Surviving pediatric intensive care: from mortality to morbidity
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Summary
The development of pediatric (intensive) care has led to a decrease in pediatric mortality and an increasing number of children surviving into adulthood. At the same time, this resulted in a shift from mortality to morbidity and subsequently the number of children with chronic illnesses increased. The increase in the number of pediatric intensive care unit (PICU) survivors has intensified the need to investigate the long term consequences for survivors.

The aim of our studies was standardized evaluation of physical sequelae, HRQoL and psychological functioning in PICU survivors and development of ideas on an adequate follow-up program for PICU survivors in The Netherlands. We therefore, developed an on-going explorative research program on physical sequelae, HRQoL and psychological sequelae in children after PICU survival. The program was developed in collaboration with the psychosocial department of our children’s hospital. The children and their parents were invited to visit the out-patient follow-up clinic for structured medical examination by a pediatric intensivist followed by psychological screening by a psychologist.

This thesis reports the results of a comprehensive literature search of available studies reporting different aspects of physical sequelae, health-related quality of life (HRQoL) and psychological sequelae in PICU survivors; and the results of our recent studies performed at our own institution, to evaluate these sequelae as well as HRQoL. The studies were performed in two patient cohorts. The first cohort consisted of previously healthy children unexpectedly referred to our PICU with an acute life threatening illness between December 2002 and October 2005. We excluded children with known underlying illnesses or patients with scheduled elective surgery. We included all previously healthy patients with respiratory or circulatory insufficiency and all trauma patients irrespective of length of PICU stay and we included patients admitted to the PICU for other reasons for 7 days or more. Exclusion criteria were admission due to abuse or self-intoxication and the inability to complete Dutch questionnaires because of a language barrier. The second cohort consisted of septic shock survivors admitted to our PICU between 1995 and 2005 with ≥ 24 hours of inotropic and/or vasoconstrictive support (dopamine, dobutamine and/or (nor)epinephrine) and a follow-up time longer than 6 months after PICU discharge.

In the first cohort, we evaluated physical sequelae, HRQoL and psychological sequelae (posttraumatic stress disorder (PTSD)), three and nine months after PICU discharge. In the second cohort, we evaluated cardiac performance, HRQoL, cognitive functioning and psychological sequelae (anxiety and depression).

In chapter 1, the general introduction, the history of the development of pediatric intensive care medicine is described and the background of the shift from mortality to morbidity as outcome measure in PICU survivors.

The main concern of the PICU teams and parents in the late 1970s and early 1980s was whether the children survived PICU admission. After PICU discharge, children were admitted to a general pediatric ward and subsequently visited an outpatient clinic of a general pediatrician or a subspecialist (e.g. pediatric cardiologist or pediatric surgeon), when indicated. Advanced preventive, diagnostic and technical modalities and global movement have changed the natural
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course of numerous illnesses both in adult and pediatric medicine and have changed the spectrum of life-threatening diseases. These changes over time resulted in one of the major advances of pediatric intensive care: decrease of mortality. Improved survival in children with critical illnesses has led to new disease patterns due to long-term complications and effects of the original illness and its treatment. Therefore, evaluation of physical and psychological sequelae is important in PICU survivors. Particularly in children, long term follow-up studies are important against the background of the development, maturation and ageing of organs. Consider, for example, respiratory distress syndrome of the prematurely born infant (IRDS) and acute lung injury (ALI) in older children. Both have long term pulmonary consequences. The primary insult occurs when the lung is exposed to a damaging process, (IRDS or ALI); the secondary insult is caused by mechanical ventilation.
Systematic and standardized evaluation and follow-up care of these sequelae in PICU survivors is therefore warranted. Knowledge of these sequelae may lead to improvement of care and support during and after PICU admission, in an aim to reduce morbidity and improve QoL and psychological functioning.
Nowadays in The Netherlands 4000-5000 children, aged 0–18 years of age are annually admitted to a PICU. About 40% (±1600-2000 children) of them is electively admitted after a planned procedure such as postoperative care after cardiac surgery. Of the remaining 60%, about two-third (±1600-2000 children) is admitted unexpectedly and was healthy before admission.

Chapter 2 is the literature review performed in 2006. Only 27 studies including 3444 PICU survivors were found in which one or more aspects of long-term sequelae in PICU survivors and or their families were described. The small numbers, heterogeneity of the studied populations and the used measurement tools, the frequent use of non-validated measurement tools and the various aspects of outcome studied, make aggregation of data and therefore strong conclusive statements difficult. In most studies indications are found that PICU survivors and their parents may have substantial physical and psychological sequelae and impaired HRQoL. Complications of intensive care procedures per se, (e.g. vascular complications due to intra-vascular catheters and side-effects of ototoxic drugs and sedatives) are not evaluated. One can assume the exact incidence of physical sequelae to be higher than has been reported so far.
The reviewed studies have a number of methodological limitations. Heterogeneity is the most important one. Consensus on all aspects of follow-up research is essential for well-founded conclusions. Multi-centre studies as proposed by the Collaborative Pediatric Critical Care Research Network (CPCCRN) in the USA with a uniform approach will provide the necessary answers either in general PICU cohorts or in disease oriented study groups. Because of longer life expectancy, longer follow-up time is warranted, emphasizing the consequences for health care in children. We believe that pediatric intensivists and psychologists should be involved as members of follow-up teams, as they are familiar with possible risks and complications of PICU treatment; besides that, notifying complications of PICU procedures might serve as a valuable tool of providing feedback on procedures in the acute phase.
In chapter 3, physical sequelae are reported in the first patient cohort. A total of 186 of 250 eligible children were evaluated three months after PICU discharge. Only 58 (31%) of 186 evaluated children were healthy and 128 (69%) children still had physical complaints three months after discharge. Upper airway disease, pulmonary and neurological problems accounted for almost half of persisting complaints. Of these 128 children, 55 (43%) children had a so far unknown underlying illness (pre-PICU morbidity) that was diagnosed during PICU admission. Seventy-three (57%) of these 128 children were healthy before PICU admission and had acquired morbidity. The complaints in these 73 children were diverse and some children had a combination of problems. Complaints consisted of (a) pulmonary complaints (after admission due to RSV infection) or upper airway problems (tracheotomy) after endotracheal intubation; (b) neurological or neuro-cognitive problems caused by among other factors, hypoxic-ischemic brain injury, traumatic brain injury, meningitis or intracerebral bleeding; (c) scars after meningococcal disease, trauma, operations, pleural drains, and (central) venous lines; (d) hoarseness three months after extubation (e) Post Thrombotic Syndrome after central venous catheterization; (f) miscellaneous illnesses like renal insufficiency, adrenal insufficiency, and gastro-enterologic problems. In at least 15 (8%) children morbidity was related to complications of PICU procedures, such as post thrombotic syndrome after central venous catheterization and hoarseness after endotracheal intubation.

To evaluate the extent of neurocognitive sequelae we used Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) scores 24 hours before PICU admission, at discharge and at three months' follow-up. Three months after discharge 143 (77%) children had normal PCPC scores and 58 (31%) had normal POPC scores. Three months after discharge in respectively 39 (21%) and 93 (50%) children scores deteriorated compared to scores before admission.

In chapter 4, physical sequelae (cardiac performance) in the second cohort. A total of 108 of 144 eligible children were evaluated. Cardiac performance recovered excellently in most patients. No children had abnormalities at history taking and physical examination attributable to cardiac dysfunction. Six (6%) of 108 children had cardiac abnormalities, consisting of polymorphic premature ventricular contractions during exercise and twenty-four hour electrocardiography registration (2 patients), decreased left ventricular function (2 patients), decreased left ventricular function and polymorphic premature ventricular contractions (1 patient) and decreased right ventricular function (1 patient). No statistically significant differences were found between children with and without cardiac abnormalities with respect to gender, age at PICU admission, age at follow-up, follow-up time, risk of mortality, length of ventilation and length of PICU stay. No correlations were found between cardiac abnormalities and the different inotropic and vasoconstrictive agents used, the duration of treatment with inotropic and or vasoconstrictive agents and the dosages of the inotropic and vasoconstrictive agents used.
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We conclude that in pediatric septic shock survivors there is excellent recovery of cardiac performance in a majority of patients. In a limited number of children we found rhythm disturbances and decreased left ventricular function.

In **chapter 5**, HRQoL is reported in the first cohort. A total of 142 children fulfilled the inclusion criteria. Eighty-one children or their parents completed one or both questionnaires. The evaluation of HRQoL in the previously healthy children showed statistically significant differences with the normative population on a number of domains in all age groups. The parents of 1-6 year old children reported statistically significant lower scores on the domains 'lung problems' and 'liveliness'; but statistically significant higher scores on the emotional domains 'problem behaviour' and 'appetite', 3 months after discharge. Parents of 6-12 year old children and 12-15 year old children scored statistically significant lower on 'motor functioning', 3 months after discharge. Nine months after discharge, almost all statistically significant differences with the healthy Dutch population leveled out, except for impaired 'motor functioning' in almost all age groups and increased 'lung problems', decreased 'positive mood' and 'liveliness' in 1-6 year old children.

In **chapter 6** HRQoL, cognitive functioning and psychological functioning (anxiety and depression) is reported in the second cohort. Fifty of 82 eligible children completed the questionnaires. Mean follow-up time was 6,5 years and ranged from 1.5 to 10.1 years. HRQoL, anxiety, and depression scores are on average better or similar to scores of children of the same age and gender in the general population. However, cognitive functioning is worse in children compared to the norm population and a larger number of children than can be expected attend special education. In this study, younger age of the child at PICU admission is associated with lower cognitive functioning. Children with worse cognitive functioning had statistically significant more negative emotions, more problems with their parents, and reported statistically significant more bullying and higher anxiety and depression scores compared to children with better cognitive functioning.

In **chapter 7** psychological sequelae (PTSD) are reported in the first patient cohort three and nine months after PICU discharge and compared with children that survived a fire disaster. Thirty-six of 63 eligible children completed one or two questionnaires. The comparison group consisted of 355 children that actually witnessed and/or survived a fire disaster in the Netherlands on New Year's Eve 2001, in a popular club in Volendam. Almost 200 children had to be hospitalised; 14 of them died. Data analyses at the three month follow-up showed that 10 out of 29 (34.5%) children had at least subclinical levels of PTSD. Of these 10 children, four (13.8%) were likely to meet criteria for PTSD. At the nine month follow-up, 10 out of 28 (35.7%) children had at least subclinical levels of PTSD. Of these 10 children, five (17.9%) were likely to meet criteria for PTSD. No statistically significant changes over time were found for symptoms of PTSD.
PICU children and Volendam fire disaster children had the same number of symptoms of PTSD. Parental stress reactions, particularly, PTSD in the mother’s, appeared to be the most important indicator for development of PTSD in PICU children compared to the nature of the medical event and the characteristics of the child.

In the discussion the results of our studies are reviewed and implications for future research and patient care are discussed. Although our studies as well as other studies have some limitations, patterns emerge that should lead to standardized follow-up research and care of PICU survivors, as in neonatal ICU survivors. In neonatology long term follow-up of preterms led to knowledge of sequelae such as chronic lung disease and neurocognitive problems with great impact on daily life. Consequently, early intervention, education and rehabilitation are expected to improve daily life. In The Netherlands this has led to consensus on standardized long term follow-up programs for preterms.

We conclude that the development of pediatric intensive care has led to an increase in morbidity, leading to an increased number of children and adults with chronic illnesses. The results of our studies on sequelae in PICU survivors, led us to the conclusion that both physical and psychological sequelae are substantial necessitating future studies and improvement of care. Follow-up research should be focus on prevalence’s of sequelae and their determinants to assess necessary adjustment of care and support during and after PICU admission. Multi-centre follow-up studies are warranted to overcome limitations of follow-up studies in PICU survivors and should be feasible in The Netherlands.