Surviving pediatric intensive care: from mortality to morbidity
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General introduction and outline of the thesis
History of pediatric critical care medicine

The development of modern pediatrics began in the second half of the 19th century when the infant mortality rate of Western Europe was 200 infants per 1,000 live births. Unsanitary infant feeding practices and infectious diseases such as dysentery, pneumonia, measles, diphtheria, and pertussis were the main causes of death in children. Mortality in children decreased due to improved hygiene, vaccination programs, the development of antibiotics, an improved understanding of infant nutrition, and enhanced socio-economic circumstances. The term pediatrics was introduced in 1858, and professional specialty organizations subsequently began to form; the Dutch Pediatric Society was founded in 1892 and the American Academy of Pediatrics (AAP) was founded in 1930. (1)

In 1952, a severe poliomyelitis epidemic in Denmark that resulted in hundreds of paralyzed patients with respiratory problems led to the establishment of the first Intensive Care Unit (ICU) for adult patients in Europe. This successful experience, as almost 60% of the patients survived, spurred the development of mechanical ventilators, humidifiers, monitoring equipment and equipment for blood gas measurements. Advances in the areas of resuscitation, such as defibrillators, perioperative care and the development of kidney replacement therapy, contributed to the improvement of multidisciplinary critical care medicine. (2) In conjunction with new initiatives in neonatology, general pediatric surgery, pediatric cardiac surgery, and pediatric anaesthesiology, these developments enabled the foundation of specialized units and centers for pediatric critical care medicine. (3)

The first multidisciplinary Pediatric Intensive Care Unit (PICU) was opened in 1955 at the Children's Hospital in Gothenburg, Sweden. (4) The first PICUs in The Netherlands were established in the late 1970s and early 1980s. In 1992, the Society of Critical Care Medicine (SCCM) created a section of pediatric critical care within the SCCM. Criteria for subspecialty certification and guidelines for PICUs were defined. (5;6)

The goals of pediatric critical care were defined as restoration of health in children who are suffering from a life-threatening conditions with a minimum of pain, anxiety, and complications and provision of comfort and guidance to the children's families. (7)

Organisation of pediatric critical care in The Netherlands

In The Netherlands, 4,000-5,000 children aged 0–18 years are admitted annually to a PICU. About 40% (±1,600-2,000 children) are electively admitted after a planned procedure such as postoperative care after cardiac surgery. Of the remaining 60%, about two-thirds (±1,600-2,000 children) are admitted unexpectedly and were healthy before the event leading to admission. There are a total of eight PICUs in The Netherlands, containing 105 beds (2.4 beds per 100,000 children), all of which are situated within university hospitals. The attending physicians at the PICUs consist of 35 pediatric-intensivists and pediatric-anaesthetists accompanied by 8-15 fellows. All PICUs in
the Netherlands belong to the Section of Pediatric Intensive Care (SICK) of the Dutch Pediatric Society (NVK) and collaborate in research and patient care programs.

**Changes over time**

The reduction of infant and child mortality at the end of the 19th and the beginning of the 20th centuries was mainly caused by improved socio-economic conditions. Soon thereafter, a further decline in mortality was achieved by major contributions from modern pediatrics and the development of pediatric surgical interventions, such as general pediatric surgery, and pediatric cardiac surgery and anaesthesiology. This progress also laid the foundation for the development of modern neonatology and pediatric intensive care.

**Changing characteristics of PICU patients**

Patient populations of the first PICUs in The Netherlands during the late 1970s and early 1980s consisted mainly of (1) previously healthy children admitted because of serious infectious disease or trauma; (2) children admitted after major surgical procedures, for which PICU admission may not have been foreseen pre-operatively; and (3) children with life-threatening congenital diseases that could not be admitted to the neonatal intensive care unit. The main concern of the PICU teams and parents was survival. After PICU discharge, children were admitted to a general pediatric ward then received follow up care at the outpatient clinic of a general pediatrician or subspecialist (e.g., pediatric cardiologist or pediatric surgeon) as necessary.

Current patient populations of PICUs consist of (1) previously healthy children admitted because of serious infectious disease or trauma; (2) children admitted after elective (surgical) procedures, for which PICU care is foreseen and planned pre-operatively; (3) children with congenital diseases; and (4) technology dependent children and children with chronic illnesses.

For example, children admitted to the PICU with respiratory insufficiency due to a viral or bacterial pneumonia in the 1970s were considered healthy when they could be discharged to a general pediatric ward. Pediatric-intensivists thought that the children had been lucky and only needed additional time to recover completely. After hospital discharge, the general pediatrician saw them at an outpatient clinic only when additional treatment was necessary. General pediatricians and pediatric-intensivists were convinced that the children and their families could then go on with their lives.

**Development of pediatrics and PICU patient population**

Advanced preventive, diagnostic and technical modalities have changed the natural course of numerous illnesses in both adult and pediatric medicine. These changes have resulted on one hand in less mortality, but on the other, in increased morbidity. Children who previously would have died now survive, dependent upon technology or affected by chronic illness. Consequently, the number of reoperations and concurrent diseases necessitating PICU admissions has increased.
Examples of these developments are vaccination programs, new diagnostic tools, advanced surgical skills, new technological modalities and improvement of pediatric intensive care. Vaccination programs have led to a decrease of patients with meningococcal disease, meningitis and epiglottitis due to Hemophilus influenzae. New diagnostic tools have identified other infectious diseases such as Respiratory Syncitial virus and Parvovirus. Well-known illnesses such as Reye syndrome have vanished completely due to the development of tests for inborn metabolic disorders. (8-12) Advanced surgical skills combined with new technological modalities have contributed to improved management and survival of children with major congenital anomalies, such as Hypoplastic Left Heart Syndrome (HLHS). Before 1980, 90% of children with HLHS died within the first 30 days of life. The development of pediatric cardiac intensive care, echocardiographic imaging, pharmacologic circulation manipulation, the Norwood procedure, and heart transplantation substantially improved survival. As a consequence, the number of children with congenital anomalies surviving into adulthood increased. (13-15) Improvement of pediatric intensive care led to increased survival of children with diseases such as Cystic Fibrosis and Duchenne's muscular dystrophy at the cost of more children living with acute and chronic respiratory insufficiency. (16-18)

Changes in disease patterns of PICU patients
While improvements in survival are generally considered benefits, they are not without drawbacks. The decreases in mortality has been accompanied by: (1) an increase of children with neurodevelopmental problems, decreased exercise performance and reduced quality of life; (2) an increased need for reoperations and other pediatric intensive care admissions due to concurrent diseases; (3) an increase in the number of technology dependent children (i.e., children who need both a medical device to compensate for the loss of a vital body function, and substantial and ongoing nursing care to avert death or further disability); and (4) an increase in iatrogenic complications (e.g., increased infection and associated mortality among low-risk patients undergoing invasive procedures such as endotracheal intubation and central venous catheterization, or mechanical ventilation induced lung damage among children with Adult Respiratory Distress Syndrome). (19-26)

Global migration and PICU patient population
Globalization and the associated increases in international travel and migration have also impacted the PICU patient population. Travel has facilitated the spread of infectious diseases such as Severe Acute Respiratory Syndrome, HIV and tuberculosis. Immigrant populations may bring genetic diseases uncommon to their adopted lands; e.g., an increase in immigrants to The Netherlands has been accompanied by an increase in sickle cell anaemia. In 2007, the migrant population of The Netherlands comprised 3.2 million (19.4%) of 16.4 million total inhabitants; nearly half (48.6%) of Amsterdam’s 740,000 inhabitants were migrants, and 65% of the city’s pediatric age group (under age 14 years) were migrants. (Data from Dutch Health Statistics, www.cbs.nl)
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Quality of life of PICU patients and their families
As a consequence of improved survival, evaluation of the well being of both the children and their families has become an important concern. Health Related Quality of Life (HRQoL) is used as an outcome measure to evaluate patient's well being. In 1948, the World Health Organization defined health as 'a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. Quality of life (QoL) is defined as an individual's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns. (27) HRQoL consists of QoL to which a dimension of personal judgement over one's health and disease has been added. (28) For children, HRQoL is influenced by the severity of disease, and the extent to which the child can participate with peer groups and be involved in developmentally appropriate activities.

Psychological side-effects in PICU patients and their families
PICU admission of a child leads to stress reactions in the child and parents both during the PICU stay and after discharge. Stress theories have named three properties of events that increase associated levels of stress: novelty, unpredictability and uncertainty. Uncertainty, the threat of losing a child, and the absence or loss of control lead to more stress symptoms (29;30) The pediatric medical traumatic stress model (PMTS), as proposed by Kazak et al., is helpful in understanding these psychological consequences. PMTS acknowledges the direct threat to life and provides a framework for conceptualizing and treating ongoing stress. (31) Pediatricians should be aware of the psychological impact on a child's critical illness on both children and their parents.

Psychological sequelae in children and parents consist of anxiety, depression, symptoms of posttraumatic stress disorder (PTSD), or the full psychiatric diagnosis of PTSD. (32-35) PTSD is an anxiety disorder that develops after one or more stressful events. (36) Historically, PTSD has been related to war veterans and survivors of severe disasters. Only recently has PTSD been acknowledged as an important patient-reported outcome following injury and illness. (37;38) In adults, it includes symptoms from three clusters: intrusions, avoidance and hyperarousal. In children, PTSD includes these three clusters plus new fears, aggressive behaviour and loss of previously acquired developmental skills. Among adults and children, PTSD can persist for months or even years, resulting in co-morbidities (e.g., anxiety, substance abuse and depression disorder). (36;39) When not properly diagnosed and treated, PTSD can result in substantial impairment of occupational, social, relational and academic function. (40;41).

Conclusion
Overall, these medical and technological breakthroughs have resulted in one of the major advances of pediatric intensive care: decreased mortality. The successes of pediatrics as a whole and pediatric intensive care in particular have resulted in a shift of commonly seen diseases, a change in disease patterns, a disappearance of distinct diagnoses and the introduction of new diagnostic groups. As a consequence we now face long term physical and psychological sequelae with lifelong implications.
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for growth, development and HRQoL for survivors and their families. Systematic and standardized evaluation and follow-up care of these sequelae in PICU survivors is therefore warranted.

Evaluation and follow-up of sequelae

In children, physical, psychological, cognitive and social development into adulthood is of utmost importance to become a productive member of society. (42) Disruption of normal development by a serious illness may have lifelong consequences. Therefore, evaluation of sequelae in PICU survivors should include evaluation of physical, psychological and cognitive function; and evaluation of HRQoL (43;44)

Since the well being of a child is also dependent upon the well being of its parents, evaluation of their physical and psychological function and HRQoL is also important. (45)

Physical function

In a multidisciplinary PICU, children are admitted for numerous reasons: (1) postoperative care after (elective) surgery; (2) life-threatening complications of underlying diseases (e.g., septic shock in oncology patients); and (3) previously healthy children who are admitted either due to acute illness such as meningococcal disease, or trauma such as traffic accidents or near drowning. In some previously healthy children, a pre-existing underlying disease (pre-PICU morbidity) is diagnosed, for example cyanosis caused by an undiagnosed congenital heart defect, or an apparent life threatening event based on a Medium-chain acyl CoA dehydrogenase deficiency. Physical sequelae (morbidity) in PICU survivors can be the inevitable consequence of the pre-PICU morbidity (e.g., congenital heart defect) or can be caused by the illness for which PICU admission and PICU treatment was needed (acquired morbidity). Acquired morbidity can be caused by the disease itself (e.g., amputation of an extremity due to meningococcal infection), by the treatment that was needed (e.g., complications of PICU procedures such as Post Thrombotic Syndrome after central venous catheterization), or a combination of both. (Figure 1)

The cornerstone for restoration of normal functional health is resolution of organ system dysfunction after PICU survival. (46) For that reason, consensus on a structured evaluation of various organ system functions following PICU treatment is essential for follow-up research. A standardized and validated tool such as The Pediatric Logistic Organ Dysfunction (PELOD) score, or the morbidity free day concept (e.g., ventilator free days) could be an excellent method of structured organ dysfunction assessment. (47-49)

Quality of life

Several challenges exist to measuring QoL in children, including (1) lack of consensus on appropriate instruments, (2) the need for different instruments for different age groups, and (3) the need of proxy reporting by parents or clinicians for children younger than 8 years of age. (50;51)

Consensus on appropriate questionnaires to evaluate HRQoL is essential. The ideal questionnaire
should measure all aspects of QoL or HRQoL, and be reported by the children themselves (≥6-8 years of age). Proxy investigation, necessary for children below 6-8 years of age, is a secondary choice because proxy reports do not always correspond with self-evaluations and can vary by the health aspect being examined. For example, concordance for items and domains concerning functional limitations are higher compared to items and domains concerning emotional and social well being. (52-54) Agreement also varies by proxy respondent; physicians are typically not valid respondents for QoL and HRQoL of their patients. (55;56)

Cognitive function
Problems in cognitive function can be expected not only after traumatic brain injury and meningitis, but also after possibly brain damaging incidents such as hypoperfusion and hypoxia. It is possible
that the younger brain is more vulnerable. Evaluation of cognitive function among pediatric survivors of traumatic brain injury and meningitis shows substantial problems that interfere with daily life. Contrary to illnesses with neurological involvement, cognitive function in children with life threatening illnesses of other organ systems (e.g., septic shock) is not evaluated. Among adult survivors of septic shock or Adult Respiratory Distress Syndrome (ARDS), neuro-cognitive sequelae are substantial.

**Psychological function**

Studies on psychological sequelae in PICU survivors and their parents are scarce. Long term effects such as PTSD have been reported in PICU survivors, but other psychological problems such as anxiety and depression have hardly been reported and need to be studied as well. Studies on PTSD often differ in terms of study sample, methods or in timing of assessment, which prohibits comparison. To determine the exact prevalence, the natural time course, and determinants of PTSD, longitudinal studies are required.

The prevention of psychological sequelae through early detection and intervention is important to reduce the harmful effects that a child’s critical illness can have on the wellbeing of both children and parents. Treatment should not end after discharge. Follow-up care is necessary, and research should focus on the prevention and reduction of these symptoms. Psychological consequences can be minimized by anticipatory guidance and stress-reduction interventions during and after PICU treatment.

**Conclusion**

The development of pediatric intensive care has led to a decrease in pediatric mortality and an increase in morbidity. It also has led to an increase in chronically ill children and adolescents. At the same time, increased attention to psychological reactions to this traumatic event, and an extension of concern to the context of the family has emerged. The increased number of chronically ill patients will have an impact on needs for health care, social services, support systems and possibilities for social participation. These provisions will have major socio-economic consequences. Therefore, standardized evaluation of long term sequelae in PICU survivors to assess future costs and benefits is important. Knowledge of these sequelae may lead to improvement of care and support during and after PICU admission, with the aim to reduce morbidity and improve QoL and psychological function.

**Aim of our study**

The aim of our study was to complete a standardized evaluation of physical sequelae, HRQoL and psychological function in PICU survivors. We performed a systematic review of sequelae in PICU survivors and developed an on-going explorative research programme on physical sequelae, HRQoL and psychological sequelae in children after PICU survival. The program was developed in...
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collaboration with the psychosocial department of our children's hospital. The children and their parents were invited to participate in a structured medical examination by a pediatric intensivist followed by a psychological screening by a psychologist.

Outline of the thesis

Chapter 2 is the literature review, which was performed in the beginning of 2006. Chapter 3 and 4 report the results of the studies performed to investigate physical sequelae. In chapter 3, physical sequelae in previously healthy children three months after PICU discharge are reported; in chapter 4, cardiac function in septic shock survivors admitted to our PICU between 1995 and 2005 is reported. Chapter 5 and 6 report the results of the studies performed to investigate HRQoL. In chapter 5, HRQoL in previously healthy children at three and nine months after discharge is reported; in chapter 6, HRQoL, cognitive and psychological function (i.e., anxiety and depression) in septic shock survivors are reported. In chapter 7, psychological sequelae (i.e., PTSD) in previously healthy children at three months after PICU discharge are reported. The thesis closes with chapter 8 with a discussion of the significance of these findings for the treatment of critically ill children and a discussion of suggestions for future research.

References

Introduction

Introduction

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