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Cognitive impairment following pediatric critical illness: time to pay attention

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With innovations in pediatric critical care that support more children to survive critical illness, a different challenge has emerged – meeting the needs of children with new cognitive, emotional, and physical morbidity following critical illness^{1,2}. Families of these children also face their own challenges in caring for a child with new deficits, including financial and emotional difficulties^{3,4}. Despite the increasing number of children surviving critical illness, very few studies have rigorously examined the recovery trajectories of these children following discharge from the pediatric intensive care unit (PICU). For example, long-term neuropsychological outcomes in patient populations with undeniable brain pathology, including cardiac arrest or traumatic brain injury (TBI), are better characterized^{5,6}, but much remains unknown regarding the long-term morbidities in the heterogeneous population of children surviving critical illness^{6–8}. Cognitive impairment in childhood has potentially long lasting effects into adolescence and adulthood, making it imperative to identify modifiable risk factors as well as effective interventions. In this timely systematic review, Kachner et al⁹ evaluate the current literature to identify risk factors specific to cognitive impairment in a cohort of critically ill children without known premorbid neurological disease or impairment.

This systematic review included twelve studies that examined cognitive outcomes in critically ill children other than those with cardiac arrest, TBI, or genetic anomalies associated with neurocognitive impairment. Nine studies included subjects with sepsis or septic shock (the remainder included a variety of illnesses) and all were assessed for quality using the Newcastle-Ottawa Quality Assessment Scale. Studies analyzed included subjects aged 3–18 years at the time of follow-up from PICU care and included objective standardized neuropsychological tests measuring at least one domain of cognitive function.

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All twelve studies were observational (six case-control and six prospective cohort studies) with healthy controls or normed population data for comparison to study subjects. There was substantial variability in the time to outcome evaluation, ranging from 3 months to 16 years.

The authors found that ten studies reported poorer cognitive functioning relative to healthy controls or population norms in at least one domain, and seven studies reported poorer cognitive functioning in more than one cognitive domain. Cognitive impairments were variably reported across domains examined, including intelligence, memory, attention, executive functions, and visuomotor integration and motor development and were found across the wide follow-up period. Findings of neuropsychological testing impairments were buttressed by several studies also reporting more parent- and teacher-reported academic and behavior difficulties, as well as special education needs, relative to healthy peers.

Regarding the primary objective of the study, independently associated risk factors for poor cognitive outcomes included: younger age at critical illness, older age at follow-up, lower socioeconomic status (SES), oxygen and mechanical ventilation requirements, and opioid administration. The “growing into deficits” hypothesis¹⁰ is referenced as a possible explanation for the finding of younger age at illness and older age on follow up given the complexity of development in childhood with the potential to see more deficits over time. Regardless, these are not modifiable risk factors. Older age at follow up is a complex finding without the context of additional details regarding other potentially confounding variables. The use of ICU interventions, such as support for respiratory failure or sedative agents for patient safety and comfort, are often unavoidable therapies based on a patient’s clinical needs. The lack of clinical information related to these interventions makes interpretation difficult. Growing evidence exists for cognitive risks associated with use of sedative agents in critical care and anesthesia¹¹, which is reiterated in findings of one study included in this review¹². These findings suggest thoughtful use of these agents when possible. SES is a risk factor for cognitive and developmental delays independent from critical illness¹³; although not necessarily modifiable, supports could be provided by the medical team, including through the assistance of social work, to attempt to remediate some of the potential mechanisms underlying this association with SES, such as insufficient follow-up care or rehabilitation interventions due to lack of resources and barriers to access.

As we gather more data on risk factors for cognitive dysfunction following critical pediatric illness, this information can be used to inform both directions for clinical research as well as improve clinical care of these patients. Recommendations exist for the developmental follow up of children at risk for neurodevelopmental delays in cohorts similar to PICU patients, for instance in the pediatric congenital heart disease population¹⁴. Similarly, the Outcomes after Critical Illness and Surgery (OACIS) group recently published a set of core domains and core outcome measures in adult acute respiratory failure survivors^{15,16}. At present, however, there are no formal recommendations for the assessment strategy of functioning following pediatric critical illness. Determining core outcome domains that reflect functional outcomes valued by patients, families, and key stakeholders, followed by implementation of assessment measures specific to these domains, are the next steps in understanding morbidity following pediatric critical illness. Clinically, increasing knowledge regarding risk factors for cognitive impairment following pediatric critical illness has the potential for

identifying patients at greatest risk for impairment for the purposes of closer monitoring and multidisciplinary follow-up, referral for more comprehensive neuropsychological evaluation, and provision of earlier and more targeted interventions and environmental accommodations.

The results summarized in this systematic review provide a timely first step towards demonstrating cognitive morbidity among heterogeneous populations of children following critical illness. The review also highlights, however, the many ways in which future studies can improve upon these initial investigations. A more rigorous approach going forward would involve prospective studies of more homogeneous groups of children with critical illness so that morbidity profiles and their specific risk factors can be determined for each unique pathology. In addition, studies should attempt to better characterize premorbid cognitive functioning (for example, through crystallized measures of intelligence and/or parent-report measures of premorbid function) so that the effects of illness and ICU-factors can be better isolated. Comparison with healthy community controls rather than population norms allows for better control of confounding factors that may increase risks of both premorbid cognitive impairments and critical illness. Finally, evaluation of emotional and behavioral difficulties should also be included in future studies, as emerging evidence suggests significant difficulties following pediatric critical illness in these domains¹⁷.

Our job caring for our critically ill pediatric patients is not complete at discharge from the PICU. The results of this review suggest that many children are left with new cognitive and other morbidities that can have potentially life-long consequences for functional independence and quality of life. Increasing our understanding of the short- and long-term morbidities, and their specific risk factors, following pediatric critical illness is time sensitive and crucial.

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