Does critical illness and intensive care unit treatment contribute to neurocognitive and functional morbidity in pediatric patients?

Ramona O. Hopkins*

Increasing attention has been paid to the proposition that critical illness may have adverse implications for neurocognitive functioning and may play a significant causal role in the development of incident neurocognitive impairment in adults,[1] which may adversely affect their functional status and quality of life. Data are beginning to accumulate in survivors of the pediatric intensive care unit (PICU) suggesting that these patients also experience significant neurocognitive and functional morbidity after critical illness and intensive care unit (ICU) treatment.[2] Data in patients treated in the newborn ICU support this finding. For example, infants with very low birth weight (< 1,500 g) treated in the ICU have neurosensory deficits, neurocognitive impairments, poor academic achievement and other behavioral disorders years after ICU discharge.[3] While research is limited and there are major gaps in our knowledge, the investigations to date using validated rating scales suggest that substantial numbers of critically ill pediatric patients treated in the PICU develop unfavorable neurocognitive and functional morbidity.

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Alievi and colleagues in this issue assessed neurocognitive and functional outcomes of 443 PICU survivors.[4] Outcomes were assessed at PICU admission and discharge using the pediatric cerebral performance category (PCPC) and the pediatric overall performance category (POPC) scales, modified from scales that assess brain injury in adult populations.[5] The POPC scale quantifies overall functional (general adaptive/physical morbidity) and the PCPC scale quantifies neurocognitive impairment.[2] The POPC and PCPC are six-point scales that rate increasing disability from normal function to death. The scores for the PCPC are 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, and 6 = brain death and the scores for the POPC are 1 = good overall performance, 2 = mild overall disability, 3 = moderate overall disability, 4 = severe overall disability, 5 = coma or vegetative state, 6 = brain death (see Fisher et al.[2] for a detailed description).

Alievi at al.[4] found that patients' median PCPC at ICU admission was normal but declined to mild disability at PICU discharge, and that mean POPC at admission was mild overall disability that declined to moderate overall disability at PICU discharge. Improvement in POPC scores from ICU admission to discharge occurred in only 4.7% of cases, similar to findings in other outcome studies.[2] Furthermore, the authors note that a large number of patients (46%) had some degree of preexisting neurocognitive disability and 66% had preexisting functional disability at PICU admission. Of the survivors with preexisting neurocognitive and functional disability, 110 (24.8%) of the patients scores declined on the PCPC and 151 (36.3%) scores declined on the POPC indicating that critical illness and PICU treatment contributed to significant decline in neurocognitive and functional performance in these patients. Data addressing the ecological validity (real world impact) of neurocognitive and functional morbidity comes from one study that assessed outcomes using the same rating scales which found that patients with mild to moderate disability at PICU discharge had poor neurocognitive performance at school (e.g., requiring special education classrooms) and the functional impairments adversely affected their competitive performance at school.[2]

The finding that a large percentage of pediatric critically ill patients are admitted to the PICU with preexisting neurocognitive and functional disability that further declines during their critical illness and PICU treatment raises a number of important questions. These questions include but are not limited to: what is the trajectory of the neurocognitive and

* PhD. Department of Medicine, Pulmonary and Critical Care Division, LDS Hospital, Salt Lake City, Utah, USA. Psychology Department and Neuroscience Center, Brigham Young University, Provo, Utah, USA.

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functional impairments? What are the mechanisms and risk factors of the neurocognitive and functional impairments? What are the long-term (e.g., 5 and 10 year) outcomes after PICU discharge? What tools should be used to *best* assess neurocognitive and functional outcomes in this population? Are there neuropathological lesions or brain atrophy in patients with neurocognitive disability? What are the effects of neurocognitive and functional disability on behavior and educational performance?

Assessing the trajectory of functioning in patients admitted to the ICU with preexisting neurocognitive of functional impairment due to preexisting disorders such as neurologic disorders, HIV, rare genetic syndromes, inborn errors of metabolism, or other medical diseases or syndromes can be difficult but essential in understanding the neurocognitive and functional morbidity in these patients. The assessment of such risk factors for critical illness associated with neurocognitive and functional impairments in pediatric patients has received little attention and is especially important in light of the high rate of neurocognitive and functional disability in these patients at PICU admission. In addition, are there tools such as the dementia rating scale used in adult populations that could be used to assess preexisting neurocognitive and functional performance in pediatric patients? Do preexisting genetic and neurologic syndromes in these patients make them vulnerable to critically illness and PICU treatment and its associated neurocognitive and functional decline? Do preexisting genetic and neurologic syndromes place these patients at higher risk for adverse outcomes? Do critically ill individuals with specific disease states – such as renal or cardiac disease – have qualitatively different neurocognitive impairments compared to patients with pulmonary or liver disease? While younger age is related to higher survival rates in pediatric ICU populations[6] the effect of age, intelligence, educational abilities, and ICU length of stay and other markers of illness severity on neurocognitive and functional outcomes in these patients are unknown.

Another concern is identification of the mechanisms of the cognitive and functional morbidity in pediatric patients. Multiple physiological and pharmacologic perturbations have both direct and indirect effects on the central nervous system and may be a direct cause of exacerbated brain injury. The etiology of neurocognitive impairments is likely multifactorial and dynamic with a number of more or less significant factors interacting with premorbid variables resulting in adverse outcomes. Potential mechanisms in adult populations include hypoxemia,[7] sedatives or analgesics,[8] hypotension,[9] delirium,[10] hyperglycemia[11] and the cumulative dose of some sedatives.[8] To date there is a paucity of data in pediatric critically ill populations and it is unknown if the above mechanisms contribute to adverse outcomes in PICU populations. Attention to the mechanisms, pathophysiology and risk factors associated with neurocognitive and neuromuscular outcomes in PICU survivors should be an important research priority.

Neurocognitive impairments or disability in the pediatric critically ill population has predominately been assessed using instruments or questionnaires that rely on more qualitative measurement methods that use clinical judgment, the direct observation of patients, and interaction with families to determine outcomes. Neurocognitive impairments identified using clinical rating scales has been shown to be a poor proxy for neurocognitive functioning measured using a standardized neuropsychological tests. Neuropsychological tests are sensitive and objective tools designed to identify and measure neurocognitive abilities and the relationships between brain functioning and behavior. Further, studies indicate that formal neuropsychological tests have greater sensitivity and specificity in detecting neurocognitive impairments than validated rating scales.[12] Thus, the observed rates of neurocognitive impairments in current PICU outcome studies are likely underestimates of the true rate of impairment. Neuropsychological tests should be incorporated in neurocognitive outcome research as they can detect frank and subtle neuropsychological impairments and track changes in neurocognitive function over time, as has been done in newborn ICU populations.[3] Studies using formal neuropsychological tests to assess neurocognitive function are needed to determine the extent and severity of the neurocognitive deficits.

The societal burdens of an enlarging population of pediatric critically ill survivors with neurocognitive impairment could be tremendous, as was demonstrated by longitudinal studies in very low birth weight infants.[13] Survivors of the PICU with neurocognitive and functional disability are likely to have unique treatment needs, whether in primary or secondary school or in higher education programs[3] as they may require special education placement and substantial support. Because neurocognitive deficits may be associated with attention and/or other behavioral problems, behavior assessment and possible management strategies are needed.[14] Over the last decade, ICU-related neurocognitive impairment has been identified as a significant public health problem and is now the focus of several large cohort studies in adults and pediatric populations, although much remains unclear. Well-designed multidisciplinary and transdisciplinary outcome studies that assess preexisting neurocognitive and functional disability, longitudinal outcomes, and ecological validity or real world outcomes (school performance and social integration) should be the focus of future pediatric critical care outcome research.

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Indirect calorimetry: a potential but as yet unrealized technique for guiding nutritional management

William W. Hay Jr.,[1] Patti J. Thureen[2]

Among those who study nutrition in preterm and small for gestational age (SGA) newborn infants, there is the hope that someday there will be a simple, reliable, and accurate bedside measure of nutrient utilization to help guide nutritional management, much like blood gas and pulse oximetry measurements help guide the use of respirators and oxygen. This certainly is a hope well expressed in the very interesting article by Soares et al.[1] ("Indirect calorimetry: a tool to adjust energy expenditure in very low birth weight infants") in this edition of the Jornal de Pediatria. In the meantime, we are limited to using tables and charts of nutrient utilization that have been based on sophisticated (and definitely not "bedside") direct and indirect calorimetry research in newborn infants. Most of the existing guidelines for feeding preterm neonates are based on the nutrition required by normally grown term infants who are fed milk or formula. However, these guidelines are not particularly useful when attempting to address the highly variable metabolism and growth of preterm and SGA infants. This failure to define optimal nutrition in different neonatal populations likely contributes significantly to our inability to achieve normal growth rates in these infants. Indeed, most centers still report that close to 100% of preterm infants are growth restricted and SGA by term gestation.

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1. MD. Professor of Pediatrics and Neonatology. Director, Neonatal Clinical-Translational Research Center, Health Sciences Center, University of Colorado, Aurora and Denver, Colorado, USA.
2. MD. Professor of Pediatrics and Neonatology, Department of Pediatrics, University of Colorado Health Sciences Center, Aurora and Denver, Colorado, USA.

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