to treat comorbidities like pain, depression, anxiety, and posttraumatic stress when present. Many clinicians begin with behavior and lifestyle modifications or melatonin supplementation and then consider adding additional pharmacological support like trazadone or clonidine if sleep disturbances persist depending on the sleep phenotype [76]. Healthy sleep is vital for brain maturation and neuronal healing after injury and sleep represents a crucial area of intervention research in PNCC survivors [64, 77–80].

Seizures can additionally complicate chronic recovery after PNCC, and outpatient providers are tasked with management of seizure medications. Many PNCC patients start antiepileptic medications to treat early seizures as well as for prophylaxis of seizures. In severe TBI, guidelines recommend 7 days of prophylaxis for early posttraumatic seizures [11••]. There is a lack of data on optimal duration of therapy for many PNCC patients with seizures secondary to primary processes like TBI, meningitis, or stroke and known adverse effects of many antiepileptic drugs. Some medications like phenobarbital are associated with cognitive and developmental delays [81]. One of the most common medications for treating seizures in the acute PNCC setting, levetiracetam, is associated with aggression and irritability that is likely to impact a return to normal daily life and confound screening for PICS after discharge [82]. There is evidence that concomitant treatment with pyridoxine may mitigate some behavioral side effects; however, these data are limited [83].

Spasticity is often managed medically with physical therapy and medications [84], including baclofen, gabapentin, clonidine, botox injections, and benzodiazepines. Most of these therapies have side effects like sedation and unstudied effects on cognitive and psychosocial outcomes in PNCC patients [84]. Other interventions to optimize physical rehabilitation for paresis and spasticity have mostly focused on pediatric stroke using constraint-induced movement therapy (CIMT) and transcranial stimulation—either transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS). Study populations have been limited to perinatal stroke, but demonstrate the ability to enhance recovery years after initial injury. CIMT involves splinting the nonaffected upper extremity to limit its use and force use of the weak upper extremity to promote motor function in the affected extremity [85, 86]. Although safe and feasible, trials of tDCS for pediatric stroke motor recovery have been largely negative to date [87•]. Repetitive TMS paired with CIMT or motor learning may enhance upper extremity function in stroke [88].

Cognitive sequelae treatment

Over 50% of all PNCC survivors report cognitive sequelae in memory and attention, and benefit from early evaluation and management with neuropsychologists [9•, 10•]. A recent systematic review of cognitive morbidities associated with pediatric critical care found lower scores across cognitive domains (attention, processing speed, executive functioning, and memory) [54•]. Few studies have investigated cognitive rehabilitation interventions in the PNCC population. Current strategies for cognitive rehabilitation involve interventions designed to reestablish previously learned behaviors or establish new patterns of compensatory mechanisms in impaired cognitive domains [89, 90]. Attention and memory may be improved through daily attention training in children with heterogeneous neurologic diseases or brain malignancy [90, 91]. Self-instruction and diary training improved everyday memory, attention, and mood in a small cohort of children with acquired brain injury from TBI, stroke, and CA [92]. Data in ICU survivors also suggests cognitive benefit of combining physical and cognitive therapies in multifaceted rehabilitation programs [93, 94]. Age and developmental stage at time of injury likely affect response to cognitive rehabilitation and an individual patient's trajectory of recovery [95]. Data supporting effectiveness of specific cognitive rehabilitation strategies in PNCC survivors is limited.

Among children with TBI, cognitive sequelae persist for years in domains of executive function, learning, attention, processing speed, and memory that significantly affect school performance and developmental trajectories [95, 96]. Many cognitive sequelae are severity of injury related, but even patients with mild TBI have chronic cognitive deficits in some studies [95, 96]. A few small studies have evaluated interventions in pediatric TBI patients showing promise for computerized and in-person cognitive rehabilitation programs [97•, 98, 99]. Limited evidence supports the use of pharmacologic management with stimulants like methylphenidate after TBI, though they are often used in patients with concurrent attention deficit/hyperactivity disorder [98]. Evidence suggests early interventions targeting parental education and problem solving can improve function after pediatric TBI particularly among low-socioeconomic status families [100–102], and that family function is a key determinant of

patient outcome [103]. Intensive supports for rehabilitation delivered by families can also improve cognitive outcomes [104].

Approximately 50% of all children with ischemic or hemorrhagic stroke will have long-term cognitive problems [105•, 106•, 107]. Although therapeutic interventions have not specifically targeted the cognitive effects poststroke, efforts to reduce infarct size and minimize physical deficits may improve cognitive outcomes, as these are potentially modifiable factors associated with worse cognitive outcomes [106•, 107]. Memory training, paired with academic tutoring, may improve cognitive outcomes in children after ischemic stroke in the setting of sickle cell disease [108, 109].

Emotional, social, and family sequelae treatment

A growing body of research shows negative psychological sequelae in critical care survivors, including increased levels of anxiety, depression, posttraumatic stress symptoms (PTSS) or disorder (PTSD), and behavioral symptoms [110, 111]. Among PNCC patients, mood disturbances are commonly reported at follow-up including anxiety (35%), behavior changes (26%), and depressive symptoms (16%) [9•]. Parents of PNCC survivors report significant social sequelae in their child and themselves including loss of employment, high financial burden, loss of relationships with family and friends, and difficulty making new friends [5•, 21•, 112]. Parents also suffer high rates of emotional and psychological sequelae including anxiety, depression, PTSS, and PTSD [113•, 114, 115]. Understanding, preventing, and treating PICS-F is not only important for the well-being of the family members but also directly impacts the child through interference with the ability to provide ongoing care and emotional support for the child [116•, 117, 118]. The research is still in its infancy, but data suggest interventions can reduce child and family morbidity [113•], most using psychoeducational and direct intervention methodology.

Psychoeducational interventions include handouts, face-to-face communication, videos, computer modules, and directed activities. Simple interventions like providing informational brochures to parents are feasible and helpful to reduce parent anxiety [119, 120]. Esses et al. examined the effectiveness of educating parents on PICS and PICS-F via three different modes of delivery (brochure, scripted conversation, short video) and found that all interventions increased knowledge about and understanding of PICS [121••]. Studies also demonstrate that parents who spoke about their feelings during the admission [122] experienced greater social support during the ICU admission [123], and those who were involved with medical decision-making [124] had better psychological outcomes. Involvement of psychology and social work during the inpatient stay can also improve the family experience during hospitalization and help prepare the family for discharge [125]. ICU diaries are an emerging intervention with limited pediatric data, but studies show good feasibility and acceptability among families of critically ill children [126•]. A systematic review of the impact of ICU diaries on psychological outcomes of adult ICU patients and their families found significant evidence that ICU diaries decrease anxiety and depression among ICU survivors and improve health-related quality of life [127].

Direct intervention studies often focus on parents as opposed to children. Melnyk et al. evaluated the Creating Opportunities for Parent Empowerment

(COPE) program showing reduced parent stress during pediatric critical care hospitalization, reduced parent psychological sequelae after hospitalization, and improved emotional and behavioral outcomes in children 12 months postdischarge [128]. A study of soothing intervention, the Touch & Talk (T&T) program, promoted quicker return to physiological baseline following invasive procedures in infants and toddlers in the ICU [129]. A later iteration of the intervention consisting of comforting touch, reading, and music via soft headbands in children showed the intervention lowered child and parent anxiety in the hospital and after discharge [130••]. Peer support both during and after the ICU is of growing interest in adult critical care with promising results on PICS and PICS-F [131], but the impact of support groups on patient and family outcomes in pediatrics is unknown.

ICU follow-up

Several studies have evaluated the feasibility and impact of offering follow-up to patients and families after discharge. A study evaluating the combination of a psychoeducational tool and follow-up phone call for critically ill children showed the majority of parents found the intervention was useful (82%) and reduced anxiety and concern (77%), with small effects on lowering PTSD and depressive symptoms in parents and behavioral concerns in the children [132]. Literature shows follow-up clinics are feasible as a method to deliver interventions and typically include a paired visit with a psychologist/psychiatrist and medical staff (physician or nurse) within 8 weeks of discharge [9•, 10•, 133–135]. High-risk parents may particularly benefit from reductions in anxiety and depressive symptoms [134]. Multidisciplinary programs spanning inpatient and outpatient care are increasing, have high rates of follow-up, and offer exciting opportunities to learn more about PICS and PICS-F [9•, 10•]. Programs that include pediatric critical care, neurology, and neuropsychology in combined follow-up visits report high rates of follow-up (≥ 66%), frequent symptoms requiring ongoing care in 85% of children, and high rates of parent satisfaction [9•, 10•]. Having multiple professions in one clinic allows an individualized and holistic approach to treatment of PICS. For instance, headaches may be treated pharmacologically, but treatment paired with sleep management strategies and psychotherapeutic intervention for comorbidities like anxiety and acute stress may improve effectiveness. Similarly, cognitive interventions that include management of physical sequelae like sleep disturbance and pain, in addition to strategies harnessing relative cognitive strengths, will maximize effectiveness. It is clear that focusing on one domain of PICS in isolation would substantially limit recovery potential and requires a multidisciplinary approach. Follow-up clinics are ideal to deliver this coordinated care.

Conclusion

Children surviving PNCC and their families suffer chronic morbidities encompassed by PICS. Few interventions have been studied in this population, and clinicians managing children and families with PICS are left with little evidence base to guide care. The breadth of PICS morbidities requires multidisciplinary management integrated into clinical care beginning with the acute admission and extending longitudinally after discharge. Research on acute

interventions to prevent PICS and therapeutic interventions to treat PICS are needed across the spectrum of physical, cognitive, emotional, and social domains of PICS in children and families.

Funding Information

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer
The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.   Wainwright MS, Hansen G, Piantino J. Pediatric neurocritical care in the 21st century: from empiricism to evidence. Curr Opin Crit Care. 2016:1–7.
2.   Moreau JF, Fink EL, Hartman ME, Angus DC, Bell MJ, Linde-Zwirble WT, et al. Hospitalizations of children with neurologic disorders in the United States. Pediatr Crit Care Med. 2013;14(8):801–10.
3.•   Williams CN, Piantino J, McEvoy C, Fino N, Eriksson CO. The burden of pediatric neurocritical care in the United States. Pediatr Neurol. 2018;89:31–8.
Using a national administrative database, this work evaluated common PNCC diseases highlighting billions of dollars in hospital costs, frequent need for critical care interventions, and poor neurologic outcomes.
4.•   Choong K, Fraser D, Al-Harbi S, et al. Functional recovery in critically ill children, the "WeeCover" multicenter study. Pediatr Crit Care Med. 2018;19(2):145–54.
A multi-center prospective study showing PNCC patients are at highest risk for persistent or worsening of functional impairments among pediatric ICU survivors.
5.•   Williams CN, Eriksson C, Piantino J, et al. Long-term sequelae of pediatric neurocritical care: the parent perspective. J Pediatr Intensive Care. 2018;7(4):173–81.
A qualitative study evaluating the burden of PNCC on long-term survivors and families highlighting the significant emotional, psychological, and social impacts of PNCC diseases on patients and families.
6.•   Watson RS, Choong K, Colville G, et al. Life after critical illness in children-toward an understanding of pediatric post-intensive care syndrome. J Pediatr. 2018;198:16–24.
Recent review of PICS highlighting the multidimensional sequelae of critical care and need for research.
7.   Manning JC, Pinto NP, Rennick JE, Colville G, Curley MAQ. Conceptualizing post intensive care syndrome in children-the PICS-p framework. Pediatr Crit Care Med. 2018;19(4):298–300.
8.•   Herrup EA, Wieczorek B, Kudchadkar SR. Characteristics of postintensive care syndrome in survivors of pediatric critical illness: a systematic review. World J Crit

Care Med. 2017;6(2):124–34.
Recent review of PICS highlighting the symptomatology within PICS domains.

9.•   Williams CN, Kirby A, Piantino J. If you build it, they will come: initial experience with a multi-disciplinary pediatric neurocritical care follow-up clinic. Children (Basel). 2017;4(9):1–8.
A case series and descriptive study evaluating PNCC survivors at follow-up within a unique multidisciplinary clinic that includes pediatric critical care, neurology, and neuropsychology. PICS outcomes evaluated highlight the high rates of PICS morbidities in survivors.

10.•   Dodd JN, Hall TA, Guilliams K, et al. Optimizing neurocritical care follow-up through the integration of neuropsychology. Pediatr Neurol. 2018;89:58–62.
Study describing integration of neuropsychology into PICS follow-up programs for PNCC patients showing high rates of parent satisfaction and intervention needs among patients.

11.••   Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the management of pediatric severe traumatic brain injury, third edition: update of the brain trauma foundation guidelines. Pediatr Crit Care Med. 2019;20(3S Suppl 1):S1–S82.
The most recent (2019) guidelines for the management of severe TBI in pediatrics including literature review and expert consensus opinions.

12.   Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med. 2015;372(20):1898–908.

13.••   Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med. 2017;376(4):318–29.
Results of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial for in-hospital cardiac arrest showing no benefit of hypothermia over normothermia for death or functional outcomes at 1 year. This was similar to prior publications for out-of-hospital cardiac arrest published in 2015.

14.   Adelson PD, Wisniewski SR, Beca J, Brown SD, Bell M, Muizelaar JP, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. Lancet Neurol. 2013;12(6):546–53.

15.   Rivkin MJ, de Veber G, Ichord RN, et al. Thrombolysis in pediatric stroke study. Stroke. 2015;46(3):880–5.

16.   Bernard TJ, Rivkin MJ, Scholz K, deVeber G, Kirton A, Gill JC, et al. Emergence of the primary pediatric stroke center: impact of the thrombolysis in pediatric stroke trial. Stroke. 2014;45(7):2018–23.

17.•   Slomine BS, Silverstein FS, Christensen JR, et al. Neuropsychological outcomes of children 1 year after pediatric cardiac arrest: secondary analysis of 2 randomized clinical trials. JAMA Neurol. 2018;75(12):1502–10.
Secondary analysis of THAPCA showing the majority of survivors have cognitive and neuropsychological deficits after cardiac arrest, including 71% of those classified as having good functional outcomes. This highlights the need for screening with performance-based neuropsychological tests in addition to caregiver reports and measures of functional outcomes.

18.•   Slomine BS, Nadkarni VM, Christensen JR, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: neurobehavioral outcomes in initially comatose children. Resuscitation. 2017;115:178–84.
Secondary analysis of THAPCA showing poor neurobehavioral outcomes were high for this subgroup of cardiac arrest survivors.

19.•   Silverstein FS, Slomine BS, Christensen J, et al. Functional outcome trajectories after out-of-hospital pediatric cardiac arrest. Crit Care Med. 2016;44(12):e1165–e74.
Secondary analysis of THAPCA out-of-hospital arrest at high risk of functional impairments showing that discharge and 3-month functional scores predicted 12-month performance well in survivors.

20.•   Meert K, Slomine BS, Silverstein FS, et al. One-year cognitive and neurologic outcomes in survivors of paediatric extracorporeal cardiopulmonary resuscitation. Resuscitation. 2019;139:299–307.
Secondary analysis of THAPCA showing many extracorporeal resuscitation survivors had favorable outcomes at 12 months that were similar to comatose children after resuscitation without extracorporeal support.

21.•   Meert K, Slomine BS, Christensen JR, et al. Burden of caregiving after a child's in-hospital cardiac arrest. Resuscitation. 2018;127:44–50.
Secondary analysis of THAPCA showing that caregiver burden is high in the first year after hospitalization especially among for caregivers of children with worse neurobehavioral dysfunction.

22.••   Ferriero DM, Fullerton HJ, Bernard TJ, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2019;50(3):e51–96.
Expert guidelines for the management of pediatric stroke.

23.   Natale JE, Joseph JG, Helfaer MA, Shaffner DH. Early hyperthermia after traumatic brain injury in children: risk factors, influence on length of stay, and effect on short-term neurologic status. Crit Care Med. 2000;28(7):2608–15.

24.•   Benedetti GM, Silverstein FS. Targeted temperature management in pediatric neurocritical care. Pediatr Neurol. 2018;88:12–24.
Review of clinical indications and experimental physiology studies for use of TTM in PNCC.

25.   Hutchison JS, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358(23):2447–56.

26.   Beca J, McSharry B, Erickson S, et al. Hypothermia for traumatic brain injury in children-a phase II randomized controlled trial. Crit Care Med. 2015;43(7):1458–66.

27.   Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31.

28. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11–21.

29. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708–18.

30. Wilson JL, Eriksson CO, Williams CN. Endovascular therapy in pediatric stroke: utilization, patient characteristics, and outcomes. Pediatr Neurol. 2017;69:87–92 e2.

31. Shoirah H, Shallwani H, Siddiqui AH, Levy EI, Kenmuir CL, Jovin TG, et al. Endovascular thrombectomy in pediatric patients with large vessel occlusion. J Neurointerv Surg. 2019;11:729–32.

32. Buompadre MC, Andres K, Slater LA, Mohseni-Bod H, Guerguerian AM, Branson H, et al. Thrombectomy for acute stroke in childhood: a case report, literature review, and recommendations. Pediatr Neurol. 2017;66:21–7.

33. Lee S, Heit JJ, Albers GW, Wintermark M, Jiang B, Bernier E, et al. Neuroimaging selection for thrombectomy in pediatric stroke: a single-center experience. J Neurointerv Surg. 2019;11:940–6.

34. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222–9.

35. Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006;5(9):769–79.

36. Topjian, A.A., Gutierrez-Colina, A.M., Sanchez, S.M., et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically ill children. Crit Care Med 2013;41(1):215-23.

37. Payne ET, Zhao XY, Frndova H, McBain K, Sharma R, Hutchison JS, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain. 2014;137(Pt 5):1429–38.

38. Abend NS, Wagenman KL, Blake TP, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav. 2015;49:238–44.

39.• Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. Pediatr Clin North Am. 2017;64(5):1117–32.
Review of pediatric delirium epidemiology, evaluation, and management in pediatric ICU.

40.• Traube C, Silver G, Gerber LM, et al. Delirium and mortality in critically ill children: epidemiology and outcomes of pediatric delirium. Crit Care Med. 2017;45(5):891–8.
Single-center study showing association between delirium and worse outcomes in pediatric ICU patients.

41. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med. 2019;47(1):3–14.

42. Hsieh SJ, Otusanya O, Gershengorn HB et al. Staged implementation of awakening and breathing, coordination, delirium monitoring and management, and early mobilization bundle improves patient outcomes and reduces hospital costs. Crit Care Med 2019;47(7):885–893.

43. Arias-Fernandez P, Romero-Martin M, Gomez-Salgado J, Fernandez-Garcia D. Rehabilitation and early mobilization in the critical patient: systematic review. J Phys Ther Sci. 2018;30(9):1193–201.

44. Walker TC, Kudchadkar SR. Early mobilization in the pediatric intensive care unit. Transl Pediatr. 2018;7(4):308–13.

45. Colwell BRL, Olufs E, Zuckerman K, Kelly SP, Ibsen LM, Williams CN. PICU early mobilization and impact on parent stress. Hosp Pediatr. 2019;9(4):265–72.

46.• Cuello-Garcia CA, Mai SHC, Simpson R, Al-Harbi S, Choong K. Early mobilization in critically ill children: a systematic review. J Pediatr. 2018;203:25–33 e6.
Recent review of early mobilization therapies and protocols for pediatric ICU patients.

47.•• Fink EL, Beers SR, Houtrow AJ, et al. Early protocolized versus usual care rehabilitation for pediatric neurocritical care patients: a randomized controlled trial. Pediatr Crit Care Med. 2019;20(6):540–50.
Randomized controlled trial of protocolized early mobilization therapies for PNCC patients showing good feasibility outcomes.

48. Treble-Barna A, Beers SR, Houtrow AJ, Ortiz-Aguayo R, Valenta C, Stanger M, et al. PICU-based rehabilitation and outcomes assessment: a survey of pediatric critical care physicians. Pediatr Crit Care Med. 2019;20(6):e274–e82.

49. Colwell BRL, Williams CN, Kelly SP, Ibsen LM. Mobilization therapy in the pediatric intensive care unit: a multidisciplinary quality improvement initiative. Am J Crit Care. 2018;27(3):194–203.

50. Konigs M, Beurskens EA, Snoep L, Scherder EJ, Oosterlaan J. Effects of timing and intensity of neurorehabilitation on functional outcome after traumatic brain injury: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2018;99(6):1149–59 e1.

51. Hopkins RO, Choong K, Zebuhr CA, Kudchadkar SR. Transforming PICU culture to facilitate early rehabilitation. J Pediatr Intensive Care. 2015;4(4):204–11.

52. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. Am J Respir Crit Care Med. 2008;177(9):976–82.

53.• Harris J, Ramelet AS, van Dijk M, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med. 2016;42(6):972–86.
Expert recommendations for pediatric ICU delirium.

54.• Kachmar AG, Irving SY, Connolly CA, Curley MAQ. A systematic review of risk factors associated with

cognitive impairment after pediatric critical illness. Pediatr Crit Care Med. 2018;19(3):e164–e71.
Recent systematic review highlights risk factors for cognitive impairment in pediatric ICU survivors.

55.   Williams C, Bratton SL. More science for the art of dexmedetomidine administration in pediatric critical care. Minerva Anestesiol. 2019;85(2):118–20.

56.   Lin EP, Lee JR, Lee CS, Deng M, Loepke AW. Do anesthetics harm the developing human brain? An integrative analysis of animal and human studies. Neurotoxicol Teratol. 2017;60:117–28.

57.•   Ong C, Lee JH, Leow MK, Puthucheary ZA. Functional outcomes and physical impairments in pediatric critical care survivors: a scoping review. Pediatr Crit Care Med. 2016;17(5):e247–59.
Recent systematic review highlighting the physical domain of PICS in pediatric ICU survivors.

58.   Blume HK, Vavilala MS, Jaffe KM, Koepsell TD, Wang J, Temkin N, et al. Headache after pediatric traumatic brain injury: a cohort study. Pediatrics. 2012;129(1):e31–9.

59.   Pinchefsky E, Dubrovsky AS, Friedman D, Shevell M. Part I–evaluation of pediatric post-traumatic headaches. Pediatr Neurol. 2015;52(3):263–9.

60.   Pinchefsky E, Dubrovsky AS, Friedman D, Shevell M. Part II–management of pediatric post-traumatic headaches. Pediatr Neurol. 2015;52(3):270–80.

61.   Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses. Pediatrics. 2003;112(1 Pt 1):e1–5.

62.   Slover R, Neuenkirchen GL, Olamikan S, Kent S. Chronic pediatric pain. Adv Pediatr Infect Dis. 2010;57(1):141–62.

63.   Williams CN, Lim MM, Shea SA. Sleep disturbance after pediatric traumatic brain injury: critical knowledge gaps remain for the critically injured. Nat Sci Sleep. 2018;10:225–8.

64.   Sandsmark DK, Elliott JE, Lim MM. Sleep-wake disturbances after traumatic brain injury: synthesis of human and animal studies. Sleep. 2017;40(5):1–18.

65.   Gagner C, Landry-Roy C, Laine F, Beauchamp MH. Sleep-wake disturbances and fatigue after pediatric traumatic brain injury: a systematic review of the literature. J Neurotrauma. 2015;32(20):1539–52.

66.   Chang CH, Chen SJ, Liu CY. Pediatric sleep apnea and depressive disorders risk: a population-based 15-year retrospective cohort study. PLoS One. 2017;12(7):e0181430.

67.   Gozal D, Kheirandish-Gozal L. Neurocognitive and behavioral morbidity in children with sleep disorders. Curr Opin Pulm Med. 2007;13(6):505–9.

68.   Owens JA. Neurocognitive and behavioral impact of sleep disordered breathing in children. Pediatr Pulmonol. 2009;44(5):417–22.

69.   Aaro Jonsson CC, Emanuelson IM, Charlotte Smedler A. Variability in quality of life 13 years after traumatic brain injury in childhood. Int J Rehabil Res. 2014;37(4):317–22.

70.   Keegan LJ, Reed-Berendt R, Neilly E, Morrall MC, Murdoch-Eaton D. Effectiveness of melatonin for sleep impairment post paediatric acquired brain injury: evidence from a systematic review. Dev Neurorehabil. 2014;17(5):355–62.

71.   Galland BC, Elder DE, Taylor BJ. Interventions with a sleep outcome for children with cerebral palsy or a post-traumatic brain injury: a systematic review. Sleep Med Rev. 2012;16(6):561–73.

72.   Bogdanov S, Naismith S, Lah S. Sleep outcomes following sleep-hygiene-related interventions for individuals with traumatic brain injury: a systematic review. Brain Inj. 2017;31(4):422–33.

73.   Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. Arch Dis Child. 2018;103(12):1155–62.

74.   Barlow KM, Esser MJ, Veidt M, Boyd R. Melatonin as a treatment after traumatic brain injury: a systematic review and meta-analysis of the pre-clinical and clinical literature. J Neurotrauma. 2018.

75.   Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res. 2012;21(6):700–9.

76.   Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. Pharmacotherapy. 2016;36(1):84–98.

77.   Volk C, Huber R. Sleep to grow smart? Arch Ital Biol. 2015;153(2–3):99–109.

78.   Ringli M, Huber R. Developmental aspects of sleep slow waves: linking sleep, brain maturation and behavior. Prog Brain Res. 2011;193:63–82.

79.   Jan JE, Reiter RJ, Bax MC, et al. Long-term sleep disturbances in children: a cause of neuronal loss. Eur J Paediatr Neurol. 2010;14(5):380–90.

80.   Kocevska D, Muetzel RL, Luik AI, et al. The developmental course of sleep disturbances across childhood relates to brain morphology at age 7: the generation R study. Sleep. 2017;40(1):1–9.

81.   Maitre NL, Smolinsky C, Slaughter JC, Stark AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. J Perinatol. 2013;33(11):841–6.

82.   Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. PLoS One. 2016;11(3):e0149686.

83.   Major P, Greenberg E, Khan A, Thiele EA. Pyridoxine supplementation for the treatment of levetiracetam-induced behavior side effects in children: preliminary results. Epilepsy Behav. 2008;13(3):557–9.

84.   Popernack ML, Gray N, Reuter-Rice K. Moderate-to-severe traumatic brain injury in children: complications and rehabilitation strategies. J Pediatr Health Care. 2015;29(3):e1–7.

85.   Taub E, Griffin A, Uswatte G, Gammons K, Nick J, Law CR. Treatment of congenital hemiparesis with pediatric constraint-induced movement therapy. J Child Neurol. 2011;26(9):1163–73.

86.   Willis JK, Morello A, Davie A, Rice JC, Bennett JT. Forced use treatment of childhood hemiparesis. Pediatrics. 2002;110(1 Pt 1):94–6.

87.•   Mirkowski M, McIntyre A, Faltynek P, et al. Nonpharmacological rehabilitation interventions for motor and cognitive outcomes following pediatric stroke: a systematic review. Eur J Pediatr. 2019;178(4):433–54.
Recent systematic review highlights interventions for motor and cognitive impairment after pediatric stroke.

88.   Kirton A, Andersen J, Herrero M, Nettel-Aguirre A, Carsolio L, Damji O, et al. Brain stimulation and constraint for perinatal stroke hemiparesis: the PLASTIC CHAMPS Trial. Neurology. 2016;86(18):1659–67.

89.   Stuss DT, Winocus G, Robertson IH. Cognitive neurorehabilitation : evidence and application. 2nd ed. Cambridge; New York: Cambridge University Press; 2008. p. xvii, 606.

90.   Slomine B, Locascio G. Cognitive rehabilitation for children with acquired brain injury. Dev Disabil Res Rev. 2009;15(2):133–43.

91.   Hooft IV, Andersson K, Bergman B, et al. Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study. Brain Inj. 2005;19(7):511–8.

92.   Ho J, Epps A, Parry L, Poole M, Lah S. Rehabilitation of everyday memory deficits in paediatric brain injury: self-instruction and diary training. Neuropsychol Rehabil. 2011;21(2):183–207.

93.   Jackson JC, Ely EW, Morey MC, Anderson VM, Denne LB, Clune J, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. Crit Care Med. 2012;40(4):1088–97.

94.   Hopkins RO, Suchyta MR, Farrer TJ, Needham D. Improving post-intensive care unit neuropsychiatric outcomes: understanding cognitive effects of physical activity. Am J Respir Crit Care Med. 2012;186(12):1220–8.

95.   Babikian T, Merkley T, Savage RC, Giza CC, Levin H. Chronic aspects of pediatric traumatic brain injury: review of the literature. J Neurotrauma. 2015;32(23):1849–60.

96.   Babikian T, Asarnow R. Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature. Neuropsychology. 2009;23(3):283–96.

97.•   Treble-Barna A, Sohlberg MM, Harn BE, Wade SL. Cognitive intervention for attention and executive function impairments in children with traumatic brain injury: a pilot study. J Head Trauma Rehabil. 2016;31(6):407–18.
Pilot study of 13 children with TBI compared with 11 controls evaluating the effects of a cognitive rehabilitation program. The intervention improved measures of attention and executive function.

98.   Backeljauw B, Kurowski BG. Interventions for attention problems after pediatric traumatic brain injury: what is the evidence? PM R. 2014;6(9):814–24.

99.   Catroppa C, Stone K, Hearps SJ, et al. Evaluation of an attention and memory intervention post-childhood acquired brain injury: preliminary efficacy, immediate and 6 months post-intervention. Brain Inj. 2015;29(11):1317–24.

100.   Wade SL, Kurowski BG, Kirkwood MW, Zhang N, Cassedy A, Brown TM, et al. Online problem-solving therapy after traumatic brain injury: a randomized controlled trial. Pediatrics. 2015;135(2):e487–95.

101.   Wade SL, Michaud L, Brown TM. Putting the pieces together: preliminary efficacy of a family problem-solving intervention for children with traumatic brain injury. J Head Trauma Rehabil. 2006;21(1):57–67.

102.   Wade SL, Walz NC, Carey JC, Williams KM. Preliminary efficacy of a web-based family problem-solving treatment program for adolescents with traumatic brain injury. J Head Trauma Rehabil. 2008;23(6):369–77.

103.   Kurowski BG, Taylor HG, Yeates KO, Walz NC, Stancin T, Wade SL. Caregiver ratings of long-term executive dysfunction and attention problems after early childhood traumatic brain injury: family functioning is important. PM R. 2011;3(9):836–45.

104.   Braga LW, Da P, Ylvisaker AC, M. Direct clinician-delivered versus indirect family-supported rehabilitation of children with traumatic brain injury: a randomized controlled trial. Brain Inj. 2005;19(10):819–31.

105.• Hawks C, Jordan LC, Gindville M, et al. Educational placement after pediatric intracerebral hemorrhage. Pediatr Neurol. 2016;61:46–50.
Single-center study highlighting high rates of educational support and school-based interventions among pediatric hemorrhagic stroke survivors.

106.• Greenham M, Anderson V, Mackay MT. Improving cognitive outcomes for pediatric stroke. Curr Opin Neurol. 2017;30(2):127–32.
Recent review highlighting high prevalence of cognitive impairments in pediatric stroke and the lack of rehabilitation strategies with evidence base in pediatric survivors.

107.   Studer M, Boltshauser E, Capone Mori A, Datta A, Fluss J, Mercati D, et al. Factors affecting cognitive outcome in early pediatric stroke. Neurology. 2014;82(9):784–92.

108.   King AA, White DA, McKinstry RC, Noetzel M, Debaun MR. A pilot randomized education rehabilitation trial is feasible in sickle cell and strokes. Neurology. 2007;68(23):2008–11.

109.   Yerys BE, White DA, Salorio CF, McKinstry R, Moinuddin A, DeBaun M. Memory strategy training in children with cerebral infarcts related to sickle cell disease. J Pediatr Hematol Oncol. 2003;25(6):495–8.

110.   Davydow DS, Richardson LP, Zatzick DF, Katon WJ. Psychiatric morbidity in pediatric critical illness survivors: a comprehensive review of the literature. Arch Pediatr Adolesc Med. 2010;164(4):377–85.

111.   Rennick JE, Rashotte J. Psychological outcomes in children following pediatric intensive care unit hospitalization: a systematic review of the research. J Child Health Care. 2009;13(2):128–49.

112.   Hooper SR, Alexander J, Moore D, et al. Caregiver reports of common symptoms in children following a traumatic brain injury. NeuroRehabilitation. 2004;19(3):175–89.

113.•   Baker SC, Gledhill JA. Systematic review of interventions to reduce psychiatric morbidity in parents and children after PICU admissions. Pediatr Crit Care Med. 2017;18(4):343–8.
Recent systematic review highlighting the low number of evidenced-based therapies to improve psychiatric morbidity in children and parents after pediatric ICU admission.

114.   Nelson LP, Gold JI. Posttraumatic stress disorder in children and their parents following admission to the pediatric intensive care unit: a review. Pediatr Crit Care Med. 2012;13(3):338–47.

115.   Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. Crit Care Med. 2012;40(2):618–24.

116.•   Nelson LP, Lachman SE, Li SW, Gold JI. The effects of family functioning on the development of posttraumatic stress in children and their parents following admission to the PICU. Pediatr Crit Care Med. 2019;20(4):e208–e15.
Single-center study evaluating PTSS and PTSD in children and parents after pediatric ICU admission showing acute stress was a predictor of post-traumatic stress.

117.   Landolt MA, Ystrom E, Sennhauser FH, Gnehm HE, Vollrath ME. The mutual prospective influence of child and parental post-traumatic stress symptoms in pediatric patients. J Child Psychol Psychiatry. 2012;53(7):767–74.

118.   Yeates KO, Taylor HG, Walz NC, Stancin T, Wade SL. The family environment as a moderator of psychosocial outcomes following traumatic brain injury in young children. Neuropsychology. 2010;24(3):345–56.

119.   Linton S, Grant C, Pellegrini J. Supporting families through discharge from PICU to the ward: the development and evaluation of a discharge information brochure for families. Intensive Crit Care Nurs. 2008;24(6):329–37.

120.   Bouve LR, Rozmus CL, Giordano P. Preparing parents for their child's transfer from the PICU to the pediatric floor. Appl Nurs Res. 1999;12(3):114–20.

121.•• Esses SA, Small S, Rodemann A, Hartman ME. Post-intensive care syndrome: educational interventions for parents of hospitalized children. Am J Crit Care. 2019;28(1):19–27.
Randomized trial evaluating methods to improve education of parents regarding PICS. Multiple methods were effective and well supported, including brochures which are a low-cost and easily implemented method of delivery.

122.   Colville GA, Gracey D. Mothers' recollections of the paediatric intensive care unit: associations with psychopathology and views on follow up. Intensive Crit Care Nurs. 2006;22(1):49–55.

123.   Mitchell ML, Courtney M. Reducing family members' anxiety and uncertainty in illness around transfer from intensive care: an intervention study. Intensive Crit Care Nurs. 2004;20(4):223–31.

124.   Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171(9):987–94.

125.   Harvey MA, Davidson JE. Postintensive care syndrome: right care, right now…and later. Crit Care Med. 2016;44(2):381–5.

126.•   Herrup EA, Wieczorek B, Kudchadkar SR. Feasibility and perceptions of PICU diaries. Pediatr Crit Care Med. 2019;20(2):e83–90.
Pilot study showing the use of ICU diaries is feasible and well received in the pediatric ICU setting.

127.   McIlroy PA, King RS, Garrouste-Orgeas M, Tabah A, Ramanan M. The effect of ICU diaries on psychological outcomes and quality of life of survivors of critical illness and their relatives: a systematic review and meta-analysis. Crit Care Med. 2019;47(2):273–9.

128.   Melnyk BM, Alpert-Gillis L, Feinstein NF, Crean HF, Johnson J, Fairbanks E, et al. Creating opportunities for parent empowerment: program effects on the mental health/coping outcomes of critically ill young children and their mothers. Pediatrics. 2004;113(6):e597–607.

129.   Johnston CC, Rennick JE, Filion F, Campbell-Yeo M, Goulet C, Bell L, et al. Maternal touch and talk for invasive procedures in infants and toddlers in the pediatric intensive care unit. J Pediatr Nurs. 2012;27(2):144–53.

130.•• Rennick JE, Stremler R, Horwood L, et al. A pilot randomized controlled trial of an intervention to promote psychological well-being in critically ill children: soothing through touch, reading, and music. Pediatr Crit Care Med. 2018;19(7):e358–e66.
A pilot randomized trial of 10 patients who received the soothing intervention versus 10 controls showing the intervention was acceptable and feasible. The intervention group trended toward lower parent and child anxiety.

131.   Haines KJ, Beesley SJ, Hopkins RO, McPeake J, Quasim T, Ritchie K, et al. Peer support in critical care: a systematic review. Crit Care Med. 2018;46(9):1522–31.

132.   Als LC, Nadel S, Cooper M, Vickers B, Garralda ME. A supported psychoeducational intervention to improve family mental health following discharge from paediatric intensive care: feasibility and pilot randomised controlled trial. BMJ Open. 2015;5(12):e009581.

133.   Colville GA, Cream PR, Kerry SM. Do parents benefit from the offer of a follow-up appointment after their child's admission to intensive care?: an exploratory randomised controlled trial. Intensive Crit Care Nurs. 2010;26(3):146–53.

134.   Samuel VM, Colville GA, Goodwin S, Ryninks K,
        Dean S. The value of screening parents for their risk of
        developing psychological symptoms after PICU: a
        feasibility study evaluating a pediatric intensive care
        follow-up clinic. Pediatr Crit Care Med.
        2015;16(9):808–13.
135.   Gledhill J, Tareen A, Cooper M, Nadel S, Garralda ME.
        Joint paediatric and psychiatric follow-up for families
        following paediatric intensive care unit admission: an
        exploratory study. Adv Crit Care. 2014;2014(1):1–5.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.