Surviving pediatric intensive care: from mortality to morbidity
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Discussion and implications for the future
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Introduction

The development of pediatric (intensive) care has led to a decrease in pediatric mortality, increasing the number of children surviving into adulthood. (1;2) This simultaneously resulted in a shift from mortality to morbidity and subsequently an increase in the number of children with chronic illnesses, in particular, those with neurodevelopmental problems. (3;4) Some must stay in the pediatric intensive care unit (PICU) for a prolonged period of time and remain technology dependent. Following discharge, these children are more susceptible to acute deterioration, leading to an increased incidence of intercurrent diseases and necessitating admission to the PICU. (5;6) As a result, outcome measures such as mortality, length of stay, and days on a ventilator are therefore extended, affecting the patient's long-term physical and psychological sequelae as well as their quality of life. Standardized evaluation of long-term sequelae in PICU survivors is important to assess the needs for health care and future costs and benefits. Awareness of the significance and the impact of sequelae may lead to the improvement of care and support during and after PICU admission, with the aim to further reduce morbidity and improve the quality of life.

The aim of the studies described in this thesis was to gain insight into sequelae in PICU survivors, and to develop ideas and initiate guidelines for standardized evaluation of physical sequelae, Health-Related Quality of Life (HRQoL) and psychological function in PICU survivors based on these findings.

Main conclusions of our studies

In the literature review we found indications that PICU survivors and their parents have physical and psychological sequelae affecting quality of life. Small numbers, methodological limitations and quantitative and qualitative heterogeneity hamper the interpretation of data.

In our study investigating the physical sequelae in 186 previously healthy children, we found that only 31% of the evaluated children were completely healthy three months after discharge, while complications from PICU procedures led to morbidity in approximately 8% of the children, and that neurocognitive sequelae could be substantial.

In a study investigating cardiac performance after septic shock survival in 108 children, we found an excellent recovery of cardiac performance in most patients. We found rhythm disturbances and/or decreased ventricular function in only six children.

We also investigated HRQoL in 81 previously healthy children that were unexpectedly admitted to the PICU, and found differences in HRQoL with the norm population three and nine months after discharge.

In the study investigating HRQoL, psychological and cognitive sequelae in 50 septic shock survivors, we found that HRQoL, anxiety and depression were equal or slightly better compared to the norm population. Furthermore, cognitive function was decreased, especially in children admitted at a younger age.
Finally, in the study investigating psychological sequelae (posttraumatic stress disorder (PTSD)) in 36 previously healthy children older than eight years of age, we found that over one third of the children had subclinical PTSD three and nine months after PICU discharge. One out of seven children were likely to meet criteria for the full diagnosis of PTSD, and these scores failed to change over time.

Critical review

After our literature review from 2006 and the studies reported in this thesis, twenty studies regarding PICU survivors have been published. Some have confirmed that long-term physical sequelae, such as renal dysfunction after acute renal failure, and vascular, cutaneous and osseous sequelae occurring after meningococcal septic shock may be substantial. (7;8) Studies investigating the complications of PICU treatment have concluded that critical illness polyneuropathy and myopathy, venous thrombo-embolisms in children with central venous catheters, and re-admission to the PICU after discharge are all associated with morbidity after PICU discharge. (9-11) Some studies on HRQoL have concluded that a substantial portion of PICU survivors have ongoing health problems, while other studies have concluded that HRQoL in PICU survivors is comparable to that of the norm population. (4;12-17) Evaluation of neuropsychological function showed impaired memory and attention and a possible association between memory anomalies and emotional behavioural problems. (18) Studies on psychological sequelae have concluded that PTSD in PICU survivors and their parents occurs and that PTSD may be associated with behaviour before PICU admission, stress experienced during PICU admission, cognitive coping styles, and support during and after PICU admission and not with medical characteristics. Furthermore, morphine administration may be associated with a decrease in symptoms of PTSD, PTSD in mothers may be negatively associated with the child's adjustment after discharge and early intervention using a psychological debriefing format does not decrease the incidence of PTSD. (19-23) These findings should lead to improvement of care and support during and after PICU admission, and possibly prevent and treat the sequelae in PICU survivors. We believe that pediatric intensivists and psychologists should be involved as members of follow-up teams, as they are familiar with the possible risks and complications of PICU treatment; besides that, notifying potential complications associated with PICU procedures may also serve as a valuable tool that will provide feedback on procedures in the acute phase.

Although many of these studies have limitations, patterns have emerged that should lead to standardized follow-up research and care of PICU survivors similar to those in neonatal ICU survivors. In neonatology, long-term follow-up of preterm infants led to knowledge of sequelae such as chronic lung disease and neurocognitive problems, having great impact on daily life. (24) Consequently, early intervention, education and rehabilitation are expected to improve daily life. (25;26) In The Netherlands, this has led to a consensus on standardized long-term follow-up programs for preterm infants. (27;28) Follow-up of adult intensive care survivors also shows substantial long-term physical and psychological sequelae and consequences for HRQoL. In adult intensive care survivors, most follow-up studies have been
performed in disease-specific groups of survivors (e.g., Adult Respiratory Disease Syndrome (ARDS) or septic shock. (29-31) Follow-up studies in adult intensive care survivors, however, have not yet led to a consensus on standardized long-term follow-up programs.

Suggestions for future research

The limitations of our and other follow-up studies on PICU survivors should be addressed in future studies. These limitations include the loss to follow-up, retrospective design, small study sample sizes due to suboptimal response, refusal to participate, and the heterogeneity of the study populations. (12;32;33) Furthermore, the lack of consensus on measurement tools make comparisons between different studies impossible, and conclusions on sequelae over an extended period cannot be drawn since the follow-up time is often short. The majority of PICU admissions is comprised of young children. Evaluation of HRQoL and psychological function in children younger than eight is only possible by proxy report, which is less reliable than self report. (34;35) Evaluation of the pre-morbid state is also an important determinant of outcome, but this is difficult to assess and seldom performed. (36) In addition, evaluation of cognitive function with appropriate tests is expensive and time consuming and is therefore seldom performed in PICU survivors. Since studies in neonatal and adult ICU survivors show substantial cognitive dysfunction with great impact on daily life, adequate evaluation of cognitive function is important. (24;31) Inclusion of sex- and age-matched healthy control groups is rarely done. Finally, considering the small numbers and diverse populations of evaluated patients, evaluations of the risk factors of sequelae is difficult. Risk factor analysis give rise to ideas for preventive interventions and adequate support during and after PICU admission. Consequently, consensus on outcome measurement tools, on study populations and on length of follow-up is essential for well-founded conclusions. A prospective cohort study with a large enough sample size and an adequate age- and disease matched control group is theoretically the only way to obtain reliable and clinically significant results. For that reason, multi-centre studies (as proposed by the Collaborative Pediatric Critical Care Research Network (CPCCRN)) with a uniform approach will provide answers both in general PICU cohorts and in disease-oriented study groups. (37)

Blueprint for structured follow-up research

The character and magnitude of physical and psychological morbidity after PICU discharge is determined both by circumstances before PICU admission, such as premorbid physical and psychological health status, and circumstances during PICU treatment, such as the underlying disease, PICU treatment and physical, cognitive and emotional resilience. (38) Follow-up research should lead to ideas for preventive interventions. Determinants of morbidity after PICU discharge are shown in Figure 1. Structured and standardized follow-up studies should consist of the evaluation of these determinants and the prevalence of physical and psychological sequelae as well
as their impact on daily life. The follow-up time has to be long because of the growth, development and longer life expectancy of children. In the Amsterdam region, 49% of all people and 65% of children younger than 14 years of age are not of Dutch origin. It is therefore important to develop a research program that is also applicable to these children and their families. (39) Loss of data due to the lack of follow-up should also be addressed (e.g., interviews by telephone or website). Research on the costs and benefits of PICU admissions and cost-effectiveness analysis may be important by measuring, for example, the quality adjusted life years (QALYs, i.e., combining life years gained from a health intervention with preference-weighted health states). (40) Suggestions for structured follow-up research are described in Table 1. A consensus on a structured evaluation of organ system function is essential for follow-up research. For that reason, a standardized and validated tool, such as the Paediatric Logistic Organ Dysfunction (PELOD) Score or the morbidity-free day concept (e.g., the number of ventilator-free days since admission), could be an excellent way to structure the follow-up of organ dysfunction. (41;42) Particularly in children, long-term follow-up studies may be important for the evaluation of the development and maturation of organs. Consider, for example, acute lung injury (ALI) in older children with long-term pulmonary consequences. The primary insult occurs when the lung is exposed to a damaging process (ALI) and the secondary insult is caused by mechanical ventilation. (43;44) This concept of a 'two-hit model' may be applicable to other organs, such as cardiac function, as we hypothesized in our study of septic shock survivors.

In our studies of physical sequelae in previously healthy children and of septic shock survivors, we found indications that physical and neurocognitive sequelae may be substantial. Standardized neurocognitive evaluation is warranted, as neurocognitive abnormalities have a sizeable impact on the (HR)QoL. Adequate rehabilitation programs may prevent future health problems.

**Figure 1.** Determinants before and during PICU stay of morbidity after PICU discharge.
Discussion and implications for the future

Early intervention, education, and rehabilitation may improve the daily lives of children with neurocognitive, developmental and psychological problems. (25-28) The relevance for social aspects such as relationships and employment, however, still needs to be defined.

In at least 8% of our previously healthy patients, morbidity was associated with complications of PICU procedures. Hoarseness and impaired growth of extremities was never spontaneously mentioned. Complications of PICU treatment (e.g., invasive procedures and drug treatment) should therefore be evaluated during standardized follow-up research. Awareness of these potential complications may have implications for treatment during the acute phase. (45)

Evaluation of the HRQoL of survivors and their families may lead to a better understanding of the long-term effects of physical and psychological sequelae, consequently leading to an improvement in support after PICU discharge. A consensus on adequate questionnaires is essential, as the measurement of the HRQoL and resulting feedback as part of the daily clinical practice of an outpatient clinic may improve management of individual patients. (46;47)

Table 1. Recommendations for structured follow-up research in PICU survivors, with examples of sequelae found in our studies.

<table>
<thead>
<tr>
<th>Physical sequelae</th>
<th>Example</th>
<th>Standardized evaluation</th>
<th>By whom</th>
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¹ PELOD score (Paediatric Logistic Organ Dysfunction score), ² POPC (Pediatric Overall Performance Category score), ³ PCPC (Pediatric Cerebral Performance Category score), ⁴ PTS (post thrombotic syndrome), ⁵ PTSD (posttraumatic stress disorder)
Psychological sequelae, such as PTSD, have been established in 14% of the previously healthy children in our study and in 10-14% of the survivors and parents in other studies. Other psychological sequelae, such as anxiety, depression and behavioural problems, are rarely studied. Risk factors reported to account for hampered psychological outcomes differ. (39;48) Further research of risk and overprotection factors and parents' wishes is essential to establish the appropriate duration and extent of the necessary psychological support. (39;49) Psychological support may consist of the improvement of coping strategies, prevention of overprotection and specialized programs for children. (50;51) A protocol to inform and prepare parents for transfers out of the PICU could offer a foundation for security and safety, therefore reducing distress. (52)

Studies of psychological sequelae in the siblings of PICU survivors are important as they may have substantial psychological sequelae as well (e.g., siblings of cancer patients). (39;53)

Compassion fatigue, burnout and PTSD are also found in health care providers in PICUs. Studies on the psychological abilities and function of health care providers may therefore also be warranted, as the number of chronically ill children increases and communication with children and families becomes increasingly difficult. (54-56)

The development of a structured follow-up program is only possible in an environment that stimulates this research and with adequate financial support. Follow-up teams should consist of pediatric-intensivists, psychologists, pediatric intensive care nurses and a data manager. In addition, the close collaboration of PICU members and psychologists is important.

**Suggestion for future research in The Netherlands**

Our studies and other Dutch studies in PICU populations confirm the findings that long-term sequelae are substantial and that knowledge of these sequelae may improve patient care during and after PICU admission. (14;15;23;57;58)

In The Netherlands, 4000-5000 children (0–18 years of age) are admitted to a PICU annually. Approximately 40% of these are electively admitted after a planned procedure. Of the remaining 60%, about two-thirds (1600-2000 children) are admitted unexpectedly and were healthy before admission. Applying the results of our study on the physical and psychological sequelae in previously healthy children to The Netherlands would mean that every year (a) 1100-1400 children (69%) will still have health problems requiring care by medical specialists three months after discharge; (b) 130-160 children (8%) will have problems associated with PICU treatment; (c) 540-680 children (34%) will have subclinical PTSD; and (d) 220-280 children (14%), 240-300 (15%) mothers and 140-180 (9%) fathers will have the full diagnosis of PTSD. (19)

In The Netherlands, all children with two or more organ system failures and all children younger than one year of age needing artificial ventilation are admitted to one of the eight PICUs that are situated in university hospitals. All PICU physicians in The Netherlands are members of the Section of Pediatric Intensive Care (SICK) of the Dutch Pediatric Society (NVK). Multi-centre follow-up studies with a uniform approach are the only way to provide answers, in either general PICU cohorts or in disease-oriented study groups.
on the long-term sequelae of PICU survivors. (37) The situation in The Netherlands, with concentration of almost all PICU patients in the eight PICUs and the collaboration of PICU physicians in the SICK may be ideal to perform such studies. Collaboration an adequate multi-centre, follow-up studies with adequate sample sizes and patient care programs should therefore be feasible. Since a substantial number of follow-up studies in PICU survivors are performed in The Netherlands, the acquired knowledge and experience should be used to reach a consensus on measurement tools, study populations and length of follow-up in the SICK. It should therefore be possible to develop a PICU follow-up network with standardized follow-up of all previously healthy children surviving PICU admission.

**Clinical implications**

Intensive care has been considered a ‘service stop-over’ for many years, and intensivists have had little concern for where their patients came from and where they went to after discharge. In these situations, follow-up was performed by the physicians involved with either the admission or discharge diagnosis. (59) Physical and psychological sequelae due to underlying diseases and due to PICU treatment are, however, often unrecognized by general pediatricians or family doctors. Knowledge of physical and psychological sequelae in PICU survivors should lead to changes in the acute phase of PICU treatment. For example, post-thrombotic syndrome after central venous catheterization should lead to evaluation of indication, way of introduction and management of central venous catheters. (60) Knowledge of psychological sequelae and their risk factors could lead to changes in the approaches of physicians and nurses when necessary (e.g., more compassionate care), to more ethical considerations in relation to ongoing technical possibilities and modalities, and improved psychological support during and after PICU admission. Support of PICU survivors and their parents should not stop when the children are discharged. Standard aftercare should include psychological screening and counselling when necessary.

We speculate that since a substantial part of the problems are related to PICU treatment, pediatric-intensivists and nurses should be core members of follow-up teams. Notifying health care practitioners about physical and psychological sequelae might serve as a valuable tool that will provide feedback on procedures and influence technical and ethical considerations as well as decisions and communications during the acute phase of treatment. Furthermore, we believe that the outpatient follow-up clinic should be part of the training program for pediatric intensive care fellows.

**Clinical implications in our PICU**

Since a substantial number of patients in our studies had physical and/or psychological sequelae, we decided to change the processes for treatment and support during and after PICU admission in our unit.
Psychological support during PICU admission was standardized in an attempt to decrease psychological problems. The standardized program now consists of: (a) weekly multidisciplinary team meetings with the nurses, attending physicians, social workers, and psychologists from the psychosocial department; (b) regular meetings with a social worker or psychologist for parents of children that will be admitted for more than three weeks; (c) a discharge protocol; and (d) additional communication training for all nurses and physicians. The discharge protocol consists of a meeting with a nurse and a doctor the day before or the day of the discharge of the child. The parents receive a brochure listing the most important differences between a general pediatric ward and a PICU, with information on possible psychological problems they and their child may encounter after discharge and information on the outpatient follow-up clinic with telephone numbers in case questions or problems should arise. When the child is discharged to a general ward in our hospital, the ward is shown to the parents beforehand. The communication training consisted of information and education on normal stress reactions in the child and parents during PICU stay and after discharge, on psychological sequelae and on the negative effect of debriefing. (61) Furthermore, communication with parents was practiced with role-playing.

We invite all PICU survivors that were healthy before PICU admission and were unexpectedly admitted to visit the outpatient follow-up program three months after discharge. Since we found physical sequelae in 69% of the children in our study, a pediatric-intensivist evaluates the physical sequelae in a structured way and arranges additional investigations and treatment when necessary. A psychologist evaluates PTSD, anxiety, depression, coping styles, acute stress disorders and HRQoL in children and their parents, arranging support when necessary. Both the pediatric-intensivist and the psychologist study the prevalence and determinants of physical and psychological sequelae. Long-term cardiac performance is evaluated in all septic shock survivors by a pediatric-cardiologist, and long-term vascular problems are evaluated in all children that had central venous catheters.

**Conclusion**

The development of pediatric intensive care has resulted in a decrease in pediatric mortality and an increase in morbidity, leading to an increase in children and adults with chronic illnesses. The results of our studies on the 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 focused on the prevalence of sequelae and their determinants in order to assess the necessity of adjustments in care and support during and after PICU admission. Knowledge of sequelae has led to changes of care and support during and after PICU admission in our unit. The outpatient follow-up clinic has become part of a standard procedure to evaluate physical and psychological sequelae. Multi-centre follow-up studies are warranted in order to overcome the limitations of follow-up studies in PICU survivors, and should be feasible in The Netherlands.
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