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EDITORIAL

Out of the PICU and Beyond!**

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Nowadays the authors can give more and more assurance to highly stressed families who have a child suddenly admitted to a Pediatric Intensive Care Unit (PICU) that their loved one will most likely survive!

Indeed, PICU mortality has been steadily decreasing over the last 3 decades, reaching indexes of 2-3% in most advanced centers in North America. Even in Brazil, despite many structural and resource limitations, mortality rates are already below 10% in centers of reference.[1,2]

Now, intensivists are much more concerned about understanding the morbidity and short- and long-term consequences related to the PICU stay.[3]

In 2020, a multinational group of pediatric intensivists published recommendations for priorities on clinical and research programs that aimed to improve outcomes for children with critical illness and their families. Four of such priorities are within "Global Domains" (Cognitive, Emotional, Physical, and Overall Health) and four are "Specific Outcomes" (Child Health-Related Quality of Life, Pain, Survival, and Communication). Families were consulted and also set some priorities for PICU outcomes research, including Family Function, Overall Health, Emotional Function, and Physical Function.[4]

The idea of evaluating pediatric patients pre and post-PICU admission started with the scores developed by Debra Fiser in 1992, known as the Pediatric Cerebral and Overall Performance Categories (PCPC/POPC).[5] More recently, Pollack et al. developed and tested the FSS (Function and Scoring System). The FSS examines six function domains as follows: (1) mental status, (2) sensory functioning, (3) communication, (4) motor functioning, (5) feeding, and (6) respiratory status. Each domain is scored from 1 point (normal) to 5 points (very severe dysfunction). A significant new change in functional status or new morbidity had been defined as an increase in FSS $\geq$ 3 points between PICU admission and discharge.[6] The evidence is now out that FSS performs better than PCPC/POPC and reflects more closely the possible changes in the child baseline status after PICU and can be assessed at hospital discharge as well.[7]

In this issue of the Jornal de Pediatria, Santos et al. evaluated a group of 1002 Brazilian pediatric patients with cancer at admission to an Oncologic PICU and at the hospital discharge time utilizing the FSS, which was obtained retrospectively. The mortality rate was 12.5% (128 patients) during PICU admission, leaving 855 patients that were included in the post-survival assessment. After almost a year, the total mortality rate reached 22%. However, they have found that 5.3% (45/855) have developed a new morbidity, defined by an increase of at least 3 points on FSS, compared to admission scores. Interestingly, only 7.3% (63/855) had improvement in their admission FSS score. Almost 50% of the study population were patients with brain tumors, with 25% presenting with other malignancies (hepatoblastomas, carcinomas, retinoblastomas, germ cell tumors, etc.). The most important cause for PICU admission was post-operatory support, totaling 67% of patients; 8% presented with respiratory failure needing mechanical ventilation (MV) and only 2.6% had sepsis or septic shock. The worsening FFS was mainly in the motor and feeding domains of the surviving patients. The independent factors for new morbidity post ICU admission on multi-regression analysis were being sicker to begin with (high PRISM IV score), need for MV, being younger age (< 5 y old), and having a CNS tumor. They also described that those new morbidities correlated with lower odds of

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survival after hospital discharge, considering all causes of death, and this was actually an independent predictive of death. A shortening in the life span of 14.2% was atributed for such new morbidities.[8]

What is noticeable in this manuscript is that there was a worse FSS score in 12.1% of patients, characteristically in the motor and feeding domains. One needs to realize that almost 50% of the patients had central nervous system (CNS) tumors, hence it is not surprising that such were the areas mostly affected.

The reported mortality rate is not too different from similar studies in the literature; a systematic review of 31 observational studies covering the past 30 years (up to 2017) showed the mortality of pediatric cancer patients admitted to PICU as high as 28%, and index that is five-fold higher than the current mortality rate of the general PICU population (2-4% in N America).[9]

In 2017, Pereira et al. utilized the FSS scoring 24 hrs after PICU discharge in 50 patients and correlated the obtained scores with readmissions to the unit. Surprisingly, 40% needed readmission to the PICU during the same hospital stay, and 12% of them eventually died. The group of patients readmitted had a higher level of dysfunction as per FSS assessment (worse in motor, respiratory and feeding domains) than the patient who did not readmit. A longer length of stay in the PICU and prolonged MV was observed in individuals who presented greater overall functional impairment.[10] It is clear that the degree of dysfunction in FSS revealed the significant complexity and consequent higher risk of dying, similar to the oncologic patients of the present study. Another study utilizing FSS from the same southern Brazilian center reported a prevalence of a functional decrease in 68% of patients at PICU discharge, a very high rate. Young age ($<$ 12 months) and MV time $\geq$ 11 days increased by 1.44 and 1.74, respectively, the chances of poor functional results at PICU discharge.[11] Similarly, for the oncology patients of the study of Santos et al., acute respiratory failure requiring invasive MV, plus higher PRISM IV, age $<$ 5 years and CNS tumors were independent predictors of new morbidity. Unfortunately, the authors of the present study did not quantify ventilation days and their correlation with such findings; one assumes that the majority of intubated patients post-surgery for brain tumors got extubated within 24 hrs, and only the most severe cases required prolonged ventilation courses, hence the increased probability of respiratory dysfunction.[12]

Looking at a sample of general PICU patients, Matics et al. found that 14% had new morbidity or mortality at 6 months and 23% at 3 years. Such new morbidities mostly include physical, psychosocial, and neurocognitive deficits that interfere with daily life and normal development.[13] In oncology patients, Santos et al. reported the need to address feeding as an important element of such acquired deficits. The need for gastric tube feeding due to neurologic impairment, for example, may significantly alter the quality of life of the child and significantly disrupt the family life.[14]

The Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial with 1330 patients reported a decline of functional status, using PCPC and POPC scales in 20% of their survivor cohort, with underlying prematurity or malignancy and longer duration of MV being risk factors,[15] a finding that matches the study of PICU oncology survivors by Santos et al. on this issue of the Jornal de Pediatria.

Henceforth, one can pick different populations and evaluate their *baseline* and *post PICU* admission status. The authors of the present paper went beyond the PICU and checked the patients at the hospital discharge. One can ascertain the effects of multiple "therapies" administered in the PICU and look at the disease progression this way. Further assessment can be done months and years later, by following these patients at multidisciplinary clinics. Such clinics exist already in many centers, including one of the author's (DG) own center in Edmonton, Alberta, in Canada ("The Complex Pediatric Therapies Follow-up Program), where former premature kids, infants with congenital heart disease who underwent surgery, ECMO patients, etc. are followed.[16]

The importance of these follow-up clinics is not just "academic curiosity". The idea is to discover problems that once detected, can be potentially traced back to the ICU stay, and then make an effort to modify practices to improve patient outcomes. The most striking example of such discoveries at the University of Alberta follow-up program was a change in how to administer Furosemide in PICU. After detecting a high percentage of hearing impairment in children operated for single ventricle, Furosemide in rapid administration (bolus) was found to be the culprit.[17] A Quality initiative project took place and Furosemide administration was modified; this drug is no longer administered as a bolus, rather it is only given diluted and slowly (over a minimum of 20 min), or as continuous infusion. The change in outcome was striking: a reduction in hearing loss from 17% to 0% was noticed in the next similar group of patients studied at 4 years of age. A good lesson learned through the PICU follow-up clinic![18]

Santos et al. described 45 patients with new morbidity post-ICU admission, and 16 (35.5%) of them died during the study assessment period (compared to 21.9% who died without new morbidity). The former patients likely died from their original cancer, although the authors do not describe the reasons for death in this group. A new morbidity was not the only factor detected that increased the risk of death in this population; ``malnutrition" and "cancer recurrence" were independent predictors of death as well. Malnutrition could be a potentially modifiable risk factor for such a population, with emphasis on more aggressive enteral nutrition, use of Gastrostomy tubes, or early utilization of Parenteral nutrition when patients are intolerant to food due to chemotherapy; this needs to be carefully evaluated. Of course, as pointed out by Santos et al., the association is not equivalent to causation in such retrospective studies. Also, new morbidity can be the result of unmeasured factors (i.e., a natural complication of the disease) rather than acquired by failures in the quality of care provided in the PICU.

Overall, the work published by the oncology PICU group on this issue of Jornal de Pediatria helps us to understand better the outcomes of children with cancer admitted to PICU, not just focusing on mortality but also giving us important insights on the functional status of this population at the time of hospital discharge. An important complementary work would be to systematically follow up those children and their families to evaluate their quality of life not only after cancer diagnosis, but compare with groups of children

with cancer who needed ICU admission for complications such as sepsis. Several instruments could be used for such assessments, the Pediatric Quality of Life Inventory (PedsQL 4.0) being one of them. There are subgroups of PICU patients who have been evaluated under these lenses, such as traumas,[19] infants after cardiac surgery,[16] etc. This journal already has published important Brazilian studies on patients' overall health-related quality of life (HRQoL) post-PICU stay. Cunha et al. in 2012 assessed 320 patients before and again 252 of those at 6 months after PICU admission, demonstrating that 21% had their HRQoL unchanged, 40% improved, and 38% worsened.[20]

Studies like the one by Santos et al. published in this issue of the Jornal de Pediatria are of extreme value for the pediatricians who will eventually follow these children, by giving them tools to counsel families at times of great stress and uncertainties, but also by pointing to the need for specific community support systems, rehabilitation efforts and other targeted therapies to enhance their recovery.

After all, there is more to it than just surviving the admission to the Intensive care unit!

Conflicts of interest

The authors declare no conflicts of interest.

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