Disease specific outcome in paediatric intensive care

Sjef van Gestel

ISBN: 978-94-61080-02-8

Cover: vrije impressie van “Disease specific outcome in paediatric intensive care” door Kester van Zijl (6 jaar)

Printed by: Gildeprint Drukkerijen, Enschede

Disease specific outcome in paediatric intensive care

Ziekte specifieke outcome van behandeling op de kinderintensive care
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op
gezag van de rector magnificus, prof.dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 14 januari 2010 des middags te 2.30 uur

door

Josephus Petrus Johannes van Gestel

geboren op 25 februari 1966 te Waalwijk

Promotoren: Prof.dr. A.J. van Vught
Prof.dr. J.L.L. Kimpen

Co-promotor: Dr. C.W. Bollen

Contents

Chapter 1

INTRODUCTION AND OUTLINE OF THE THESIS

"Some patients are clearly salvaged by intensive care unit admission; others are clearly harmed. The relative distribution of these patients is important to establish in guiding our approach to intensive care generally [1]"

Introduction

Evolutions of critical care

The foundations for modern intensive care units were laid in Denmark in the middle of the last century, when there was a catastrophic poliomyelitis epidemic. Due to the infection, so many patients suffered from respiratory muscle weakness and severe hypoventilation, that the hospital in Copenhagen was overwhelmed with patients requiring artificial ventilation. Until then, an occasional patient with respiratory failure had been treated with a negative pressure ventilator. However, a high proportion of patients in Denmark suffered from bulbar poliomyelitis, in which the brainstem and cranial nerves are involved in the disease, leading to swallowing difficulties with stagnation of secretions in the upper airways. Ventilation with negative pressure ventilators had proven nearly futile in these patients with mortality rates being over 90%. These circumstances urgently required therapeutic improvisations and new ways of artificial ventilation. Following the common practice in operating theatres, one of the anaesthesiologists proposed to put a rubber tube into the trachea of affected patients through a tracheotomy. The tracheal tube was then attached to a bag. By squeezing the bag, air was inflated into the lungs of the patient. In order to keep patients alive, a student had to sit next to the bed of each patient and squeeze the bag every few seconds for hours at a stretch. Already during the first weeks of the epidemic, about 200 medical students had been employed daily to deliver intermittent bag ventilation. It is important to acknowledge that recovery from muscle paralysis could take several months. By the time the polio epidemic was over 1,500 students had been bagging their patients for more than 160,000 hours. As a result of these interventions, mortality rates from respiratory failure due to bulbar poliomyelitis had fallen to 40% [2]. With this improvement in outcome, assisted ventilation became the central feature of care for the seriously ill. It was a strong incentive for the founding of intensive care units, although it took several years before other medical specialists (i.e. surgeons) accepted the idea of prolonged ventilation for their patients.

Nowadays, intensive care has evolved from mere mechanical ventilation to multidisciplinary treatment of frequently complex medical and surgical conditions. The common characteristic of patients admitted to an intensive care unit is that they have sustained, or are at risk of sustaining, acutely life threatening, single or multi-organ system failures due to disease or injury. In daily clinical practice, populations

in paediatric intensive care consist of: (1) previously healthy children admitted because of life threatening respiratory, circulatory or neurological conditions, mostly due to serious infection or trauma, (2) children after surgical procedures, for which intensive care is generally foreseen pre-operatively, (3) children with life threatening congenital anomalies and (4) children with chronic diseases with vital complications due to the disease or its therapy (such as severe infections in children on chemotherapy, respiratory failure in children with a neuromuscular disorder or increase in seizures in children known with epilepsy). The rapid evolution in intensive care medicine is particularly true for paediatric intensive care, being an even younger discipline than its adult counterpart. In a relatively short time span, it underwent an impressive progress in technology, organisation and education, all of which will be briefly discussed below.

Technological developments have greatly facilitated complex critical care. For example, sophisticated mechanical ventilators have been designed, which make it possible to accurately give small tidal volumes to infants and children, thereby contributing to lung protective ventilation and improvements in survival [3]. The response time and sensitivity of these ventilators have improved, which makes adaptation to the ventilator easier. Less sedatives and neuromuscular blocking agents are therefore required, and the patient can start earlier with spontaneous breathing in a ventilatory support mode. Both can reduce the duration of mechanical ventilation [4]. Alternative methods of mechanical ventilation, like high frequency ventilation, have been developed for patients with severe lung disease [5, 6]. When both these ways of respiratory support fail, more complex technical solutions like extracorporeal membrane oxygenation can be used to secure oxygenation and ventilation [7]. Recently, the first clinical experiences with pumpless extracorporeal carbon dioxide removal in children have been reported [8].
Technological developments have enhanced sophisticated diagnostic strategies in medicine. Techniques like the polymerase chain reaction created the possibility to confirm infections at a very early stage or identify pathogens which are difficult to culture. This can be of vital importance in immunocompromised patients [9, 10]. In patients requiring haematopoietic stem cell transplantation, molecular techniques enabled improved antigenic typing quality, leading to more precise matching between graft and host, which resulted in fewer complications after the transplantation [11].

The organisation of paediatric intensive care has considerably changed over the years. In the past, critically ill children were treated on general paediatric wards, or on adult intensive care units. Nowadays it is standard of care that these children are treated in specialised paediatric intensive care units, where they are treated by physicians and nurses who are specifically trained in paediatric anaesthesia or

paediatric critical care. Dedicated paediatric intensive care specialists significantly improved patient outcome [12-14], as did centralisation of paediatric intensive care [15, 16]. The most optimal staffing and organisation of intensive care units remains topic of research [17-19]. In the Netherlands, there are eight paediatric intensive care units, all situated within university medical centres. For a small country like the Netherlands, it can be questioned if optimal centralisation has already been achieved: there is evidence that a greater volume of patients improves both quality and efficiency of paediatric critical care [20, 21].
Since 2004, transport of critically ill children in the Netherlands from general hospitals to paediatric intensive care units is well organised and done by specialist retrieval teams. Before 2004, such transports were often done by referring paediatricians with little training in critical care, which resulted in more complications [22].

Over time, education in paediatric intensive care has professionalized. A number of training courses in early stabilisation of critically ill patients are available in the Netherlands, like the Advanced Paediatric Life Support (APLS), the European Paediatric Life Support (EPLS) or the Advanced Trauma Life Support (ATLS) courses. Each year, over 200 physicians are currently trained in the APLS, leading to an increase in their self-efficacy when confronted with acutely ill children [23]. It is very likely that these courses contributed to an improvement in outcome of critically ill children [24, 25].
Most paediatric intensive care units in the Netherlands have fellows in training for intensivist. Paediatric intensive care units with critical care training programs are generally associated with better risk adjusted mortality rates than intensive care units without such fellowship training programs [26]. There are joint schooling days for all fellows from paediatric intensive care units in the Netherlands, where various subjects are discussed in depth. Certification for paediatric critical care fellows in the Netherlands is clearly defined, and includes at least one publication in a peer reviewed journal. This reflects the increased attention in paediatric intensive care for research, which is further underscored by the steep rise in the number of PhD theses in the Netherlands addressing paediatric critical care.

Outcome assessment in paediatric critical care
Despite all progress in critical care medicine, some of the typical characteristics of intensive care treatment have remained unchanged. One of the reported disadvantages of bag ventilation in the first intensive car unit in Denmark was that “the assistance of well-trained personnel all round the clock is essential and costly [2].” Expensive technological equipment, highly classified personnel, extensive diagnostic tests and pharmaceutical services continue to make intensive care very costly [27-29]. Moreover, intensive care is literally intensive, with a considerable

burden for patients, their relatives and for the professionals who deliver this care. This necessitates the need for clear and current data about outcome of intensive care. It is highly undesirable to give a patient a false feeling of hope and expose this patient to a costly and burdensome therapy, when it is very unlikely to be of any benefit. On the other hand there is a strong drive to try any therapy at any cost, especially for those who suffer from a disease with a bad short term prognosis. These patients and their doctors are often willing to rescue any therapy, even if chances for success are minimal.

For many years, advancements in medical knowledge were based on experimental and innovative therapies without proven efficacy; the delivery of prolonged mechanical ventilation in Denmark during the polio epidemic can be seen as a clear example for this. In modern and safety-conscious medicine, advancements are based much more on objective scientific methods. Nowadays, survival in paediatric intensive care is known to be very good for the vast majority of diseases, which is underscored by solid scientific evidence [28]. However, daily clinical care is refractory, and deciding if intensive care is beneficial to an individual patient, and which treatment on the intensive care unit is best is highly complex for several reasons. First, the overall decrease in mortality in paediatric intensive care has been accompanied by an increase in morbidity. A considerable number of survivors are confronted with long term physical and psychological sequelae with implications for growth, development and quality of life for themselves and their families [30-33]. Attention for these long term consequences of intensive care began only recently, and literature on this subject therefore still is scarce. As a result, for many treatments there is still insufficient knowledge about long term outcome. Second, in rarely occurring diseases outcome is often simply unknown. Seemingly contradictory, rare diseases are regularly encountered in paediatric critical care. Third, outcome may have improved over time as a result of novel therapies or overall improvements in medical care. Some of these improvements advance at such high speed that scientific evidence for clinical decision making inevitably falls behind. Altogether, therefore, there are multiple reasons why patients, parents and health care professionals are regularly confronted with considerable uncertainty about the outcome of intensive care. It underscores the need for a continuous critical evaluation of critical care.

There are several strategies to inform clinicians about patient's outcomes and chances for survival. At first, several scoring methods have been developed to assess the severity of illness on admission to the intensive care. The Pediatric Risk of Mortality (PRISM) score [34] and the Paediatric Index of Mortality (PIM) score [35] are examples of such scoring systems. They are the most frequently used generic scoring systems for infants and children. In both scoring systems, deteriorations of

clinical and laboratory parameters like systolic blood pressure, pupillary reflexes and acid base status at entry into the intensive care unit (PIM) or during the first 24 hours of admission to the intensive care unit (PRISM) are assessed. For each parameter, an abnormal range with a number of points is assigned. The number of points of each variable is proportional to its capacity to predict mortality. The total sum of these points can subsequently be converted into a risk of mortality by means of a logistic regression technique. Both scoring systems are well validated with large sample sizes involving different paediatric intensive care units, and they are used worldwide. They are mainly used for two reasons: first, to assess the quality of an intensive care unit by comparing the actual mortality rate with the predicted mortality rate, and second, to describe the severity of illness on admission to the intensive care unit in clinical trials or descriptive studies.

There are several limitations to generic scoring systems such as PRISM and PIM. At first, scoring during development and validation of PRISM and PIM was mostly done by a small number of dedicated and well-trained professionals, which resulted in an acceptable interobserver reliability [36, 37]. In daily clinical practice, however, scoring will be done by various persons with varying degrees of experience, which may result in significant degrees of interobserver variability [38]. Training, strict guidelines and regular auditing are required to improve the reliability [39]. Second, mortality changes over time and scoring systems therefore have to be updated and recalibrated regularly. The last recalibration of the PIM score has been in 2003 [37], while the PRISM III score is continuously recalibrated. The PRISM III score, however, is not used in many paediatric intensive care units outside the United States of America [40]. Moreover, the PRISM score includes data from the first 24 hours in the intensive care unit, which may result in early treatment bias [40]. Another limitation of generic scoring systems is that they are generic, and by definition therefore, are case-mix dependent. For groups of patients with a specific disease, generic scoring systems have shown to be of limited value in accurately predicting mortality [41-43]. For individual patients, generic scoring systems are unsuitable. An individual patient either survives to discharge or dies in the intensive care unit. For individual patients, their relatives, and those involved with the care for these patients it is far more informative to know the clinical course and outcome (both mortality and morbidity) of other patients with comparable diseases. For frequently occurring diseases, such as respiratory failure due to an infection with respiratory syncytial virus, the clinical course and outcome often are well known. In other diseases, the clinical course may be less obvious, or uncertainty about outcome may be considerable. This includes rarely occurring diseases, or diseases for which the benefits of critical care have long been doubted. This holds true for example for respiratory failure in patients with cystic fibrosis or patients after bone marrow transplantation. In these patients it was observed that outcome of intensive care treatment was very poor [44, 45]. However, as mentioned before, medical care

advanced significantly over the years. Up to date outcome data and accurate prognostic indicators for these diseases are urgently needed: starting mechanical ventilation when the patient is certain to die is futile and therefore unethical, but the decision to refrain from intensive care treatment is difficult, especially when survivors of intensive care treatment have a long life ahead, even if the chances to survive are slim.

In conclusion, medical care in general and paediatric critical care specifically, have greatly advanced over the years. This has resulted in a steady decrease in mortality over time. A critical re-examination of outcome of diseases for which critical care previously was found to be without chance is therefore required. This is especially important, since generic scoring systems often are unreliable in accurately predicting mortality for these specific disease categories.

Aims and outline of the thesis

The studies presented in this thesis concentrate on the following questions:

1. What are the current epidemiological characteristics, clinical course and intensive care unit mortality rates of diseases, which traditionally were considered to have an unfavourable outcome?
2. What are the intensive care unit mortality trends over time in these patient categories?
3. What are the prognostic factors associated with mortality in these patient categories?

Chapter 1 is a general introduction to intensive care, more specifically paediatric intensive care, and to the question of outcome assessment.

Respiratory failure is the leading cause of death among patients with cystic fibrosis. The use of mechanical ventilation in the treatment of acute respiratory failure in cystic fibrosis patients has long been discouraged because of very poor outcome [44]. In **chapter 2** we describe the outcome of assisted ventilation for respiratory failure in a recent cohort of patients with cystic fibrosis, and the risk factors associated with outcome in these patients.

Haematopoietic stem cell transplantation is a potentially life saving treatment for a wide variety of diseases, which previously had little hope for cure. Nevertheless, it remains a high risk procedure and a considerable number of patients require transfer to the intensive care unit because of complications related to the transplantation. The first studies reported that nearly all children who required intensive care after their transplantation died [45, 46], but several authors have suggested that survival

improved over time. In **chapter 3** we performed a meta-regression analysis on all studies in which outcome of critical care treatment in children after haematopoietic stem cell transplantation was assessed. Since current outcome data of mechanical ventilation in these children were lacking, we assessed survival in a recent group of children from our own department. The results of that study are described in **chapter 4**.

Children with severe developmental delay often have respiratory problems. It is assumed by many clinicians that mortality rates are very high once these children require mechanical ventilation, but there are no published reports to confirm this. In **chapter 5** we describe the outcome of mechanical ventilation for respiratory failure in children with severe developmental delay in our department.

Case fatality rates from meningococcal septic shock have remained high for many years [47-49]. Only in the last decade, a reduction in mortality has been reported [24, 50, 51]. This was mainly attributed to a raised awareness for the disease, and to better medical training, leading to earlier recognition and more appropriate initial treatment [25, 52-54]. In **chapter 6** we reviewed the outcomes for all patients with meningococcal disease admitted to our PICU over a 13 years' period, and assessed the influences of critical care treatment strategies on their survival.

In **chapter 7** we describe the clinical course and outcome of children treated in our department with propofol or thiopental for refractory status epilepticus (RSE). Previous studies in children with RSE reported high morbidity and mortality rates 55-57]. Thiopental is often used as a last treatment in RSE [58, 59]. It is an effective treatment, but the possible side-effects are impressive. Because of these side-effects, propofol has been suggested as an alternative [60], but there is little evidence for its safety and efficacy in the treatment of RSE.

Finally, the results from the studies above are summarized in **Chapter 8.** Their potential implications are discussed in the same chapter.

"Much of modern medicine would benefit from a critical examination. Critical care medicine, as an infant discipline, would benefit particularly [1]"

References

1 Robin ED. A critical look at critical care. *Crit Care Med* 1983; 11: 144-148

2 Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet* 1953; 1: 37-41

3 Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347-354

4 Putensen C, Muders T, Varelmann D, Wrigge H. The impact of spontaneous breathing during mechanical ventilation. *Curr Opin Crit Care* 2006; 12: 13-18

5 Butler WJ, Bohn DJ, Bryan AC, Froese AB. Ventilation by high-frequency oscillation in humans. *Anesth Analg* 1980; 59: 577-584

6 Froese AB, Kinsella JP. High-frequency oscillatory ventilation: lessons from the neonatal/pediatric experience. *Crit Care Med* 2005; 33: S115-S121

7 Kopp R, Dembinski R, Kuhlen R. Role of extracorporeal lung assist in the treatment of acute respiratory failure. *Minerva Anestesiol* 2006; 72: 587-595

8 Conrad SA, Green R, Scott LK. Near-fatal pediatric asthma managed with pumpless arteriovenous carbon dioxide removal. *Crit Care Med* 2007; 35: 2624-2629

9 Sulahian A, Boutboul F, Ribaud P, et al. Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. *Cancer* 2001; 91: 311-318

10 Cesaro S, Murrone A, Mengoli C, et al. The real-time polymerase chain reaction-guided modulation of immunosuppression enables the pre-emptive management of Epstein-Barr virus reactivation after allogeneic haematopoietic stem cell transplantation. *Br J Haematol* 2005; 128: 224-233

11 Tiercy JM. Molecular basis of HLA polymorphism: implications in clinical transplantation. *Transpl Immunol* 2002; 9: 173-180

12 Pollack MM, Katz RW, Ruttimann UE, Getson PR. Improving the outcome and efficiency of intensive care: the impact of an intensivist. *Crit Care Med* 1988; 16: 11-17

13 Goh AY, Lum LC, Abdel-Latif ME. Impact of 24 hour critical care physician staffing on case-mix adjusted mortality in paediatric intensive care. *Lancet* 2001; 357: 445-446

14 Pronovost PJ, Angus DC, Dorman T, et al. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002; 288: 2151-2162

15 Pearson G, Shann F, Barry P, et al. Should paediatric intensive care be centralised? Trent versus Victoria. *Lancet* 1997; 349: 1213-1217
16 Fraser J, Maskrey C, Taylor H. Evaluation of the Paediatric Index of Mortality in children managed on adult intensive care units. *Arch Dis Child* 2004; 89: 974-976
17 Gajic O, Afessa B, Hanson AC, et al. Effect of 24-hour mandatory versus on-demand critical care specialist presence on quality of care and family and provider satisfaction in the intensive care unit of a teaching hospital. *Crit Care Med* 2008; 36: 36-44
18 Tenner PA, Dibrell H, Taylor RP. Improved survival with hospitalists in a pediatric intensive care unit. *Crit Care Med* 2003; 31: 847-852
19 Groves RH, Jr., Holcomb BW, Jr., Smith ML. Intensive care telemedicine: evaluating a model for proactive remote monitoring and intervention in the critical care setting. *Stud Health Technol Inform* 2008; 131: 131-146
20 Tilford JM, Simpson PM, Green JW, et al. Volume-outcome relationships in pediatric intensive care units. *Pediatrics* 2000; 106: 289-294
21 Marcin JP, Song J, Leigh JP. The impact of pediatric intensive care unit volume on mortality: a hierarchical instrumental variable analyis. *Pediatr Crit Care Med* 2005; 6: 136-141
22 Vos GD, Nissen AC, Nieman FH, et al. Comparison of interhospital pediatric intensive care transport accompanied by a referring specialist or a specialist retrieval team. *Intensive Care Med* 2004; 30: 302-308
23 Turner NM, Dierselhuis MP, Draaisma JM, ten Cate OT. The effect of the Advanced Paediatric Life Support course on perceived self-efficacy and use of resuscitation skills. *Resuscitation* 2007; 73: 430-436
24 Booy R, Habibi P, Nadel S, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001; 85: 386-390
25 Ninis N, Phillips C, Bailey L, et al. The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. *BMJ* 2005; 330: 1475-1480
26 Pollack MM, Patel KM, Ruttimann E. Pediatric critical care training programs have a positive effect on pediatric intensive care mortality. *Crit Care Med* 1997; 25: 1637-1642
27 Chalom R, Raphaely RC, Costarino AT, Jr. Hospital costs of pediatric intensive care. *Crit Care Med* 1999; 27: 2079-2085
28 Carcillo JA. What's new in pediatric intensive care. *Crit Care Med* 2006; 34: S183-S190
29 Truog RD. Will ethical requirements bring critical care research to a halt? *Intensive Care Med* 2005; 31: 338-344

30 Gemke RJ. Outcome assessment of pediatric intensive care: principles and applications [*thesis*]. Utrecht: Utrecht University; 1995
31 Buysse CMP. Outcome of meningococcal septic shock in childhood [*thesis*]. Rotterdam: Erasmus University Rotterdam; 2008
32 Knoester H. Surviving Pediatric Intensive Care. From mortality to morbidity [*thesis*]. Amsterdam: University of Amsterdam; 2008
33 Gischler SJ, Mazer P. Children with anatomical congenital anomalies; a portrait. Follow-up over five years [*thesis*]. Rotterdam: Erasmus University Rotterdam; 2008
34 Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16: 1110-1116
35 Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med* 1997; 23: 201-207
36 Gemke RJ, Bonsel GJ. Comparative assessment of pediatric intensive care: a national multicenter study. Pediatric Intensive Care Assessment of Outcome (PICASSO) Study Group. *Crit Care Med* 1995; 23: 238-245
37 Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med* 2003; 29: 278-285
38 Van Keulen JG, Polderman KH, Gemke RJ. Reliability of PRISM and PIM scores in paediatric intensive care. *Arch Dis Child* 2005; 90: 211-214
39 Van Keulen JG, Gemke RJ, Polderman KH. Effect of training and strict guidelines on the reliability of risk adjustment systems in paediatric intensive care. *Intensive Care Med* 2005; 31: 1229-1234
40 Lacroix J, Cotting J. Severity of illness and organ dysfunction scoring in children. *Pediatr Crit Care Med* 2005; 6: S126-S134
41 Tissieres P, Prontera W, Chevret L, Devictor D. The pediatric risk of mortality score in infants and children with fulminant liver failure. *Pediatr Transplant* 2003; 7: 64-68
42 Ben Abraham R, Toren A, Ono N, et al. Predictors of outcome in the pediatric intensive care units of children with malignancies. *J Pediatr Hematol Oncol* 2002; 24: 23-26
43 Schneider DT, Lemburg P, Sprock I, Heying R, Gobel U, Nurnberger W. Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children. *Bone Marrow Transplant* 2000; 25: 1079-1086
44 Davis PB, di Sant'Agnese PA. Assisted ventilation for patients with cystic fibrosis. *JAMA* 1978; 239: 1851-1854
45 Todd K, Wiley F, Landaw E, et al. Survival outcome among 54 intubated pediatric bone marrow transplant patients. *Crit Care Med* 1994; 22: 171-176

46 Nichols DG, Walker LK, Wingard JR, et al. Predictors of acute respiratory failure after bone marrow transplantation in children. *Crit Care Med* 1994; 22: 1485-1491
47 Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J* 1996;15: 967-978
48 Havens PL, Garland JS, Brook MM, et al. Trends in mortality in children hospitalized with meningococcal infections, 1957 to 1987. *Pediatr Infect Dis J* 1989; 8: 8-11
49 Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. *N Engl J Med* 2001; 344: 1378-1388
50 Thorburn K, Baines P, Thomson A, Hart CA. Mortality in severe meningococcal disease. *Arch Dis Child* 2001; 85: 382-385
51 Maat M, Buysse CM, Emonts M, et al. Improved survival of children with sepsis and purpura: effects of age, gender, and era. *Crit Care* 2007; 11: R112
52 Pollard AJ, Britto J, Nadel S, et al. Emergency management of meningococcal disease. *Arch Dis Child* 1999; 80: 290-296
53 Pollard AJ, Nadel S, Ninis N, et al. Emergency management of meningococcal disease: eight years on. *Arch Dis Child* 2007; 92: 283-286
54 Nadel S, Britto J, Booy R, et al. Avoidable deficiencies in the delivery of health care to children with meningococcal disease. *J Accid Emerg Med* 1998; 15: 298-303
55 Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. *J Child Neurol* 2002; 17: 106-110
56 Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. *Epilepsia* 2001; 42: 1461-1467
57 Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. *J Child Neurol* 1999; 14: 602-609
58 Holtkamp M, Masuhr F, Harms L, et al. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. *J Neurol Neurosurg Psychiatry* 2003; 74: 1095-1099
59 Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002; 43: 146-153
60 Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother* 1998; 32: 1053-1059

Chapter 2

OUTCOME OF ASSISTED VENTILATION FOR ACUTE RESPIRATORY FAILURE IN CYSTIC FIBROSIS

Intensive Care Medicine 2006; 32: 754-758

MG Slieker
JPJ van Gestel
HGM Heijerman
GA Tramper-Stranders
F Teding van Berkhout
CK van der Ent
NJG Jansen

Abstract

Objectives: To assess outcome of assisted ventilation in cystic fibrosis (CF) patients with acute respiratory failure (ARF), to identify risk factors associated with poor outcome and to compare long-term outcome of children who were mechanically ventilated for ARF with unventilated CF controls.
Design: Retrospective cohort study.
Setting: Two large CF centres in the Netherlands.
Patients: CF patients who required assisted ventilation for ARF and unventilated CF controls.
Interventions: None.
Measurements and results: Thirty-one CF patients required assisted ventilation for ARF between January 1990 and March 2005. All 5 children (under 2 years of age) and 7 adults (27%) survived. In the total population, age was a statistically significant risk factor for poor outcome (p=0.02). In adult CF patients who required invasive mechanical ventilation, acute on chronic respiratory failure was associated with poor outcome. In children who required mechanical ventilation for ARF, lung function and CF related complications 5 years later were not significantly different compared with controls matched for age, gender and genotype.
Conclusions: CF patients younger than 2 years old, who are ventilated because of ARF, have a good prognosis and their long-term outcome seems identical to unventilated CF controls. ARF in adult CF patients still is associated with high mortality, especially among patients with acute on chronic respiratory failure.

Abbreviations

ARF	acute respiratory failure
CF	cystic fibrosis
ICU	intensive care unit
NIV	noninvasive ventilation
IMV	invasive mechanical ventilation
LTX	lung transplantation
BMI	body mass index
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
SDS	standard deviation scores
OR	odds ratio
CI	confidence interval

Introduction

Mechanical ventilation for acute respiratory failure (ARF) in patients with cystic fibrosis (CF) has long been discouraged because of poor outcome [1]. In recent decades, however, life expectancy has increased significantly [2], and management of CF [3-6] and intensive care treatment principles [7-9] have changed dramatically.
These developments necessitate re-evaluation of outcome of mechanical ventilation in CF patients [10-12]. Mortality in adults varies between 45 and 80%. Although different studies tried to identify risk factors associated with poor outcome, results are not conclusive [10, 11]. Results of mechanical ventilation in infants and children with CF are reported as favourable, but little is known about their long-term outcome [11, 13].
This study aimed to assess outcome of assisted ventilation in CF patients with ARF, to identify risk factors associated with poor outcome and to compare long-term outcome in children who were mechanically ventilated for ARF with unventilated CF controls. Some of the results of this study have been published as an abstract [14].

Materials and methods

Setting
This study was performed at the University Medical Centre Utrecht (Utrecht, the Netherlands) and at the Haga Teaching Hospital (The Hague, the Netherlands). These centres provide care for approximately half the Dutch CF population. Treatment strategies are similar in both centres [15].

Subjects
All CF patients who had been admitted to the intensive care unit (ICU) between January 1990 and March 2005 were identified from the electronic hospital databases. Medical records of these patients were reviewed. Only patients who were admitted to the ICU for ARF were included. ARF was defined as respiratory deterioration requiring assisted ventilation, due to an acute illness in a previously stable patient [11]. Assisted ventilation could be non-invasive (NIV) via nasal or full face mask, or invasive (IMV) via endotracheal tube. Patients with pneumothorax, haemoptysis or allergic reaction without respiratory exacerbation according to the criteria of Fuchs [16] were not included, because of significantly better prognosis [12]. Patients with a history of lung transplantation (LTX) were excluded.

Ventilatory support
Children only received IMV. Adults were initially treated with NIV to avoid adverse effects of tracheal intubation [7, 9]. When adequate gas exchange could not be maintained, IMV was offered and initiated after informed consent.

Risk factors for poor outcome
To identify risk factors for mortality, the following data were recorded: age, sex, body mass index (BMI), best forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in the year prior to ICU admission, presence of chronic respiratory failure, mode of ventilation, steroid use before admission, pancreatic insufficiency, history of CF related diabetes and CF related liver disease, history of haemoptysis or pneumothorax, sputum microbiology, and presence of allergic broncho-pulmonary aspergillosis.
Chronic respiratory failure was defined as consistent increase in arterial partial pressure of carbon dioxide above 45 mm Hg during spontaneous breathing of room air in the period prior to the acute exacerbation [17]. Sputum microbiology samples were collected at hospital admission. Arterial blood gasses on admission were not available for most subjects and could therefore not be included as potential risk factor for poor outcome.

Long-term outcome in children
To assess long-term outcome in infants who survived assisted ventilation for ARF, a retrospective follow-up study was performed. Cases were matched with controls (5 per patient) with the same gender, genotype and age (± 1 year) without a history of ARF. Lung function, anthropometrics (standard deviation scores (SDS) of height and BMI) [18] and presence of CF related complications 5 years after admission to the ICU were compared between cases and controls.

Statistical analysis
The association between potential risk factors and outcome was quantified using univariate logistic regression analysis. Differences in demographic and clinical variables between cases and controls 5 years after IMV were analysed using Fisher's exact test and Mann-Whitney test.

Results

In the inclusion period, 83 CF patients were admitted to the ICU. Details on indications for admission are displayed in Supplementary Table A. Thirty-one patients fulfilled the criteria of ARF. Their demographic and clinical data are summarized in Table 1. Two patients had a readmission for ARF > 1 year after the

first. Only the first admission was included in the analysis. Two adults (1 receiving IMV, 1 NIV) underwent LTX during their stay in the ICU. Because they probably would have died otherwise, they were analysed as non-survivors.

Table 1
Demographic and clinical data of cystic fibrosis patients admitted to the ICU for acute respiratory failure

	children	adults
number of patients	5	26
mean age (range)	6 months (2-18)	26 years (15-41)
male gender (%)	3 (60)	16 (62)
endotracheal intubation (%)	5 (100)	17 (65)
FVC (% predicted) (SD)	-	39 (12)
FEV_1 (% predicted) (SD)	-	25 (8)
BMI (kg/m^2) (SD)	-	18 (3)

ICU, intensive care unit; FVC, forced vital capacity; SD, standard deviation; FEV_1, forced expiratory volume in one second; BMI, body mass index

The 31 patients consisted of 5 children (aged between 2 months and 18 months), 2 adolescents (aged 15 years and 16 years) and 24 adults (aged ≥18 years). All 5 children were admitted because of pneumonia. Because of the age distribution, 2 groups of patients were defined: 'children' (aged <2 years) and 'adults' (aged ≥15 years). Detailed patient characteristics of the adults are displayed in Supplementary Table B.

Outcome

All 5 children survived (100%). Seven of 26 adults (27%) survived. When the 2 patients who underwent LTX were excluded from analysis, survival in adults was 29%. Nine adults received only NIV; 17 adults underwent endotracheal intubation. Mortality was 56% in patients receiving NIV and 82% in patients receiving IMV. After discharge from ICU, all patients survived more than 1 year.

Risk factors for poor outcome

In the total population, age was a significant risk factor for poor outcome (p=0.02). Results of univariate logistic regression analyses in adults are shown in Table 2. None of the demographic or clinical data could predict mortality significantly. This did not change when the patients who underwent LTX were excluded from analyses. Because mortality and presence of potential risk factors differed between patients receiving IMV and NIV, a subgroup analysis was performed. In patients receiving only NIV, no significant predictors of outcome were found. In patients receiving IMV, acute on chronic respiratory failure was a significant predictor of mortality

(odds ratio (OR) = 26.0, 95% confidence interval (CI) 1.12-604). The association remained significant when the patient who underwent LTX was excluded.

Table 2
Comparison between surviving and non-surviving adult cystic fibrosis patients with acute respiratory failure. The capacity to predict outcome is also shown

	survivors	non-survivors[a]	odds ratio	*p*-value
N	7	19		
IMV versus NIV (%)	3 (43)	14 (74)	3.73	0.15
acute on chronic (%)	5 (71)	17 (95)	3.40	0.28
age (years) (SD)	26 (6)	26 (7)	1.01[b]	0.90
male gender (%)	5 (71)	11 (58)	0.55	0.53
FVC (% predicted) (SD)	40 (19)	39 (9)	0.99[b]	0.83
FEV_1 (% predicted) (SD)	25 (11)	25 (7)	0.99[b]	0.83
BMI (kg/m^2) (SD)	17 (2)	19 (4)	1.15[b]	0.33
steroid use (%)	2 (29)	7 (37)	1.46	0.70
pancreatic insufficiency (%)	7 (100)	19 (100)	–[c]	
CF related diabetes (%)	3 (43)	10 (53)	1.48	0.66
CF related liver disease (%)	3 (43)	6 (32)	0.62	0.59
history of haemoptysis (%)	2 (29)	9 (48)	2.25	0.40
history of pneumothorax (%)	2 (29)	7 (37)	1.46	0.70
P. aeruginosa (%)	6 (86)	19 (100)	–[c]	
B. cepacia (%)	0 (0)	2 (11)	–[c]	
ABPA (%)	0 (0)	2 (11)	–[c]	

[a]Group includes 2 patients who underwent LTX
[b]Odds ratio per unit of variable
[c]Odds ratio could not be calculated
IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; SD, standard deviation; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; BMI, body mass index; CF, cystic fibrosis; ABPA, allergic broncho-pulmonary aspergillosis.

Long-term outcome in children

No differences in long-term outcome were observed between cases and controls (Table 3). Since 1 infant was born in 2001, no 5-year follow-up data for this child were available.

Table 3
Comparison in long-term outcome between ventilated CF children and controls

	patients (n=4)	controls (n=20)	*p*-value
age (years)	5.6	5.6	0.88
FVC (% predicted)	96	95	0.88
FEV_1 (% predicted)	96	102	0.35
history of haemoptysis (%)	0	0	-
history of pneumothorax (%)	0	0	-
height (SDS)	-0.1	-0.8	0.14
BMI (SDS)	0.1	0.0	0.91
pancreatic insufficiency (%)	100	100	-
CF related diabetes (%)	0	0	-
CF related liver disease (%)	25	10	0.44
P. aeruginosa (%)	0	20	0.46
B. Cepacia (%)	0	0	-
ABPA (%)	0	5	0.83

FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; SDS, standard deviation score; BMI, body mass index; CF, cystic fibrosis; ABPA, allergic broncho-pulmonary aspergillosis

Discussion

This is the first European study in which outcome of assisted ventilation in CF patients with ARF was assessed. All children survived, and their long-term outcome was similar to non-ventilated CF-controls. In adults, ARF still was associated with a high mortality, despite improvements in ICU and CF management.

Two other studies [11, 13] reviewed survival of assisted ventilation in children with CF. In both studies, as in our study, a favourable outcome was found. Assisted ventilation may result in long-term complications [19]. In infants this was assessed in only 1 other study, published in 1989 [13]. In that study, with a variable follow-up time, clinical status was identical between 5 ventilated children and their controls. In our study, lung function and CF-related complications 5 years after IMV did not differ between cases and controls, matched for age, gender and genotype. However, the number of children in our study is small, and most CF-related complications develop later in life. Conclusions regarding long-term outcome must be therefore be made with caution.

In 3 recent studies, mortality in adults requiring ICU admission varied between 45 and 80% [10-12]. The reason for ICU admission and the possibility to perform LTX varied widely between studies. Despite these differences, all 3 studies found that most adults with ARF died, unless LTX was performed [12].

With the high mortality in adult CF patients, predictors for outcome are urgently needed. Sood et al. found no significant predictors [12]. Berlinski et al. found age as a significant risk factor [11]. Also in our total population, age was significantly

associated with mortality. However, within the group of adults, age did not affect outcome. In a recent Australian study, FEV_1 < 24% of predicted and BMI < 18 kg/m^2 were associated with poorer outcome [10]. However, in that study, 25% of patients did not have ARF, but disorders with comparatively good outcome, and specifically these patients on average had a higher FEV_1 and BMI.

In patients requiring IMV in our study, acute on chronic respiratory failure was a significant risk factor for mortality. Patients with chronic respiratory failure generally are in a poor clinical condition and the capacity to recover from an acute exacerbation probably is substantially lower.

Like the recent American and Australian studies [10-12], our study was limited by its retrospective nature and by the relatively small number of patients included, especially were it concerns the paediatric patients. A prospective multi-centre study, with well-defined treatment strategies and inclusion criteria, in centres having ample experience with NIV is needed to identify clear risk factors for poor outcome and to compare efficacy of NIV with IMV.

In conclusion, CF patients aged 2 years or younger who are ventilated because of ARF have a good prognosis. Assisted ventilation should not be withheld from these patients. ARF in adult CF patients still is associated with high mortality, especially in patients with acute on chronic respiratory failure. For these patients, mechanical ventilation should be undertaken with caution.

References

1 Davis PB, di Sant'Agnese PA. Assisted ventilation for patients with cystic fibrosis. *JAMA* 1978; 239:1851-1854

2 Slieker MG, Uiterwaal CSPM, Sinaasappel M, et al. Birth prevalence and survival in cystic fibrosis - A national cohort study in the Netherlands. *Chest* 2005; 128: 2309-2315

3 Kulich M, Rosenfeld M, Goss CH, Wilmott R. Improved survival among young patients with cystic fibrosis. *J Pediatr* 2003; 142: 631-636

4 Hodson ME, McKenzie S, Harms HK, et al. Dornase alfa in the treatment of cystic fibrosis in Europe: A report from the Epidemiologic Registry of Cystic Fibrosis. *Pediatric Pulmonology* 2003; 36: 427-432

5 Charman SC, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. *J Heart Lung Transplant* 2002; 21: 226-232

6 Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation among patients with cystic fibrosis. *JAMA* 2001; 286: 2683-2689

7 Piper AJ, Parker S, Torzillo PJ, et al. Nocturnal nasal IPPV stabilizes patients with cystic fibrosis and hypercapnic respiratory failure. *Chest* 1992; 102: 846-850

8 Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347-354

9 Hodson ME, Madden BP, Steven MH, et al. Non-invasive mechanical ventilation for cystic fibrosis patients--a potential bridge to transplantation. *Eur Respir J* 1991; 4: 524-527

10 Vedam H, Moriarty C, Torzillo PJ, et al. Improved outcomes of patients with cystic fibrosis admitted to the intensive care unit. *J Cyst Fibros* 2004; 3: 8-14

11 Berlinski A, Fan LL, Kozinetz CA, Oermann CM. Invasive mechanical ventilation for acute respiratory failure in children with cystic fibrosis: outcome analysis and case-control study. *Pediatr Pulmonol* 2002; 34: 297-303

12 Sood N, Paradowski LJ, Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. *Am J Respir Crit Care Med* 2001; 163: 335-338

13 Garland JS, Chan YM, Kelly KJ, Rice TB. Outcome of infants with cystic fibrosis requiring mechanical ventilation for respiratory failure. *Chest* 1989; 96: 136-138

14 Slieker MG, van Gestel JPJ, Tramper-Stranders GA, et al. Survival and prognosis after assisted ventilation for acute respiratory failure in cystic fibrosis (abstract). *J Cyst Fibros* 2005; 3(S1): 71

15 Van der Laag J, Sinaasappel M, Heijerman HG. Diagnostiek en behandeling van cystic fibrosis [*Diagnosis and treatment of cystic fibrosis*]. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing, Utrecht, 1998

16 Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994; 331: 637-642
17 Serra A, Polese G, Braggion C, Rossi A. Non-invasive proportional assist and pressure support ventilation in patients with cystic fibrosis and chronic respiratory failure. *Thorax* 2002; 57: 50-54
18 TNO Preventie en Gezondheid. TNO Growth Calculator. http://groeiweb.pgdata.nl/calculator.asp Date last updated: 1/1/2004. Date last accessed: 1/6/2005
19 Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet* 2003; 361: 332-340

supplementary Table A
Reasons for ICU admission of cystic fibrosis patients

indication	number of admissions		
	males	females	all
	(45 patients)	(38 patients)	(83 patients)
acute respiratory failure	20	13	33
lung transplantation	10	7	17
postoperative monitoring	13	11	24
haemoptysis	6	1	7
pneumothorax	4	0	4
initiation of HMV	2	3	5
other	3	7	10
all indications*	58	42	100

Because some patients had multiple admissions during the study period, the total number of admissions (100) is higher than the total number of patients admitted to the ICU (83)

supplementary Table B
Characteristics of adult cystic fibrosis patients with acute respiratory failure

pat	hosp	sex	age (y)	FEV_1	FVC	BMI	CF-related complications
1	UMCU	M	29.1	20	28	16.7	PI, LD
2	UMCU	M	24.9	28	34	18.5	PI, DM, ABPA
3	UMCU	F	32.1	24	54	20.1	PI, DM, LD, HAEM
4	UMCU	F	25.1	30	50	16.0	PI, LD, DM
5	UMCU	F	37.7	21	31	19.5	PI, DM, HAEM
6	UMCU	M	27.3	18	32	17.6	PI, PTX
7	UMCU	M	23.8	27	31	15.2	PI, LD, PTX
8	UMCU	M	20.1	20	31	13.6	PI, LD
9	UMCU	M	23.8	20	31	14.8	PI, HAEM
10	UMCU	F	26.8	19	33	14.0	PI, DM, PTX
11	UMCU	F	41.3	36	52	19.7	PI, LD, HAEM
12	UMCU	M	23.8	23	35	27.5	PI, LD
13	UMCU	M	23.6	21	45	18.3	PI, DM, HAEM
14	UMCU	F	18.9	33	51	12.8	PI
15	UMCU	F	29.6	32	43	18.6	PI, DM, LD, HAEM
16	UMCU	M	23.5	20	27	19.6	PI, HAEM, ABPA
17	UMCU	M	27.4	15	27	22.7	PI, DM, HAEM
18	UMCU	M	20.7	16	24	17.9	PI
19	UMCU	M	23.6	23	37	21.7	PI, DM, HAEM
20	UMCU	M	17.0	39	47	18.1	PI, PTX
21	UMCU	F	15.4	26	44	12.6	PI, DM, PTX
22	HAGA	F	18.6	50	82	19.9	PI, DM
23	HAGA	M	29.6	22	38	18.8	PI, DM, HAEM, PTX
24	HAGA	F	39.7	24	34	20.2	PI, DM, PTX
25	HAGA	M	30.4	19	35	22.0	PI, HAEM, PTX
26	HAGA	M	22.3	22	42	19.2	PI, LD,PTX

supplementary Table B
continued

pat	mo sputum	LOS ICU (d)	LTX	steroids	acute on chronic	IMV	survival
1	PA	19	no	no	yes	yes	yes
2	PA, AF	11	no	yes	yes	yes	no
3	PA	41	no	no	yes	yes	no
4	PA	1	no	no	yes	yes	no
5	PA, AF	7	no	yes	yes	no	yes
6	PA	8	no	no	yes	no	yes
7	SA, SP, HI	3	no	no	yes	no	yes
8	PA	3	no	no	yes	no	yes
9	PA	9	yes	no	yes	yes	yes*
10	PA, AF	4	no	no	yes	yes	no
11	PA	5	no	yes	yes	yes	no
12	PA, AF	4	no	no	no	no	no
13	PA	2	no	no	no	yes	yes
14	PA	6	no	no	yes	yes	no
15	PA	7	no	no	yes	yes	no
16	PA, AF	10	no	yes	yes	yes	no
17	PA	2	no	no	yes	no	no
18	PA	12	no	no	yes	yes	no
19	PA	2	yes	yes	yes	no	yes*
20	PA, BC	4	no	no	no	yes	no
21	PA, SM, SH	33	no	no	yes	yes	no
22	PA	9	no	yes	no	yes	yes
23	PA	4	no	no	yes	yes	no
24	PA	1	no	yes	yes	yes	no
25	PA	1	no	yes	yes	no	no
26	PA, BC	2	no	yes	yes	no	no

UMCU, University Medical Center Utrecht; HAGA, Haga Teaching Hospital; F, female; M, male; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; PI, pancreatic insufficiency; DM, diabetes mellitus; LD, liver disease; HAEM, haemoptysis; PTX, pneumothorax; ABPA, allergic broncho-pulmonary aspergillosis; MO, micro-organism; PA, Pseudomonas aeruginosa; AF, Aspergillus fumigatus; BC, Burkholderia Cepacia; SA, staphylococcus aureus; SH, streptococcus haemolyticus; LOS ICU, length of stay in intensive care unit; LTX, lung transplantation; IMV, invasive mechanical ventilation.

Chapter 3

INTENSIVE CARE UNIT MORTALITY TRENDS IN CHILDREN AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION: A META-REGRESSION ANALYSIS

Critical Care Medicine 2008; 36: 2898-2904

JPJ van Gestel
CW Bollen
I van der Tweel
JJ Boelens
AJ van Vught

Abstract

Background: There is ongoing discussion whether intensive care unit (ICU) mortality has decreased over time for children after haematopoietic stem cell transplantation (HSCT).
Objective: To analyse ICU mortality trends in children after HSCT.
Data sources: Search of MEDLINE, EMBASE and Cochrane databases and a manual review of reference lists.
Study selection: Prospective and retrospective cohort studies containing ICU mortality data of children after HSCT.
Data extraction: Mortality statistics and features associated with mortality were abstracted from studies of interest. To assess mortality over time, the median years of inclusion in original studies were included as risk factor. A multiple random-effects meta-regression analysis was conducted to assess the independent contribution of prognostic factors on mortality.
Data synthesis: Twenty-three studies were included, reporting on 1101 ICU admissions. Overall ICU mortality was 60% (range 25% - 91%). Once mechanical ventilation was necessary (n=822), mean ICU mortality was 71% (range 25% - 91%). Over the years, significantly fewer ICU admitted patients received mechanical ventilation ($p<0.001$).
Univariable analysis in all ICU admitted patients showed a significant decrease in mortality associated with year of inclusion. Mechanical ventilation and pulmonary disease were associated with increased mortality. In the multiple meta-regression analysis, only pulmonary disease remained significantly associated with mortality (OR=1.21, 95% CI 1.01-1.46 per 10% increase in the number of patients with pulmonary disease in studies). The association between year of inclusion and ICU mortality was less pronounced (OR=0.92, 95% CI 0.84-1.01).
Conclusion: There is a widely held impression that ICU mortality clearly decreased in children after HSCT. However, characteristics of ICU admitted patients significantly changed over time. After correcting for this, an improvement in ICU survival was less evident. More studies are needed before a true improvement in ICU survival can be confirmed.

Abbreviations

HSCT	haematopoietic stem cell transplantation
ICU	intensive care unit

Introduction

Haematopoietic stem cell transplantation (HSCT) is a potentially life saving treatment for a wide variety of diseases, which previously had little hope for cure. Nevertheless, it remains a high risk procedure, and a considerable number of patients require transfer to the intensive care unit (ICU) after transplantation. ICU admissions of HSCT recipients historically were associated with very high mortality rates. Over the years advances have been made in transplantation medicine and in the management of critical care patients [1-4]. According to a number of authors, this has led to a noticeable and steady decrease in ICU mortality for HSCT recipients [5-11]. However, 2 recent studies in large cohorts of paediatric patients could not confirm these claims [12, 13] and in several editorials an increase in ICU survival in children after HSCT has been questioned [14, 15]. Whether ICU survival really has improved over time is therefore still a matter of debate.
To analyze ICU mortality trends and the main prognostic factors associated with mortality in paediatric HSCT recipients, we systematically reviewed the literature. Mortality statistics and features associated with mortality were abstracted from studies of interest, and a meta-regression analysis was applied.

Materials and methods

Literature search
A comprehensive literature search was performed in the MEDLINE and EMBASE databases and in the Cochrane Library. The last search was performed in August 2006. Combinations of the following search terms were used: (1) (stem) cell transplant(ation)(s), blood transplant(ation)(s), BMT; (2) intensive care (unit), (P)ICU, critical care, mechanical ventilation, respiratory failure; (3) child, p(a)ediatric, infant. These search terms were used in titles and abstracts of published papers to identify all eligible studies. Additionally, corresponding Medical Subject Heading (Pubmed) or Emtree (EMBASE) keywords were identified and used to obtain the broadest range of potentially relevant articles. Reference lists of included studies were screened for additional studies.

Study selection
Two reviewers independently assessed the titles and abstracts of all articles retrieved by the search to identify potentially relevant studies for inclusion. Discrepancies were resolved through discussion.
All retrospective and prospective observational studies were included if they contained ICU mortality data of cohorts of patients younger than 18 years who had undergone HSCT. Inclusion criteria of the original studies could vary, but within a

study, the total cohort of HSCT patients who fulfilled those inclusion criteria within a specified time frame had to be described. ICU mortality data of more than 80% of included patients in the original study had to be accounted for. We excluded letters, case reports, review articles and editorials. Only studies in English language were included.

Data extraction

From the included studies, we extracted demographic data, transplantation and ICU treatment details, ICU mortality data and reported features associated with mortality. HSCT comprised all types of stem cell transplantations (allogeneic, autologous, (un)related donor, stem cells from cord blood, peripheral blood, bone marrow). Requirement of mechanical ventilation only included endotracheal mechanical ventilation. Pulmonary disease was defined as requirement of mechanical ventilation for a pulmonary disorder. In most studies this was objectified by an increased oxygenation index or decreased P_aO_2 / F_iO_2 ratio, and diffuse pulmonary consolidations on chest radiograph with exclusion of cardiogenic pulmonary oedema. Airway control was defined as the need for intubation in case of upper airway obstruction or decreased mental status. Multiple organ failure was defined according to criteria defined by Wilkinson et al. [16, 17], otherwise comparable criteria were used. Graft versus host disease was diagnosed and graded following standard criteria [18]. Human Leukocyte Antigen mismatch was not further specified in any of the studies. We defined mortality as death at discharge from the ICU. Only data that specifically presented children after HSCT and specifically mentioned ICU mortality were used for analysis. To assess the influence of time on mortality, the median of the inclusion dates of individual studies were used as risk factor.

Statistical analysis

For each risk factor in each cohort, the proportion of patients with that risk factor was calculated. ICU mortality rates were transformed to their logit values, i.e. ln p/(1-p), where p is the mortality rate and ln is the natural logarithm. The asymptotic within-study variance was estimated by (1/x + 1/(n-x)), where n is the number of patients in the study and x the number of patients who died (i.e. x/n=p). Odds ratios were calculated per 10% increase in incidence of risk factors, or per year for age, year of inclusion and year of publication.

Since there was considerable heterogeneity between studies in ICU mortality rates, a random-effects model was used for the multiple meta-regression analysis [19]. Meta-analysis was performed using SAS PROC MIXED (version 8). To calculate the contribution of risk factors to heterogeneity, the between-study variance from the regression model (BSVR) was divided by the estimated between-study variance

from the meta-analysis (BSVM) without these risk factors, i.e. (1 - BSVR/BSVM) x 100%.

Results

Initially, 185 papers were identified with the MEDLINE search. No additional studies were identified in EMBASE or in the Cochrane Library. Two studies were found by screening reference lists. Ninety-four studies were excluded based on title and abstract. The remaining 93 studies were considered potentially relevant, of which 23 were included [8, 9, 12, 13, 20-38]. The other 70 studies were excluded, because they did not contain or specify ICU outcome data in children after HSCT, did not fulfil all inclusion criteria [39, 40], or because they were double publications [41-44]. Diaz et al. [20] and Gonzalez-Vicent et al. [21] published 2 studies from the same centre with a 3 years' overlap in inclusion time in a total inclusion period of 9 years. Since this was considered a minor overlap, both studies were included in the meta-analysis.

Details of included studies, ICU mortality rates and the most prominent features associated with mortality found within individual studies are shown in Table 1. Across studies there was considerable variation in underlying disorders necessitating HSCT, in the number of autologous versus allogeneic transplantations, in indications for transfer to the ICU, in indications for intubation and in time interval between transplantation and admission to the ICU. Transplantation details, like source of stem cells or information from the donor, were not consistently reported in studies.

Table 1
Overview of studies reporting intensive care unit mortality rates and prognostic features associated with intensive care unit mortality in paediatric haematopoietic stem cell transplantation recipients

ref.	inclusion period	n	% of HSCT patients	ICU mort	characteristics of included patients
24	1973-1990	54	19%	89%	all intubated patients
25	1976-1992	196	23%	60%	patients requiring MV > 24 hours
26	1978-1988	23	7%	91%	intubated patients with ARF
27	1981-1987	5	NR	80%	all patients admitted to the ICU
13	1983-1996	121	11%	84%	patients requiring MV > 24 hours
22	1986-1993	43	NR	88%	intubated patients with ARF
28	1986-1995	39	11%	56%	patients requiring MV, except short postoperative ventilation
8	1987-1996	28	NR	46%	all patients admitted to ICU
23	1989-1998	28	16%	50%	all patients admitted to ICU, except short postoperative stay
29	1990-1995	4	13%	25%	all intubated patients
30	1990-1999	86	NR	59%	patients requiring MV
12	1990-2002	132	NR	30%	patients with sepsis
31	1991-1995	31	18%	45%	all patients admitted to ICU
32	1991-2000	44	29%	70%	all patients admitted to ICU, except short postoperative stay
33	1992-2002	19	15%	58%	all patients admitted to ICU
9	1992-2004	81	44%	43%	all patients admitted to ICU, except postoperative patients
20	1993-2001	42	18%	69%	all patients admitted to ICU
34	1994-1998	40	19%	63%	all patients admitted to ICU
35	1995-2001	6	4%	83%	patients with diffuse alveolar haemorrhage
36	1996-2000	7	5%	43%	patients with diffuse alveolar haemorrhage
37	1998-1999	13	NR	38%	patients with septic shock
38	1998-2001	23	18%	65%	all patients admitted to ICU, except short (postoperative) monitoring
21	1998-2002	36	18%	53%	all patients admitted to ICU
total		1101			

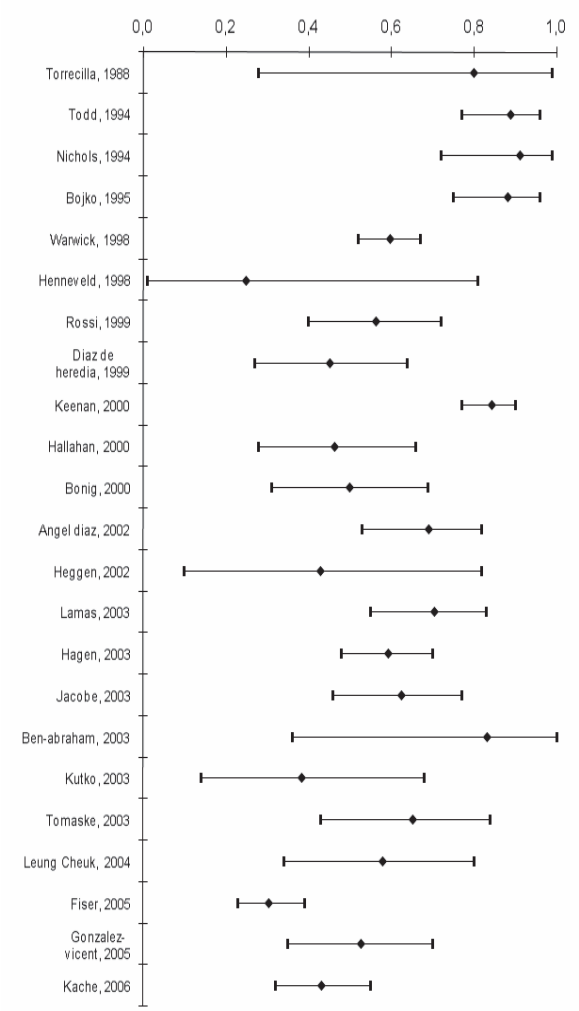
Table 1
continued

ref.	most prominent risk factors associated with mortality	most prominent risk factors not associated with mortality
24	≥ 2 organs failing, indication for MV	NR
25	indication for MV, underlying disease, absence of GvHD	duration of MV
26	NR	NR
27	NR	NR
13	indication for MV, pulmonary infection, ≥ 2 organs failing	underlying disease, duration of MV, GvHD, RRT
22	NR	NR
28	≥ 4 organs failing, PRISM score, deterioration of pulmonary function	lung disease on admission, duration of MV, underlying disease, GvHD
8	NR	NR
23	cardiovascular instability, multiple organ failure	type of HSCT
29	NR	multiple organ failure, prolonged mechanical ventilation
30	HFOV, indication for MV	duration of MV, multiple organ failure
12	NR	NR
31	lung disease, requirement of MV, ≥ 4 organs failing	type of HSCT
32	requirement of MV, lung injury, ≥3 organs failing, GvHD, male gender	renal failure, ARDS
33	requirement of MV, PRISM score, macroscopic haemorrhage	GvHD
9	malignancy, renal failure requiring RRT	GvHD, PRISM score, source of stem cells
20	multi-organ failure	NR
34	requirement of MV, HFOV, RRT, ≥ 3 organs failing	duration of intubation, PRISM score
35	NR	NR
36	NR	NR
37	NR	NR
38	duration of MV > 5 days	underlying disease, age, PRISM score
21	O-PRISM score	NR

ref, reference number of study; n, number of patients included in study; ICU, intensive care unit; mort, mortality; NR, not recorded; ARF, acute respiratory failure; MV, mechanical ventilation; HSCT, haematopoietic stem cell transplantation; GvHD, graft-versus-host disease; PRISM, pediatric risk of mortality; HFOV, high frequency oscillatory ventilation; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome.

The 23 included studies reported ICU mortality rates from 1101 children. Depending on the study, 4% to 44% of children after HSCT were transferred to the ICU [9, 35], and their ICU mortality rates varied between 25% and 91% (mean 60%) [26, 29]. A historical overview of ICU mortality rates from individual studies is shown in Figure 1a. In this Figure, studies were ranked chronologically based on their year of publication, suggesting a decrease in mortality over time.

Figure 1a
Intensive care unit mortality rates (95% confidence interval) of paediatric patients admitted to the ICU after haematopoietic stem cell transplantation. Studies are ranked chronologically according to their year of publication



In 19 of the 23 studies, ICU mortality rates of mechanically ventilated children were reported (n=822). Depending on the study, 4% to 30% of children after HSCT received mechanical ventilation [9, 35, 36]. Once mechanical ventilation was necessary, ICU mortality ranged between 25% and 91% (mean 71%) [26, 29]. In Figure 1b, a historical overview of ICU mortality rates in the subgroup of ventilated children is shown. In this Figure, studies were ranked chronologically based on their year of publication. This Figure is less suggestive for a decrease in mortality over time than Figure 1a.

Figure 1b
Intensive care unit mortality rates (95% confidence interval) of the subgroup of mechanically ventilated paediatric patients after haematopoietic stem cell transplantation. Studies are ranked chronologically according to their year of publication

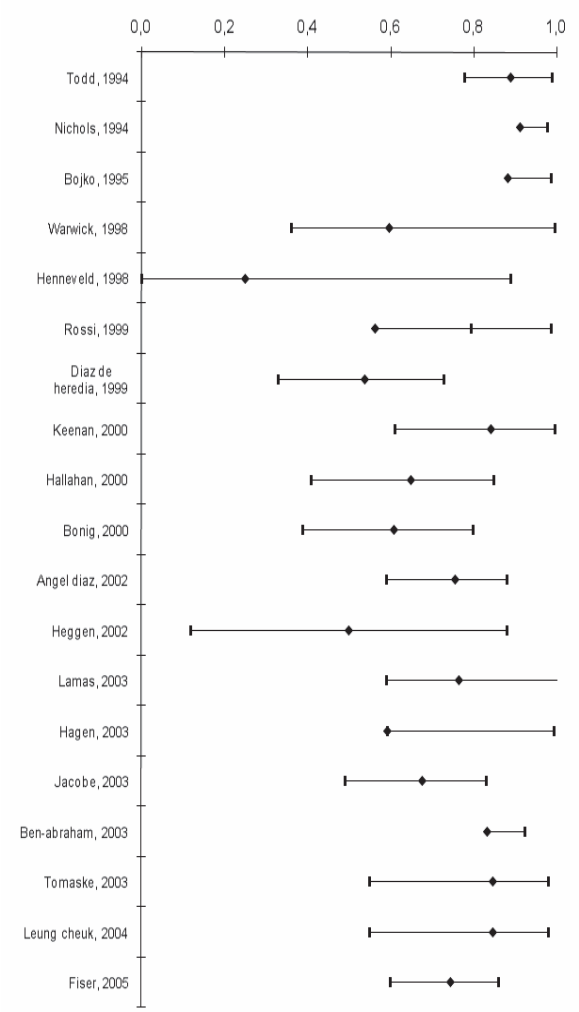
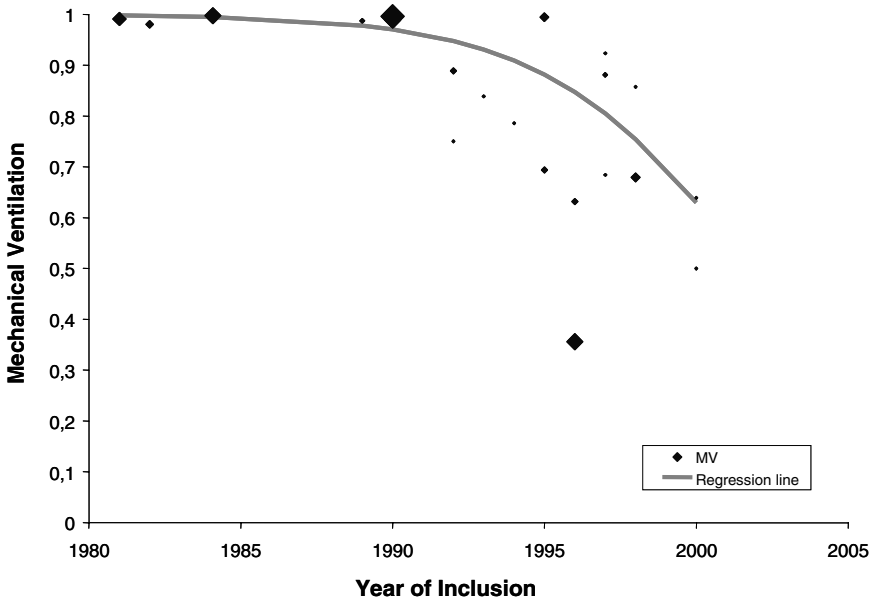


Figure 2 shows the result of a regression analysis between year of inclusion and proportion of mechanically ventilated patients in the cohorts as dependent variable. In more recent years, significantly fewer ICU admitted patients received mechanical ventilation ($p<0.001$).

Figure 2
Result of a linear regression analysis between year of inclusion and proportion of mechanically ventilated patients after haematopoietic stem cell transplantation within separate studies as dependent variable. The sizes of dots depend on the number of patients included in a study



MV, requirement of mechanical ventilation

Mean values of potential risk factors associated with mortality, their level of significance in the univariable regression analysis and the number of studies which reported these risk factors, are summarized in Table 2. In the univariable analysis, year of publication and year of inclusion were significantly associated with a decrease in mortality over time. Requirement of mechanical ventilation and presence of pulmonary disease were associated with an increase in mortality.

Table 2
Mean values for (risk factors for) mortality, their level of significance in the univariable analysis, and the number of studies included in the meta-regression analysis in which these risk factors were reported.

all ICU patients	mean	sign	number of studies
mortality	60%		23
year of publication	2000	< 0.01	23
year of inclusion	1992	< 0.01	23
age	5.4	0.14	17
male	48%	0.53	17
mechanical ventilation	80%	0.01	19
pulmonary disease	35%	0.08	14
high frequency ventilation	3%	0.18	11
airway control	6%	0.39	11
multi-organ failure grade 3[a]	30%	0.46	7
multi-organ failure grade 4[a]	15%	0.96	4
GvHD grade 2[b]	8%	0.11	6
GvHD grade 3[b]	6%	0.37	7
malignancy	47%	0.10	15
immune deficiency	10%	0.14	13
unrelated donor	19%	0.56	14
autologous transplant	15%	0.72	19
mismatch	13%	0.12	10
irradiation	10%	0.69	10
renal support therapies	7%	0.06	9
hepatic failure	9%	0.64	6

ICU, intensive care unit; GvHD, graft-versus-host disease
[a]multi-organ failure was graded according to Wilkinson et al. [16, 17]
[b]GvHD was graded according to Glucksberg et al. [18]

Due to the limited availability of data, only the most important and consistently reported confounders were included in the multiple random-effects meta-regression analysis, using year of inclusion instead of year of publication. Therefore, the 14 studies which contained information on year of inclusion, requirement of mechanical ventilation and presence of pulmonary disease were included in the multiple meta-regression analysis. The results of this analysis are summarized in Table 3.

Table 3
Results of the multiple regression analysis in all paediatric patients admitted to the intensive care unit after haematopoietic stem cell transplantation

		95% confidence interval for OR		
all ICU patients	**OR**	**lower bound**	**upper bound**	**number of studies (n)**
year of inclusion[a]	0.92	0.84	1.01	14 (760)
mechanical ventilation[b]	0.93	0.64	1.35	(721)
pulmonary disease[c]	1.21	1.01	1.46	(464)

ICU, intensive care unit; OR, odds ratio; no. studies, number of studies which assessed all 3 risk factors; n, number of subjects with specified risk factor
[a]OR was calculated per year of inclusion; the median year of inclusion from the 14 studies ranged between 1981 and 1998
[b]OR was calculated per 10% increase in the number of patients requiring mechanical ventilation in studies
[c]OR was calculated per 10% increase in the number of patients with pulmonary disease in studies.

For all studies, mortality decreased by 0.08 for each year beyond 1981 that the study started to accrue patients. For each 10% increase in the number of patients in a study identified as having pulmonary disease (i.e. intubation and mechanical ventilation for a pulmonary disorder), mortality increased by 1.21. Presence of pulmonary disease, requirement of mechanical ventilation and year of inclusion explained 53% of the heterogeneity in ICU mortality rates between studies.

Discussion

There is a widely held impression that ICU mortality significantly decreased in the past decades in children after HSCT [6, 11]. A first glance at the currently available data from literature does suggest a clear improvement in ICU outcome. However, in more recent years fewer ICU admitted patients received mechanical ventilation. After adjusting for mechanical ventilation and pulmonary disease, a decrease in ICU mortality was less pronounced.
A trend for a decrease in ICU mortality by year was noted, but was not statistically significant. This may be due to the limited power of this meta-regression analysis: all included studies were observational and retrospective, and most studies included only a limited number of patients. Only 1 study was multimember [35]. Patients after HSCT are a highly heterogeneous population, and inclusion criteria varied widely between studies, as well as reasons for admission to the ICU and indications to start mechanical ventilation. Power was further diminished since we were not informed which patients in a given report had which covariates at risk for mortality.

Moreover, certain risk factors, like source of stem cells or presence of multiple organ dysfunction at admission to the ICU, were not consistently reported in all studies. Correcting for other confounders than mechanical ventilation and presence of pulmonary disease could therefore not be done. Results of our study therefore have to be interpreted with caution. With all these limitations, firm conclusions about ICU mortality trends in children after HSCT can not be drawn. On the other hand, the impression that ICU mortality clearly improved can not be confirmed either with the currently available data.

There are several explanations which might explain the findings in our study. First, most of the data in this meta-analysis come from relatively old studies [8, 13, 22, 24-29, 31]; Only 3 studies in ventilated patients started with their inclusion after 1995 [35, 36, 38]. These studies report on 25 children, which is only 3% of all ventilated patients in the meta-regression analysis. More recent studies are needed to assess current results of mechanical ventilation. Second, characteristics of transplanted patients have changed over the years: indications for transplantation have expanded [45-48] and due to better supportive care, transplantations probably are performed in sicker patients nowadays. It is difficult to assess whether severity of illness changed over time: only 3 studies reported the actual predicted risk of mortality in their patients [22, 29, 34], and only few studies reported the Pediatric Risk of Mortality [49] or Paediatric Index of Mortality scores [50]. Third, because physicians might have had the impression that ICU mortality decreased, their practices in advising parents and children about accepting mechanical ventilation may have changed over time. From none of the studies it could be retrieved, to what extent this patient selection occurred.

Our conclusions differ from several previous authors, who have claimed a clear improvement of ICU survival [7-10]. The study of Hallahan et al. [8] included only 20 mechanically ventilated patients. In the study of Kache et al. [9], 30% of HSCT recipients required mechanical ventilation, which is substantially higher than in other studies (mean 14%). This could imply a low threshold to start mechanical ventilation, which makes it difficult to compare their results with other ICUs. The review done by Naeem et al. [10] did not include 10 of the studies we found, and the review done by Martin et al. [7] did not report on 5 of the studies we found. Secondary to larger sample size, mortality trends were assessed with more power in our study. Moreover, by correcting for pulmonary disease and mechanical ventilation, a more realistic assessment of ICU mortality was obtained in our study.

Paediatric HSCT recipients form a totally different population than adult HSCT recipients, which hampers a true comparison in ICU mortality trends between them. On the other hand, both groups experienced the same improvements in critical care and transplantation medicine over time. In a recent multimember study in adults receiving mechanical ventilation after allogeneic transplantation, survival was nearly identical as 20 years ago. [51] Thiery et al. [52] suggested that ICU mortality rates

in adult HSCT recipients mainly decreased over time because of a change in patient selection. Results in both these studies are in line with our findings.
The burden of ICU treatment for patients and their parents is enormous. At the same time, it is difficult to withhold ICU treatment, when its results are uncertain and transplantation potentially cures the underlying disease. This underscores the need for clear and up to date ICU mortality data. Prospective studies of all children eligible for ICU care are urgently needed. Such studies should collect detailed information on previously identified risk factors associated with mortality. Only data from well designed prospective studies can provide more confidence in predicting ICU mortality in children after HSCT.

Conclusions

There is a widely held impression that ICU survival clearly improved over time in children after HSCT. However, with the currently available data from literature no firm conclusions about ICU mortality trends can be drawn. In more recent years, significantly fewer patients received mechanical ventilation after ICU transfer. After correcting for mechanical ventilation and pulmonary disease, an improvement in ICU survival was less evident. More recent data are needed to assess whether advancements in critical care and transplantation medicine can be translated in a true decrease in ICU mortality.

References

1 Singh N, Paterson DL. Aspergillus infections in transplant recipients. *Clin Microbiol Rev* 2005; 18: 44-69

2 Vij R, Khoury H, Brown R, et al. Low-dose short-course intravenous ganciclovir as pre-emptive therapy for CMV viremia post allo-PBSC transplantation. *Bone Marrow Transplant* 2003; 32: 703-707

3 Corbacioglu S, Greil J, Peters C, et al. Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. *Bone Marrow Transplant* 2004; 33: 189-195

4 Corbacioglu S, Honig M, Lahr G, et al. Stem cell transplantation in children with infantile osteopetrosis is associated with a high incidence of VOD, which could be prevented with defibrotide. *Bone Marrow Transplant* 2006; 38: 547-553

5 Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med* 1996; 125: 625-633

6 Sullivan KJ, Goodwin SR, Sandler E, et al. Critical care of the pediatric hematopoietic stem cell recipient in 2005. *Pediatr Transplant* 2005; 9 (Suppl 7): 12-24

7 Martin PL. To stop or not to stop: how much support should be provided to mechanically ventilated pediatric bone marrow and stem cell transplant patients? *Respir Care Clin N Am* 2006; 12: 403-419

8 Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. *Crit Care Med* 2000; 28: 3718-3721

9 Kache S, Weiss IK, Moore TB. Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. *Pediatr Transplant* 2006; 10: 299-303

10 Naeem N, Reed MD, Creger RJ, et al. Transfer of the hematopoietic stem cell transplant patient to the intensive care unit: does it really matter? *Bone Marrow Transplant* 2006; 37: 119-133

11 Soubani AO. Critical care considerations of hematopoietic stem cell transplantation. *Crit Care Med* 2006; 34: S251-S267

12 Fiser RT, West NK, Bush AJ, et al. Outcome of severe sepsis in pediatric oncology patients. Pediatr Crit Care Med 2005; 6: 531-536

13 Keenan HT, Bratton SL, Martin LD, et al. Outcome of children who require mechanical ventilatory support after bone marrow transplantation. *Crit Care Med* 2000; 28: 830-835

14 Bojko T, Notterman DA. Reversal of fortune? Respiratory failure after bone marrow transplantation. *Crit Care Med* 1999; 27: 1061-1062
15 Keenan HT, Bratton SL. Pediatric intensive care unit mortality and the oncology patient: has survival really changed? *Pediatr Crit Care Med* 2005; 6: 610-611
16 Wilkinson JD, Pollack MM, Glass NL, et al. Mortality associated with multiple organ system failure and sepsis in pediatric intensive care unit. *J Pediatr* 1987; 111: 324-328
17 Wilkinson JD, Pollack MM, Ruttimann UE, et al. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med* 1986; 14: 271-274
18 Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974; 18: 295-304
19 Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002; 21: 589-624
20 Angel Diaz M, Vicent MG, Prudencio M, et al. Predicting factors for admission to an intensive care unit and clinical outcome in pediatric patients receiving hematopoietic stem cell transplantation. *Haematologica* 2002; 87: 292-298
21 Gonzalez-Vicent M, Marin C, Madero L, et al. Risk score for pediatric intensive care unit admission in children undergoing hematopoietic stem cell transplantation and analysis of predictive factors for survival. *J Pediatr Hematol Oncol* 2005; 27: 526-531
22 Bojko T, Notterman DA, Greenwald BM, et al. Acute hypoxemic respiratory failure in children following bone marrow transplantation: an outcome and pathologic study. *Crit Care Med* 1995; 23: 755-759
23 Schneider DT, Lemburg P, Sprock I, et al. Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children. *Bone Marrow Transplant* 2000; 25: 1079-1086
24 Todd K, Wiley F, Landaw E, et al. Survival outcome among 54 intubated pediatric bone marrow transplant patients. *Crit Care Med* 1994; 22: 171-176
25 Warwick AB, Mertens AC, Shu XO, et al. Outcomes following mechanical ventilation in children undergoing bone marrow transplantation. *Bone Marrow Transplant* 1998; 22: 787-794
26 Nichols DG, Walker LK, Wingard JR, et al. Predictors of acute respiratory failure after bone marrow transplantation in children. *Crit Care Med* 1994; 22: 1485-1491
27 Torrecilla C, Cortes JL, Chamorro C, et al. Prognostic assessment of the acute complications of bone marrow transplantation requiring intensive therapy. *Intensive Care Med* 1988; 14: 393-398

28 Rossi R, Shemie SD, Calderwood S. Prognosis of pediatric bone marrow transplant recipients requiring mechanical ventilation. *Crit Care Med* 1999; 27: 1181-1186
29 Henneveld HT, Wulffraat NM, Gemke RJ, et al. Mechanical ventilation in bone marrow transplanted children; do they benefit? *Eur J Pediatr* 1998; 157: 441-442
30 Hagen SA, Craig DM, Martin PL, et al. Mechanically ventilated pediatric stem cell transplant recipients: effect of cord blood transplant and organ dysfunction on outcome. *Pediatr Crit Care Med* 2003; 4: 206-213
31 Diaz de Heredia C, Moreno A, Olive T, et al. Role of the intensive care unit in children undergoing bone marrow transplantation with life-threatening complications. *Bone Marrow Transplant* 1999; 24: 163-168
32 Lamas A, Otheo E, Ros P, et al. Prognosis of child recipients of hematopoietic stem cell transplantation requiring intensive care. *Intensive Care Med* 2003; 29: 91-96
33 Cheuk DK, Ha SY, Lee SL, et al. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. *Hematol Oncol* 2004; 22: 1-9
34 Jacobe SJ, Hassan A, Veys P, et al. Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. *Crit Care Med* 2003; 31: 1299-1305
35 Ben-Abraham R, Paret G, Cohen R, et al. Diffuse alveolar hemorrhage following allogeneic bone marrow transplantation in children. *Chest* 2003; 124: 660-664
36 Heggen J, West C, Olson E, et al. Diffuse alveolar hemorrhage in pediatric hematopoietic cell transplant patients. *Pediatrics* 2002; 109: 965-971
37 Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. *Pediatr Crit Care Med* 2003; 4: 333-337
38 Tomaske M, Bosk A, Eyrich M, et al. Risks of mortality in children admitted to the paediatric intensive care unit after haematopoietic stem cell transplantation. *Br J Haematol* 2003; 121: 886-891
39 DiCarlo JV, Alexander SR, Agarwal R, et al. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. *J Pediatr Hematol Oncol* 2003; 25: 801-805
40 Drew B, Peters C, Rimell F. Upper airway complications in children after bone marrow transplantation. *Laryngoscope* 2000; 110: 1446-1451
41 Crawford SW, Schwartz DA, Petersen FB, et al. Mechanical ventilation after marrow transplantation. Risk factors and clinical outcome. *Am Rev Respir Dis* 1988; 137: 682-687

42 Bonig H, Schneider DT, Sprock I, et al. 'Sepsis' and multi-organ failure: predictors of poor outcome after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 2000; 25: S32-34
43 Schneider DT, Cho J, Laws HJ, et al. Serial evaluation of the oncological pediatric risk of mortality (O-PRISM) score following allogeneic bone marrow transplantation in children. *Bone Marrow Transplant* 2002; 29: 383-389
44 DeBruin W, Notterman DA, Magid M, et al. Acute hypoxemic respiratory failure in infants and children: clinical and pathologic characteristics. *Crit Care Med* 1992; 20: 1223-1234
45 Grewal SS, Shapiro EG, Krivit W, et al. Effective treatment of alpha-mannosidosis by allogeneic hematopoietic stem cell transplantation. *J Pediatr* 2004; 144: 569-573
46 Wulffraat NM, Vastert B, Tyndall A. Treatment of refractory autoimmune diseases with autologous stem cell transplantation: focus on juvenile idiopathic arthritis. *Bone Marrow Transplant* 2005; 35: S27-29
47 Al-Ahmari A, Ayas M, Al-Jefri A, et al. Allogeneic stem cell transplantation for patients with congenital amegakaryocytic thrombocytopenia (CAT). *Bone Marrow Transplant* 2004; 33: 829-831
48 Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. *J Inherit Metab Dis* 2006; 29: 413-420
49 Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16: 1110-1116
50 Shann F, Pearson G, Slater A, et al. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med* 1997; 23: 201-207
51 Pene F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *J Clin Oncol* 2006; 24: 643-649
52 Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. *J Clin Oncol* 2005; 23: 4406-4413

Chapter 4

SURVIVAL IN A RECENT COHORT OF MECHANICALLY VENTILATED PAEDIATRIC ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

Biology of Blood and Marrow Transplantation 2008; 14: 1385-1393

JPJ van Gestel
CW Bollen
MB Bierings
JJ Boelens
NM Wulffraat
AJ van Vught

Abstract

There is ongoing discussion whether survival improved for children requiring mechanical ventilation after haematopoietic stem cell transplantation (HSCT). We reviewed the outcomes of 150 children who received an allogeneic HSCT between January 1999 and April 2007 in a paediatric university hospital in the Netherlands.
Thirty-five of the 150 patients received mechanical ventilation on 38 occasions. None of the recorded risk factors was significantly associated with the requirement of mechanical ventilation. Sixteen admissions resulted in death on the intensive care unit (ICU), giving a case fatality rate of 42% (95% confidence interval 26% - 58%). ICU mortality was associated with multi-organ failure on the second day of admission and with the use of high frequency oscillatory ventilation. Patients had higher paediatric risk of mortality scores than in previous studies, reflecting higher acuity of illness on admission to the ICU. Six-month survival in patients discharged from the ICU was 82%.
Compared to previous studies, we found an improvement in ICU survival and survival six months after ICU discharge in a recent cohort of ventilated children after allogeneic HSCT, even though our patients were more severely ill. Our results are promising, but they need to be confirmed in larger, preferably multi-centre, studies.

Abbreviations

HSCT	haematopoietic stem cell transplantation
GvHD	graft-versus-host disease
ICU	intensive care unit
HFOV	high frequency oscillatory ventilation
PRISM	paediatric risk of mortality
CI	confidence interval

Introduction

Despite all its progress over the years, paediatric haematopoietic stem cell transplantation (HSCT) remains a high risk procedure, which necessitates transfer to the intensive care unit (ICU) in up to 44% of patients [1]. Mortality in ventilated children after HSCT historically was reported to be very high. Whether outcome improved over the years is still a matter of debate: a clear decrease in mortality over time could not be detected in a recent meta-regression analysis [2], mostly because current outcome data in ventilated patients were lacking. Two studies from the United States, published after the inclusion period of the meta-regression analysis, revealed conflicting results: survival had clearly improved over time in one study [3], while it did not differ by year of study in the other [4]. More outcome data in this population are therefore needed.
Only few studies investigated, which factors were associated with an increased risk of ICU admission in children after HSCT [5-8]. A considerable proportion of patients in these studies underwent autologous transplantations, which may have limited general applicability of results. Moreover, patients in previous studies often did not require mechanical ventilation during their ICU stay, while this specifically is the most uniform ICU treatment, and it is associated with the largest increase in risk of mortality [4].
The main goal of the present study was to assess outcome in a recent cohort of children requiring mechanical ventilation after allogeneic HSCT. Secondly, we wanted to identify predictors for mortality in this cohort and predictors for the requirement of mechanical ventilation.

Materials and methods

Setting
This study was performed at the Wilhelmina Children's Hospital, which is part of the University Medical Center Utrecht (Utrecht, the Netherlands). In this hospital, about 30 allogeneic HSCTs in children are performed annually. The multidisciplinary 14-bed paediatric ICU has approximately 650 admissions each year, about 80% of them receive invasive mechanical ventilation. The generally applied ventilation strategies aim to limit tidal volumes to < 8 mL/kg and to restrict peak inspiratory pressures to < 30 cm H_2O, while applying high positive end expiratory pressures. Patients are ventilated in a pressure control or pressure support mode. Patients requiring peak inspiratory pressures above 30 cm H_2O or patients with an oxygenation index ([mean airway pressure x FiO_2 x 100] / PaO_2) > 20 proceed to high frequency oscillatory ventilation (HFOV). Ventilation is delivered by a Servo 300 or Servo-*i* (Maquet, Sweden) for conventional mechanical

ventilation and a Sensormedics 3100A or 3100B (Viasys healthcare, USA) for HFOV.

Patients

All children younger than 19 years of age, who received an allogeneic HSCT in our hospital between January 1999 and April 2007, were identified from the HSCT database. Patients admitted to the ICU after HSCT were identified from a prospectively maintained ICU database. They were included when they had received invasive mechanical ventilation for more than 24 hours. Prior to the start of the HSCT procedure, all parents, and when appropriate, all patients, gave written informed consent to analyze de-identified clinical data for study purposes.

Data collection

Patient data were collected from medical charts and from the HSCT database. Data that were abstracted included demographic information, pre-existing diagnosis requiring HSCT, number and type of transplantations, type of donor and source of stem cells. For those patients admitted to the ICU for mechanical ventilation, the following additional information was recorded: presence of neutropenia, grade of graft-versus-host disease (GvHD), cytomegalovirus status, time interval between HSCT and admission to the ICU, reason for intubation, duration of intubation, use of HFOV, paediatric risk of mortality (PRISM) score [9], highest oxygenation index during the first day of admission and severity of organ dysfunction during the first three days of admission to the ICU.

Definitions

Indications for HSCT were categorized in the following groups: malignancy, inborn error of metabolism, immunodeficiency, bone marrow failure syndrome and miscellaneous inborn error (including thalassaemia, Morbus Glanzmann). GvHD was diagnosed and graded according to Glucksberg et al. [10]. Cytomegalovirus status at admission to the ICU was categorized as negative, infection (including reactivation) or carrier. Neutropenia was defined as a polymorphonuclear leukocyte count of less than 500 cells per cubic millimetre of blood. Reasons for admission to the ICU were grouped in the following categories: respiratory failure, neurological deterioration, sepsis, arrest, bleeding and postoperative [11]. Number and severity of organ dysfunction was assessed following the criteria of Wilkinson et al. [12]. The PRISM score [9] was used to assess severity of illness on admission to the ICU. It is a validated scoring system, applied by paediatric ICUs worldwide. It is based on deteriorations of a number of physiological variables measured during the first 24 hours of ICU admission. Human leukocyte antigen matching was based on high-resolution typing for class I and class II antigens for bone marrow and peripheral blood stem cell donors (10 antigens: A, B, C, DR and DQ). For cord blood donors

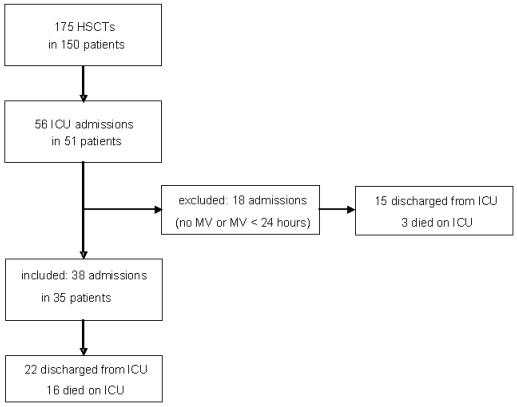
intermediate resolution criteria were used (Loci A and B serologically and DRB1 by high resolution typing) [13]. A DPB1 mismatch was not taken into account. For the analyses, patients were simply divided into a matched or mismatched group. Identical cord blood grafts according to the intermediate resolution criteria mentioned above, were regarded as matched.
Primary outcome of the study was outcome (survival or death) at discharge from the ICU; secondary endpoint was outcome (survival or death) six months after discharge from the ICU.

Statistical analysis
Differences in categorical demographic and clinical variables were analyzed using Fisher's exact test. Continuously distributed data were evaluated using Student's t-tests. The association between potential risk factors and ICU admission or ICU mortality was quantified using univariable logistic regression analysis. This was followed by stepwise multiple logistic regression analysis to identify those factors independently associated with ICU admission or ICU mortality. A *p*-value of less than 0.05 was considered to indicate statistical significance. Data were analyzed using SPSS version 12.0.2 (SPSS, Chicago, IL).

Results

A flow chart of HSCTs and ICU admissions is given in Figure 1. During the inclusion period, 175 HSCTs were performed in 150 patients: a second transplantation was done in 23 patients and one patient received three transplantations. Fifty-one patients were admitted to the ICU on 56 occasions: two patients were admitted twice, one patient was admitted to the ICU on five occasions. Eighteen admissions (16 patients) did not receive mechanical ventilation for more than 24 hours and they were excluded. Three of the excluded patients died in the ICU: one patient was admitted because of a sepsis, which rapidly deteriorated. Despite intubation and resuscitation he died within one hour after admission. In two patients it was decided (in agreement with the patients' and parents' wishes) to give maximum support, but refrain from mechanical ventilation. Both patients died within three days after ICU admission.

Figure 1
Flow chart of ICU admissions and outcomes of children after allogeneic haematopoietic stem cell transplantation

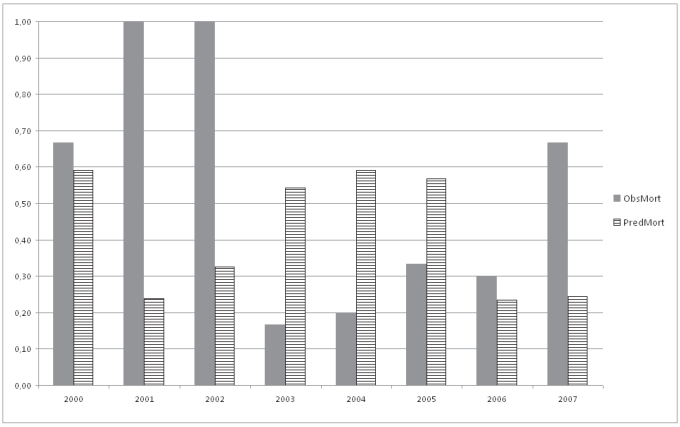


HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; MV, mechanical ventilation

The remaining 35 patients (23% of all HSCT recipients) were included in the study. Since three patients required two episodes of mechanical ventilation, mechanical ventilation was given on 38 occasions. Readmissions for mechanical ventilation occurred two days, 214 days and 219 days after the first admission. They were considered to be separate treatment episodes and were analyzed accordingly. None of the included patients had received non-invasive ventilation before intubation or during weaning. The reasons to start mechanical ventilation were respiratory failure (n=26), neurological deterioration (n=6), sepsis (n=4), cardiac arrest (n=1), and postoperative (n=1).

Sixteen patients died in the ICU, resulting in a case fatality rate of 42% (95% confidence interval (CI) 26%–58%). The cause of death for patients in the ICU was respiratory failure (n=6), multiple organ system failure (n=7), sepsis (n=1), Epstein Barr encephalitis (n=1) and post transplantation lymphoproliferative disorder (n=1). All three patients who received two episodes of mechanical ventilation died on the ICU. During ICU treatment two patients received renal replacement therapy, both died on the ICU. The observed ICU mortality (42%) corresponded to PRISM based predicted mortality (37%). However, there was a wide variation between annually observed and predicted ICU mortality (Figure 2).

Figure 2
Predicted mortality rates (based on PRISM scores) and observed mortality rates in children requiring mechanical ventilation after allogeneic haematopoietic stem cell transplantation.



ObsMort, observed ICU mortality rate; PredMort, predicted ICU mortality rate based on PRISM score [9]

Three patients who were discharged from the ICU died shortly afterwards: one patient after 10 days (refractory GvHD), one after 20 days (refractory GvHD, Epstein Barr reactivation and pulmonary aspergillosis) and one patient died 34 days after ICU discharge (idiopathic pneumonia syndrome, multiple viral infections). Early mortality rate (i.e. death on the ICU or shortly after discharge from the ICU) therefore was 50% (95% CI 34%-66%). Eighteen patients who were discharged from the ICU were still alive six months later. Altogether, therefore, 18 out of 38 ICU admissions (47%) could be discharged from the ICU and lived at least six months afterwards.

Risk factors for the requirement of mechanical ventilation
Characteristics of all HSCT recipients are summarized in Table 1. In this Table, a comparison is made between ventilated and non-ventilated children. Data are analyzed per patient. When data were analyzed with each transplantation as a separate event (i.e. n=175 instead of n=150), comparable results were found (data not shown).

Table 1
Characteristics of paediatric allogeneic haematopoietic stem cell transplantation recipients

	all HSCT recipients (n=150)	**HSCT recipients not receiving MV** (n=115)	**HSCT recipients requiring MV** (n=35)	***p*-value**
gender (female)	39%	37%	46%	0.43
median age (years)	6.5	6.6	4.7	0.56
diagnosis				
malignancy	54%	56%	49%	0.56
immunodeficiency	17%	17%	20%	0.62
bone marrow failure	13%	16%	6%	0.16
inborn error of metabolism	10%	8%	17%	0.12
miscellaneous inborn error	5%	4%	9%	0.39
type of transplant				
bone marrow	69%	70%	63%	0.41
cord blood	17%	15%	23%	0.30
peripheral blood stem cells	16%	17%	14%	1.00
type of donor (related)	43%	47%	29%	0.06
HLA mismatch	33%	32%	31%	0.68
more than 1 transplantation	15%	17%	6%	0.11
year of transplantation	1999-2007	1999-2007	1999-2007	0.05

HSCT, hematopoietic stem cell transplantation; MV, mechanical ventilation; HLA, human leukocyte antigen

In the univariable analysis, year of transplantation and type of donor were associated with the risk of requiring mechanical ventilation (see Table 1). In the multiple regression analysis, both year of transplantation (odds ratio 1.15, 95% CI 0.94-1.39, p=0.17) and type of donor (odds ratio 0.56, 95% CI 0.24-1.35, p=0.20) lost significance.

Risk factors for mortality in ventilated patients

Clinical characteristics of ventilated patients who survived to ICU discharge are summarized in supplementary Table A. Clinical characteristics of ventilated patients who died during their ICU admission are summarized in supplementary Table B.

Results from the statistical comparison between survivors and non-survivors are given in Table 2. In the univariable analysis, presence of organ system failure on day two and HFOV were significantly related with ICU mortality. Both organ system failure on day two (odds ratio 3.45, 95% CI 1.12-10.63, p=0.03) and HFOV (odds ratio 6.28, 95% CI 1.16-34.12, p=0.03) remained significantly associated with mortality in the multivariable analysis.

Table 2
Demographic and clinical data of the children requiring mechanical ventilation after allogeneic haematopoietic stem cell transplantation; comparison between survivors and non-survivors

	ventilated patients		95% CI for OR			
	surv n=22	non-surv n=16	OR	lower	upper	*p*-value
female gender	59%	31%	0.32	0.08	1.22	0.11
median age (years)	4.3	8.7	1.00	1.00	1.00	0.29
diagnosis						
malignancy	55%	38%	0.50	0,13	1.86	0.34
immunodeficiency	14%	25%	2.11	0.40	11.13	0.43
bone marrow failure	5%	6%	1.40	0.08	24.20	1.00
inborn error of metabolism	18%	25%	1.50	0.31	7.19	0.70
miscellaneous inborn error	9%	6%	0.67	0.06	8.06	1.00
type of transplant						
bone marrow	59%	69%	1.52	0.39	5.91	0.74
cord blood	23%	31%	1.55	0.36	6.61	0.71
PBSC[a]	18%	0%				0.12
HLA mismatch	27%	44%	2.07	0.53	8.10	0.32
type of donor (related)	27%	25%	0.89	0.20	3.87	1.00
CMV status						
negative	59%	56%	0.89	0.24	3.28	1.00
infection/reactivation	14%	25%	2.11	0.40	11.13	0.43
carrier	27%	19%	0.62	0.13	2.95	0.71
days on ventilation	14 (2-50)	14 (3-42)	1.01	0.96	1.06	0.66
ICU after Tx (days)	70 (7-412)	32 (4-319)	1.00	0.99	1.01	0.54
OI at admission	10 (2-36)	11 (2-37)	0.99	0.92	1.07	0.87
HFOV	14%	44%	4.93	1.03	23.63	0.05
neutropenia at admission	23%	42%	2.04	0.49	8.45	0.47
GvHD > grade 2	9%	12%	3.33	0.53	21.03	0.20
PRISM score	20 (4-40)	21 (9-36)	1.02	0.95	1.10	0.64
predicted risk of mortality	35% (2-97)	37% (5-94)				
n of organs failing day 1	2 (1-3)	2 (1-4)	1.95	0.86	4.41	0.11
n of organs failing day 2	2 (1-3)	2 (1-5)	3.10	1.06	9.05	0.04
n of organs failing day 3	2 (1-4)	3 (1-6)	2.45	0.98	6.13	0.06
indication for MV						
respiratory failure	59%	81%	3.00	0.66	13.66	0.18
neurological deterioration	18%	13%	0.64	0.10	4.03	1.00
sepsis	14%	6%	0.42	0.04	4.48	0.62
postoperative[a]	5%	0%				
arrest[a]	5%	0%				

CI, confidence interval; OR, odds ratio; surv, survivors; non-surv, non-survivors; PBSC, peripheral blood stem cells; HLA, human leukocyte antigen; CMV, cytomegalovirus; ICU, intensive care unit; Tx, transplantation; OI, oxygenation index; HFOV, high frequency oscillatory ventilation; GvHD, graft-versus-host disease; PRISM, pediatric risk of mortality, n, number.
Data are presented as median (range) or percentage, unless specified otherwise. Organ dysfunction was assessed following the criteria of Wilkinson et al. [12]. GvHD was graded according to Glucksberg et al. [10].
[a] = odds ratio and 95% confidence interval could not be calculated since no patients died in the ICU with specified risk factor

Discussion

We assessed risk factors for and outcomes of mechanical ventilation in a recent cohort of children after allogeneic HSCT. The main finding is that ICU mortality rate was considerably lower than in previous studies. ICU discharge was followed by a low medium-term mortality rate. Our results are promising, but they need to be confirmed in larger multimember studies.

There is ongoing discussion whether ICU outcome improved over time for children after HSCT. A recent meta-regression analysis [2] could not detect a significant improvement over the years, but conclusions were hampered by the limited availability of current data. After the inclusion period of the meta-regression analysis, two additional studies on this subject were published. Bratton et al. [4] found a decrease over the years in complications requiring ICU transfer in children after HSCT. However, once mechanical ventilation was necessary, mortality remained unchanged in the years studied. This study benefited from a very large sample size from a database of over 3000 hospitals in the United States, but it did not focus on ICU treatment or ICU outcomes. It therefore included only limited information on the reason for ICU transfer, or the acuity of illness on admission to the ICU, which limits interpretation of their results. Tamburro et al. [3] reviewed outcomes of mechanical ventilation in a large cohort of paediatric HSCT recipients between 1996 and 2004 and found a significant improvement over the years. Our findings are in line with their results, and even suggest an ongoing improvement in outcomes in more recent years, both for ICU survival (40% in the study of Tamburro et al. versus 58% in our study) as for 6-month survival (25% in the study of Tamburro et al. versus 47% in our study).

Our results need to be interpreted cautiously: they are limited by the retrospective nature of the study and by the relatively small number of patients included from only a single centre. This is especially important, since ventilated children after HSCT form a heterogeneous population, which makes it difficult to compare results between studies. Moreover, we do not know in which patients ICU admission was denied because it was considered futile. Triage decisions can influence ICU outcome, as has been shown in adult cancer patients [14]. With these limitations in mind, we can conclude that results are promising, but need to be confirmed in other, preferably multi-centre, studies. Since transplantation and critical care medicine are rapidly evolving, future research on ICU treatment in HSCT recipients would be helped with a prospectively collected database by a group of dedicated ICUs. Only then some of the remaining questions in this complex group of patients can be answered.

There may be several explanations for the improved survival we found. First, it is likely that advancements in medical care contributed to better outcomes. Second, improvements in outcome can be explained by a lower threshold to start mechanical

ventilation, and by intubating less severely ill patients. In our study, 23% of transplanted children required mechanical ventilation, which is comparable to the proportion of patients after allogeneic HSCT in previous European studies [6, 8, 15]. However, in the study of Bratton et al. [4], only 10% of children after allogeneic HSCT received mechanical ventilation. In this study, 45% of non-survivors died without receiving mechanical ventilation, which may suggest a restrictive use of ICU care in a considerable number of children. Patients in our study had higher PRISM scores than patients in other studies [1, 7, 16, 17], and their PRISM based risk of mortality (37%) was considerably higher than in previous studies (18% [11], 19% [18] and 26% [19]). It is therefore unlikely that a lower threshold to start mechanical ventilation or a lower severity of illness explains the improved outcome in our patients.

An interesting finding in the present study is that the duration of mechanical ventilation (median 14 days, range 2 – 50) was considerably longer than reported in previous studies. This may coincide with a higher severity of illness on admission to the ICU. Furthermore, therapeutic options for complications after HSCT have extended, which may lead to prolonged treatment in patients who would have already died previously. The shorter duration of mechanical ventilation in other studies may reflect withdrawal or limitation of ICU treatment, since the need for prolonged mechanical ventilation has been considered predictive for death by many physicians [11, 20-23]. However, the results from the current study emphasize that the decision to stop or limit ICU treatment should not be based solely on the duration of mechanical ventilation.

Organ failure was associated with ICU mortality, but only on the second day of admission. This suggests that lack of improvement or even progression of organ failure despite ICU treatment gives the largest increase in risk of mortality. The relation between organ failure and ICU mortality is a consistent finding in nearly all other ICU studies in HSCT recipients. It is also reflected in the association between HFOV and mortality, since HFOV is used in patients with the most severe form of respiratory failure. On the other hand, 30% of patients who received HFOV in our study survived, as did the patient with the highest PRISM score, and the patient with the highest oxygenation index. This underscores the difficulty of identifying survivors and non-survivors in a way accurate enough to guide clinical decision making.

In conclusion, there is ongoing discussion whether ICU outcome improved over time for ventilated children after HSCT. Compared to previous studies, we found significantly better outcomes. This holds true both for ICU survival as for survival six months after discharge from the ICU. The ICU survival rate of more than 50% in the present study is promising, but needs to be confirmed in other, preferably multi-centre, studies.

References

1 Kache S, Weiss IK, Moore TB. Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. *Pediatr Transplant* 2006; 10: 299-303

2 van Gestel JPJ, Bollen CW, van der Tweel I, et al. Intensive care unit mortality trends in children after hematopoietic stem cell transplantation: a meta-regression analysis. *Crit Care Med* 2008; 36: 2898-29043

3 Tamburro RF, Barfield RC, Shaffer ML, et al. Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. *Ped Crit Care Med* 2008; 9: 270-277

4 Bratton SL, Van Duker H, Statler KD, et al. Lower hospital mortality and complications after pediatric hematopoietic stem cell transplantation. *Crit Care Med* 2008; 36: 923-927

5 Warwick AB, Mertens AC, Shu XO, et al. Outcomes following mechanical ventilation in children undergoing bone marrow transplantation. *Bone Marrow Transplant* 1998; 22: 787-794

6 Diaz de Heredia C, Moreno A, Olive T, et al. Role of the intensive care unit in children undergoing bone marrow transplantation with life-threatening complications. *Bone Marrow Transplant* 1999; 24: 163-168

7 Cheuk DK, Ha SY, Lee SL, et al. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. *Hematol Oncol* 2004; 22: 1-9

8 Angel Diaz M, Vicent MG, Prudencio M, et al. Predicting factors for admission to an intensive care unit and clinical outcome in pediatric patients receiving hematopoietic stem cell transplantation. *Haematologica* 2002; 87: 292-298

9 Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16: 1110-1116

10 Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974; 18: 295-304

11 Jacobe SJ, Hassan A, Veys P, et al. Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. *Crit Care Med* 2003; 31: 1299-1305

12 Wilkinson JD, Pollack MM, Glass NL, et al. Mortality associated with multiple organ system failure and sepsis in pediatric intensive care unit. *J Pediatr* 1987; 111: 324-328

13 Tiercy JM. Molecular basis of HLA polymorphism: implications in clinical transplantation. *Transpl Immunol* 2002; 9: 173-180

14 Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. *J Clin Oncol* 2005; 23: 4406-4413
15 Gonzalez-Vicent M, Marin C, Madero L, et al. Risk score for pediatric intensive care unit admission in children undergoing hematopoietic stem cell transplantation and analysis of predictive factors for survival. *J Pediatr Hematol Oncol* 2005; 27: 526-531
16 Rossi R, Shemie SD, Calderwood S. Prognosis of pediatric bone marrow transplant recipients requiring mechanical ventilation. *Crit Care Med* 1999; 27: 1181-1186
17 Schneider DT, Lemburg P, Sprock I, et al. Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children. *Bone Marrow Transplant* 2000; 25: 1079-1086
18 Henneveld HT, Wulffraat NM, Gemke RJ, van Vught AJ. Mechanical ventilation in bone marrow transplanted children; do they benefit? *Eur J Pediatr* 1998; 157: 441-442
19 Bojko T, Notterman DA, Greenwald BM, et al. Acute hypoxemic respiratory failure in children following bone marrow transplantation: an outcome and pathologic study. *Crit Care Med* 1995; 23: 755-759
20 Tomaske M, Bosk A, Eyrich M, et al. Risks of mortality in children admitted to the paediatric intensive care unit after hematopoietic stem cell transplantation. *Br J Haematol* 2003; 121: 886-891
21 Todd K, Wiley F, Landaw E, et al. Survival outcome among 54 intubated pediatric bone marrow transplant patients. *Crit Care Med* 1994; 22: 171-176
22 Hagen SA, Craig DM, Martin PL, et al. Mechanically ventilated pediatric stem cell transplant recipients: effect of cord blood transplant and organ dysfunction on outcome. *Pediatr Crit Care Med* 2003; 4: 206-213
23 Keenan HT, Bratton SL, Martin LD, et al. Outcome of children who require mechanical ventilatory support after bone marrow transplantation. *Crit Care Med* 2000; 28: 830-835

supplementary Table A
Clinical characteristics of the 22 ventilated paediatric haematopoietic stem cell transplantation recipients who survived to ICU discharge

	diagnosis necessitating Tx	indication for MV	diagnosis necessitating MV	Tx-ICU (d)	MV (d)	surv after ICU	aGvHD	neut	viral inf
1	GM1-gangliosidosis	resp fail	IPS	7	9	>6 mo	1	Y	n
2	AML I	resp fail	engraftment syndrome, hepatic VOD	10	12	>6 mo	1	n	n
3	MPS I	resp fail	DAH	11	19	>6 mo	0	y	adeno react
4	β thalassaemia major	resp fail	hepatic VOD, pulmonary oedema	14	8	>6 mo	0	y	n
5	MDS	resp fail	IPS, hepatic VOD	24	20	>6 mo	0	n	n
6	MDS	resp fail	hepatic VOD, pulmonary oedema, aGvHD	25	15	10 d	4	n	n
7	AML	resp fail	intox cyclosporine, pleural effusions, MOF	29	2	>6 mo	0	n	CMV react
8	Niemann-Pick disease	resp fail	IPS, pulmonary VOD	66	31	>6 mo	3	n	n
9	α-mannosidosis	resp fail	IPS	82	17	34 d	1	n	adeno react
10	MDS	resp fail	interstitial pneumonitis	90	9	>6 mo	1	n	rhino
11	MPS IV	resp fail	bronchiolitis obliterans, no MO identified	94	11	>6 mo	1	n	n
12	CID	resp fail	IPS, subglottic stenosis	117	8	>6 mo	NA	n	n
13	SAA	resp fail	lobar pneumonia, no MO identified	171	21	>6 mo	NA	n	n
14	T-cell ALL	neurol	Guillain –Barré syndrome	68	50	>6 mo	0	n	n
15	cartilage hair hypoplasia	neurol	acinetobacter sepsis with encephalopathy	71	5	144 d	0	y	system adeno
16	relapsed AML	Neurol	CNS toxoplasmosis	171	37	>6 mo	NA	n	n

supplementary Table A continued

	diagnosis necessitating Tx	indication for MV	diagnosis necessitating MV	Tx-ICU (d)	MV (d)	surv after ICU	aGvHD	neut	viral inf
17	AML	neurol	CNS, pulmonary and intestinal aspergillosis	244	39	>6 mo	NA	n	n
18	AML	sepsis	Klebsiella pneumoniae sepsis with ARDS	69	17	>6 mo	0	n	CMV react
19	HLH	sepsis	stenotrophomonas sepsis	72	5	>6 mo	0	n	VZV, adeno react
20	ALL high risk	sepsis	septic shock, no MO identified	412	6	>6 mo	NA	n	n
21	AML	postop	external CSF drainage for hydrocephalus, BAL	12	3	20 d	0	y	EBV, HHV6 react
22	AML	arrest	pulmonary VOD with pulmonary hypertension	94	23	>6 mo	0	n	n

Tx, transplantation; MV, mechanical ventilation; ICU, intensive care unit; d, days; surv, survival; aGvHD, (grade of) acute graft-versus-host disease; neut, neutropenia on admission to ICU; inf, infection; AML, acute myeloid leukaemia; MPS, mucopolysaccharidosis; MDS, myelodysplastic syndrome; CID, combined immune deficiency; SAA, severe aplastic anaemia; ALL, acute lymphocytic leukaemia; HLH, haemophagocytic lymphohistiocytosis; resp fail, respiratory failure; neurol, neurological deterioration; postop, postoperative; IPS, idiopathic pneumonia syndrome; VOD, veno-occlusive disease; DAH, diffuse alveolar haemorrhage; intox, intoxication; MO, micro-organism; CNS, central nervous system; ARDS, acute respiratory distress syndrome; CSF, cerebrospinal fluid; BAL, broncho-alveolar lavage; NA, not applicable; react, reactivation; system, systemic; CMV, cytomegalovirus; VZV, varicella zoster virus; EBV, Epstein Barr virus; HHV, human herpes virus.

supplementary Table B
Clinical characteristics of the 16 ventilated paediatric haematopoietic stem cell transplantation recipients who died during their ICU admission

	diagnosis necessitating Tx	indication for MV	diagnosis necessitating MV	Tx-ICU (d)	MV (d)	aGvHD	neut	viral inf
1	relapsed ALL	resp fail	aGvHD, hepatic VOD	7	29	3	y	n
2	MDS	resp fail	IPS	9	26	4	n	n
3	lymphoproliferative syndrome	resp fail	pulmonary microbacterial and nocardia infection	10	34	0	n	n
4	Morbus Glanzmann	resp fail	IPS, DAH	13	42	1	y	n
5	osteopetrosis	resp fail	IPS	22	33	0	n	n
6	SAA	resp fail	pulmonary aspergillosis	23	11	0	n	n
7	Morbus Wolman	resp fail	IPS, DAH	25	30	1	n	CMV inf
8	cartilage hair hypoplasia	resp fail	CMV pneumonia	40	17	2	y	CMV pneumonia, adeno and EBV react
9	CVID	resp fail	EBV PTLD	56	3	2	n	EBV PTLD
10	relapsed ANLL	resp fail	Adeno infection	60	7	0	y	adeno inf
11	Wiskott-Aldrich syndrome	resp fail	CMV, EBV infection	64	11	0	n	CMV, EBV inf
12	α-mannosidosis	resp fail	IPS	104	30	1	n	adeno inf
13	Niemann-Pick disease	resp fail	candida sepsis with ARDS	319	6	NA	n	n
14	relapsed AML	neurol	RPLS	118	3	NA	y	EBV, adeno react
15	AML	neurol	cerebral EBV infection	248	11	NA	n	EBV inf
16	relapsed ALL	sepsis	septic shock, no MO identified	4	3	0	y	n

Tx, transplantation; MV, mechanical ventilation; ICU, intensive care unit; d, days; surv, survival; aGvHD, (grade of) acute graft-versus-host disease; neut, neutropenia on admission to ICU; inf, infection; ALL, acute lymphocytic leukaemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anaemia; CVID, common variable immunodeficiency; ANLL, acute non-lymphocytic leukaemia; AML, acute myeloid leukaemia; resp fail, respiratory failure; neurol, neurological deterioration; postop, postoperative; IPS, idiopathic pneumonia syndrome; VOD, veno-occlusive disease; DAH, diffuse alveolar haemorrhage; CMV, cytomegalovirus; EBV, Epstein Barr virus; PTLD, post transplantation lymphoproliferative disease; ARDS, acute respiratory distress syndrome; RPLS, reversible posterior leukoencephalopathy syndrome; MO, micro-organism; NA, not applicable; react, reactivation.

Chapter 5

MECHANICAL VENTILATION FOR RESPIRATORY FAILURE IN CHILDREN WITH SEVERE NEUROLOGICAL IMPAIRMENT: IS IT FUTILE MEDICAL TREATMENT?

Developmental Medicine & Child Neurology, in press

JPJ van Gestel
AH Robroch
CW Bollen
CK van der Ent
AJ van Vught

Abstract

Aim: To assess outcome for children with severe neurological impairment receiving invasive mechanical ventilation for respiratory failure.
Method: Medical charts for all these children treated in our intensive care unit (ICU) between January 2003 and July 2008 were reviewed. Outcomes were compared with those for children with moderate neurological impairment.
Results: Twenty-two children with severe neurological impairment were included (nine females, 13 males; median age 7y 10mo; range 4 mo-17y). The median duration of mechanical ventilation was 16 days. Six children had an uneventful 1-year survival, the others required reintubation or readmission to the ICU, or died. Eleven children were still alive 1 year after discharge from the ICU. Nine patients died of respiratory failure. Eleven children with moderate neurological impairment were included (nine females, three males; median age 1 year 1 month (range 4mo–13y). Four children had an uneventful 1-year survival. Eight children were still alive 1 year after discharge from the ICU. Two of the three non-survivors died of their heart defects.
Interpretation: Mechanical ventilation for respiratory failure in children with severe neurological impairment is complex and associated with limited survival. However, it cannot be regarded as futile medical treatment. Further studies are urgently needed for the rational guidance of clinical decision making.

Abbreviations

ICU intensive care unit

Introduction

Children with severe neurological impairment often have respiratory problems.[1] The aetiology is multifactorial and includes recurrent aspiration,[2] gastro-oesophageal reflux,[2,3] swallowing difficulties, poor coughing, respiratory muscle weakness, kyphoscoliosis, hypo-activity and poor nutritional status. The exact magnitude of the respiratory problems is not well documented in the literature, but the finding that children with severe developmental delay often die of respiratory causes confirms their relevance.[4–6]

When children with severe neurological impairment present with respiratory failure, the difficult decision has to be made whether or not to intubate and initiate mechanical ventilation. On the one hand, it is believed that mechanical ventilation cannot serve as a bridge to recovery in most of these patients: their neurological condition is the main contributor to the respiratory problems, and there is no therapy to improve this condition. In view of this, mechanical ventilation is futile medical treatment, which explains the reluctance of intensivists to admit this category of patients to the intensive care unit (ICU). The idea of futility is especially important, because treatment in the ICU is often perceived to be difficult and protracted, with considerable suffering for the patient. On the other hand, sometimes parents, caregivers or physicians favour maximal therapy, even if chances of survival are poor.

The decision to initiate or withhold mechanical ventilation has important consequences and requires careful consideration. Unfortunately, the literature does not provide any evidence to support parents and clinicians in making this decision. We hypothesized that mechanical ventilation in this population often has a complicated clinical course and is associated with high mortality rates. The aim of the present study was to investigate whether this assumption was correct.

Methods

Setting

This study was performed at the ICU of the Wilhelmina Children's Hospital, which is part of the University Medical Center Utrecht (Utrecht, the Netherlands). It is a tertiary, multidisciplinary, 14-bed ICU with approximately 600 admissions each year. The hospital's Ethical Committee granted exemption from the requirement of informed consent for this study.

Patients

All ICU admissions between January 2003 and July 2008 were reviewed. We wished to select patients with neurological impairment who had been admitted for

respiratory failure. Respiratory failure was defined as the need for endotracheal mechanical ventilation for respiratory problems, such as upper respiratory tract infection, lower respiratory tract infection, small airways disease, or a combination of these. At first screening, the following admissions were therefore excluded: children who had not been intubated, children who had been on home mechanical ventilation before admission to the ICU, elective (postoperative) admissions, children who were intubated for acute neurological problems (e.g. refractory status epilepticus, diminished Glasgow coma score or metabolic derangement) and children who were intubated for circulatory support (e.g. severe dehydration or cardiac decompensation). The medical charts of the remaining patients were separately reviewed in depth by two observers (AHR, JPJvG) for final inclusion. In case of disagreement, the opinion of a third observer (AJvV) was sought. All included patients were followed for 1 year to assess outcome after discharge from the ICU.

Neurological impairment was defined according to the American Association on Intellectual Disabilities as a disability characterized by significant limitations both in intellectual functioning and in adaptive behaviour as expressed in conceptual, social and practical adaptive skills, originating before the age of 18 years.[7] In none of the included children was an intelligence test performed. A descriptive classification was therefore used, partly following the DSM-IV-TR criteria.[8] Patients were classified as severely impaired when they suffered from profound developmental delay, required around-the-clock care and support, were completely dependent on a wheelchair and had no or very limited possibilities for communication. The outcomes for children with severe neurological impairment were compared with those for children with moderate impairment. Children were classified as moderately impaired when they were delayed in their psychomotor development but were considered trainable and had adequate communication skills. They required assistance in navigating through everyday life and it was expected that they could not live independently as adults. All information to identify and classify developmental disabilities was obtained from existing records. In cases that were uncertain the opinion of the child's paediatrician was asked.

Data collection

The following data were recorded: pre-existing respiratory condition, pre-existing co-morbidities, Paediatric Index of Mortality 2 score,[9] details of the ventilator settings during the first 24 hours of mechanical ventilation (highest peak inspiratory pressure, highest oxygenation index defined as 100 times the mean airway pressure times the fraction of inspiratory oxygen divided by the partial pressure of arterial oxygen), length of stay in the ICU, and duration of mechanical ventilation.

The primary endpoint was uneventful 1-year survival. This was defined as successful weaning and extubation on first attempt, discharge from the ICU and survival for 1 year after discharge without requirement for readmission to the ICU.

Results

During the inclusion period 3377 patients were admitted to the ICU, of whom 33 (1%) fulfilled the inclusion criteria. None of the included patients had received non-invasive mechanical ventilation before intubation.
Twenty-two of the included patients were categorized as severely impaired. Characteristics of these patients are shown in Table 1.
Eleven of the included patients were categorized as moderately impaired.
Characteristics of these patients are shown in Table 2.
An overview of the clinical course and outcome data for all included patients is given in Table 3, in which a comparison is made between children with moderate and severe neurological impairment. The most prominent differences are the higher 1-year mortality rate, the higher incidence of chronic respiratory problems and the higher reintubation rate for sputum retention in children with severe neurological impairment. The median length of stay for all our ICU-admitted patients was 6 days, which means that patients with moderate impairment and those with severe impairment required prolonged admission.
A flow chart of ICU admission of the children with severe neurological impairment is given in Figure 1. As can be seen, six patients had an uneventful 1-year survival. The remaining patients required reintubation or readmission to the ICU, or died. Overall, 11 children were still alive 1 year after discharge from the ICU. Seven of the survivors and all 11 non-survivors had chronic respiratory problems. Two children died during their first admission to the ICU. One of them was admitted with human metapneumovirus pneumonia. Her pulmonary situation gradually declined with recurrent pneumothoraces. Despite maximum support, she died of respiratory failure after an admission period of 11 days. For the other child, it was decided to refrain from reintubation after an admission period of 36 days and failed first extubation. She died 2 days after the second extubation. Six children died after their discharge from the ICU (after 3, 4, 27, 54, 68 and 289 days, respectively). For all these children it was decided to refrain from readmission to the ICU; five of them died of respiratory failure, and one died as a result of a refractory status epilepticus. The three remaining non-survivors were readmitted to the ICU, at 19, 39 and 61 days after their first discharge. One died in the ICU as a result of *Candida* sepsis despite maximum therapy. The other two were discharged but died 30 days and 104 days later from respiratory failure. For these two patients it was decided to refrain from treatment in the ICU after the second admission.

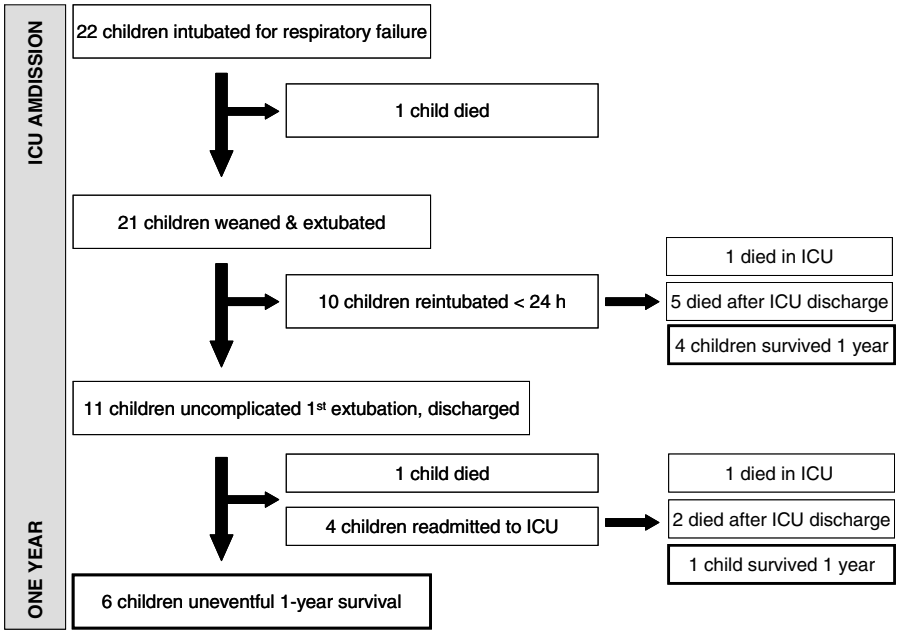
Table 1
Characteristics of the 22 patients with severe neurological impairment

pat	cause of neurol impairment	comorbidities	age	sex	chron resp prob	1-year outcome
1	unknown	none	4 m	M	+	died
2	unknown	diaphragmatic hernia, tracheo-broncho-malacia, re-entry tachycardia, dextrocardia, blindness	5 m	M	+	died
3	unknown	epilepsy	6 m	M	+	died
4	unknown	broncho-malacia, spasticity, epilepsy	7 y	F	+	died
5	1p36 deletion	epilepsy, spasticity	7 y	F	+	died
6	unknown	epilepsy	9 y	F	+	died
7	asphyxia	CVIT, spasticity	13 y	M	+	died
8	Aicardi syndrome	epilepsy	14 y	F	+	died
9	trisomy 21	epilepsy, cerebral paresis, AVSD, AV-block, pulm emphysema	15 y	F	+	died
10	perinatal asphyxia	epilepsy, spasticity	16 y	F	+	died
11	unknown	epilepsy	17 y	M	+	died
12	translocation 8/18	epilepsy	5 m	F	-	surv
13	mitochondrial encephalopathy	epilepsy	6 m	F	+	surv
14	Joubert syndrome	central hypoventilation	7 m	M	+	surv
15	hydranencephaly	epilepsy, VPD, cataract	1 y	M	+	surv
16	mitochondrial encephalopathy	epilepsy	3 y	F	-	surv
17	ring chromosome 21	epilepsy, ToF, deafness, blindness	4 y	M	+	surv
18	Miller Dieker	epilepsy, spasticity	8 y	M	-	surv
19	unknown	cerebral paresis	11 y	M	+	surv
20	hemi-mega encephaly	epilepsy	13 y	M	+	surv
21	unknown	epilepsy	13 y	M	+	surv
22	unknown	epilepsy	17 y	M	-	surv

pat, patient; neurol, neurological; chron resp prob, chronic respiratory problems; m, months; y, years; F, female; M, male; CVIT, Catecholamine Induced Ventricular Tachycardia; AVSD, atrioventricular septal defect; AV-block, atrioventricular block; VPD, ventriculoperitoneal drain; ToF, tetralogy of Fallot; surv, survived.

Reintubation within 24 hours after extubation was required in 10 patients, four of whom were still alive 1 year after discharge from the ICU. In four of the children, reintubation was required because of sputum retention. Only one of these four was still alive 1 year after discharge from the ICU.

Figure 1
Flow chart of intensive care unit admission for respiratory failure in 22 patients with severe neurological impairment



ICU, intensive care unit; h, hours.

All children with moderate neurological impairment were discharged from the ICU. Four of them had an uneventful 1-year survival. Overall, eight children were still alive 1 year after discharge from the ICU. One child died shortly after discharge from the ICU. He was admitted to the ICU because of croup caused by an adenovirus. After extubation he had persistent obstruction of the upper airway because of swallowing difficulties and disturbed muscle tone of the upper airways due to severe spasticity. Non-invasive mechanical ventilation and hyoidthyroidpexia could not improve the obstruction. After extensive discussion with his paediatrician, the ear–nose–throat physicians and the parents it was decided not to do a tracheotomy. The boy was discharged from the ICU after an admission of 41 days and he died 2 days later. The other two non-survivors died after intervention for their heart defects. One of them was readmitted to the ICU after cardiac catheterization, which was performed because of pulmonary hypertension. After the

catheterization she developed necrotizing enterocolitis, which deteriorated despite maximal therapy. The third non-survivor had an intracerebral bleeding with herniation as a complication of cardiac surgery.
Reintubation within 24 hours after extubation was required in five patients; in all of these, stridor was the reason for reintubation (Table 2). Five of the children with moderate neurological impairment had chronic respiratory problems; all survived. Two of the six children with cardiac disease died (see Table 2).

Table 2
Characteristics of the 11 patients with moderate neurological impairment

pat	cause of neurological impairment	comorbidities	age	sex	chron resp probl	1-year outcome
1	trisomy 21	duodenal atresia, ASD, pulm hypertension, tracheostomy	4 m	F	-	died
2	unknown	pulm atresia, VSD, MAPCA, Peter's anomaly	6 m	F	-	died
3	perinatal asphyxia	epilepsy, spasticity	13 y	M	-	died
4	trisomy 21	ASD	4 m	F	-	surv
5	trisomy 21	small airways disease, ASD, VSD	6 m	F	+	surv
6	trisomy 21	insulin dependent diabetes	1 y	F	+	surv
7	trisomy 21	none	1 y	M	-	surv
8	trisomy 21	ASD, pulm hypertension	1 y	F	+	surv
9	trisomy 21	subglottic stenosis, pulm hypertension	3 y	F	+	surv
10	VACTERL association	VACTERL association	5 y	M	+	surv
11	unknown	none	7 y	F	-	surv

pat, patient; chron resp probl, chronic respiratory problems; ASD, atrial septal defect; pulm, pulmonary; VSD, ventricular septal defect; MAPCA, multiple aorto-pulmonary connecting arteries; VACTERL, nonrandom association of birth defects including Vertebral anomalies, Anal atresia, Cardiac defects, Tracheo-Esophageal abnormalities, Renal abnormalities and Limb abnormalities; m, months; y, years; F, female; M, male.

Table 3
Clinical course and outcome data of mechanical ventilation for respiratory failure in children with moderate and severe neurological impairment

	children with moderate neurological impairment	**children with severe neurological impairment**
	n = 11 patients	**n = 22 patients**
ICU mortality	0 / 11	2 / 22
predicted ICU mortality rate (based on PIM2 score)	5.4% (0.9 - 27)	4.3% (1 - 41)
overall one-year mortality	3 / 11	11 / 22
length of stay in ICU (days)	22 (5 - 58)	18 (4 - 36)
duration of mechanical ventilation (days)	20 (4 - 57)	16 (3 - 34)
carbon dioxide level before intubation (mmHg)	63[1] (40-73)	68[2] (34-117)
highest oxygenation index on day of admission	9.7 (2 - 36)	8 (2 - 55)
highest peak inspiratory pressure on day of admission (cm H2O)	27 (9-36)	29 (18-54)
number of children requiring reintubation because of failed first extubation	5 / 11	10 / 22
stridor main reason for reintubation	5 / 5	6 / 10
sputum retention main reason for reintubation	0	4 / 10
number of children with chronic respiratory complaints	5 / 11	18 / 22
mortality in children with chronic respiratory complaints	0 / 5	11 / 18

ICU, intensive care unit; PIM2, Paediatric Index of Mortality 2 [9]
Data are presented as median (range) unless otherwise specified.
[1] Carbon dioxide levels before intubation could not be retrieved in 5 patients
[2] Carbon dioxide levels before intubation could not be retrieved in 8 patients

DISCUSSION

Our study is the first to describe the clinical course and outcome of mechanical ventilation for respiratory failure in children with severe neurological impairment. The main finding is that survival rates were low and that repeated, prolonged and complicated ICU admission was often required. However, mechanical ventilation could not be regarded as invariably futile. This underscores the urgent need for more studies in this population to guide clinical decision making.

There are several limitations to this study. First, it is a retrospective study from a single centre. This is an important limitation because there is risk of misclassifying the degree of neurological impairment. In none of the included children was an intelligence test performed to objectify intellectual functioning, and the criteria by which patients were categorised as moderately or severely impaired were not robust. However, all children with severe neurological impairment were without doubt more severely affected than patients with moderate impairment. We tried to avoid misclassification in the diagnosis of respiratory failure by critically reviewing all medical charts separately by two researchers, or by a third person in case of disagreement. We excluded all patients who required intubation for an elective procedure, for acute neurological problems or for support of the circulation. The high carbon dioxide levels before admission and the high oxygenation index and peak inspiratory pressures during the first 24 hours of admission confirm the presence of pulmonary problems in most patients. A second limitation of our study design is the risk of holding a self-fulfilling prophecy: when mechanical ventilation is expected to be futile, intensivists will be inclined to aim at early extubation and limitation of ICU care. It is not likely that such a limitation of care occurred in our patients, given the prolonged length of stay in the ICU and the high rate of reintubations. A third limitation of the present study is that we assessed only survival, and did not look at morbidity or physical and emotional functioning after discharge from the ICU. Treatment in the ICU often results in serious sequelae for patients and their families,[10,11] and it is unlikely that the consequences will be less in patients with cognitive disabilities. The retrospective nature of our study impeded a concise assessment of morbidity and complications related to treatment in the ICU. This point is highly relevant in terms of weighing the benefits and harms of mechanical ventilation in this population, and it should deserve attention in future prospective studies. It would then be very interesting to know whether the parents thought that treatment in the ICU had been worthwhile. A fourth limitation is that the patients we studied were a selection of children with severe neurological impairment. There probably were children with the same problems for whom it was decided beforehand not to start invasive mechanical ventilation. We therefore cannot make any statements about the natural course of respiratory failure in this

population, or about beneficial effects of alternative techniques such as non-invasive ventilation and cough assist machines.
There is generally no question of not starting mechanical ventilation when children with moderate neurological impairment present with respiratory failure. We therefore wished to compare their outcome with the outcome in children with severe neurological impairment. Such a comparison could also clarify the influence of severity of neurological impairment on outcome. It is interesting to see that outcome for children with moderate impairment was not influenced by their pre-admission respiratory condition, but was influenced much more by their heart defects. In children with severe impairment, mortality rates were highest when they had chronic respiratory complaints or required reintubation for sputum retention. These children were probably in a delicate respiratory balance with a limited capacity to recover from an acute exacerbation. For reasons given above, our study does not allow firm conclusions to be made with respect to predictors of outcome, so these findings require confirmation in future studies.
The results of our study shed some light on the difficult choice of whether or not to start mechanical ventilation in children with severe neurological impairment who present with respiratory failure. Medical care keeps improving, and patients are surviving diseases that were previously lethal. This is accompanied by an increase in the number of patients with neurodevelopmental problems.[12] At the same time, the life expectancy of patients with severe neurological impairment has increased.[13,14] This makes it likely that in the near future more physicians will be confronted with this dilemma. Good clinical practice requires evidence, and parents ask for well-grounded information about therapeutic options. This underscores the urgent need for prospective studies.

Conclusions

Uneventful survival in children with severe neurological impairment who received mechanical ventilation for respiratory failure was low. Repeated, prolonged and complicated admission to the ICU was often required. However, outcome was not uniformly dismal, which underscores the urgent need for further research for the rational guidance of clinical decision making in this population.

References

1 Seddon PC, Khan Y. Respiratory problems in children with neurological impairment. *Arch Dis Child* 2003; 88: 75-78

2 Morton RE, Wheatley R, Minford J. Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. Dev Med Child Neurol 1999; 41: 329-334

3 Gustafsson PM, Tibbling L. Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage. Acta Paediatr 1994; 83: 1081-1085

4 Carter G, Jancar J. Mortality in the mentally handicapped: a 50 year survey at the Stoke Park group of hospitals (1930-1980). J Ment Defic Res 1983; 27: 143-156

5 Hollins S, Attard MT, von Fraunhofer N, et al. Mortality in people with learning disability: risks, causes, and death certification findings in London. Dev Med Child Neurol 1998; 40: 50-56

6 Plioplys AV, Kasnicka I, Lewis S, Moller D. Survival rates among children with severe neurologic disabilities. South Med J 1998; 91: 161-172

7 Luckasson R, Reeve A. Naming, defining, and classifying in mental retardation. Ment Retard 2001; 39: 47-52

8 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision. American Psychiatric Association, 2000, Washington, DC

9 Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003; 29: 278-285

10 Knoester H, Bronner MB, Bos AP. Surviving pediatric intensive care: physical outcome after 3 months. Intensive Care Med 2008; 34: 1076-1082

11 Bronner MB, Knoester H, Bos AP, et al. Follow-up after paediatric intensive care treatment: parental posttraumatic stress. Acta Paediatr 2008; 97: 181-186

12 Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261-269

13 Plioplys AV. Survival rates of children with severe neurologic disabilities: a review. Semin Pediatr Neurol 2003; 10: 120-129

14 Puri BK, Lekh SK, Langa A, Zaman R, Singh I. Mortality in a hospitalized mentally handicapped population: a 10-year survey. J Intellect Disabil Res 1995; 39: 442-446

Chapter 6

INITIAL INTENSIVE CARE TREATMENT AND SURVIVAL IN CHILDREN WITH SEVERE MENINGOCOCCAL DISEASE

submitted

JPJ van Gestel
A Miedema
NJG Jansen
CW Bollen
AJ van Vught

Abstract

Purpose: To assess survival trends in children admitted to the paediatric intensive care unit (PICU) for severe meningococcal disease and to determine the effect of early critical care treatment of shock on survival.
Methods: All children with severe meningococcal disease who were admitted to the PICU of a university hospital in the Netherlands between January 1991 and January 2004 were identified. Demographic data and PICU treatment details were collected from their medical charts. Multiple logistic and linear regression analyses were used to assess the association of these data with PICU survival.
Results: 239 patients were included, of whom 37 patients died (case fatality rate 15.5%). Over time, children were more severely ill on admission. When corrected for severity of disease, mortality significantly decreased in the same time period ($p=0.009$). More fluids were given (each year 3.7 millilitre per kilo more, $p=0.0004$) and dopamine (each year 0.06 hours earlier, $p=0.022$) and dobutamine (each year 0.12 hours earlier, $p<0.001$) were started earlier. However, in a logistic regression model, only year of admission remained strongly associated with mortality. There was no independent effect of amounts of fluids administered or start of cardiovascular drug therapy on mortality.
Conclusion: Over time, children with meningococcal disease were more severely ill on admission to the PICU. Mortality corrected for severity of disease decreased in the same time period. This could not be explained by more aggressive fluid resuscitation or earlier start of cardiovascular drug therapy. Our findings suggest improvements in other supportive treatments over time.

Abbreviations

PICU	paediatric intensive care unit
PIM	paediatric index of mortality

Introduction

Meningococcaemia is characterised by an abrupt onset of fever and petechial or purpuric rash, which can rapidly progress to refractory septic shock and may cause death within hours after initial presentation [1]. Despite advances in medical care, case fatality rates from meningococcal septic shock have remained fairly stable at around 20-40% for many years [2, 3]. Only in the last decade, a reduction in mortality has been reported [4, 5]. This was mainly attributed to a raised awareness for the disease, and to better medical training, leading to earlier recognition and more appropriate initial treatment [6-9].
Thus far, only few studies investigated the specific influence of intensive care treatment on outcome of children with severe meningococcal disease. Three studies showed that paediatric intensive care unit (PICU) mortality rates have decreased over time, while disease severity had remained unchanged or even increased [4, 5, 10]. This reflects that overall intensive care performance improved, but it gives no insight which factors specifically contributed to this improvement. To further explore effects of early treatment on survival, we reviewed clinical data of patients with meningococcal disease admitted to our PICU over a 13 years' period, and performed a logistic regression analysis on these data. Our main focus was on the early treatment of shock, being the most prominent feature of severe meningococcal disease, and taken the recently emphasised importance of early and aggressive haemodynamic support in children presenting with shock [11-13].

Methods

This study was performed at the PICU of the Wilhelmina Children's Hospital, the Netherlands. It is a tertiary, multidisciplinary, 14-beds unit with approximately 600 admissions each year.
Eligible patients were identified from the PICU admission records. All children admitted for meningococcal disease between January 1991 and January 2004 were included. Data from included patients were retrieved from written and computerised medical charts, and included demographic information, the Paediatric Index of Mortality version 2 (PIM2) score [14], amount of fluids administered during the first six hours of admission to the PICU, type of cardiovascular drug therapy used, time interval between admission to the PICU and start of cardiovascular drug therapy, length of stay in the PICU and outcome (survival or death) at discharge from the PICU.
Meningococcal disease was confirmed by isolation of Neisseria meningitidis from blood or cerebral spinal fluid. Patients, whose cultures were negative, but who had characteristic clinical signs of meningococcal disease (features of infection with

characteristic meningococcal petechiae or purpura) were included, if no alternative organism for the illness was identified.
Primary endpoint of the study was outcome (survival or death) at discharge from the PICU. The hospital's Ethical Committee waived informed consent.

Statistical analysis
The association between treatment strategies and PICU survival was quantified using univariable logistic regression analysis. This was followed by stepwise multiple logistic regression analysis to identify those factors independently associated with PICU survival. The Kruskal-Wallis test has been used to compare clinical data between survivors and non-survivors. Raw PIM2 scores between survivors and non-survivors were compared using independent sample t-test. A *p*-value of less than 0.05 was considered to indicate statistical significance. Data were analyzed using SAS (SAS 9.1.3. Service Pack 2, SAS Institute Inc., Cary, NC, USA).

Results

From January 1991 until January 2004, 239 patients with meningococcal disease were admitted to the PICU. Their median age at admission was 3.4 years (range 2 months - 17.2 years). The male-to-female ratio was 1.3. Thirty-seven patients died, resulting in a case-fatality rate of 15.5%. Characteristics of all included patients are shown in Table 1. In this Table a statistical comparison is made between survivors and non-survivors.

During the study, actual mortality did not decrease significantly (p=0.10). In the same time period, the predicted risk of mortality (based on PIM2 scores) increased (p=0.01), indicating that more severely ill patients were admitted (Figure 1). Over the years, more fluid was administered in the first six hours after admission to the PICU (each year 3.7 millilitres per kilo more, p=0.0004). Dopamine (each year 0.06 hours earlier, p=0.02) and dobutamine (each year 0.12 hours earlier, p<0.001) were started earlier after PICU admission. Fluid resuscitation in the first hour after admission (each year 0.7 millilitres per kilo more, p=0.06) and the start of norepinephrine (each year 0.03 hours earlier, p=0.34) did not change significantly over time. Use of corticosteroids within the first 6 hours decreased over time (in 0.013 patients per year, p=0.001).

When corrected for severity of disease, mortality significantly decreased during the study (odds ratio 0.80 per year, 95% confidence interval 0.70-0.91; p<0.001). When year of admission, PIM2 score, start of dopamine, start of dobutamine, start of

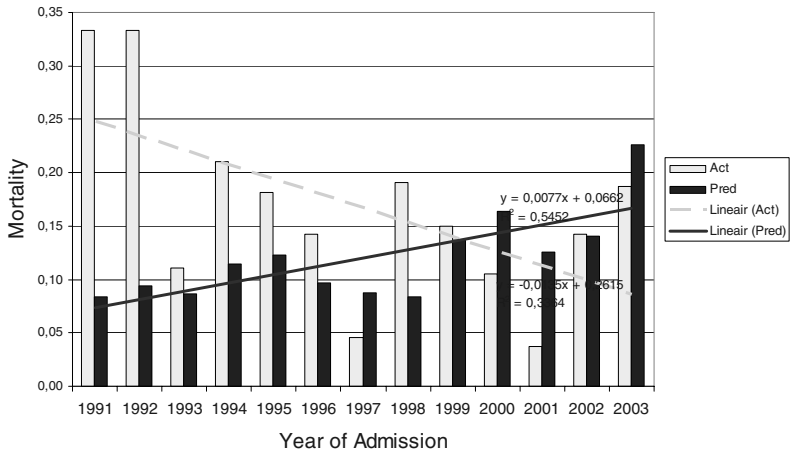
norepinephrine, fluid resuscitation and whether or not corticosteroids were given within the first 6 hours, were entered simultaneously into a logistic regression, only year of inclusion remained strongly associated with mortality (odds ratio 0.60 per year, 95% confidence interval 0.47-0.76; p=0.002). There was no independent effect of fluid resuscitation (p=0.50), start of dopamine (p=0.55), start of dobutamine (p=0.17), start of norepinephrine (p=0.48) and use of corticosteroids (p=0.98) on standardised mortality. This indicates that the decrease in corrected mortality could not be explained by changes in these initial treatment modalities.

Table 1
Demographic and clinical characteristics of 239 children admitted to the paediatric intensive care unit with severe meningococcal disease; comparison between surivors and non-survivors

	non-survivors (n = 37)	**survivors** (n = 202)	**overall** (n = 239)	***p*-value**
actual mortality rate	0%	100%	15.5%	
predicted mortality rate (PIM2)	36.2%	7.8%	12.2%	<0.001
male-to-female ratio	2.0	1.1	1.3	0.14
age (years)	2.4 (0.4 - 13.6)	3.7 (0.1 - 17.2)	3.4 (0.1 - 17.2)	0.54
base excess (miliMol/Liter)	-12 (-34 to -1)	-6.3 (-18 to 1.8)	-6.9 (-34 to 1.8)	0.03
amounts of fluids in first 6 hours of PICU stay (mililitre/kg)	75 (0 to 192)	42 (0 to 367)	47 (0 to 367)	<0.001
length of stay in PICU (days)	1 (1 to 45)	6 (1 to 169)	5 (1 to 169)	<0.001

PIM2, Paediatric index of Mortality version 2 score [14]; PICU, paediatric intensive care unit
Data are expressed as percentage or median (range).

Figure 1
Predicted (based on PIM2 score [14]) and actual mortality rates of 239 consecutive children with severe meningococcal disease admitted to the paediatric intensive care unit between 1991 and 2004



act, actual mortality rate; pred, predicted mortality rate.

Discussion

The primary goal of the present study was to assess the effect of initial treatment of shock on mortality of children with severe meningococcal disease. Over the years, mortality corrected for severity of disease decreased significantly. Over the same period, more fluids were administered and dopamine and dobutamine were started earlier in the course of the disease. Corticosteroids were given less frequently within the first 6 hours. However, this could not explain the reduction in standardised mortality.

Generous fluid resuscitation and early of start of cardiovascular drug therapy is nowadays generally accepted best practice in the treatment of severe septic shock [11-13, 15]. It has been reported that in current practice, children with septic shock are systematically under-resuscitated in the first hours [15] and an even more aggressive approach would be beneficial [11, 16]. These views are by no means disputed by the results of the present study; with our study we did not assess the optimal treatment of septic shock, or compare different treatment strategies. On the other hand, our data revealed no indications that more aggressive fluid resuscitation or earlier start of cardiovascular drug therapy could explain the apparent improvement of survival corrected for PIM2 score, neither when variables were tested simultaneously, nor independently. There may be several explanations for these findings. The first could be that a priori outcome on admission to PICU has

improved over time, which is not covered by PIM2 predicted mortality. This is unlikely, since PIM2 scores have been validated in a large cohort of critically ill children from several PICUs, and it has been recalibrated recently [14]. The PIM2 score has been shown to have a good predictive value [17], also in children with meningococcal disease [18]. The improvement in survival could also be explained by other advancements in critical care treatment over time. The most striking changes over time are earlier intubation in patients with severe sepsis [6] and the implementation of lung protective ventilation strategies. The retrospective design of the present study hampered accurate retrieval of time of intubation, delivered tidal volumes and levels of positive end-expiratory pressure in all patients. Their influence on survival could therefore not be assessed in this study. With our findings in mind, these items deserve attention in future studies.

A comparison between PICUs in management and outcome of severe meningococcal disease is difficult and prone to confounding. The case fatality rate (15.5%) in our study is identical to others [10, 19], but it is higher than two PICUs in the United Kingdom (8.9% and 10% [4, 5]). It can therefore not be excluded that treatment of shock in our PICU can be further improved by an even more aggressive approach [15]. On the other hand, our patients received more fluids than patients in a recent study, whose therapy was based on central venous oxygen saturation measurements [11], which is hypothesised to result in 'therapeutic hypervolaemia' [16].

A number of scoring systems have been developed to identify the degree of severity of meningococcal disease [20]. We used the PIM2 score, since it is the most commonly used scoring system that requires variables which are collected in the first hour as part of routine clinical care. The PIM2 score has been shown to discriminate well between survivors and non-survivors in patients with meningococcal disease [18]. PIM2 score has been recalibrated recently and may therefore underestimate mortality in the first years of our study. However, the consistent use of this scoring system throughout the study period does allow an analysis of trends in disease severity and standardised mortality rates.

In conclusion, we found that, over the years, children with meningococcal disease were more severely ill on admission to the PICU. Mortality corrected for severity of disease decreased in the same time period. This could not be explained by more aggressive fluid resuscitation or earlier start of cardiovascular drug therapy and could point to improvement of other supportive treatments over time. Early start of mechanical ventilation or improved ventilatory strategies may be important contributing factors.

References

1 Hazelzet JA. Diagnosing meningococcemia as a cause of sepsis. *Pediatr Crit Care Med* 2005; 6: S50-S54

2 Havens PL, Garland JS, Brook MM, et al. Trends in mortality in children hospitalized with meningococcal infections, 1957 to 1987. *Pediatr Infect Dis J* 1989; 8: 8-11

3 Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. *N Engl J Med* 2001; 344: 1378-1388

4 Booy R, Habibi P, Nadel S, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001; 85: 386-390

5 Thorburn K, Baines P, Thomson A, Hart CA. Mortality in severe meningococcal disease. *Arch Dis Child* 2001; 85: 382-385

6 Pollard AJ, Britto J, Nadel S, et al. Emergency management of meningococcal disease. *Arch Dis Child* 1999: 80: 290-296

7 Pollard AJ, Nadel S, Ninis N, et al. Emergency management of meningococcal disease: eight years on. *Arch Dis Child* 2007; 92: 283-286

8 Nadel S, Britto J, Booy R, et al. Avoidable deficiencies in the delivery of health care to children with meningococcal disease. *J Accid Emerg Med* 1998; 15: 298-303

9 Ninis N, Phillips C, Bailey L, et al. The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. *BMJ* 2005; 330: 1475

10 Maat M, Buysse CM, Emonts M, et al. Improved survival of children with sepsis and purpura: effects of age, gender, and era. *Crit Care* 2007; 11: R112

11 de Oliveira CF, de Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008; 34: 1065-1075

12 Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37: 666-688

13 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296-327

14 Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med* 2003; 29: 278-285

15 Inwald DP, Tasker RC, Peters MJ, Nadel S. Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. *Arch Dis Child* 2009; 94: 348-353
16 Peters MJ, Brierley J. Back to basics in septic shock. *Intensive Care Med* 2008; 34: 991-993
17 Slater A, Shann F. The suitability of the Pediatric Index of Mortality (PIM), PIM2, the Pediatric Risk of Mortality (PRISM), and PRISM III for monitoring the quality of pediatric intensive care in Australia and New Zealand. *Pediatr Crit Care Med* 2004; 5: 447-454
18 Festa MS, Tibby SM, Taylor D, et al. Early application of generic mortality risk scores in presumed meningococcal disease. *Pediatr Crit Care Med* 2005; 6: 9-13
19 Peters MJ, Ross-Russell RI, White D, et al. Early severe neutropenia and thrombocytopenia identifies the highest risk cases of severe meningococcal disease. *Pediatr Crit Care Med* 2001; 2: 225-231
20 Leteurtre S, Leclerc F, Martinot A, et al. Can generic scores (Pediatric Risk of Mortality and Pediatric Index of Mortality) replace specific scores in predicting the outcome of presumed meningococcal septic shock in children? *Crit Care Med* 2001; 29: 1239-1246

Chapter 7

PROPOFOL AND THIOPENTAL FOR REFRACTORY STATUS EPILEPTICUS IN CHILDREN

Neurology 2005; 65: 591-592

JPJ van Gestel
HJ Blussé van Oud-Alblas
M Malingré
FFT Ververs
KPJ Braun
O van Nieuwenhuizen

Abstract

To assess safety and efficacy of propofol and thiopental for refractory status epilepticus (RSE) in children, we reviewed 34 episodes of RSE. Thiopental was effective in most patients, but there were serious side-effects. Propofol was used according to a strict protocol. It was effective in most patients, so that thiopental was not needed. Side-effects were infrequent, of minor severity and fully reversible. We suggest the use of propofol before thiopental.

Abbreviations

RSE	refractory status epilepticus
ICU	intensive care unit
CSE	continuing status epilepticus
DSF	decrease of seizure frequency
SF	seizure free
D	death
PD	progressive deterioration
RTB	returned to baseline
ADEM	acute disseminated encephalomyelitis
ND	seizure control could not be determined

Introduction

Thiopental is commonly used as a last treatment in refractory status epilepticus (RSE) [1]. Side-effects of thiopental are well described, but little is known about their frequency and impact on clinical practice. Because of the adverse effects of thiopental, several guidelines recommend propofol as an alternative therapy before thiopental. However, propofol is associated with potentially fatal outcome [2, 3], and its efficacy in the treatment of RSE is mainly based on case reports and small case series.
To assess safety and efficacy of propofol and thiopental in the treatment of RSE in children, we reviewed all patients treated with these drugs in our department.

Methods

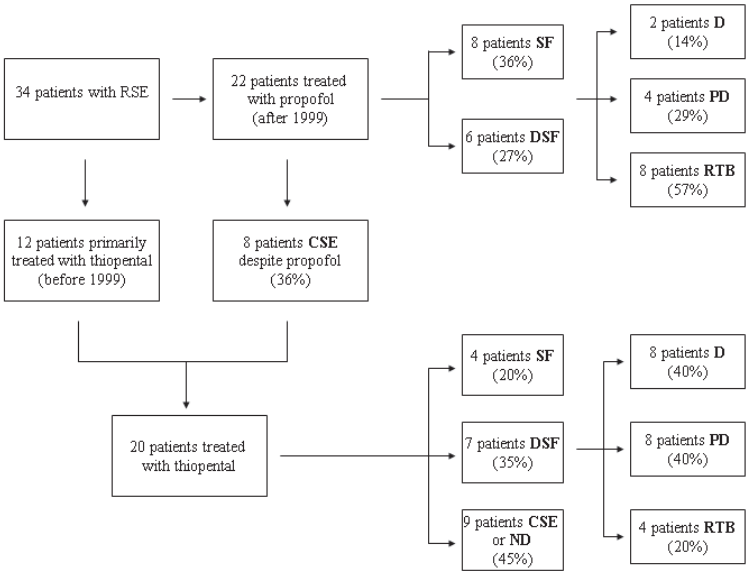
Between January 1993 and 2004, 33 patients were treated for 34 episodes of RSE in the intensive care unit (ICU) of the Wilhelmina Children's Hospital, the Netherlands. Patient 12 was admitted twice; during his first admission RSE was terminated with propofol. During the second admission, 5 months later, thiopental was necessary.
RSE was defined as continuous seizure activity clinically and on the EEG, which failed to respond to phenytoin and high doses of midazolam (0.5 – 1.0 mg/kg/h), and persisted for more than 60 minutes. RSE was generalized or multifocal in 29 patients and focal in 5. Focal RSE had persisted for several days before propofol or thiopental was started and was accompanied by serious discomfort.
Before 1999, patients with RSE were primarily treated with thiopental. After 1999, propofol was administered systematically to all children before thiopental was started, reserving thiopental for those who suffered from side-effects of propofol or did not respond to it.
When propofol was used, a bolus of 1-2 mg/kg was given, followed by continuous infusion of 1-2 mg/kg/h. If necessary, maintenance infusion was increased to a maximum of 5 mg/kg/h. Side-effects were regularly monitored, and infusion was stopped if side-effects emerged. Goal of treatment with propofol was disappearance of clinical seizures and epileptic activity on the EEG.
Thiopental was started according to a dosing scheme made by the pharmacy department, based on pharmacokinetic data of previously treated patients. A loading dose was given, aiming at a blood level of 20 mg/ml after 6 hours. This was followed by continuous infusion, which was adjusted when necessary according to the EEG. The goal of treatment with thiopental was complete control of seizures with a burst suppression pattern on the EEG.

In patients treated with propofol, special attention was paid to blood levels of lactate, triglycerides, creatine kinase, and blood gas analyses. In patients treated with thiopental, special attention was paid to respiratory, circulatory and infectious complications.
Short-term seizure control was assessed at discharge from the ICU and classified as complete seizure freedom (SF), decrease of seizure frequency (DSF) or continuing status epilepticus (CSE). At discharge from hospital, short-term neurological outcome was assessed and classified as returned to baseline (RTB), progressive deterioration (PD), or death (D) [4].

Results

Effects of propofol and thiopental on seizure activity and short-term neurological outcome are summarized in Figure 1. Tables E-1 and E-2 contain clinical characteristics of included patients.

Figure 1
Effects of propofol and thiopental on seizure activity and neurological outcome



Seizure control assessed at discharge from the ICU: SF, seizure free; DSF, decrease of seizure frequency; CSE, continuing status epilepticus; ND, seizure control could not be determined because of progressive cerebral herniation or death during thiopental treatment.
Neurological outcome assessed at discharge from hospital: RTB, returned to baseline; PD, progressive deterioration; D, death.

Propofol

Propofol was used in 22 episodes of RSE. All children had a convulsive status epilepticus. Mean duration of treatment with propofol was 57 hours (range 10 – 264 hours). Propofol had to be stopped on 4 occasions (18%) because of side-effects: 1 patient suffered from rhabdomyolysis (patient 8) and 3 patients developed hypertriglyceridaemia (patients 1, 16, 17). The elevation of triglycerides and creatine kinase normalized quickly after propofol was stopped. In patients 16 and 17, RSE was not terminated when propofol was stopped because of side-effects. Both patients were treated with thiopental afterwards.

In 14 of the 22 episodes treated with propofol (64%), RSE could be adequately controlled. Two patients who were successfully treated with propofol died. Their death was attributed to severe neurological damage after bacterial meningitis, and not related to the use of propofol.

Thiopental

Twenty patients were treated with thiopental. Nineteen had a convulsive status epilepticus. One child (patient 27) received muscle relaxants, when an EEG showed status epilepticus. Clinical signs of convulsions could obviously not be assessed. Mean duration of thiopental infusion was 8.6 days (range 2 - 33 days).

Seizure control with thiopental was achieved in 11 out of 20 children (55%). In 6 of the children who died, death was related to the underlying disorder and could not be avoided despite treatment. In 2 patients, thiopental probably contributed to their deaths: patient 21 died of acute hepatic failure induced by thiopental, patient 32 died of progressive pulmonary damage during thiopental infusion.

All children required extra fluids and inotropes. With these measures, circulation was adequate in all but 1 child (patient 20). She developed multiple organ dysfunction syndrome with acute tubular necrosis, for which peritoneal dialysis was necessary. After thiopental was stopped, she had complete recovery of organ functions.

All children required mechanical ventilation. Fifteen children (75%) developed infiltrates on their chest X-rays, and required higher airway pressures and supplemental oxygen during thiopental infusion. Eleven patients (55%) developed pleural effusions. Patient 32 died due to progressive pulmonary abnormalities, while all other children had a complete recovery of their respiratory status.

Eighteen children (90%) were treated with antibiotics during thiopental coma, mostly because of fever and suspected pneumonia. Sputum cultures, however, were positive in only 33% of patients. Three children had a sepsis from their central lines during ICU admission.

Discussion

We found that propofol is a safe, effective drug in the treatment of paediatric RSE. With propofol, treatment with thiopental could be prevented in a considerable subgroup of patients.

Our study is the first that assesses safety and efficacy of propofol and thiopental in the treatment of RSE in children. Compared to other studies, the number of patients included is relatively high. However, it is a retrospective study and randomization between the 2 treatment strategies did not take place: patients were either treated with thiopental (before 1999) or with propofol followed by thiopental when necessary (after 1999). With this study it is therefore not possible to compare safety and efficacy of propofol and thiopental.

There are several advantages in using propofol: effective seizure suppression can be achieved in most patients [5, 6]. Since it is a very fast acting drug, quicker seizure control can be obtained with propofol than with thiopental [5]. Even if propofol fails to terminate RSE, little time is lost.

The main concern with respect to propofol is in its potentially fatal side-effects [2, 3]. However, several studies reported that it is safe to use propofol, if the maximum dose during prolonged infusion does not exceed 5 mg/kg/h [7, 8] and if infusion is stopped when side-effects emerge. Studies that compared propofol versus barbiturates [5] or midazolam [6] found a higher mortality rate in patients treated with propofol, but dosages in those studies were far above 5 mg/kg/h. Only the minority of our patients suffered from side-effects, which were of limited severity and fully reversible. Mortality rate in children treated with propofol was low, supporting the conclusion that it is safe to use propofol under the aforementioned restrictions.

The findings in our patients confirm, that haemodynamic problems during thiopental infusion can be adequately managed [9, 10]. The influence of thiopental on the respiratory tract was larger than expected. Most patients suffered from suspected pneumonia, while other infections were not often encountered.

We recommend that before thiopental is started in children with RSE, treatment with propofol should be considered, with a dosage up to 5 mg/kg/h, under strict observation of potential side-effects.

References

1 Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002; 43: 146-153

2 Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology* 1998; 50: 301-303

3 Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992; 305: 613-616

4 Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. *Epilepsia* 2001; 42: 1461-1467

5 Stecker MM, Kramer TH, Raps EC, et al. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; 39: 18-26

6 Prasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of refractory status epilepticus. *Epilepsia* 2001; 42: 380-386

7 Cremer OL, Moons KG, Bouman EA, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357: 117-118

8 Cornfield DN, Tegtmeyer K, Nelson MD, et al. Continuous propofol infusion in 142 critically ill children. *Pediatrics* 2002; 110: 1177-1181

9 Schalen W, Messeter K, Nordstrom CH. Complications and side effects during thiopentone therapy in patients with severe head injuries. *Acta Anaesthesiol Scand* 1992; 36: 369-377

10 Parviainen I, Uusaro A, Kalviainen R, et al. High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. *Neurology* 2002; 59: 1249-1251

Table E-1
Characteristics of children treated with propofol for refractory status epilepticus

pat	age	sex	aetiology	seizure control	neurol. outcome	duration of infusion
A. RSE successfully treated with propofol						
1	4 mo	M	pneumococcal meningitis	SF	D	17h
2	4 mo	M	post hypoxic ischaemic encephalopathy	DSF	PD	18h
3	5 mo	F	post hypoxic ischaemic encephalopathy	SF	RTB	45h
4	6 mo	F	pneumococcal meningitis	SF	D	25h
5	6 mo	F	complex 1 deficiency	DSF	PD	240h
6	9 mo	F	cortical dysplasia	SF	RTB	66h
7	17 mo	F	post hypoxic ischemic encephalopathy	SF	PD	49h
8	21 mo	F	pneumococcal meningitis	SF	PD	39h
9	22 mo	F	symptomatic generalized epilepsy	DSF	RTB	23h
10	2 y	F	symptomatic generalized epilepsy	DSF	RTB	67h
11	7 y	M	idiopathic generalized epilepsy	SF	RTB	21h
12	12 y	F	idiopathic generalized epilepsy	SF	RTB	122h
13	12 y	M	Sturge Weber syndrome	DSF	RTB	264h
14	15 y	M	frontal cysts	DSF	RTB	69h
B. persistent RSE despite propofol, requiring thiopental (see table 2)						
13*	13 y	M	Sturge Weber syndrome	CSE	See table 2	24h
15	11 mo	M	ADEM	CSE	See table 2	37h
16	15 mo	M	suspected mitochondrial disorder	CSE	See table 2	23h
17	17 mo	M	complex I deficiency	CSE	See table 2	28h
18	2 y	M	prolonged hypoglycaemia, glycerol kinase deficiency	CSE	See table 2	10h
19	3 y	F	progressive myoclonic epilepsy	CSE	See table 2	18h
20	4 y	F	idiopathic focal epilepsy	CSE	See table 2	32h
21	11 y	M	mitochondrial Alpers-Huttenlocher disease	CSE	See table 2	18h

SF, seizure free; DSF, decrease of seizure frequency; CSE, continuing status epilepticus; RTB, returned to baseline; PD, progressive deterioration; D, death; y, year; mo, month; F, female; M, male, h, hour; ADEM, acute disseminating encephalomyelitis.
Seizure control assessed at discharge from ICU, neurological outcome assessed at discharge from hospital.
* previous episode was successfully treated with propofol, second episode required thiopental.

Table E-2
Characteristics of children treated with thiopental for refractory status epilepticus

pat	age	sex	aetiology	seizure control	neurol. outcome	number of courses
A. prior unsuccessful treatment with propofol						
13*	13 y	M	Sturge Weber syndrome	CSE	D	2
15	11 mo	M	ADEM	DSF	PD	1
16	15 mo	M	suspected mitochondrial disorder	SF	RTB	1
17	17 mo	M	complex I deficiency	DSF	PD	1
18	2 y	M	prolonged hypoglycaemia, glycerol kinase deficiency	ND[1]	D	1
19	4 y	F	idiopathic focal epilepsy	SF	PD	2
20	3 y	F	progressive myoclonic epilepsy	SF	RTB	2
21	11 y	M	mitochondrial Alpers-Huttenlocher disease	DSF	D	1
B. primarily treated with thiopental						
22	20 mo	M	post hypoxic ischaemic encephalopathy	ND[2]	D	1
23	23 mo	F	mitochondrial disorder	CSE	D	1
24	2 y	F	suspected mitochondrial disorder	CSE	D	2
25	6 y	M	encephalitis	DSF	PD	2
26	6 y	F	Sturge Weber syndrome	SF	RTB	1
27	8 y	M	Lennox-Gastaut in down syndrome	DSF	PD	2
28	11 y	M	encephalitis	DSF	PD	2
29	11 y	F	Rasmussen's encephalitis	CSE-N	PD	1
30	12 y	F	progressive multifocal leuko-encephalopathy	CSE	D	1
31	12 y	M	Rasmussen's encephalitis	CSE-N	RTB	1
32	13 y	M	Rasmussen's encephalitis	ND[2]	D	1
33	14 y	F	MELAS syndrome	DSF	PD	1

SF, seizure free; DSF, decrease of seizure frequency; CSE, continuing status epilepticus; CSE-N, continuing or recurrent status epilepticus requiring neurosurgery; ND, seizure control could not be determined due to [1] = progressive cerebral herniation; [2] = died during thiopental treatment; RTB, returned to baseline; PD, progressive deterioration; D, death; y, year; mo, month; F, female; M, male; ADEM, acute disseminating encephalomyelitis; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.
Seizure control assessed at discharge from ICU, neurological outcome assessed at discharge from hospital.
* previous episode was successfully treated with propofol, second episode required thiopental.

Chapter 8

SUMMARY AND GENERAL DISCUSSION

Medical care in general and paediatric critical care specifically have greatly advanced over the years. This has resulted in a steady decrease in mortality over time for a large number of diseases that are regularly encountered in paediatric intensive care. However, there still are a considerable number of diseases for which outcome is uncertain. Being informed about results of intensive care treatment is of vital importance, since it is expensive and associated with considerable burden for patients and their relatives. It is undesirable to expose a patient to a costly and burdensome therapy, when it is unlikely to be of any benefit. On the other hand it is difficult to refrain from intensive care, when survivors have a long life ahead, even if the chances to survive are slim. The lack of knowledge about results of intensive care typically applies to rarely occurring diseases, to diseases for which outcome traditionally was considered to be unfavourable or to diseases for which novel therapies have emerged. Especially for these disease categories, a regular (re-)examination of outcome of critical care is therefore needed. The studies described in this thesis assessed epidemiological characteristics, clinical course and intensive care unit mortality rates of conditions belonging to these disease categories.

Respiratory failure is the leading cause of death among patients with cystic fibrosis (CF). The use of mechanical ventilation in the treatment of acute respiratory failure in CF patients has long been discouraged because of very poor outcome [1]. In **chapter 2** we show that adult CF patients who require mechanical ventilation for acute respiratory failure still have high mortality rates. Acute on chronic respiratory failure is a significant risk factor associated with poor outcome. None of the children requiring mechanical ventilation for acute respiratory failure in this study died. Although their number was small, long-term outcome of these children was similar to that of non-ventilated CF control patients matched for gender, age and genotype.

Haematopoietic stem cell transplantation (HSCT) has revolutionized outcome of a wide variety of diseases which previously had little hope for cure. Nevertheless, it remains a high risk procedure and a considerable number of patients require transfer to the intensive care unit because of complications related to the transplantation. In the first reports, about 90% of children requiring intensive care after HSCT died [2, 3]. In **chapter 3** it was shown that literature suggests a clear increase in survival over the years for these children. However, this increase in survival was accompanied by a decrease in the proportion of patients requiring mechanical ventilation after their transfer to the intensive care unit. In the group of ventilated post-HSCT patients, an appreciable improvement of survival could not be proven. Current outcome data in this group of patients, however, were scarce. We therefore assessed outcome in a recent cohort of mechanically ventilated children after HSCT from our own department **(chapter 4).** We found an improvement of intensive care survival and in survival six months after discharge from intensive care. Multiple

organ failure and the use of high frequency ventilation were predictors of poor outcome in our patients.

Children with severe developmental delay often have respiratory problems. In order to make a rational decision about intensive care treatment for these children, knowledge of its benefits and harms is required. It is assumed by many clinicians that mechanical ventilation in children with severe neurological impairment who present with respiratory failure is futile medical treatment, but there are no published reports to confirm this. In **chapter 5** we show that in our department, these children often had prolonged and complicated admission to the intensive care unit. However, 50% of them were still alive one year after discharge from intensive care. This underscores the urgent need for further research to help those involved in making a well-informed decision about therapeutic options when a patient with severe developmental delay develops respiratory failure.

Despite advances in medical care, case fatality rates from meningococcal septic shock have remained fairly stable at around 20-40% for many years [4-6]. Only in the last decade, a reduction in mortality has been reported [7-9]. To assess survival trends in our department, we reviewed the outcome of 239 consecutive patients with meningococcal disease (**chapter 6**). Over time, children were more severely ill on admission. Mortality corrected for severity of disease decreased in the same time period. More fluids were administered in the first hours of admission, and dopamine and dobutamine were started earlier in the course of the disease, following the generally accepted guidelines in treatment of shock. The improvement in survival could however not be explained by this more aggressive resuscitation.

In **chapter 7** we describe the clinical course and outcome of children treated with propofol or thiopental for refractory status epilepticus (RSE). Previous studies in children with RSE reported high morbidity and mortality rates [10-12]. Most intensive care units use thiopental as a last treatment in RSE [13, 14]. It is an effective treatment, but the possible side-effects are impressive. Because of the side-effects of thiopental, some authors recommend propofol as an alternative therapy [15]. Its rapid onset and short duration of action are advantageous in the treatment of RSE, but it has been associated with a combination of potentially fatal adverse effects [16]. Moreover, the efficacy of propofol in the treatment of RSE is almost exclusively based on case reports and very small case series.
In our department, patients with RSE were traditionally treated with thiopental. Since 1999, propofol is administered systematically to all children with RSE before thiopental is started. Thiopental is thus reserved for those children who suffer from side-effects of propofol or who do not respond to propofol treatment. Short-term neurological outcome of all children with RSE in our study showed deterioration in

roughly one third of patients, one third had a return to their baseline situation and one third died. Both propofol and thiopental were effective in terminating RSE. When correctly used, propofol resulted in few side-effects. Complications were frequently encountered during treatment with thiopental, some of which were potentially life-threatening. Together with its favourable pharmacological properties, we therefore suggest to consider propofol before thiopental in the treatment of RSE in children.

For many centuries, innovations have been the driving force in the advancement of medical knowledge. Nowadays, we look less to innovations to solve clinical problems, and more to science to provide evidence for clinical decision making. In classic evidence-based medicine teaching, there is a hierarchy in grading the quality of research studies. On top of strength for evidence are the randomised controlled trials. They can give a good estimate of treatment effect and are thus applied to assess statistically the degree to which the effect of a studied treatment compares with standard treatment. In other words: randomised trials are important to bring a final evaluation of medical interventions, but in themselves they offer little scientific novelty. Case reports and case series provide weaker strength of evidence, but they are equally important in the progress of medical science. Casual clinical observations strike when they are unexpected. They will therefore challenge previously held beliefs and will lead to new ideas and theories. With their high sensitivity for detecting novelty, case reports and case series remain one of the cornerstones of medical progress [17].
Most studies in this thesis describe the clinical course and outcome of series of patients with rarely occurring diseases, or conditions for which survival traditionally has been shown to be very poor. For children with RSE, children requiring mechanical ventilation after HSCT and severely retarded patients with respiratory failure, our studies show that survival nowadays is better than expected. That finding in itself is highly relevant, and it justifies the initiation of intensive care treatment in the aforementioned patient groups.

However, a little caution is warranted.
Firstly, when a treatment is found to be beneficial, there is always the risk of a "random high": the studied treatment is truly beneficial, but chance added an extra benefit in this particular study, and the magnitude of its effect is then overestimated. This may partly explain why literature is often somewhat optimistic [18].
Secondly, most studies in this thesis were single-centre and performed only in the paediatric intensive care unit of the University Medical Center Utrecht. The advantage of such a study is that retrieval of clinical data occurs in a consistent way and therefore may be of superior quality. A disadvantage of single-centre studies, however, is that they often are underpowered due to small population sizes.

Additionally, results from single-centre studies with their specific case-mix of patients may not be necessarily applicable in other centres. This is especially important when populations are highly heterogeneous, which applies to children with RSE, children with severe mental retardation and children after haematopoietic stem cell transplantation. Outcome studies in this last category of patients are additionally hampered by the very rapid evolution in transplantation medicine: indications for transplantation keep expanding, knowledge about potential complications is rapidly growing, and therapeutic possibilities to treat these complications are continuously increasing. As a result, case series of children requiring mechanical ventilation after HSCT are nearly outdated once they are published. To overcome this problem, continuous monitoring of outcome of intensive care treatment is required, for example through a central registry or database. Both the association for blood and marrow transplantation in the United States (American Society of Blood and Marrow Transplantation, ASBMT) and its counterpart in Europe (European Group for Blood and Marrow Transplantation, EBMT) have such a database, which contains transplantation details from all accredited HSCT centres. Centres have to report in order to get their accreditation, which offers some guarantee that it is done concisely. However, intensive care treatment details, or even admissions to the intensive care unit are not yet reported in the ASBMT or EBMT registry. Considering their specificity, which falls outside the specific expertise of haematologists/immunologists, it can be questioned if critical care treatment details should become part of these registries. To make such a database part of a general critical care registry has the disadvantage that most paediatric intensive care units do not treat children post-HSCT on a regular basis. In the Netherlands, the number of children admitted to intensive care after HSCT is too small to use the Dutch paediatric intensive care registry (Paediatric Intensive Care Evaluation, PICE) to assess survival trends. Moreover, PICE contains too few critical care treatment details to assess their influence on survival. Apart from the discussion where such a registry should be placed, there are other difficulties to overcome. Reporting data to a central registry is an enormous amount of extra work requiring specific measures to ensure ongoing reporting in a consistent, accurate, complete and timely way [19-22]. Reporting data to a registry requires patients to give their consent, when these data are used for purposes not directly related to treatment. Merely the process of obtaining consent has shown to be labour intensive and unlikely to be successful without additional resources and support [23]. As a potential promising alternative, we are currently setting up a prospective database containing critical care treatment details of children after HSCT with a small group of dedicated European paediatric intensive care units.

Conclusions

Diseases described in this thesis are relatively rare and often highly heterogeneous, which limits the possibility for large scale interventional studies and the determination of potential predictors of outcome. Traditionally, these diseases were considered to have an unfavourable outcome, but improvements in medical care have resulted in increased survival. A well-designed prospective database is required to continuously monitor outcome and assess factors affecting the clinical course in these complex groups of patients.

References

1 Davis PB, di Sant'Agnese PA. Assisted ventilation for patients with cystic fibrosis. *JAMA* 1978; 239: 1851-1854

2 Todd K, Wiley F, Landaw E, et al. Survival outcome among 54 intubated pediatric bone marrow transplant patients. *Crit Care Med* 1994; 22: 171-176

3 Nichols DG, Walker LK, Wingard JR, et al. Predictors of acute respiratory failure after bone marrow transplantation in children. *Crit Care Med* 1994; 22: 1485-1491

4 Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J* 1996; 15: 967-978

5 Havens PL, Garland JS, Brook MM, et al. Trends in mortality in children hospitalized with meningococcal infections, 1957 to 1987. *Pediatr Infect Dis J* 1989; 8: 8-11

6 Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. *N Engl J Med* 2001; 344: 1378-1388

7 Booy R, Habibi P, Nadel S, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001; 85: 386-390

8 Thorburn K, Baines P, Thomson A, Hart CA. Mortality in severe meningococcal disease. *Arch Dis Child* 2001; 85: 382-385

9 Maat M, Buysse CM, Emonts M, et al. Improved survival of children with sepsis and purpura: effects of age, gender, and era. *Crit Care* 2007; 11: R112

10 Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. *J Child Neurol* 2002; 17: 106-110

11 Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. *Epilepsia* 2001; 42: 1461-1467

12 Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. *J Child Neurol* 1999; 14: 602-609

13 Holtkamp M, Masuhr F, Harms L, et al. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. *J Neurol Neurosurg Psychiatry* 2003; 74: 1095-1099

14 Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002; 43: 146-153

15 Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother* 1998; 32: 1053-1059

16 Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia* 2007; 62: 690-701
17 Vandenbroucke JP. In defense of case reports and case series. *Ann Intern Med* 2001; 134: 330-334
18 Vandenbroucke JP. Case reports in an evidence-based world. *J R Soc Med* 1999; 92: 159-163
19 Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer* 2009; 45: 747-755
20 Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. *Eur J Cancer* 2009; 45: 756-764
21 Van Keulen JG, Gemke RJ, Polderman KH. Effect of training and strict guidelines on the reliability of risk adjustment systems in paediatric intensive care. *Intensive Care Med* 2005; 31: 1229-1234
22 Van Keulen JG, Polderman KH, Gemke RJ. Reliability of PRISM and PIM scores in paediatric intensive care. *Arch Dis Child* 2005; 90: 211-214
23 McKinney PA, Jones S, Parslow R, et al. A feasibility study of signed consent for the collection of patient identifiable information for a national paediatric clinical audit database. *BMJ* 2005; 330: 877-879

Nederlandse samenvatting

De onderzoeken in dit proefschrift richten zich op de resultaten van behandeling op de kinderintensive care. Zij trachten een antwoord te vinden op de volgende vragen: [1] Hoe is het huidige klinische beloop en de overleving van ziektebeelden, waarvan in het verleden beschreven is dat de kans op een goede afloop minimaal is? en [2] Welke factoren kunnen mogelijk de uitkomst van behandeling van deze ziektebeelden voorspellen?

Hoofdstuk 1
Dit hoofdstuk biedt een algemene inleiding over de ontwikkelingen in de intensive care geneeskunde, en beschrijft het probleem van onzekerheid over de resultaten van behandeling op de intensive care.
De intensive care geneeskunde vindt zijn oorsprong in het midden van de vorige eeuw. Ten gevolge van een polio epidemie ontwikkelden veel mensen verlamming van hun ademhalingsspieren. Deze verlamming kon zodanig ernstig zijn, dat de ademhaling dramatisch tekort schoot en de patiënt kwam te overlijden. De ernst en omvang van deze polio epidemie vormde de aanleiding tot het oprichten van speciale beademingsafdelingen, waar patiënten kunstmatig beademd konden worden. Dankzij de kunstmatige beademing nam het aantal mensen dat de ziekte overleefde op indrukwekkende wijze toe. Deze verbetering in overleving gaf een sterke prikkel tot verdere ontwikkeling van de zorg voor ernstig zieke patiënten. Aanvankelijk richtte deze zorg zich puur op ondersteuning van de ademhaling, maar in de loop van de jaren groeide het uit tot de multidisciplinaire behandeling van vaak complexe medische en chirurgische aandoeningen. Het gemeenschappelijke kenmerk van patiënten die opgenomen worden op een intensive care afdeling is, dat zij een acute en levensbedreigende stoornis hebben in hun ademhaling, bloedsomloop en/of hersenfunctie, of een reële kans hebben op het krijgen van een stoornis in deze orgaansystemen.
In de loop van de jaren heeft de medische zorg grote vooruitgang geboekt. Deze vooruitgang geldt in het bijzonder voor de kinderintensive care. In een relatief korte tijd onderging de kinderintensive care een indrukwekkende vooruitgang in kennis, technische mogelijkheden, organisatie en opleiding. Deze vooruitgang heeft geleid tot een geleidelijke verbetering in de resultaten van de behandeling van vele ziektebeelden. Voor sommige aandoeningen is de uitkomst van intensive care behandeling echter nog steeds onzeker, terwijl het van groot belang is om te weten hoe deze resultaten zijn: het is letterlijk intensieve en zeer belastende behandeling voor patiënt en familie. Bovendien is intensive care duur. Het is onethisch om een patiënt bloot te stellen aan een belastende en dure behandeling, als deze behandeling geen schijn van kans heeft. Aan de andere kant is het moeilijk om af te zien van behandeling op een intensive care, als degenen die deze behandeling overleven nog

een lang leven voor zich hebben, ook al zijn de kansen op overleving gering. Onzekerheid over de uitkomsten van intensive care behandeling geldt in het bijzonder voor ziektebeelden die heel zeldzaam zijn, voor ziektebeelden waarvoor belangrijke nieuwe behandelmogelijkheden zijn gekomen en voor ziektebeelden waarvan in het verleden de kansen op overleving minimaal bleken te zijn. In het huidige proefschrift worden de resultaten van intensive care behandeling van enkele van deze ziektebeelden onder de loep genomen.

Hoofdstuk 2

Bij patiënten met de taaislijmziekte (cystic fibrosis, CF) raken de longen als gevolg van hun ziekte geleidelijk steeds meer beschadigd, wat uiteindelijk resulteert in het tekortschieten van de ademhaling. Patiënten met CF hebben dan ook een verkorte levensverwachting en overlijden vaak als gevolg van ademhalingsfalen. Kunstmatige beademing is voor deze patiënten lange tijd sterk afgeraden, omdat beademing een uitermate moeizame behandeling bleek, die bovendien gepaard ging met slechts een minimale overleving voor zowel kinderen als volwassenen.

In hoofdstuk 2 worden de resultaten beschreven van alle patiënten met CF die tussen 1990 en 2005 beademd zijn geweest in het Haga Ziekenhuis in Den Haag of in het UMC Utrecht vanwege een falende ademhaling. In totaal betrof het 31 patiënten (5 kinderen, 26 volwassenen). Alle 5 de kinderen overleefden de beademing. Hun longfunctie 5 jaar na de beademing bleek vergelijkbaar te zijn met een controlegroep. Voor volwassen patiënten met CF bleek de overleving nog altijd beperkt (27%). Van de volwassenen die invasieve beademing nodig hadden, bleken degenen met chronisch falen van de ademhaling het grootste risico te hebben om te overlijden op de intensive care.

Hoofdstuk 3

Door een beenmergtransplantatie is de prognose van verschillende ziekten sterk vooruit gegaan. Dat geldt bijvoorbeeld voor diverse vormen van leukemie, voor ernstige afweerstoornissen of voor bepaalde stofwisselingsziekten. Een beenmergtransplantatie blijft echter een risicovolle behandeling, en een aanzienlijk deel van de kinderen moet opgenomen worden op de intensive care als gevolg van complicaties gerelateerd aan de transplantatie. In de eerste studies bleek dat meer dan 90% van deze kinderen de intensive care behandeling niet overleefde. In de literatuur is er doorgaande discussie of de resultaten van intensive care behandeling voor deze kinderen in de loop van de jaren zijn verbeterd.

In dit hoofdstuk worden de resultaten beschreven van een metaregressie analyse van de 23 studies die de uitkomst beschrijven van intensive care behandeling bij kinderen na een beenmergtransplantatie. In totaal betrof het 1101 patiënten met een overall intensive care overleving van 40%. Univariate analyse liet een significante verbetering zien in de loop van de jaren in het percentage patiënten dat intensive

care behandeling overleefde. In dezelfde tijdsperiode bleek echter dat het aantal kinderen dat na opname op de intensive care beademd moest worden significant afgenomen. Wanneer hiervoor werd gecorrigeerd, werd er niet langer een evidente verbetering gezien in de overleving. De conclusies van deze studie worden beperkt door een gebrek aan recente gegevens van resultaten van beademing bij kinderen na een beenmergtransplantatie.

Hoofdstuk 4
In dit hoofdstuk worden de resultaten beschreven van beademing op de intensive care van het Wilhelmina Kinderziekenhuis bij een recente groep kinderen (tussen 1999 en 2007) na een beenmergtransplantatie. In totaal betrof het 35 kinderen, die 38 keer opgenomen werden voor beademing. De ziekte-ernst voor deze kinderen leek hoger dan in voorgaande studies, maar desondanks werd een betere overleving gevonden: 58% van de kinderen overleefde de intensive care behandeling. Falen van meerdere organen en de noodzaak tot hoge frequentie beademing waren voorspellers van een slechte uitkomst in onze patiënten. Van de kinderen die de intensive care overleefden was na 6 maanden nog altijd 82% in leven. Deze uitkomsten zijn veelbelovend, maar moeten nog bevestigd worden in grotere studies waar meerdere centra aan deelnemen.

Hoofdstuk 5
Kinderen met een ernstige ontwikkelingsachterstand hebben vaak ademhalingsproblemen. Veel van deze kinderen slikken slecht, verslikken zich frequent, hoesten onvoldoende, zuchten onvoldoende, kunnen maar beperkt gemobiliseerd worden, hebben gastro-oesofageale reflux en een ernstige verkromming van de wervelkolom, wat allemaal kan bijdragen aan de ademhalingsproblemen. Het vermoeden bestaat, dat een groot percentage van deze kinderen overlijdt, wanneer eenmaal kunstmatige beademing nodig is vanwege de ademhalingsproblemen. De beslissing om te starten met beademing, of hiervan af te zien, heeft vergaande consequenties. Er zijn geen uitkomstgegevens in de literatuur bekend die besluitvorming hierover kunnen ondersteunen.
In dit hoofdstuk worden de resultaten beschreven van 22 kinderen met een ernstige ontwikkelingsachterstand die beademd moesten worden vanwege ademhalingsproblemen in het Wilhelmina Kinderziekenhuis. De gemiddelde beademingsduur bedroeg 16 dagen, wat veel langer is dan de doorsnee beademingsduur op de kinderintensive care. Zes kinderen hadden een ongestoorde 1-jaars overleving, de anderen hadden een gecompliceerd beloop op de intensive care, moesten heropgenomen worden op de intensive care of overleden. Na 1 jaar was 50% van de kinderen nog in leven. De ademhalingsfunctie vóór opname op de intensive care is vermoedelijk een belangrijke voorspeller voor de uiteindelijke kans op overleving.

Hoofdstuk 6

Ondanks vooruitgang in de medische zorg is de sterfte als gevolg van een ernstige meningococceninfectie pas het laatste decennium gedaald. In dit hoofdstuk is gekeken naar de invloed van intensive care behandeling op de overleving van kinderen met een ernstige meningococceninfectie. Alle 239 kinderen die tussen 1991 en 2004 waren opgenomen op de intensive care van het Wilhelmina Kinderziekenhuis vanwege een ernstige meningococceninfectie werden geïncludeerd. 37 Kinderen (15,5%) overleden op de intensive care. In de loop van de jaren waren de kinderen zieker bij opname. Na correctie voor ziekte-ernst bleek de sterfte significant te zijn afgenomen. Over de jaren werd de septische shock bij de ernstige meningococceninfectie steeds agressiever behandeld: er werd meer vaatvulling gegeven en er werd eerder gestart met bloeddrukondersteunende medicatie. Deze agressievere behandeling van de shock kon de verbeterde overleving echter niet verklaren. Dit suggereert verbeteringen in andere ondersteunende behandelingen, zoals bijvoorbeeld vooruitgang in beademingszorg.

Hoofdstuk 7

Vroegere studies naar de uikomsten van intensive care behandeling bij kinderen met een doorgaande ernstige epileptische aanval (refractaire status epilepticus, RSE) lieten hoge sterfte zien. De meeste intensive care afdelingen gebruiken thiopental als laatste behandeling bij RSE. De behandeling is bewezen effectief, maar de bijwerkingen van thiopental zijn indrukwekkend. Sommige auteurs raden daarom propofol aan als alternatieve behandeling bij RSE, maar de effectiviteit hiervan is slechts aangetoond door beschrijving van enkele losse casus.

In dit hoofdstuk worden de resultaten beschreven van alle kinderen die behandeld zijn voor RSE op de intensive care van het Wilhelmina Kinderziekenhuis tussen 1993 en 2004. Tot 1999 werd thiopental gebruikt, daarna werd eerst gestart met propofol voordat thiopental werd gestart. Op deze manier werd thiopental dus alleen gebruikt als propofol niet effectief was, of als er teveel bijwerkingen waren van de propofol. Eenderde van de patiënten overleed, eenderde had een duidelijke achteruitgang van het neurologisch functioneren en eenderde herstelde tot het niveau van vóór de opname. Zowel propofol als thiopental bleken effectief in de behandeling van RSE. Gebruik volgens strikte richtlijnen resulteerde in weinig bijwerkingen van propofol. Tijdens de behandeling met thiopental werden frequent bijwerkingen gezien, waarvan sommigen potentieel levensbedreigend waren. Wij stellen voor om bij RSE bij kinderen propofol te overwegen voordat met thiopental wordt gestart.

Hoofdstuk 8

In dit hoofdstuk wordt een samenvatting gegeven van de voorgaande hoofdstukken., en reflecteren we op de resultaten van de afzonderlijke studies. De ziektebeelden die in dit proefschrift worden beschreven zijn relatief zeldzaam en vaak zeer heterogeen. Dat beperkt de mogelijkheden voor grootschalig interventie-onderzoek en voor het bepalen van potentiële voorspellers van sterfte. In het verleden werd een hoge sterfte gevonden bij de behandeling van deze ziektebeelden, maar vooruitgang in de medische zorg heeft geleid tot betere overleving. Een goed ontworpen prospectieve database is noodzakelijk om continu de uitkomsten van intensive care behandeling bij deze complexe groepen patiënten te monitoren.

Dankwoord

Promoveren op leeftijd betekent dat zeer velen een zeer belangrijke rol hebben gespeeld. Teveel om op te noemen. Of het nu gaat om dr. Beekman, die me kennis liet maken met de geneeskunde, Willem Fetter, die me de opleiding induwde, opleiders uit Groningen, Enschede, Zwolle, Rotterdam of Utrecht, collega's en teamleden uit deze ziekenhuizen: allen hebben me doen groeien tot dit niveau, en bijgedragen aan dit resultaat. Het is onmogelijk hen allen te noemen. Passend in de lijn van dit proefschrift wordt dit dankwoord een soort van 'brief report.' In de wetenschap dat ik mensen tekort doe, wil ik toch een aantal personen in het bijzonder noemen.

Als eerste wil ik danken mijn promotor: Hans van Vught. Jouw begeleiding gaat veel verder dan alleen het begeleiden van het onderzoek. Nog dagelijks kan ik genieten van de onnavolgbare wijze waarop je de afdeling weet aan te sturen, en alle medische, organisatorische, wetenschappelijke en ethische 'kansen en uitdagingen' weet aan te pakken. Ik ben er trots op door jou opgeleid te zijn!

Veel dank gaat uit naar mijn tweede promotor, Jan Kimpen. In Groningen was je de opleider tijdens het laatste deel van mijn opleiding tot kinderarts, het doet me heel veel plezier dat dit deel van mijn academische carrière mede door jou wordt volbracht.

Mijn co-promotor, Casper Bollen: vooral dankzij jou heb ik de eindstreep gehaald. Jouw snelle, heldere en motiverende begeleiding wist me steeds weer in het wiel te krijgen, wanneer ik eigenlijk dacht ik het niet meer trok en uit de koers moest stappen. Jouw enthousiasme voor wetenschap en epidemiologie zijn zo aanstekelijk, dat je zelfs mij hebt weten te besmetten! Ik hoop dat we binnenkort weer een keer ook letterlijk tegen de wind in kunnen fietsen. Moet jij wel het kopwerk doen, vrees ik.

Koos Jansen: via Maastricht en Groningen zijn we uiteindelijk samen in Utrecht beland. Dank voor alle hulp, vertrouwen, enthousiasme en bemoedigende woorden. Nu is er weer tijd om samen een uitje te fruiten en een goed glas te drinken.

Het leuke van onderzoek doen met verschillende klinische disciplines, is dat je met veel verschillende mensen kunt samenwerken. Alle mede-auteurs wil ik hartelijk danken voor hun hulp bij het meedenken en schrijven van de studies in dit proefschrift. Speciale dank gaat daarbij uit naar Martijn Slieker, Kors van der Ent, Ingeborg van der Tweel, Jaap Jan Boelens, Marc Bierings, Nico Wulffraat, Afke Robroch, Annemieke Miedema, Heleen Blussé van Oud-Albas, Mirte Malingré,

Tessa Ververs, Kees Braun en Onno van Nieuwenhuizen: dank voor alle hulp, geduld, revisie van weer een aangepaste versie, discussie en nog een revisie van een gereviseerde versie. Zonder jullie was het nooit wat geworden.

Alle lof en dank voor het hele team van Pelikaan, de intensive care afdeling van het Wilhelmina Kinderziekenhuis. Jullie betrokkenheid, inzet, collegialiteit, alertheid en expertise zorgen ervoor dat alles op rolletjes loopt, en dat het er goed toeven is. Mede dankzij jullie zijn de resultaten van behandeling steeds beter geworden. Voor de hulp bij het onderzoek wil ik in het bijzonder de secretaresses bedanken, wanneer een zware stapel statussen weer ‘even’ boven water getoverd moesten worden. En liefst gisteren, als het kan. Joke, veel dank voor de onmisbare hulp bij het plannen en regelen van allerlei zaken, zowel voor het klinische werk als voor de promotie.

Mijn paranimfen: Anja en Marije. Anja, ik ben er razend trots op dat jij mijn paranimf wilt zijn. Bij jullie in Best is het altijd best vertoeven. Met alle rust, organisatietalent en bescheidenheid is je rol binnen gezin en familie groot en belangrijk. (en eigenlijk zou jij Chef moeten heten…)
Marije, met jou aan mijn zijde kan niemand me wat maken! Ik ben nog elke dag blij dat ik met je ben gaan samenwonen. Het sparren over wetenschap, werk, de tafeltennistafel, roddel of het leven vormen een belangrijk deel van het plezier in mijn werk. Dankzij jou blijf ik betrokken bij de kliniek, zelfs in de meest donkere beeldschermdagen. Je zult zien: voor je het weet ben jij aan de beurt, en zit je de Nederlandse samenvatting te typen!

Ons pa en ons ma: dank voor een onvoorwaardelijk en echt thuis, voor alle relativering, erwtensoep en gezelligheid.

En als allerlaatste, en allerallerbelangrijkste: Stans. Dien leefde, det is mien gelök! Dankzij jou is zelfs de zwaarste tocht goed te doen.

Curriculum vitae

Sjef van Gestel werd geboren op 25 februari 1966 te Waalwijk. Na het behalen van zijn VWO diploma aan het dr. Mollercollege in Waalwijk startte hij in 1984 met de studie geneeskunde aan de Rijksuniversiteit Limburg in Maastricht. In 1991 is hij gaan werken als AGNIO kindergeneeskunde in het Sophia Ziekenhuis in Zwolle. In 1992 startte hij met de opleiding tot kinderarts in de Beatrix Kinderkliniek in Groningen (opleider prof. dr. H.S.A. Heijmans). Het perifere gedeelte van zijn opleiding volgde hij in het Medisch Spectrum Twente in Enschede (opleider drs. R.F.H.M. Tummers).
Na de voltooiing van de opleiding tot kinderarts startte hij met een fellowship neonatologie in het Sophia Ziekenhuis in Zwolle (opleider dr. W.P.F. Fetter). In 1998 voltooide hij zijn opleiding tot neonatoloog in het Sophia Kinderziekenhuis in Rotterdam (opleider prof. dr. J.N. van den Anker). Daarna begon hij met een fellowship kinderintensive care op de Intensive Care Chirurgie van het Sophia Kinderziekenhuis in Rotterdam (opleider prof. dr. D. Tibboel). In 2000 is hij gaan werken op de intensive care van het Wilhelmina Kinderziekenhuis in Utrecht, aanvankelijk als fellow (opleider prof. dr. A.J. van Vught) en later als staflid. Onder supervisie van prof. dr. A.J. van Vught, prof. dr. J.L.L. Kimpen en dr. C.W. Bollen verrichtte hij het onderzoek dat resulteerde in dit proefschrift.
Na een proefperiode van bijna 20 jaar is hij in 2008 getrouwd met Stans Drossaert.

List of publications

Van Gestel JPJ, L'Hoir M, ten Berge M, Jansen NJG, Plötz FB. Risks of ancient practices in modern times. *Pediatrics* 2002; 110: e78

Van Dijk K, Kamphuis SSM, Geelen SPM, Wulffraat NM, van Gestel JPJ, Wolfs TFW. Pneumonia due to Legionella pneumophila in an immunocompromised child. *Ned Tijdschr Geneeskd* 2002; 146: 1420-1423

Van der Flier M, van Dijk NB, Fluit AC, Fleer A, Wolfs TFW, van Gestel JPJ. Fatal pneumonia in an adolescent due to community-acquired methicillin-resistant Staphylococcus aureus positive for Panton-Valentine-leukocidin. *Ned Tijdschr Geneeskd* 2003; 147: 1076-1079

Van Woensel JBM, van Aalderen WMC, de Weerd W, Jansen NJG, van Gestel JPJ, Markhorst DG, van Vught AJ, Bos AP, Kimpen JLL. Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus. *Thorax* 2003; 58: 383-387

De Graaff PMA, Heidema J, Poelen MC, van Dijk MEA, Lukens MV, van Gestel JPJ, Reinders J, Rozemuller E, Tilanus M, Hoogerhout P, van Els CACM, van der Most RG, Kimpen JLL, van Bleek GM. HLA-DP4 presents an immunodominant peptide from the RSV G protein to CD4 T cells. *Virology* 2004; 326: 220-230

Van Gestel JPJ, Jansen NJG. CF, naar de intensive care? Capita Selecta Cystic Fibrosis 2004; 37-43. ISBN 90-393-2981-8

Van Gestel JPJ, Blussé van Oud-Alblas HJ, Malingré M, Ververs FFT, Braun KPJ, van Nieuwenhuizen O. Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; 65: 591-592

Van Gestel JPJ, Merks JHM, Lo RTH, Kappelle JL, Braun KPJ. A child with multifocal arterial thrombosis. *Thromb Haemost* 2005; 93: 995-996

Markhorst DG, Van Gestel JPJ, van Genderingen HR, Haitsma JJ, Lachmann B, van Vught AJ. Respiratory inductive plethysmography accuracy at varying PEEP levels and degrees of acute lung injury. *J Med Eng Technol* 2006; 30: 166-175

Van Woerkum F, Bont LJ, Haas F, Freund MW, van Gestel JPJ. Aortoesophageal fistula due to double aortic arch and prolonged nasogastric intubation: case report and review of the literature. *Eur J Pediatr* 2006; 165: 660-661

Slieker MG, van Gestel JPJ, Heijerman HGM, Tramper-Stranders GA, Teding van Berkhout F, van der Ent CK, Jansen NJG. Outcome of assisted ventilation for acute respiratory failure in cystic fibrosis. *Intensive Care Med* 2006; 32: 754-758

Rump P, Letteboer TGW, Gille JJP, Torringa MJL, Baerts W, van Gestel JPJ, Verheij JBGM, van Essen AJ. Severe complications in a child with achondroplasia and two FGFR3 mutations on the same allele. *Am J Med Genet A* 2006; 140: 284-290

Heidema J, Lukens MV, van Maren WWC, van Dijk MEA, Otten HG, van Vught AJ, van der Werff DBM, van Gestel JPJ, Semple MG, Smyth RL, Kimpen JLL, van Bleek GM. CD8+ T Cell Responses in Bronchoalveolar Lavage Fluid and Peripheral Blood Mononuclear Cells of Infants with Severe Primary Respiratory Syncytial Virus Infections. *J Immunol* 2007; 179: 8410-8417

Boelens JJ, van Gestel JPJ. Immunologie. Leerboek Intensive-Care-Verpleegkunde Kinderen. Derde druk, 2008. Elsevier Gezondheidszorg, Maarssen; 720-728

Van Gestel JPJ, Bollen CW, Bierings MB, Boelens JJ, Wulffraat NM, van Vught AJ Survival in a Recent Cohort of Mechanically Ventilated Pediatric Allogeneic Hematopoietic Stem Cell Transplantation Recipients. *Biol Blood Marrow Transplant* 2008; 14: 1385-1393

Van Gestel JPJ, Bollen CW, van der Tweel I, Boelens JJ, van Vught AJ. Intensive care unit mortality trends in children after hematopoietic stem cell transplantation: a metaregression analysis. *Crit Care Med* 2008; 36: 2898-2904

Veldhoen ES, Hartman BJ, van Gestel JPJ. Monitoring biochemical parameters as an early sign of propofol infusion syndrome: false feeling of security. *Pediatr Crit Care Med* 2009; 10: e19-21

Van Gestel JPJ, Drossaert CHC, van Klink M, Taal E, Kampelmacher MJ, van Vught AJ. Ervaringen van kinderen en hun ouders met thuisbeademing. *Tijdschr voor Kindergeneeskd* 2009; 77: 131-136

Van Gestel JPJ, Robroch AH, Bollen CW, van der Ent CK, van Vught AJ. Mechanical ventilation for respiratory failure in children with severe neurological impairment: is it futile medical treatment? *Dev Med Child Neurol*, in press