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What's new in the long-term neurodevelopmental outcome of critically ill children

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Take-home message: Children surviving critical illness are prone to develop important long-term neurocognitive impairments, compromising quality of life. Better insight in the contributing factors is urgently needed to identify treatment opportunities to improve long-term outcome of these patients.

140-character Tweet: Understanding factors contributing to impaired neurocognitive development of critically ill children to improve their long-term outcome.

Thanks to major advances in intensive medical care, most critically ill children nowadays survive the life-threatening event requiring admission to the paediatric intensive care unit (PICU). Mortality in modern PICUs is now below 5% [1]. Strikingly, however, the improved survival revealed new concerns. Indeed, it appeared that many children who survive critical illness are confronted with significant, long-lasting morbidity, comprising amongst others neurocognitive/psychological problems, which brings about an important burden for them, their families, caregivers and society [2-6]. Moreover, more children suffer from prolonged critical illness and their long-term outcome is even worse than that of short-stay PICU patients [5, 7]. Consequently, research efforts are shifting from short-term vital outcomes to long-term morbidity and quality-of-life years after PICU discharge. We highlight several key insights in the field of long-term neurodevelopmental outcome of critically ill children gained in the last 5 years.

PICU survivors have more behavioural problems and reduced neurocognitive performance as compared to healthy peers. These effects are being recognised across an increasing number of diagnostic groups and throughout extended follow-up periods. Four years after critical illness, a large heterogeneous cohort of PICU survivors showed a 15 points lower IQ, performed 20-63% worse with regard to visual-motor integration, motor-coordination, cognitive flexibility, inhibitory control and attention, had worse memory, and showed signs of anxious and depressed behaviour [2]. These data among the “general population” of critically ill children are consistent with findings in several individual diagnostic subgroups. Patients with congenital heart disease displayed lower developmental index scores and lower performance on intelligence and alertness assessment [3, 6]. In children treated with neonatal extracorporeal membrane oxygenation, problems with concentration and behaviour were diagnosed more frequently upon long-term follow-up and significantly more children attended special education (9%) or received extra support in regular education (39%) [4]. Also children admitted with meningoencephalitis or sepsis were found to underperform on neuropsychological measures [8].

Multiple factors likely contribute to the adverse long-term outcomes following paediatric critical illness. Several pre-admission and disease-related factors (e.g. meningoen­cephalitis and cardiac arrest [9]) could be major predeterminants (Figure 1). Importantly, however, the neurocognitive deficit can be at least partially counteracted by changing medical care (Figure 1). Indeed, several factors have been identified that can affect long-term neurocognitive outcome of PICU patients. We will focus on recent insight potentially implicating exposure to certain drugs and other toxic components, and endocrine/metabolic and social/psychological factors.

With regard to drugs, many studies have focused on the potential neurodevelopmental harm of anaesthetic and analgesic agents used during PICU-treatment. Such neurotoxicity has been convincingly demonstrated in animal studies, but is much harder to investigate in humans in view of many potential confounders, as exposing children in a randomised controlled trial to anaesthetics without medical necessity would be unethical. In meningococcal septic shock survivors, opioid use during PICU stay appeared significantly associated with long-term adverse neuropsychological outcome, including IQ-scores and visual attention/executive functioning, independent of severity of illness [10]. Reassuringly, no difference was found in Bayley-score test results in a large follow-up study of 532 children randomly assigned to awake-regional or a less than one-hour sevoflurane-based general anaesthesia for inguinal herniorrhaphy in early infancy [11]. This suggests that at least some narcotics, when used sparingly, may be fairly safe for brain development.

Whereas drugs are administered intentionally, physicians may be unaware of exposing their patients to other potential toxicants via the instrumentation used for intensive care. Indeed, paediatric intensive care relies heavily on soft plastic indwelling medical devices, such as tubes and catheters. These are miniaturised for use in children and made soft and pliable most often by incorporating phthalates. As phthalates are not chemically bound to the plastic, they can leach during use. A large association study in a heterogeneous group of critically ill children found a robust association between exposure to circulating

phthalates leaching from medical devices during intensive care with the observed attention deficit four years after PICU admission [12]. This phthalate exposure effect explained half of the attention deficit. Hence, these data may provide an argument for using, whenever possible, medical devices softened with alternative, safer plasticisers.

Several endocrine and metabolic derangements can disturb a child's neurocognitive development, but their potential role in the adverse legacy of critical illness largely remains to be elucidated. The tolerable level of stress hyperglycaemia is debated, but targeting age-adjusted normoglycaemia with insulin infusion during critical illness improved motor-coordination and cognitive flexibility four years after PICU admission, despite an increased risk of hypoglycemia [2]. In contrast, triiodothyronine administration to correct the low T3-syndrome in children undergoing cardiac surgery showed acute benefits in PICU, but did not improve neurodevelopmental outcome 10 years later [13].

Finally, an observational study among patients who experienced an early childhood brain injury suggests that also psychosocial environmental factors could serve as predictor of overall functional impairment [14]. These included parental stress, less optimal home environments and parenting behaviours. These and general pre-admission factors are often not (adequately) adjusted for in neurocognitive analyses, although randomisation in RCTs likely provides similar distributions among the groups.

With the heightened awareness of adverse neurocognitive outcome after paediatric critical illness, research interest in this field has steadily increased, yielding crucial insight. Nevertheless, some studies have focused on specific patient populations, limiting generalisability of the findings to entire PICU cohorts, and many more large-scale studies are needed to unequivocally identify (other) modifiable underlying factors. In this regard, we are looking forward to the results of two ongoing studies. The RESTORE Study Investigators are following-up children 2.5 years after enrolment in a sedation protocol RCT [15] to investigate whether greater exposure to benzodiazepines and/or ketamine is associated with

worse long-term neurocognitive outcome (ClinicalTrials.gov-NCT02225041). The international PEPaNIC-consortium is documenting long-term (2-4 year) survival and neurodevelopmental outcome of the 1440 patients enrolled in the PEPaNIC-trial [1] to address long-term safety and efficacy of late versus early initiation of supplemental parenteral nutrition during PICU stay. Every further insight could pave the way for major progress in improving long-term neurocognitive outcome of critically ill children.

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Figure legend

Fig. 1 The long-term neurocognitive sequelae of paediatric critical illness

Both the pre-morbid state of the child and the acute paediatric critical illness and several factors related to its management may theoretically lead to long-term neurodevelopmental sequelae.

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