Baby steps forward
on the pathway towards improvement
of neonatal care

K.A. de Bijl-Marcus

Baby steps forward on the pathway towards improvement of neonatal care
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Baby steps forward

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Babystapjes vooruit op weg naar verbetering van de neonatale zorg

(met een samenvatting in het Nederlands)

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TABLE OF CONTENTS

Great change is made through small steps
And the science is irrefutable: small steps circumvent the brain's built-in resistance to new behavior

Dr. Robert Maurer
Klinisch psycholoog en gedragswetenschapper
(Kaizen)

CHAPTER 1

CHAPTER 1

General introduction

and outline of this thesis

1.1 GENERAL INTRODUCTION

1.1.1 Neonatal Intensive Care: Mortality Declines, Long-Term Implications Persist

During the last decades, the number of neonatal deaths in neonatal intensive care units (NICU) has declined considerably [1-3]. However, despite this progress, preterm birth remains the primary cause of mortality among children below the age of five years, resulting in a global annual mortality rate of almost 1 million infants. Additionally, the long-term outcomes of critically ill preterm born infants continue to be a matter of major concern [4,5]. The complexity of neonatal conditions, coupled with intensive care interventions, may adversely affect future growth and lead to neurodevelopmental impairments. Neonatal conditions persist as dominant contributors to global disability-adjusted life-years, even when considering all age groups [6]. Conditions such as chronic lung disease, behavioral problems, obesity, type II diabetes mellitus, hypertension, and adult-onset heart disease often are more prevalent outcomes following significant neonatal complications [7,8]. In many cases, the full extent of long-term consequences remains insufficiently understood for various neonatal adverse conditions.

1.1.2. Challenges within neonatal care

Currently, numerous neonatal care systems are facing significant challenges. These interrelated challenges encompass:

1. Increasing complexity of patient characteristics and treatments:

The landscape of neonatal care is becoming increasingly complex due to several factors. Firstly, intensive care treatment is increasingly provided to infants born with a gestational age at the threshold of viability and/or with highly complex medical conditions (e.g., infants with severe congenital anomalies). These illnesses demand specialized care and interventions that are often protracted. As a result, healthcare professionals face a growing need for expertise and resources to effectively address these intricate cases. Secondly, the constant evolution of diagnostic tools and treatment modalities adds another layer of complexity to neonatal care, emphasizing the importance for healthcare providers to stay in touch with the latest innovations in the field [9,10].

2. Escalating healthcare costs:
The heightened complexity of neonatal care directly translates into rising healthcare costs. Caring for critically ill infants, comes with substantial financial burdens. Over the past decade, the costs associated with neonatal care for this group of patients have surged by a significant 10% [9]. This increment is a result of the specialized equipment, medications, and skilled personnel required to manage the complex needs of these vulnerable infants. On average, a NICU admission costs 26,627 euros. In addition to the costs of the first hospital admission, these infants often require ongoing medical support, imposing long-term financial challenges on patients, their families, and society as a whole [9-16]. Patients, and their families, may struggle to maintain stable employment or may require social support services. This can lead to a reduction in overall economic productivity and exacerbation of (healthcare) disparities.

3. Scarcity of resources:
The challenges mentioned above are a matter of concern, given the constraints on resources, including limited personnel and restricted capacity within neonatal care units. This scarcity places significant strain on healthcare systems and professionals, which may compromise both patient safety and equal access to care [9, 12-16].

1.1.3. Quality improvement
Quality improvement in neonatal care holds the potential to address all of these challenges. Improving the quality of healthcare involves data-driven methods to systematically enhance the safety, efficiency, and effectiveness of healthcare services. This results in improved patient outcomes and the overall performance of healthcare systems. The ultimate objective is to provide care that is safe, effective, patient-centered, timely, efficient, and equitable [17]. Initiatives aimed at enhancing quality within the field of fetal and neonatal care can play a substantial role in reducing the incidence of numerous neonatal illnesses and mitigating the long-term complications associated with preterm birth [18-20]. Complications arising from preterm birth and subsequent long-term consequences exert a detrimental impact on healthcare resources and expenditures [21]. The overarching goal in the context of neonatal care is to elevate the quality of care, with a primary focus on improving outcomes for this vulnerable patient group. Simultaneously, there exists a shared responsibility to effectively manage and curtail healthcare expenses, preventing the unbridled escalation of healthcare

costs. The adoption of principles grounded in value-based healthcare emerges as a promising pathway to achieve these dual objectives.

1.1.4. Value based healthcare (VBHC)

Value-based healthcare emphasizes the achievement of optimal outcomes for patients while ensuring the efficient utilization of resources. This approach, initially articulated by Michael Porter, recognizes that attaining the most favorable patient outcomes is the fundamental objective of healthcare [22]. The value perceived by patients is closely tied to the results achieved through the care they receive. Within the context of VBHC, it's important to acknowledge that "value" is primarily determined by the patient. However, in neonatal care, an additional layer of complexity arises because the patient cannot articulate his/her perspective on value. In these cases, we rely on parents to advocate on behalf of the patient [23,24]. Focusing on improving patient outcomes alone is not enough. Given the ongoing increase in healthcare costs, and the constraints imposed by limited resource availability, the careful allocation of resources becomes paramount. Healthcare professionals bear the responsibility of integrating cost considerations into their decision-making processes. VBHC aims to achieve the most optimal patient outcomes that matter to the patient, while minimizing costs, as illustrated in Figure 1.1 [22].

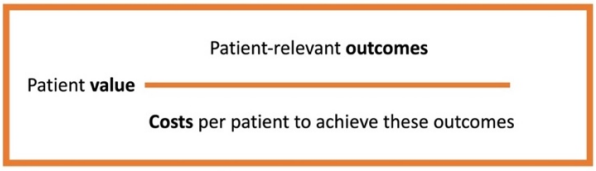

Figure 1.1: Value equation.

Measuring & enhancing outcomes

The measurement of patient outcomes is vital in determining value within healthcare. Establishing a systematic approach to measuring and improving value represents a potent strategy for driving progress in medical care [25]. In the absence of a feedback loop, the essential information necessary for providers to learn and enhance their practices is lacking. Hence, the measurement of outcomes stands as an indispensable foundation for the increment of value. Both short-term and long-term outcomes serve as the numerator within the value equation. The creation of value for the patient is a collaborative effort orchestrated by a team of healthcare providers throughout the entire care cycle [26]. The effectiveness of any intervention depends on the efficacy of other interventions across the continuum

of care. According to Porter, the outcomes associated with any medical condition can be classified within a three-tiered hierarchy, as illustrated in Figure 1.2.

Tier One: At the apex of the hierarchy, tier one encompasses the achieved health status. This includes survival or mortality (first level within tier one). The second level within tier one pertains to the extent of health or recovery attained at the short-term, encompassing freedom from disease and functional status. In view of neonatal care, aspects such as the necessity for respiratory support, or reliance on parenteral nutrition belong to this level.

Tier Two: Tier two outcomes are related to the recovery process. The first level of tier two revolves around the time required for recuperation and the restoration of normal or optimal functionality. Within neonatology, this could translate to the length of hospitalization in a neonatology department. The second level within tier two concentrates on the challenges faced during the care process, including missed diagnoses, unsuccessful treatments, short-term complications, errors, and delays in providing appropriate treatment.

Tier Three: Tier three relates to the sustainability of health. The initial level involves the recurrence of the original illness (such as re-admission to the neonatal intensive care unit) or the emergence of long-term complications (like developmental delays originating from perinatal asphyxia or preterm birth). The subsequent level within tier three encapsulates new health issues arising as a consequence of treatment. Examples of such outcomes within neonatal care include functional or aesthetic deficiencies as a result of the extravasation of parenteral fluids or limb ischemia due to an arterial catheter.

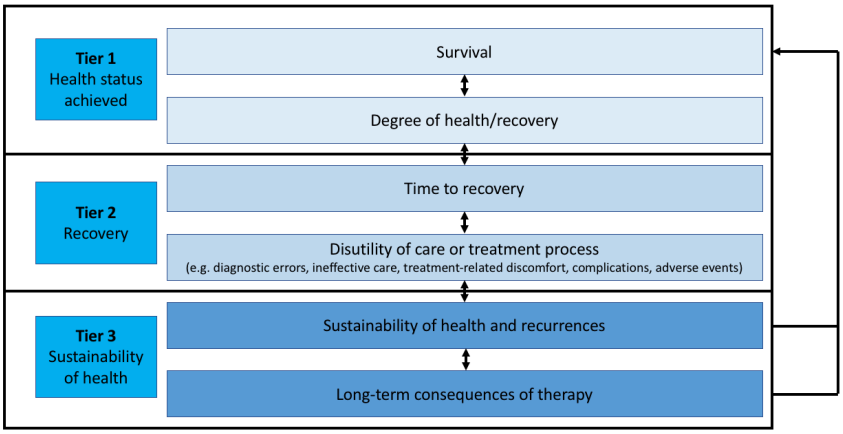

Figure 1.2: The outcome measure hierarchy according to M. Porter.
N Eng J Med 2010; 363(26): page 2479

Reducing Neonatal Care Expenditure

Given the escalating costs within neonatal care and the limitations posed by scarcity of resources, it becomes crucial to allocate resources, including finances, judiciously to activities that offer the highest value. The latest edition of the American College of Physicians Ethics Manual underscores the responsibility of physicians to deliver healthcare effectively and efficiently, emphasizing the prudent utilization of healthcare resources to provide care of high value [27]. This perspective strongly aligns with the fundamental tenets of VBHC. In the domain of neonatal care, it is imperative to recognize that the denominator of the value equation extends beyond direct medical costs. While this category encompasses factors such as equipment, medications, and the time of healthcare providers (measured in person-hours), it also encompasses non-medical costs that may not have a direct association with healthcare delivery. These non-medical costs include elements such as travel expenses, additional childcare expenditures for siblings, and the (potential) loss of current and future productivity due to missed work. These financial implications not only affect families but also have long-term effects on the patient. While essential, decisions regarding cost reduction should be approached with care, considering the potential long-term effects of such choices. The Heckman curve underscores that the highest economic returns arise from early investments in children's health [28]. The economic benefits of early investments, which nurture skill development progressively, carry profound significance. This approach enhances productivity and ultimately reduces the need for extensive societal expenditure. From this perspective, the most potent pathway for reducing

costs in neonatal healthcare lies in optimizing patient outcomes. Improved outcomes almost invariably correlate with a decrease in the denominator (costs). This phenomenon is grounded in the fact that adverse outcomes often entail enduring consequences, resulting in substantial expenses that far exceed the initial costs of the intervention itself.

1.1.5. The perspective of care professionals and patient ('s families)

A fundamental prerequisite for the development and evaluation of effective strategies to enhance healthcare provision is the assessment of care quality from both the viewpoint of healthcare professionals and the complementary perspective offered by patients or their families. This value-driven approach acknowledges that determining what constitutes value in healthcare is a collaborative endeavor, shaped by the insights of those who deliver care and those who receive it. Over the years, initiatives such as Patient-Reported Outcome Measures (PROMs), Patient-Reported Experience Measures (PREMs), and the International Consortium for Health Outcomes Measurement (ICHOM) have significantly redirected the focus within healthcare towards outcomes [29-31]. These endeavors recognize that the true value of healthcare lies in the outcomes achieved for patients and their families. PROMs and PREMs capture the patient's perspective on the effectiveness of interventions and their overall healthcare experience, respectively. ICHOM, on the other hand, standardizes outcome measurement for specific medical conditions, providing a common language for assessing results across diverse healthcare settings. These developments align harmoniously with VBHC, as well as the framework of Berwick's Triple Aim and the Quadruple Aim, as articulated by Bodenheimer [32,33]. The Triple Aim, focused on (1) elevating patient experience, (2) improving population health, and (3) controlling healthcare costs, now finds even stronger support through these outcome-oriented approaches. The Quadruple Aim adds the importance of (4) healthcare provider well-being. By embracing these initiatives and incorporating the insights of healthcare professionals and patients' families, we can collectively shape a healthcare system that delivers value by achieving meaningful outcomes and fostering patient-centered care.

1.2 OUTLINE OF THIS THESIS

Through an exploration of VBHC principles, this thesis aims to identify strategies to improve patient outcomes within neonatal care, while at the same time discuss financial and organizational implications. The three-section thesis examines the measurement of neonatal outcomes, strategies to enhance neonatal outcomes, and the perception of care by caregivers and patients, culminating in a synthesis of findings and future directions.

1.2.1 SECTION ONE: Measurement of neonatal outcome

In the first section of this thesis, we delve into various outcomes within neonatal intensive care.

Chapter two of this thesis, specifically addresses a significant, yet relatively underexplored outcome of neonatal intensive care: *renal function*. Critically ill neonates are at high risk of kidney injury. Acute kidney injury (AKI) is an outcome measure belonging to tier one. However, it is also associated with long-term renal impairment and thus predictive of tier three outcome measures. The lessons learned from this patient cohort can be used to tailor a screening protocol for AKI and serve as the foundation for a renal follow-up program in the neonatal intensive care unit as well as secondary prevention.

Chapter 3 provides an analysis of the trends in the length of stay (LoS) among patients admitted to both the NICU and level II neonatal care departments. LoS serves as a valuable indicator of care quality within a healthcare setting, providing insight into the efficiency of care delivery, occurrence of complications, effectiveness of treatment, and resource utilization. The significance of LoS is underscored by its dual role as both an outcome measure within tier two and a potential avenue for cost reduction. However, it's important to exercise caution when utilizing LoS as a cost-reduction tool, as this approach must be balanced against other quality metrics like readmission rates and complications. This consideration becomes particularly pertinent in health systems where the NICU and post-discharge healthcare environments operate distinctly. Despite these complexities, the substantial value of reducing LoS remains undeniable, particularly when acknowledging the impact of extended hospital stays on patients and their families.

1.2.2 SECTION TWO: Improving neonatal outcomes

In the second section of this thesis, we outline a range of interventions targeted at enhancing important outcomes for patients admitted to the NICU.

Chapter four of this thesis entails a systematic review investigating the impact of therapeutic hypothermia on renal and myocardial function of neonates suffering from perinatal asphyxia. Perinatal asphyxia resulting in hypoxic-ischemic encephalopathy (HIE) carries detrimental implications for various fetal organs, including the brain, heart, and kidneys. Notably, 30% of neonates with moderate HIE and 90% of those with severe HIE experience profound long-term disabilities, encompassing epilepsy, cerebral visual impairment, cognitive impairments, and cerebral palsy. Therapeutic hypothermia has proven to be an effective therapy to reduce the risk of mortality or neurocognitive disability for infants with moderate to severe HIE. This review specifically concentrates on the effects of therapeutic hypothermia on the kidney and heart, given their vulnerability to perinatal asphyxia and potential long-term complications. The effect of therapeutic hypothermia on renal and myocardial function is not well known. The aim of this review is to ascertain the potential short-term (tier one) and long-term (tier three) advantageous impacts of therapeutic hypothermia on renal and myocardial function in asphyxiated (near) term neonates.

In chapter five and six we focus on interventions aimed at reducing the incidence of germinal matrix and intraventricular hemorrhage (GMH-IVH) in preterm neonates admitted at the NICU. GMH-IVH is an important neonatal outcome measurement (tier one) since it is directly associated with long-term sequelae (tier three). Of the extremely premature infants, 20–25% will develop a GMH-IVH, with the incidence being inversely proportional to GA [34]. A large and/or complicated GMH-IVH is strongly associated with an adverse outcome, including disabilities and death in particular when the GMH-IVH is leading to venous infarction or posthemorrhagic hydrocephalus. Despite numerous efforts to prevent GMH-IVH in premature infants, the incidence of severe GMH-IVH has remained stable during the last few decades. Though seemingly harmless, routine caregiving events may affect cerebral perfusion and oxygenation in the preterm neonate and thereby the risk of developing a GMH-IVH. In an attempt to avoid (rapid) fluctuations in cerebral blood flow as well as intracranial pressure during routine care, several nursing interventions have been proposed.

In chapter five we present a systematic review of studies assessing the influence of head positioning and tilting on the incidence of GMH-IVH, as well as on cerebral

hemodynamics and cerebral oxygenation in preterm neonates. The latter two being important factors in the etiology of GMH-IVH.
In **chapter six** we present the results of a prospective cohort study in which we investigated the effect of a nursing intervention bundle (NIB), aimed at maintaining a more stable cerebral blood flow and less cerebral venous congestion on the incidence of GMH-IVH in preterm neonates. In addition, we studied the effect of the intervention on the incidence of c-PVL and mortality.

1.2.3 SECTION THREE: Learning from the perception of quality of care from the view of parents and care professionals

In the third part of this thesis, we describe the perception of safety and quality of care as observed by both healthcare professionals and parents of patients admitted to the NICU, particularly concerning the transfer of infants to a level II department. Limited understanding exists regarding how care professionals perceive the safety of the transfer process and its alignment with parental perceptions. In **chapter seven**, we present a prospective cohort study aimed at investigating the perceived level of safety regarding the transfer process. This exploration involves all relevant stakeholders, including parents, physicians, physician assistants (PAs), nurses, secretary personnel, and ambulance personnel. The study seeks to uncover areas of agreement and divergence in the perspectives of safety of these different stakeholders. This investigation will identify the factors that facilitate or hinder the attainment of a high level of perceived safety during the transfer process. The study was conducted using a Safety-II approach. Traditional safety practices, referred to as Safety-I, primarily focus on identifying and eliminating risks to prevent failures and incidents. Safety-I adopts a reactive and retrospective model, emphasizing compliance with safety regulations and procedures. In contrast, Safety-II acknowledges the complexity and adaptability of organizations and systems [35]. It recognizes that safety is not solely determined by incidents and failures but also encompasses the study of successful outcomes and normal operations, yielding valuable insights. Safety-II aims to comprehend how systems effectively function under routine circumstances. This approach takes into account the intricate and dynamic nature of the workplace, involving complex interactions and influenced by human factors. It emphasizes the necessity for flexibility and resilience within work processes and among diverse stakeholders. This perspective aims to build on positive aspects and prevent adverse outcomes. Evaluating and learning from the routine transfer of infants, considering the

viewpoints of all relevant stakeholders and focusing on the inherent success of these intricate processes, aligns well with the principles of Safety-II.

The most important findings are summarized in Chapter 8. Conclusions are presented together with suggestions for future research.
Chapter 8: The synthesis chapter brings together the key findings from the previous sections, highlighting the significance of VBHC in improving neonatal outcomes. It emphasizes the need for comprehensive, multidisciplinary strategies to enhance neonatal care efficiency, reduce complications, and promote patient safety. The chapter concludes by suggesting avenues for future research in neonatal care improvement and VBHC implementation. It underscores the potential of quality improvement initiatives and the application of VBHC principles to foster more effective, efficient, safe, and patient-centered neonatal care.

To summarize, quality improvement has a favorable effect on:
1. patient outcomes and experiences of health care
2. judicious utilization of resources.

This thesis thoroughly examines the challenges of neonatal care, proposes a value-based approach to address these challenges, and presents strategies for improving neonatal outcomes by delving into outcome measurement, quality improvement strategies, and safety perceptions.

REFERENCES

1. Zegers MJ, Hukkelhoven CWPM, Uiterwaal CSPM, Kollee LAA, Groenendaal F. Chaning Dutch approach and trends in short-term outcome of periviable preterms. Arch Dis Child Fetal Neonatal Ed 2016;101(5):F391-6.
2. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;345:e7976.
3. Stol BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sanchez PJ, van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotton CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314(10):1039-51.
4. Hug L, Alexander M, You D, Alkema L; UN Inter-agency Group for Child Mortality Estimation. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. Lancet Glob Health 2019; 7(6): e710-20.
5. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, Prieto-Merino D, Cousens S, Black RE, Liu L. Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022;6(2):106–15.
6. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396(10258):1204-22.
7. McCormick MC, Litt JS, Smith VC, Zupancic JA. Prematurity: an overview and public health implications. Annu Rev Public Health 2011;32:367–79.
8. Lane RH. Fetal programming, epigenetics, and adultonset disease. Clin Perinatol 2014;41(4):815–31.
9. Yeung T, Rios JD, Beltempo M, Khurshid F, Toye J, Ojah C, Zupancic JAF, Lee SK, Pechlivanoglou P, Shah PS. Canadian Neonatal Network (CNN) and the Canadian Preterm Birth Network (CPBN) Investigators. The Trend in Costs of Tertiary-Level Neonatal Intensive Care for Neonates Born Preterm at 220/7-286/7 Weeks of Gestation from 2010 to 2019 in Canada. J Pediatr 2022;245:72-80.
10. Keizer RACMO, Maroune A, Deden AC, van Zelst-Stams WAG, de Boode WP, Keusters WR, Henneman L, van Amstel JKP, Frederix GWJ, Vissers LELM. Medical costs of children admitted to the neonatal intensive care unit: the role and possible economic impact of WES in early diagnosis. E J Med Gen 2022;65(5):104467.
11. De Proost L, Verweij EJT, Ismaili M'hamdi H, Reiss IKM, Steegers EAP, Geurtzen R, Verhagen AAE. The edge of perinatal viability: understanding the Dutch position. Front Pediatr 2021;9:634290.
12. Derienzo C, Kohler JA, Lada E, Meanor P, Tanaka D. Demonstrating the relationships of length of stay, cost and clinical outcomes in a simulated NICU. J of Perinatol 2016;36(12):1128–31.

13. Sharma D, Murki S. Making neonatal intensive care: cost effective. J Matern Fetal Neonatal Med 2021;34(14):2375–83.
14. Walsh E, LI S, Black L, Kuzniewicz M. Incremental Cost of Prematurity by Week of Gestational Age. AJP Rep 2019;9(1):e76–83.
15. Capaciteitsorgaan. Capaciteitsplan 2020-2023. Utrecht: 2020. https://capaciteitsorgaan.nl/app/uploads/2020/11/20200119_Capaciteitsplan-FZO-AVP-2020_DEF-WEB.pdf (accessed 15 Mar 2023).
16. Wise J. Neonatal units in Wales are understaffed and under-resourced, says report. BMJ 2016;354:i3768.
17. Institute of Medicine (IOM). Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C: National Academy Press; 2001.
18. Zaka N, Alexander E, Manikam L, Norman ICF, Akhbari M, Moxon S, Ram PK, Murphy G, English M, Niermeyer S, Pearson L. Quality improvement initiatives for hospitalized small and sick newborns in low- and middle-income countries: a systematic review. Implement Sci 2018; 13(1):20.
19. Ellsbury DL, Clark RH, Ursprung R, Handler DL. Dodd ED, Spitzer AR A multifaceted approach to improving outcomes in the NICU: the Pediatrix 100 000 Babies Campaign. Pediatrics 2016;137(4): e20150389.
20. Edwards EM, Ehret DEY, Soll RF, Horbar JD. Vermont Oxford Network: a worldwide learning community. Transl Pediatr 2019 Jul; 8(3): 182–92.
21. Rolnitsky A, Unger S, Urbach D, Bell CM. The price of neonatal intensive care outcomes – in-hospital costs of morbidities related to preterm birth. Front Pediatr 2023;11:1068367.
22. Porter ME. What is value in health care? N Eng J Med 2010; 363(26):2477-81.
23. Partridge JC, Dickey BJ. Decision-making in Neonatal Intensive Care: interventions on Behalf of Preterm infants. NeoReviews 2009;10(6):e270-9.
24. Rhodes R, Holzman IR. Is the best interest standard good for pediatrics? Pediatrics 2014;134(suppl 2):S121–S129
25. Edwars EM, Ehret DEY, Soll RF, Horbar JD. Vermont Oxford Network: a worldwide learning community. Transl Pediatr 2019;8(3):182-92.
26. Bohmer RMJ. Leading clinicians and clinicians leading. N Engl J Med 2013;368(16):1468-70.
27. Sulmasy LS, Bledsoe TA, ACP Ethics Professionalism and Human Rights Committee. American College of Physicians Ethics Manual: Seventh Edition. Ann Intern Med 2019;170(2 Suppl):S1-32.
28. https://heckmanequation.org.
29. Routine provision of feedback from patient-reported outcome measurements to healthcare providers and patients in clinical practice. Cochrane Database Syst Rev. 2021; 2021(10): CD011589.
30. Austin E, LeRouge C, Hartzler AL, Segal C, Lavallee DC. Capturing the patient voice: implementing patient-reported outcomes across the health system. Qual Life Res. 2020;29(2):347–55.
31. Schouten E, Haupt J, Ramirez J, Sillett N, Nielsen C, Clarke A, Matkin L, Joseph A, Been J, Bolaños González I, Cheong J, Daly M, Kirpalani H, Mader S, Maria A, Matijasevich A, Mittal R, Mutesu-Kapembwa K, Vavouraki E, Webbe J, Wolke D, Zeitlin

J, Flemmer A. Standardized Outcome Measures for Preterm and Hospitalized Neonates: An ICHOM Standard Set. Neonatology 2022; 119(4): 443–54.

32. Berwick DM, Noal TW, Whittington J. The triple aim: care, health, and cost. Health Aff 2008;27(3):759-69.
33. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. Ann Fam Med 2014;12(6):573-6.
34. Szpecht D, Szymankiewicz M, Nowak I, Gadzinowski J. Intraventricular hemmorhage in neonates born before 32 weeks of gestation – retrospective analysis of risk factors. Childs Nerv Syst 2016;32:1399-1404.
35. Hollnagel E, Wears RL, Braithwaite J. From Safety-I to Safety-II: a white paper. Brussels (Belgium): 2013. https://www.england.nhs.uk/signuptosafety/wp-content/uploads/sites/16/2015/10/safety-1-safety-2-whte-papr.pdf

SECTION ONE

Measurement of neonatal outcome

Not everything that counts can be counted
and not everything that can be counted counts

Albert Einstein
Duits-Amerikaans natuurkundige (1879 - 1955)

CHAPTER 2

CHAPTER 2

Early acute kidney injury in preterm and term neonates:

incidence, outcome, and associated clinical features

Dario Gallo, Karen A. de Bijl-Marcus, Thomas Alderliesten, Marc Lilien, Floris Groenendaal

Neonatology, 2021

2.1 ABSTRACT

Background: Critically ill neonates are at high risk of kidney injury, mainly in the first days of life. Acute kidney injury (AKI) may be underdiagnosed due to lack of a uniform definition. In addition, longterm renal follow-up is limited.

Objective: To describe incidence, etiology, and outcome of neonates developing AKI within the first week after birth in a cohort of NICU-admitted neonates between 2008 and 2018. Renal function at discharge in infants with early AKI was assessed.

Methods: AKI was defined as an absolute serum Cr (sCr) value above 1.5 mg/dL (132 µmol/L) after the first 24 h or as stage 2–3 of the NIDDK neonatal definition. Clinical data and outcomes were collected from medical records and retrospectively analyzed.

Results: From January 2008 to December 2018, a total of 9,376 infants were admitted to the NICU of Wilhelmina Children's Hospital/UMC Utrecht, of whom 139 were diagnosed with AKI during the first week after birth. In 72 term infants, the most common etiology was perinatal asphyxia (72.2%), followed by congenital kidney and urinary tract malformations (CAKUT) (8.3%), congenital heart disease (6.9%), and sepsis (2.8%). Associated conditions in 67 preterm infants were medical treatment of a hemodynamic significant PDA (27.2%), CAKUT (21%), and birth asphyxia (19.4%). Among preterm neonates and neonates with perinatal asphyxia, AKI was mainly diagnosed by the sCr >1.5 mg/dL criterion. Renal function at discharge improved in 76 neonates with AKI associated with acquired conditions. Neonates with stage 3 AKI showed increased sCr values at discharge. Half of these were caused by congenital kidney malformations and evolved into chronic kidney disease (CKD) later in life. Neurodevelopmental outcome (NDO) at 2 years was favorable in 93% of surviving neonates with detailed follow-up.

Conclusion: During the first week after birth, AKI was seen in 1.5% of infants admitted to a level III NICU. Renal function at discharge had improved in most neonates with acquired AKI but not in infants diagnosed with stage 3 AKI. Longterm renal function needs further exploration, whereas NDO appears to be good.

2.2 BACKGROUND

Acute kidney injury (AKI) is defined by an acute reduction of kidney function, resulting in uremia, altered fluid balance, and disturbed electrolytes homeostasis. In critically ill neonates, AKI is relatively common and occurs mainly in the first days of life, secondary to hypovolemia, hypotension, and ischemia, and less frequently to primary kidney disease [1]. AKI has been traditionally defined as an increase of serum Cr (sCr) above 1.5 mg/dL (132 µmol/L) [2–7].

From 2008, the RIFLE criteria have been adapted to neonates from older infants and adults, after reports stating that residual damage might occur even after a small increase in sCr, evolving into CKD later in life [8]. Using the adapted criteria, the incidence of AKI has become higher, but longterm renal follow-up is scarce [9]. In older children, a 2- or 3-fold rise of sCr from baseline (stage 2–3 AKI) is associated with increased mortality and morbidity [10].

Moreover, diagnosis of AKI in the first days after birth is cumbersome, due to developing renal physiology and unreliable assessment of diuresis. In the present study, we aim to describe incidence, etiology, and outcomes of neonates developing AKI within the first week after birth in a cohort of neonates born between 2008 and 2018. Renal function at discharge in these infants as well as neurodevelopmental outcome (NDO) were assessed. The clinical description of a patient cohort can be used to tailor a screening protocol for AKI and serve as the foundation for a renal follow-up program in the NICU.

2.3 MATERIAL and METHODS

2.3.1 Study population and data acquisition

From January 2008 to December 2018, a total of 9,376 neonates was admitted to the NICU of Wilhelmina Children's Hospital/ University Medical Center Utrecht. These neonates were eligible for this retrospective study.

Infants admitted to the NICU had daily blood sampling for blood gases, electrolytes, glucose, and hematological examina- tions. At least one sCr measurement was obtained in case of reduced urinary output (<1 mL/kg/h over 12 h) in preterm infants and in term infants with clinical concerns. In all infants with AKI, the last sCr level before discharge was noted. In our NICU, early AKI was defined as a sCr above 1.5 mg/dL (132 µmol/L) after the first 24 h of life, despite

a normal maternal renal function, in the first week after birth [2, 3]. In addition, AKI was defined as stage 2–3 of NIDDK neonatal definition. Stage 2 was identified by a 2–2.9-fold increase of sCr from baseline, while stage 3 by a 3-fold increase or a sCr >2.5 mg/dL (221 μmol/L) [8]. Preterm and fullterm infants were analyzed separately. Clinical features and outcomes were arranged according to etiology and AKI categorization. The following clinical data were collected from medical records: maternal disease (such as preeclampsia), presence of oligo/ anhydramnion, gestational age (GA), birth weight, sex, mode of delivery, multiple birth, Apgar scores (AS) at 1 and 5 min, resuscitation, and need for mechanical ventilation. Risk factors for AKI were explored, including need for inotropes for hemodynamic instability, use of nephrotoxic drugs such as gentamycin and vancomycin, and the following neonatal conditions: perinatal asphyxia, congenital kidney and urinary tract malformations (CAKUT), congenital heart disease (CHD), treatment for hemodynamic significant patent ductus arteriosus with ibuprofen/indomethacin (NSAID) or surgical closure, arterial thrombosis, sepsis, and necrotizing enterocolitis.

Perinatal asphyxia was defined as persistence of an Apgar score <5 at 10 min or severe acidosis in umbilical cord blood gas (pH <7.00 or BE <−16 mmol/L). Routine assessment of NDO was performed in term infants with hypoxic ischemic encephalopathy and in preterm infants with a GA <30.0 weeks or a birth weight <1,000 grams. NDO included the Griffiths' Mental Development Scales (GMDS) at 15 months and the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III) at 24 months. From the BSID-III, only the cognitive (CS) and motor scales (MS) were assessed.

2.3.2 Statistical analysis

Statistical analysis was performed using IBM SPSS v 21.0 (Chicago, IL). Data were described as percentages, mean ± SD, and median ± IQR where appropriate. Renal function was described as mean sCr ± SD value. Student *t* tests or Kruskal-Wallis tests were used where appropriate. Differences were considered statistically significant at alpha 0.05.

2.4 RESULTS

2.4.1 Study population

Of the 9,376 infants admitted to the NICU over the study period, 139 (1.5%) developed AKI in the first week after birth, of whom 72 (52%) were born at term and 67 (48%) preterm. Neonatal clinical characteristics are summarized in Table 2.1.

2.4.2 Etiology

Among all neonates with early AKI, 14% had CAKUT, 81% developed AKI in association to acquired conditions, and an additional 5% because of congenital heart disease. The most frequent potential causes in preterm and fullterm infants are reported in Table 2.2. Genetic syndromes were diagnosed in 8 infants, of which 4 cases had kidney malformations. Arterial thrombosis of the aorta and subsequent renal ischemia resulted from umbilical artery catheterization in all cases. In Table 2.3, the main clinical factors are related to AKI definition and staging.

Table 2.1: Neonatal clinical features

	Preterm (*n* = 67), *n* (%)	Term (*n* = 72), *n* (%)
GA, wk (mean ± SD)	30.5 ± 4.0	39.2 ± 1.0
< 28 wk	25 (37.3)	
< 1,000 g	21 (31.3)	
Sex (male)	44 (65.7)	46 (63.9)
Birth weight, g (mean ± SD)	1,658 ± 841	3,398 ± 461
Mode of birth		
- Spontaneous vaginal	17 (25.4)	29 (40.3)
- Vacuum	1 (1.5)	8 (11.1)
- Caesarean section	49 (73.1)	35 (48.6)
Twin	16 (23.9)	2 (2.8)
Maternal disease		
- Preeclampsia	11 (16.4)	4 (5.6)
Sentinel event at birth	8 (11.9)	17 (23.6)
Oligo/anhydramnion	9 (13.4)	7 (9.7)
Apgar score (median, IQR)		
1 min	5 (4)	2 (4)
5 min	7 (4)	5 (5)
Resuscitation (chest compression)	8 (11.9)	21 (29.2)
Small for GA (< 2 SD)	5 (7.5)	
Mechanical ventilation	39 (58.2)	40 (55.6)
Inotropes	30 (44.8)	39 (54.2)

Table 2.2: Clinical factors in preterm and term infants with AKI

	Preterm (*n* = 67), *n* (%)	Term (*n* = 72), *n* (%)
CAKUT	14 (20.9)	6 (8.3)
Syndrome	5 (7.5)	3 (4.2)
Perinatal asphyxia	13 (19.4)	52 (72.2)
- HIE with TH	8 (11.9)*	34 (47.2)
Congenital heart disease	2 (3.0)	5 (6.9)
Aortic/renal artery thrombosis	3 (4.5)	1 (1.4)
Sepsis	2 (3.0)	2 (2.8)
NEC	1 (1.5)	1 (1.4)
PDA NSAID treatment	18 (26.9)	
- Indomethacin	17 (25.4)	
- Ibuprofen	1 (1.5)	
Gentamycin and/or vancomycin	14 (20.9)	8 (11.1)
No associated conditions	12 (17.9)	3 (4.2)

AKI, acute kidney injury; CAKUT, congenital kidney and urinary tract malformations; HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia; NEC, necrotizing enterocolitis; PDA, persistent ductus arteriosus; NSAID, non-steroid anti-inflammatory drug. * These preterm infants had a gestational age of 35-36 weeks.

Table 2.3: Main clinical factors related to definition of AKI

	Preterm	CAKUT	Perinatal Asphyxia	HIE with TH	CHD	PDA treatment
Stage 2, *n* (%)	12 (18)	4 (20)	4 (6)	3 (7)	2 (30)	3 (17)
Stage 3, *n* (%)	8 (12)	11 (55)	11 (17)	6 (14)	1 (13)	
> 1.5 mg/dL, *n* (%)	47 (70)	5 (25)	50 (77)	33 (79)	4 (57)	15 (83)

AKI, acute kidney injury; CAKUT, congenital kidney and urinary tract malformations; HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia; CHD, congenital heart disease; PDA, persistent ductus arteriosus.

2.4.3 Outcomes

Outcomes were analyzed separately for infants diagnosed with AKI stages 2 and 3 and with 1.5 mg/dL criterion. Serum Cr values at discharge are reported in Table 2.4. Renal function had improved in 35 term and 41 preterm infants, whereas neonates with AKI stage 3 showed significantly increased sCr values at discharge from the NICU. Table 2.5 reports follow-up data. NDO for term and preterm infants is described in Table 2.6. Among infants with acquired AKI diagnosed by 1.5 mg/dL criterion, 2 term asphyxiated neonates developed cerebral palsy and deafness, and 3 preterm neonates had a Griffiths' score at 15-18 months <−1 SD (<88); however, only in 1 patient neurodevelopment delay was persistent using the BSID-III at 2 years of age.

Table 2.4: sCr values (mg/dL) at discharge from the neonatal unit for preterm and full-term infants according to the definition of AKI

	Stage 2	Stage 3	> 1.5 mg/dL	*p* value
Full-term	0.44 ± 0.05, *n* = 3	1.73 ± 0.9, *n* = 10	0.66 ± 0.29, *n* = 32	< 0.01
Preterm	0.64 ± 0.23, *n* = 10	4.09 ± 1.7, *n* = 6	0.61 ± 0.32, *n* = 31	< 0.01

sCr, serum Cr; AKI, acute kidney injury.

Table 2.5: Follow-up data

Outcome	Stage 2 (*n* = 15), *n* (%)	Stage 3 (*n* = 21), *n* (%)	> 1.5 mg/dL (*n* = 103), *n* (%)
Died	2 (13.3)	4 (19)	35 (34)
Surviving	13	17	68
CKD	2 (15.4)	9 (53)	2 (2.9)
BPD	2 (15.4)	0	7 (10.3)
Brain injury	2 (15.4)	4 (23.5)	20 (29.4)
- Cystic PVL	1 (7.7)	0	2 (2.9)
- IVH	1 (7.7)	0	10 (14.7)
- Perinatal asphyxia	0	4 (23.5)	8 (11.8)

PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; CKD, chronic kidney disease. * Percentages of surviving infants.

Table 2.6: Neurodevelopmental outcome (mean ± SD)

Full-term infants	Stage 2 (*n* = 2)	Stage 3 (*n* = 4)	> 1.5 mg/dL (*n* = 14)
Griffiths 15–18 months	96 ± 6 (*n* = 2)	102 ± 7 (*n* = 4)	94 ± 10 (*n* = 14)
BSID 2 year cognition	145 (*n* = 1)	97 ± 6 (*n* = 3)	109 ± 9 (*n* = 9)
BSID 2 year motor	133 (*n* = 1)	111 ± 1 (*n* = 2)	118 ± 14 (*n* = 9)
Adverse			*n* = 2 *
Preterm infants	**Stage 2 (*n* = 5)**	**Stage 3 (*n* = 1)**	**> 1.5 mg/dL (*n* = 16)**
Griffiths 15–18 months	93 ± 15 (*n* = 5)	85 (*n* = 1)	96 ± 12 (*n* = 16)
BSID 2 year cognition	115 ± 0 (*n* = 2)		104 ± 12 (*n* = 17)
BSID 2 year motor	115 ± 12 (*n* = 2)		108 ± 13 (*n* = 15)
Adverse			*n* = 1 **

* 1 deafness and 1 cerebal palsy ** 1 neurodevelopmental impairment

2.5 DISCUSSION

Critically ill neonates in the NICU are at high risk of AKI due to associated comorbidity, fluid and blood pressure imbalance, and nephrotoxic drug exposure [11]. In the present study, we assessed the incidence of AKI and outcome in a cohort of term and preterm neonates. AKI was defined using a combination of 2 definitions. Given the limits of sCr as a measure of kidney function, particularly in the first week after birth [12], we used a sCr cutoff of 1.5 mg/dL [2–4]. This clinical definition describes a severe kidney impairment and is still adopted in research articles [5–7]. Among neonates with perinatal asphyxia, it showed a positive predictive value for an adverse outcome [13]. Furthermore, AKI was defined as stage 2-3 of NIDDK neonatal AKI workshop [8]. In the present study, we did not include patients with AKI stage 1 because of the scarce evidence that such mild AKI is associated with longterm consequences [14,15], whereas its incidence in the NICU is quite high [16].

Of our NICU-admitted patients, 139 (1.5%) developed AKI, of whom 20 (14%) had CAKUT. Using the sCr 1.5 mg/dL criterion, Agras et al. [3] and Mortazavi et al. [4] reported incidences of 3.4 and 2.6%, respectively. Our percentage of infants with AKI is slightly lower, and this might be caused by our focus on AKI in the first week after birth. In contrast, Charlton et al. [16] in the "AWAKEN" cohort diagnosed early AKI according to the KDIGO definition from stage 1 and found, among all enrolled infants, a higher incidence of 11%.

In line with previous reports, in our cohort of neonates, AKI was more often the result of acquired as opposed to congenital abnormalities [3]. Perinatal asphyxia was the most frequent associated condition in term neonates with AKI. Several studies confirm the high prevalence of AKI in asphyxiated neonates, as high as 72% by Hankins et al. [17], 54% by Gupta et al. [18], and 29.5% by Bozkurt and Yucesoy [19]. In more than 70% of asphyxiated neonates of our cohort, AKI was diagnosed by the 1.5 mg/dL criterion. This can be explained in the context of early kidney injury, as the first measured sCr value after birth can already be increased without a previous value to relate to. Conversely, among infants with congenital anomalies of the kidney and urinary tract, more than half had stage 3 AKI, hence showing a severe kidney impairment. All patients had a prenatal diagnosis, and oligo/anhydramnion was present in case of bilateral kidney involvement [20].

In the majority of cases (53%), the presence of the posterior urethral valves or bilateral kidney dysplasia led to CKD (stage II–V), with 2 infants requiring dialysis after the neonatal period and later kidney transplant. In the present study, a

relatively high percentage of preterm infants were born before 28 weeks of gestation, as according to a national protocol, all infants with a GA below 32 weeks are treated in level III NICUs in the Netherlands.

In these extremely preterm born infants, AKI was more frequently associated with the treatment of a hemodynamic significant PDA. AKI may result as an adverse effect of indomethacin administration and, in our cohort, indomethacin was used as a first-line therapy until 2016. In line with the literature, we find that a renal insult was common in more premature neonates [21]. However, sCr values did not reach 2.5 mg/dL as for AKI stage 3, except for infants with congenital AKI. Congenital heart disease due to coarctation of the aorta, aortic arch interruption, hypoplastic left heart syndrome, and transposition of the great arteries caused AKI as a result of systemic hypoperfusion [22]. Sepsis was a minor cause of AKI in both preterm and term neonates, in contrast with findings of Agras et al. [3] and Bolat et al. [6]. However, we looked only at early onset sepsis related to kidney injury in the first week, and the incidence of early onset sepsis in our population is low. Since long-term follow-up of renal function is missing, we assessed the last sCr before discharge as a measure of kidney function. As expected, infants with AKI stage 3 still had significantly increased sCr at discharge from the NICU and half of the patients developed CKD later in life. In infants diagnosed as stage 2 or with 1.5 mg/ dL criterion, renal function had improved at the time they could be discharged from the NICU although normal sCr values were not reached in all. In most cases, AKI was the result of systemic disease. This is reflected in the number of patients with an adverse outcome, in addition to a high mortality (35%), high incidence of bronchopulmonary dysplasia (9%), and brain injury (27%).

Previous studies reported that in infants with birth asphyxia, AKI could be associated with short-term neurological outcome [23, 24]. However, in our cohort, NDO at 2 years of age was favorable almost in all cases, including neonates with AKI due to asphyxia, and independently from AKI categorization. Furthermore, the clinical management of AKI was conservative in all but 3 infants.

2.6 STUDY LIMITATIONS

The study has several limitations. First, this is a monocentric retrospective study. Neonatal sCr levels are not assessed routinely in the first days after birth of otherwise healthy neonates and are not part of the point of care of preterm infants, in order to minimize blood loss. Furthermore, sCr is a poor marker of renal

damage. Recent studies have looked at more specific and sensitive markers, like NGAL and KIM1 in urine, although there is yet very little evidence in neonates [25]. Thus, we may have underestimated the prevalence of AKI in our population. However, sCr levels are measured during the first week after birth in at least 40% of neonates who were admitted to our level III NICU. In addition, since most fullterm infants with congenital heart malformations are not admitted to the NICU but to the PICU in our hospital, the percentage of infants with AKI in fullterm infants might be somewhat higher. To date, a uniform definition of AKI is still lacking, and, in the first week after birth, it needs to consider the developing renal physiology [26, 27]. We acknowledge that using a different definition of AKI could change its incidence in our population. Finally, we would like to emphasize that in our center, as in most NICUs, there is not a renal follow-up program for neonates with AKI.

2.7 CONCLUSION

Our study shows that, with the exception of infants with CAKUT, the majority of infants are discharged from the NICU with an improving sCr. However, we are not able to make predictions on long-term kidney function of these patients. NDO of our cohort was within the normal range in most high-risk infants with detailed follow-up examination of neurodevelopment. Assessment of renal outcome in the NICU is relevant. Ideally, measurement of sCr level, blood pressure, renal protein excretion, and tubular function testing should be performed. Further studies are needed to define the optimal timing of these follow-up assessments [28].

The study provides an overview of AKI occurring in the early clinical course of neonates admitted to a level III NICU. Neonates with acquired AKI were generally severely ill and AKI is associated with high morbidity and mortality of both preterm and term infants. Episodes of AKI were generally transient and self-limiting and were mainly diagnosed by 1.5 mg/dL criterion. The clinical management was conservative almost in all cases, although normal levels of sCr were not seen in all infants at discharge. In contrast, infants with AKI stage 3 had significantly increased sCr, confirming them to be at high risk of renal sequelae. A renal follow-up program in the NICU is needed; further studies will define the optimal timing for assessment.

REFERENCES

1. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, et al. Neonatal acute kidney injury. Pediatrics. 2015;136(2): e463–73.
2. Gouyon JB, Guignard JP. Management of acute renal failure in newborns. Pediatr Nephrol. 2000 Sep;14(10–11):1037–44.
3. Agras PI, Tarcan A, Baskin E, Cengiz N, Gurakan B, Saatci U. Acute renal failure in the neonatal period. Ren Fail. 2004;26(3):305–9.
4. Mortazavi F, Hosseinpour Sakha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3(3):136–40.
5. Viswanathan S, Manyam B, Azhibekov T, Mhanna MJ. Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. Pediatr Nephrol. 2012;27(2):303–11.
6. Bolat F, Comert S, Bolat G, Kucuk O, Can E, Bulbul A, et al. Acute kidney injury in a single neonatal intensive care unit in Turkey. World J Pediatr. 2013;9(4):323–9.
7. Bansal SC, Nimbalkar AS, Kungwani AR, Pa- tel DV, Sethi AR, Nimbalkar SM. Clinical profile and outcome of newborns with acute kidney injury in a level 3 neonatal unit in western India. J Clin Diagn Res. 2017;11(3):SC01–4.
8. Zappitelli M, Ambalavanan N, Askenazi DJ, Moxey-mims MM, Kimmel PL, Star RA, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017; 82(4):569–73.
9. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Neonatal Kidney Collaborative (NKC). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017 Nov;1(3):184–94.
10. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis. 2012; 59(4):523–30.
11. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care. 2004;8(4):R204–12.
12. Boer DP, De Rijke YB, Hop WC, Cransberg K, Dorresteijn EM. Reference values for serum creatinine in children younger than 1 year of age. Pediatr Nephrol. 2010;25(10):2107–13.
13. Aggarwal A, Kumar P, Chowdhary G, Ma- jumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. J Trop Pediatr. 2005;51(5):295–9.
14. Weintraub AS, Connors J, Carey A, Blanco V, Green RS. The spectrum of onset of acute kidney injury in premature infants less than 30 weeks gestation. J Perinatol. 2016;36(6):474– 80.
15. Maqsood S, Fung N, Chowdhary V, Raina R, Mhanna MJ. Outcome of extremely low birth weight infants with a history of neonatal acute kidney injury. Pediatr Nephrol. 2017;32(6): 1035–43.

16. Charlton JR, Boohaker L, Askenazi D, Brophy PD, D'Angio C, Fuloria M, et al. Incidence and risk factors of early onset neonatal AKI. Clin J Am Soc Nephrol. 2019;14(2):184–95.
17. Hankins GD, Koen S, Gei AF, Lopez SM, Van Hook JW, Anderson GD. Neonatal organ system injury in acute birth asphyxia sufficient to result in neonatal encephalopathy. Obstet Gynecol. 2002;99(5 Pt 1):688–91.
18. Gupta C, Massaro AN, Ray PE. A new approach to define acute kidney injury in term newborns with hypoxic ischemic encephalop- athy. Pediatr Nephrol. 2016;31(7):1167–78.
19. Bozkurt O, Yucesoy E. Acute kidney injury in neonates with perinatal asphyxia receiving therapeutic hypothermia. Am J Perinatol. 2020 Jan 27.
20. Rodriguez MM. Congenital anomalies of the kidney and the urinary tract (CAKUT). Fetal Pediatr Pathol. 2014 Oct–Dec;33(5–6):293– 320.
21. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus ar- teriosus in preterm infants. JAMA. 2018; 319(12):1221–38.
22. Agras PI, Derbent M, Ozcay F, Baskin E, Turkoglu S, Aldemir D, et al. Effect of congenital heart disease on renal function in childhood. Nephron Physiol. 2005;99(1): p10–5.
23. Sarkar S, Askenazi DJ, Jordan BK, Bhagat I, Bapuraj JR, Dechert RE, et al. Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. Pediatr Res. 2014;75(3): 431–5.
24. Shellhaas RA, Kushwaha JS, Plegue MA, Selewski DT, Barks JD. An evaluation of cerebral and systemic predictors of 18-month outcomes for neonates with hypoxic ischemic en- cephalopathy. J Child Neurol. 2015;30(11): 1526–31.
25. Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, et al. Serum and urine acute kidney injury biomarkers in asphyxiated neonates. Pediatr Nephrol. 2012; 27(9):1575–82.
26. Cleper R, Shavit I, Blumenthal D, Reisman L, Pomeranz G, Haham A, et al. Neonatal acute kidney injury: recording rate, course, and outcome: one center experience. J Matern Fetal Neonatal Med. 2019;32(20):3379–85.
27. Bruel A, Rozé JC, Quere MP, Flamant C, Boivin M, Roussey-Kesler G, et al. Renal outcome in children born preterm with neonatal acute renal failure: IRENEO: a prospective controlled study. Pediatr Nephrol. 2016; 31(12):2365–73.
28. Askenazi DJ, Morgan C, Goldstein SL, Selews- ki DT, Moxey-Mims MM, Kimmel PL, et al. Strategies to improve the understanding of long-term renal consequences after neonatal acute kidney injury. Pediatr Res. 2016;79(3): 502–8.

CHAPTER 3

CHAPTER 3

Morbidity and trends in length of hospitalization of very preterm infants born between 2008 - 2021:

A cohort study

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Submitted

3.1 ABSTRACT

Objective: This study investigated changes in length of stay (LoS) at a level III/IV neonatal intensive care unit (NICU) and level II neonatology departments until discharge home for very preterm infants and identified factors influencing these trends.

Design: Retrospective cohort study based on data recorded in the Netherlands Perinatal Registry between 2008 and 2021.

Setting: A single level III/IV NICU and multiple level II neonatology departments in the Netherlands.

Patients: NICU-admitted infants (n=2646) with a gestational age (GA) <32.0 weeks.

Main outcome measures: LoS at the NICU and overall LoS until discharge home.

Results: The results showed an increase of 6 days in overall LoS after accounting for confounding variables (95%CI: 4–8, p<0.001). This increase was primarily driven by extended LoS at level II hospitals, while LoS at the NICU remained stable. The study also indicated a strong association between severe complications of preterm birth and LoS. The revision of the Dutch perinatal guideline in 2010, which lowered the threshold for active treatment to 24.0 weeks, appears to have contributed to the increased LoS.

Conclusion: The findings of this study highlight the increasing overall LoS for very preterm infants. LoS of very preterm infants is mainly influenced by the occurrence of complications, and GA, as the occurrence of complications is negatively associated with GA at birth.

3.2 BACKGROUND

Length of stay (LoS) at the NICU is an important indicator of clinical outcomes and (economic) performance of the healthcare system [1,2]. Predicting LoS is crucial for resource planning, decision-making and parental counseling. Many factors influence LoS, including infant characteristics, quality and complexity of care, management, as well as the availability of post-discharge healthcare facilities [1,3,4]. Trends towards shorter hospital stays have been observed for many hospital populations within developed countries, attributed to enhanced patient outcomes and the delivery of more efficient care [5–7]. During the final decade of the previous century, the Vermont–Oxford Network and others reported similar trends of decreasing LoS at the NICU [8,9]. In more recent years, NICU's have implemented multiple interventions to facilitate a safe and earlier discharge of (very) preterm infants [10–14]. However, despite the implementation of these interventions, recent studies conducted in multiple developed countries have shown a consistent or even increased LoS at the NICU [8,15,16]. These studies speculated that improvements in survival may have led to higher LoS, since more infants at extremely low gestational age (GA) and/or with more severe health conditions survive to discharge [8,15,16]. If and how these changing population characteristics are related to the LoS at the NICU has not been elucidated. Furthermore, in several neonatal health care systems (including the Netherlands), infants are being transferred to a level II hospital to receive convalescent care (APPENDIX). Limited information is available regarding the overall duration of hospitalization of preterm infants until they are discharged home after being transferred.

The aims of the study are:

1. To investigate changes in the overall length of hospitalization until discharge home, encompassing both the LoS at the NICU and the level II departments, for surviving preterm infants (GA <32.0 weeks) between 2008 and 2021.
2. To identify variables that influenced trends in LoS.

These data could facilitate predicting LoS and possibly provide a deeper knowledge of developments regarding care demands of preterm infants.

3.3 MATERIAL and METHODS

3.3.1 Study design

This study is a retrospective cohort study based on data from the Netherlands Perinatal Registry (www.perined.nl), which were completed by manual medical record review of all individual records. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3.3.2 Study subjects

All infants born alive below 32.0 weeks gestation between 01-01-2008 and 31-12-2021 admitted to the level III/IV NICU of Wilhelmina Children's Hospital of Utrecht were eligible for inclusion. Exclusion criteria consisted of: (1) major congenital anomalies (defined as chromosomal anomalies, congenital anomaly requiring surgery within the neonatal period and/or congenital anomalies incompatible with life), (2) infants transferred from/to another level III/IV NICU.

3.3.3 Study period

The study period was divided into three subgroups:

1: 2008 – 2010: period in which infants with a GA <25.0 weeks were admitted to the NICU only by exception.

2: 2011 – 2015: first period after the revision of the Dutch perinatal guideline, lowering the threshold to offer active treatment from 25.0 to 24.0 weeks of gestation.

3: 2016 – 2021: for trend analyses a third period was studied.

3.3.4 Setting

The NICU of the Wilhelmina Children's Hospital is part of a Dutch university hospital with 24 level III/IV NICU beds and many pediatric medical subspecialists. The NICU is located in a highly regionalized area with four regional post-NICU/High care (HC) departments and three non-postIC/HC units. A high percentage (>90%) of infants are transferred to level II hospitals for convalescent care. Infants are transferred when all of the following criteria are met: corrected GA ≥30.0 weeks, weight ≥1000 grams, respiratory support consisting of nasal continuous positive airway pressure (nCPAP) or less (such as humidified high-flow nasal cannula, HHFNC, or low flow), and no need of specialized intensive care treatment.

3.3.5 Outcomes (of each period)

- Primary outcomes:

(1) Median LoS (days) at the NICU.

(2) Median LoS (days) until discharge home (LoS NICU + LoS level II hospital).

- Secondary outcomes:

(1) In-hospital mortality rate, which was compared to the expected mortality rate, calculated using a previously published prognostic model [17,18].

(2) Morbidity-rate of each period, defined as a composite variable of at least one of the following complications: chronic lung disease (CLD: defined as oxygen needed at 36 weeks corrected GA), intraventricular hemorrhage grade 3 (IVH-III), cerebral venous infarction (VI), posthemorrhagic ventricular dilatation needing intervention (PHVD), cystic periventricular leukomalacia (cPVL grade II/III), laser coagulation for retinopathy of prematurity (ROP) and necrotizing enterocolitis with indication for surgery (NECs) [19,20].

(3) Type of respiratory support at time of transfer since changing policies regarding (maximum) respiratory support at time of transfer could affect LoS.

(4) Readmission rate.

(5) The association between LoS and variables, such as period of birth, GA, birth weight <3rd percentile (small for GA, SGA), sex, antenatal corticosteroids, multiple pregnancy, Apgar score, outborn, cesarian section, CLD, duration of mechanical ventilation, IVH-III, VI, PHVD, cPVL, persistent ductus arteriosus with treatment (PDA), ROP, NECs, late onset sepsis, type of receiving level II department).

3.3.6 Statistical analysis

Patient characteristics and outcome variables were summarized as proportions, means and medians where appropriate. We estimated changes in medians over the study period with 95% confidence intervals (CIs). We used generalized linear models (GLM) to explore differences in LoS across the three study periods, as well as for differences regarding mortality, GA, and SGA. Factors found to change significantly over time ($p<0.05$) were incorporated as fixed effects into adjusted models by using generalized linear mixed-effect multivariable models, and interactions between periods and complications were tested. Statistical analyses were performed by using Statistical Package for Social Sciences for Windows version 26 (SPSS, Chicago, Illinois, USA) and R statistical software (http://www.r-project.org).

3.3.7 Ethical approval

The Medical Research Ethics Committee of Utrecht granted exemption from formal approval under the Dutch Medical Research Involving Human Subjects Act for the study (NedMec; number 22/588).

3.4 RESULTS

Overall, 2646 infants were included in the study. Of the 2776 live births below 32.0 weeks, 90 infants were excluded due to major congenital anomalies and 40 due to transfer from/to another NICU. Patient characteristics (potentially) affecting LoS of the included infants during the three study periods are presented in Table 3.1. There were significant differences between study periods regarding median GA, sex, birthweight, duration of mechanical ventilation and treatment of PDA. Furthermore, the incidence of late onset sepsis and severe ROP varied between study periods. Patient characteristics at time of discharge and the effect of severe complications on LoS are presented in Table 3.2 and 3.3. LoS at the NICU and corrected GA at time of transfer did not change significantly during the study period. However, the results approached statistical significance, indicating a trend towards longer duration of hospitalization. Median overall LoS increased six days during the study period (95% CI: 4 – 8, $p<0.001$). LoS at the NICU depending on GA and the occurrence of severe complications is shown in Figure 3.1. The OR for receiving intensive non-invasive respiratory support (HHFNC or nCPAP) at time of first discharge from the NICU during period three was 54 (95% CI: 17 – 166, $p<0.001$) when compared to period 1. In table 3.4 the results of multivariable analysis of LoS at the NICU and overall LoS are presented. LoS at the NICU and overall LoS of infants with NECs was only significant longer in period 2 and 3. Most infants with NECs, were also diagnosed with CLD. In survivors, there was a difference in overall LoS per period, adjusted for SGA, NECs, PHVD, CLD, late onset sepsis and ROP. The variables SGA, NECs, and CLD had significant different effects on LoS during different time periods. After adjusting for these variables: GA, mode of delivery, sex, and multiple birth were no longer significantly associated with overall LoS.

Table 3.1: Patient characteristics of study subjects during three time periods

PATIENT CHARACTERISTICS	PERIOD 1: 2008 – 2010	PERIOD 2: 2011 – 2015	PERIOD 3: 2016 – 2021	*p* value **
ALL INCLUDED INFANTS, INCLUDING DECEASED	**N = 594**	**N = 1034**	**N = 1018**	
GA (days) at birth (median – IQR)	210 @# (198 - 217)	206 # (192 - 216)	207 @ (194 - 216)	**<.001**
Sex (% male)	50.8% @	50.8% ^	55.8% @^	**.043**
Birthweight in grams (median – IQR)	1265 # (1000 - 1555)	1215 $^ (920 - 1475)	1263 ^ (970 - 1545)	**.001**
In-hospital mortality Number (%)	31 (5.2%)	65 (6.3%)	72 (7.1%)	.336
Survival rate (%)	94.8%	93.7%	92.9%	.336
Expected survival rate (mean survival prediction)*	92.5% @#	89.6% #	90.2% @	**<.001**
SURVIVORS	**N = 563 (94.8%)**	**N = 969 (93.7%)**	**N = 946 (92.9%)**	***p* value****
GA (days) at birth (median – IQR)	211 #@ (199 - 218)	208 # (194 - 216)	208 @ (196 - 217)	**.001**
Sex (% male)	51.2%	50.4%	55.3%	.077
Birthweight in grams (median – IQR)	1300 (1035 - 1570)	1235 ^ (960 - 1498)	1285 ^ (1005 - 1573)	**.001**
Birthweight percentile (median – IQR)	-0.61 @ (-1.55 – 0.33)	-0.60 ^ (-1.59 – 0.14)	-0.43 ^@ (-1.45 – 0.38)	**.004**
Small for gestational age (% < 3rd percentile)	17.6%	17.5%	15.2%	.317
Small for gestational age (% <10th percentile)	36.8%	37.5%	32.5%	.054
Multiple pregnancy (%)	32.7% @	27.9%	25.1% @	**.006**
Antenatal corticosteroids (% optimal)	53.6% @	51.7% ^	60.8% @^	**<.001**
Cesarean section (%)	54.7%	58.6%	53.9%	.253
Inborn (%)	87.6%	86.6%	89.8%	.081
Apgar score at 5 minutes (median – IQR)	9 #@ (8 - 9)	8 #^ (7 - 9)	8 ^@ (7 - 9)	**<.001**

SURVIVORS	PERIOD 1:	PERIOD 2:	PERIOD 3:	*p* value **
Intraventricular hemorrhage grade 3 and/or cerebral venous infarction (%)	5.7%	4.5%	3.7%	.196
Posthemorrhagic ventricular dilatation (%)	1.2%	1.0%	1.7%	.443
Cystic periventricular leukomalacia (%)	0.5%	0.5%	0.5%	.999
Necrotizing enterocolitis (%)	5.7%	7.4%	5.8%	.255
Necrotizing enterocolitis with laparotomy (%)	2.5%	3.2%	3.4%	.611
Mechanical ventilation (%mechanical ventilation)	42.6% @	45.1% ^	35.3% @^	**<.001**
Chronic lung disease (%)	31.6%	37.0%	32.8%	.059
Medication for persistent ductus arteriosus (%)	15.1%	19.6% ^	14.5% ^	**.006**
Surgical ligation persistent ductus arteriosus (%)	3.0%	4.4% ^	1.9% ^	**.006**
Late onset sepsis (%)	23.1% @	19.1% ^	14.6% @^	**<.001**
Retinopathy of prematurity with laser coagulation (%)	0.2% #@	1.3% #	2.1% @	**.007**
At least 1 major morbidity*** (%)	34.1%	38.4%	35.4%	.189
No major morbidities (%)	65.1%	61.6%	64.6%	
1 major morbidity (%)	27.7%	30.3%	28.9%	
2 major morbidities (%)	3.9%	5.6%	4.1%	
> 2 major morbidities (%)	2.5%	2.5%	2.4%	

GA = gestational age;

* Survival prediction calculated using model described by van Beek et al. ** Kruskal-Wallis

*** At least one of the following neonatal complications: chronic lung disease (CLD, defined as oxygen needed at 36 weeks postmenstrual age), intraventricular hemorrhage grade III and IV (IVH-III/IV, defined by Papile's classification), posthemorrhagic ventricle dilatation (PHVD) requiring intervention, cystic periventricular leukomalacia grade II and III (cPVL-II/III, defined by de Vries' classification), laser coagulation for retinopathy of prematurity (ROP) and necrotizing enterocolitis with indication for surgery

Statistically significant difference between period 0 and period 1;

@ Statistically significant difference between period 0 and period 2

^ Statistically significant difference between period 1 and period 2.

Table 3.2: Patient characteristics at time of discharge during three time periods

DISCHARGE CHARACTERISTICS	PERIOD 1: 2008 – 2010	PERIOD 2: 2011 – 2015	PERIOD 3: 2016 – 2021	*p* value **
ALL SURVIVORS	**N = 563**	**N = 969**	**N= 946**	
Corrected GA (weeks) at time of first discharge from the NICU (median – IQR)	32.6 (31.9 – 33.9)	32.4 (31.6 – 34.1)	32.7 (31.9 – 34.6)	.051
LoS of first admission at the NICU (days) (median- IQR)	18 (10 - 36)	17 (10 - 44)	20 (11 - 43)	.060
Respiratory support at time of first discharge form the NICU	None: 56% @# Low flow: 43% HHFNC: 0% nCPAP: 1%	None: 42% #^ Low flow: 55% HHFNC: 1% nCPAP: 2%	None: 44% @^ Low flow: 20% HHFNC: 24% nCPAP: 12%	**<.001**
Readmission rate (%)	8.0%	7.6%	5.5%	.092
Infants transferred to level II department (%)	98% @	96%	94% @	**.002**
Infants transferred home from level II hospital (%)	95%	94%	92%	.070
Corrected GA (weeks) at time of discharge home (from NICU or level II hospital) (median – IQR)	37.4 @# (36.6 – 39.0)	37.9 # (36.7 – 39.9)	38.0 @ (36.9 - 40.0)	**<.001**
Total duration hospitalization NICU (days) (median – IQR)	18 (11 - 39)	18 (10 - 45)	21 (11 – 44)	.070
Total duration hospitalization level II hospital (days) (median – IQR)	32@# (27 - 40)	36 # (28 - 45)	35 @ (28 - 45)	**<.001**
Total duration hospitalization: NICU + level II hospital (days) (median – IQR)	55 @# (44 - 72)	60 # (45 - 84)	61 @ (46 - 82)	**<.001**

SURVIVORS WITHOUT MAJOR MORBIDITIES *	PERIOD 1 N = 371	PERIOD 2 N = 597	PERIOD 3 N = 611	
Corrected GA (weeks) at time of first discharge from the NICU (median – IQR)	32.3 #	32.0 #^	32.1 ^	<.001
LoS of first admission at the NICU (median- IQR)	13 # (8 – 18)	11 #^ (8 – 15)	13 ^ (8 – 20)	<.001
Corrected GA (weeks) at time of discharge home (from NICU or level II hospital) (median – IQR)	37.0 (36.3 – 38.3)	37.1 ^ (36.3 – 38.3)	37.3 ^ (36.6 – 38.6)	.017
Total duration hospitalization: NICU + level II hospital (days) (median – IQR)	48 @ (40 – 58)	49 ^ (41 – 59)	51 @^ (42 – 63)	.020
SURVIVORS WITH AT LEAST ONE MAJOR MORBIDITY *	**PERIOD 1 N = 192**	**PERIOD 2 N = 372**	**PERIOD 3 N = 335**	
Corrected GA (weeks) at time of first discharge from the NICU (median – IQR)	34.1 @# (32.7 – 36.2)	35.0 # (33.0 – 37.6)	35.1 @ (33.3 – 37.6)	.003
LoS of first admission at the NICU (median- IQR)	45 @# (33 – 60)	53 # (38 – 76)	52 @ (38 – 76)	.001
Corrected GA (weeks) at time of discharge home (from NICU or level II hospital) (median – IQR)	38.6 @# (37.4 – 40.9)	39.9 # (38.1 – 42.1)	40.0 @ (38.3 – 42.1)	<.001
Total duration hospitalization: NICU + level II hospital (days) (median – IQR)	77 @# (64 – 94)	90 # (74 – 110)	88 @ (71 – 109)	<.001

GA = gestational age; LoS = length of stay; HHFNC = humidified high-flow nasal cannula; * At least one of the following neonatal complications: chronic lung disease (CLD, defined as oxygen needed at 36 weeks postmenstrual age), intraventricular hemorrhage grade III and IV (IVH-III/IV, defined by Papile's classification), posthemorrhagic ventricle dilatation (PHVD) requiring intervention, cystic periventricular leukomalacia grade II and III (cPVL-II/III, defined by de Vries' classification), laser coagulation for retinopathy of prematurity (ROP) and necrotizing enterocolitis with indication for surgery; ** Kruskal-Wallis test # Statistically significant difference between period 0 and period 1; @ Statistically significant difference between period 0 and period 2; ^ Statistically significant difference between period 1 and period 2.

Table 3.3: Patient characteristics at time of discharge depending on type of receiving level II department

DISCHARGE CHARACTERISTICS	Non-postIC/High care level II department N = 699 (31%)	PostIC/High care Level II department N = 1606 (69%)	*p* value**
GA at birth (days) (median – IQR)	212 (200 – 218)	208 (196 – 216)	**<.001**
At least 1 major morbidity* (%)	33.5%	33.7%	.899
Corrected GA at time of first discharge from the NICU (weeks) (median- IQR)	32.9 (32.1 – 34.6)	32.3 (31.4 – 33.6)	**<.001**
Respiratory support at time of first discharge form the NICU (%)	None: 55% Low flow: 38% HHFNC: 6% nCPAP: 1%	None: 38% Low flow: 43% HHFNC: 12% nCPAP: 7%	**<.001**
Corrected GA at time discharge home (weeks) (median- IQR)	38.0 (37.0 – 39.7)	37.6 (36.6 – 39.4)	**.001**

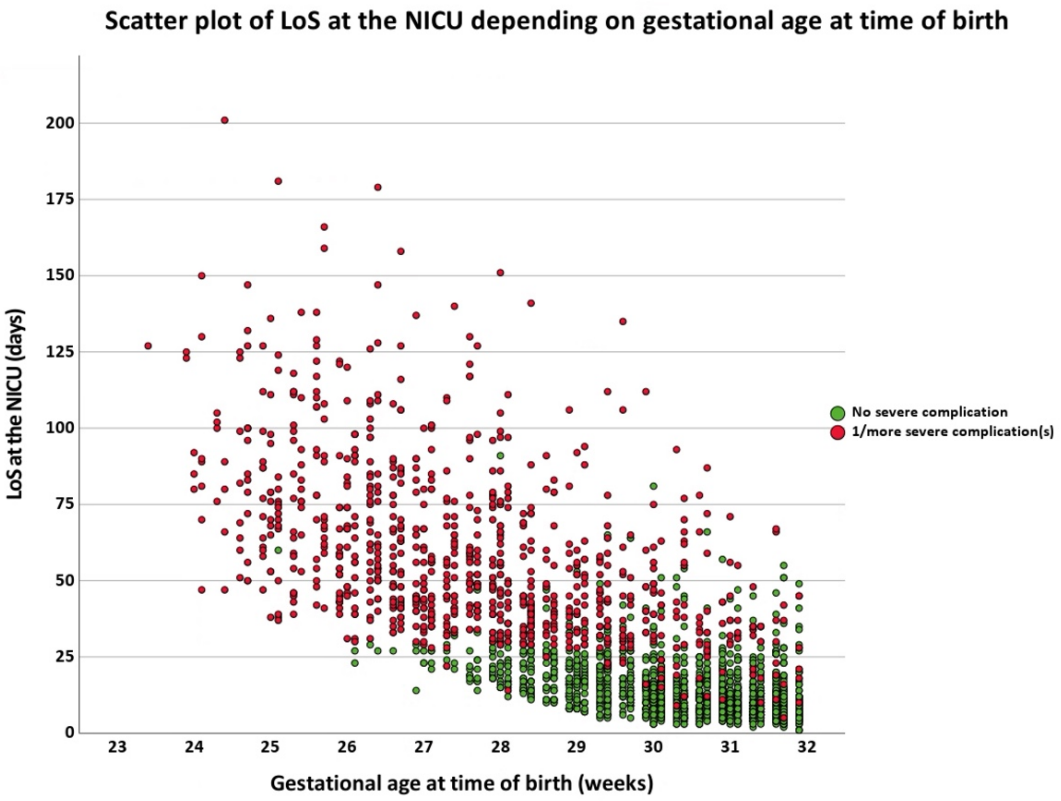
GA: gestational age; HHFNC = humidified high-flow nasal cannula; *At least one of the following neonatal complications: chronic lung disease (CLD, defined as oxygen needed at 36 weeks postmenstrual age), intraventricular hemorrhage grade III and IV (IVH-III/IV, defined by Papile's classification), posthemorrhagic ventricle dilatation (PHVD) requiring intervention, cystic periventricular leukomalacia grade II and III (cPVL-II/III, defined by de Vries' classification), laser coagulation for retinopathy of prematurity (ROP) and necrotizing enterocolitis with indication for surgery; ** Mann-Whitney U test.

Table 3.4: Best model describing LoS (days)

	MODEL: dependent variable LoS at the NICU (days) aR² 0.677			*MODEL: dependent variable overall LoS (days) hospital (NICU + level II)* aR² 0.513		
	Days of admis-sion*	95%CI Lower bound	95% CI Upper bound	Days of admis-sion*	95%CI Lower bound	95% CI Upper bound
Constant	14.9	12.9	16.9	48.2	45.9	50.5
Factors	Additional days	95%CI Lower bound	95% CI Upper bound	Additional days	95%CI Lower bound	95% CI Upper bound
SGA	2.3	0.6	3.9	7.4	2.8	12.1
Multiplet	2.0	0.6	3.5			
Period 2	-1.2	-3.1	0.8	2.0	-0.9	4.9
Period 3	1.9	-0.1	3.9	5.1	2.2	8.0
CLD	35.2	32.4	38.1	30.5	26.6	34.4
NECs**	-2.2	-11.7	7.8	-4.2	-15.6	7.3
PHVD intervention	18.4	11.7	25.0	14.3	7.1	21.6
ROP intervention	38.1	31.1	45.1	29.6	22.0	37.3
Late onset sepsis	5.2	3.5	6.9	5.9	3.6	8.1
Discharge to postIC/ HC department	-3.2	-4.6	-1.7			
Extra days CLD period 2	4.4	0.9	7.9	9.1	4.3	13.9
Extra days CLD period 3	5.5	1.9	9.1	8.2	3.3	13.1
Extra days NECs period 2	16.5	4.4	28.6	34.0	20.4	47.7
Extra days NECs period 3	5.8	-5.9	17.5	-0.9	-14.8	12.9
Extra days SGA period 2				-6.3	-12.0	-0.5
Extra days SGA period 3				-7.9	-13.9	-1.9

Best models describing LoS of first NICU admission and total duration hospitalization; GLM: general linear model; aOR = adjusted odds ratio; 95%CI = 95% confidence interval; SGA = small for gestational age, below 3rd percentile; ROP = retinopathy of prematurity; CLD = chronic lung disease; dep = department; NECs = necrotizing enterocolitis with indication for surgery; * Additional days of admission on top of 'constant'; ** NECs not significant in period 1.

Figure 3.1:



3.5 DISCUSSION

3.5.1 Increased overall LoS until discharge home

This study aimed to investigate changes in overall LoS, encompassing both the duration of stay at the NICU and the level II departments. After accounting for confounding variables, we found a median increase of six days in the overall LoS for surviving preterm infants born below 32.0 weeks of gestation between 2008 and 2021. This increase was primarily driven by extended stays at level II hospitals. Similar trends of increased LoS have been reported in other recent studies [8,15,16]. However, these studies did not differentiate between or included the LoS at the NICU and the level II hospitals.

3.5.2 Severe complications & LoS

We observed a strong association between severe complications of preterm birth and LoS at the NICU, as well as overall LoS. Infants without severe complications exhibited a consistent LoS at the NICU, with a modest increase of three days in the overall hospitalization during the study period. In contrast, infants experiencing at least one severe complication showed a substantial prolongation of seven days in NICU stay and an overall hospitalization increase of eleven days. We hypothesize that (the treatment of) severe ROP may have contributed to this extended hospitalization, considering the observed rise in the incidence of this complication during the study period. These findings underscore and confirm the significant impact of complications on LoS of very preterm infants [21]. This emphasizes the importance of comprehensive care and tailored interventions to address the complexities associated with these medical illnesses.

3.5.3. GA & LoS

Complications of preterm birth were stronger predictors of LoS when compared to GA. However, extreme preterm infants are more prone to experiencing severe complications associated with preterm birth [8]. Our observations indicate that lowering the threshold for active treatment from 25.0 to 24.0 weeks of gestation, largely contributed to an increased LoS. This supports previous research suggesting that the treatment of extremely preterm infants has a significant impact on LoS [8,15,22–25]. This is especially important considering the fact that the guideline is currently being evaluated in the Netherlands to determine whether the threshold should be lowered even further.

3.5.4. Prediction of LoS

The models described in this study can be used to predict LoS of individual infants. Factors with the greatest impact on LoS were severe complications of preterm birth occurring relatively late during the NICU-stay (e.g., CLD and ROP).

3.5.5. Improvements

Our findings did not indicate an improved survival rate, which means that the prolonged LoS cannot be attributed to more vulnerable infants surviving to discharge. However, our study did reveal several improvements in outcome and care. We observed a decrease in the frequency and median duration of mechanical ventilation, as well as a decline in the incidence of late-onset sepsis. These positive changes, along with a stable mortality rate and a lower median GA at birth, are

encouraging. They suggest advancements in preventive strategies and the overall care provided to these vulnerable infants. Furthermore, in all 3 periods the observed mortality was lower than the mortality predicted by the model of van Beek et al. [18] The increased incidence of severe ROP was expected due to the revision of guidelines regarding saturation thresholds during the study period [26].

3.5.6. Changing Patterns of Transfer

Traditionally, level II hospitals primarily received infants who were considered "feeders" and "growers" requiring minimal respiratory support after being transferred from a NICU [27]. In contrast, our study revealed a shifting trend, with more infants requiring intensive non-invasive respiratory support being transferred. This change can be attributed to the increasing demands on our NICU, operating at full capacity, due to a growing population of (extremely premature) infants with higher care needs and staffing issues [28]. Transferring stable, yet still vulnerable, infants who require intensive non-invasive respiratory support is necessary to optimize resource utilization and maintain access to care [29–31]. However, the transfer of these complex infants necessitates close coordination and communication among healthcare providers to ensure patient safety. Despite the increasing complexity and higher care needs, our study did not observe an increase in readmission rate during the study period. This finding suggests that healthcare providers at the level II hospitals have adapted to the changing needs of these infants and are providing effective treatment. Furthermore, our results revealed that infants transferred to postIC/HC level II departments more frequently were on intensive respiratory support and had a lower corrected GA at the time of transfer compared to non-postIC/HC-facilities. It is intriguing to note that despite these factors, infants transferred to post/HC-departments were discharged home at a lower corrected GA. Exploring these differences in future research may help optimize care pathways and may provide insights into ways to reduce LoS.

3.5.7. Potential consequences

Despite multiple interventions aimed at reducing LoS and transferring infants on intensive non-invasive respiratory support, our study revealed an increased overall LoS and longer LoS at the NICU for infants with major morbidities. This prolonged hospitalization has significant consequences that need to be considered. From a healthcare perspective, the increased LoS places additional strain on resources, especially when NICU's are already operating at maximum capacity [1,2,4,15,32–34]. Reaching or exceeding the capacity can lead to compromised patient safety

and places additional strain on healthcare providers. Moreover, reports have indicated a direct correlation between increased LoS and higher healthcare expenditure [15]. For the infants themselves, the extended hospitalization may result in adverse outcome since the NICU environment is associated with risks such as healthcare-associated infections [1,35–37]. Furthermore, the prolonged LoS influences the families of the infants in various ways. Parents may experience increased emotional and financial burdens due to the prolonged separation from their infants and the need to balance work and other responsibilities [38].

3.5.8. Future improvements

Efforts to optimize LoS are closely linked to those enhancing the quality of care and are both vital for improving patient outcomes, optimal resource utilization, and minimizing healthcare costs [15,16]. Our findings indicate that focusing on reducing the occurrence of severe complications associated with preterm birth could positively impact both LoS at the NICU, as well as overall LoS.

3.6 STUDY LIMITATIONS

This study examines LoS in a single, although relatively large, NICU. Previous research has identified variations in LoS across different healthcare systems [7,16]. Our NICU is located in a highly regionalized area, with a high percentage of infants being transferred. The generalizability of our findings may be limited in less regionalized areas. Additionally, organizational factors such as bed capacity were not included and accounted for in our study. In addition, we have no data regarding fetal death, death before admission to the NICU, or infants for whom it was decided not to initiate intensive care treatment in the delivery room. Another limitation is the fact that variables such as socioeconomic status, ethnicity and pregnancy related complications were not included.

3.7 CONCLUSION

Our findings demonstrate a significant increase in overall LoS for infants born with a GA below 32.0 weeks between 2008 and 2021, even after correction for confounding variables. This increase is primarily driven by the treatment of extremely premature infants and those experiencing severe complications. The prolonged LoS could potentially have far-reaching implications for healthcare systems, families, and the infants themselves.

3.8 APPENDIX

Level of neonatal care categories

LEVEL OF CARE	CARE DELIVERED	CARE PROVIDERS
LEVEL I **Well new born** neonatology department	- Provide neonatal resuscitation at every delivery - Evaluate and provide postnatal care to stable term newborn infants - Stabilize and provide care for infants born 35–37 wk gestation who remain physiologically stable - Stabilize newborn infants who are ill and those born at <35 wk gestation until transfer to a higher level of care	Pediatricians, family physicians, nurse practitioners, and other advanced practice registered nurses
LEVEL II **Special care** neonatology department	*Level I capabilities plus:* - Provide care for infants born ≥32 wk gestation and weighing ≥1500[A] g who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis - Provide care for infants convalescing after intensive care - Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both - Stabilize infants born before 32 wk gestation and weighing less than 1500[A] g until transfer to a neonatal intensive care facility	*Level I health care providers plus* Pediatric hospitalists, neonatologist, and neonatal nurse practitioners.
Level III **NICU**	*Level II capabilities plus:* - Provide sustained life support - Provide comprehensive care for infants born <32 wks gestation and weighing <1500[A] g and infants born at all gestational ages and birth weights with critical illness - Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists - Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide - Perform advanced imaging, with interpretation on an urgent basis, including computed	*Level II health care providers plus:* Pediatric medical subspecialists, pediatric anesthesiologists, pediatric surgeons, and pediatric ophthalmologists.
LEVEL IV **Regional NICU**	*Level III capabilities plus:* Located within an institution with the capability to provide: - Surgical repair of complex congenital or acquired conditions - Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site - Facilitate transport and provide outreach education	Level III health care providers plus: Pediatric surgical subspecialists

[A:] In the Netherlands, level II facilities provide care to infants born at ≥32 wk gestation and weighing ≥1200 grams. Level II post intensive care/high care department provide convalescent care to infants

[39]

REFERENCES

1 Derienzo C, Kohler JA, Lada E, et al. Demonstrating the relationships of length of stay, cost and clinical outcomes in a simulated NICU. Journal of Perinatology 2016;36:1128–31.
2 Sharma D, Murki S. Making neonatal intensive care: cost effective. Journal of Maternal-Fetal and Neonatal Medicine. 2021;34:2375–83.
3 Kim Y, Ganduglia-Cazaban C, Chan W, et al. Trends in neonatal intensive care unit admissions by race/ethnicity in the United States, 2008–2018. Sci Rep 2021;11:23795.
4 Walsh E, Ll S, Black L, et al. Incremental Cost of Prematurity by Week of Gestational Age. Am J Perinatology Reports 2019;9:e76–83.
5 Gay JC, Hall M, Morse R, et al. Observation Encounters and Length of Stay Benchmarking in Children's Hospitals. Pediatrics 2020;146. doi:10.1542/peds.2020-0120
6 Brown CM, Williams DJ, Hall M, et al. Trends in length of stay and readmissions in Children's Hospitals. Hosp Pediatr 2021;11:554–62.
7 Wen S, Liu S, Fowler D. Trends and Variations in Neonatal Length of In-hospital Stay in Canada. Canadian J of Public Health 1998;89:115–9.
8 Edwards EM, Greenberg LT, Ehret DEY, et al. Discharge age and weight for very preterm infants: 2005⇓2018. Pediatrics. 2021;147.
9 Costeloe KL, Hennessy EM, Haider S, et al. Short term outcomes after extreme preterm birth in England: Comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ (Online) 2012;345.
10 Gonya J, Martin E, McClead R, et al. Empowerment programme for parents of extremely premature infants significantly reduced length of stay and readmission rates. Acta Paediatrica, International Journal of Paediatrics 2014;103:727–31.
11 Moody C, Callahan TJ, Aldrich H, et al. Early Initiation of Newborn Individualized Developmental Care and Assessment Program (NIDCAP) Reduces Length of Stay: A Quality Improvement Project. J Pediatr Nurs 2017;32:59–63.
12 Lehtonen L, Lee SK, Kusuda S, et al. Family Rooms in Neonatal Intensive Care Units and Neonatal Outcomes: An International Survey and Linked Cohort Study. Journal of Pediatrics 2020;226:112-117.e4.
13 Örtenstrand A, Westrup B, Broström EB, et al. The Stockholm neonatal family centered care study: Effects on length of stay and infant morbidity. Pediatrics 2010;125.
14 Melnyk BM, Feinstein NF, Alpert-Gillis L, et al. Reducing premature infants' length of stay and improving parents' mental health outcomes with the Creating Opportunities for Parent Empowerment (COPE) Neonatal Intensive Care Unit Program: A randomized, controlled trial. Pediatrics 2006;118.

15 Yeung T, Rios JD, Beltempo M, et al. The Trend in Costs of Tertiary-Level Neonatal Intensive Care for Neonates Born Preterm at 220/7-286/7 Weeks of Gestation from 2010 to 2019 in Canada. Journal of Pediatrics 2022;245:72-80.e6.
16 Maier RF, Blondel B, Piedvache A, et al. Duration and time trends in hospital stay for very preterm infants differ across European regions*. Pediatric Critical Care Medicine 2018;19:1153–61.
17 Manktelow BN, Seaton SE, Field DJ, et al. Population-based estimates of in-unit survival for very preterm infants. Pediatrics 2013;131.
18 van Beek PE, Groenendaal F, Onland W, et al. Prognostic model for predicting survival in very preterm infants: an external validation study. BJOG 2022;129:529–38.
19 Papile L, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatrics 1987;92:529–34.
20 De Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49(1):1-6.
21 Seaton SE, Barker L, Jenkins D, et al. What factors predict length of stay in a neonatal unit: a systematic review.
22 Bender GJ, Koestler D, Ombao H, et al. Neonatal intensive care unit: Predictive models for length of stay. Journal of Perinatology 2013;33:147–53.
23 Zhang M, Wang YC, Feng JX, et al. Variations in length of stay among survived very preterm infants admitted to Chinese neonatal intensive care units. World Journal of Pediatrics 2022;18:126–34.
24 Seaton SE, Barker L, Jenkins D, et al. What factors predict length of stay in a neonatal unit: a systematic review.
25 Seaton SE, Draper ES, Abrams KR, et al. Can we estimate the length of stay of very preterm multiples? Arch Dis Child Fetal Neonatal Ed. 2019;104:F568–70.
26 Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. Cochrane Database of Systematic Reviews. 2017;2017.
27 Lainwala S, Perritt R, Poole K, et al. Neurodevelopmental and growth outcomes of extremely low birth weight infants who are transferred from neonatal intensive care units to level I or II nurseries. Pediatrics 2007;119:e1079-1087.
28 Capaciteitsorgaan. Capaciteitsplan 2020-2023. Utrecht: 2020. https://capaciteitsorgaan.nl/app/uploads/2020/11/20200119_Capaciteitsplan-FZO-AVP-2020_DEF-WEB.pdf (accessed 15 Mar 2023).
29 Wise J. Neonatal units in Wales are understaffed and under-resourced, says report. BMJ Published Online First: July 2016.
30 Rogowski JA, Staiger D, Patrick T, et al. Nurse staffing and nicu infection rates. JAMA Pediatr 2013;167:444–50.
31 Rogowski JA, Staiger DO, Patrick TE, et al. Nurse Staffing in Neonatal Intensive Care Units in the United States. Res Nurs Health 2015;38:333–41.

32 Rolnitsky A, Unger SL, Urbach DR, et al. Cost of neonatal intensive care for extremely preterm infants in Canada. Transl Pediatr 2021;10:1630–6.
33 Perin J, Mulick A, Yeung D, et al. Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022;6:106–15.
34 Zein H, Yusuf K, Paul R, et al. Elective transfers of preterm neonates to regional centres on non-invasive respiratory support is cost effective and increases tertiary care bed capacity. Acta Paediatrica, International Journal of Paediatrics 2018;107:52–6.
35 Merritt TA, Pillers DA, Prows SL. Early NICU discharge of very low birth weight infants: A critical review and analysis. Seminars in Neonatology. 2003;8:95–115.
36 Santos J, Pearce SE, Stroustrup A. Impact of hospital-based environmental exposures on neurodevelopmental outcomes of preterm infants. Curr Opin Pediat. 2015;27:254–60.
37 Flacking R, Lehtonen L, Thomson G, et al. Closeness and separation in neonatal intensive care. Acta Paediatrica, International Journal of Paediatrics. 2012;101:1032–7.
38 Caporali C, Pisoni C, Gasparani L, et al. A global perspective on parental stress in the neonatal intensive care unit: a meta-analytic study. Journal of peinatology 2020;40:1739–52.
39 Barfield WD, Papile LA, Baley JE, et al. Levels of neonatal care. Pediatrics. 2012;130:587–97.

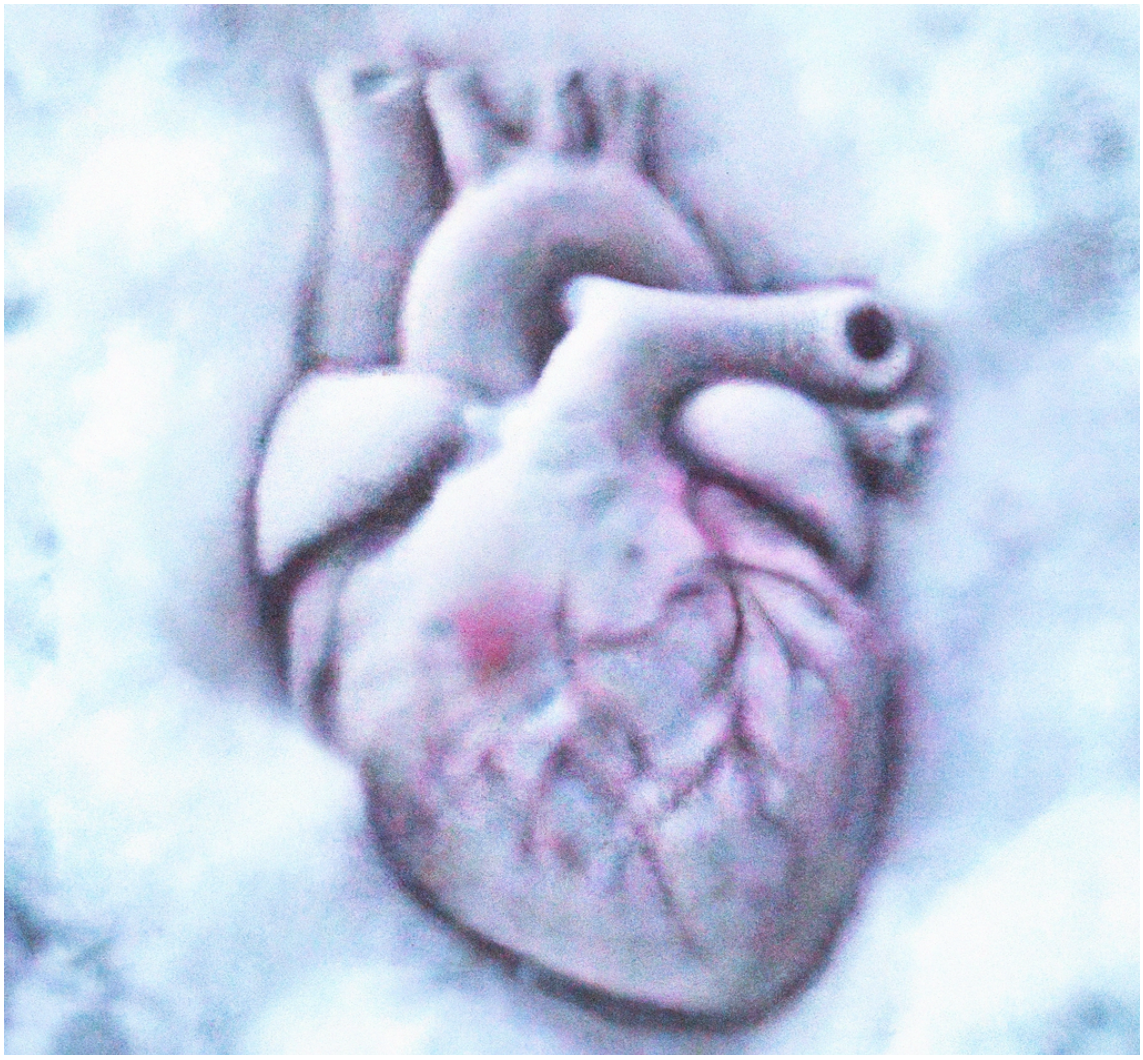
SECTION TWO

Improving neonatal outcome

We all labor against our own cure
since death is the cure of all diseases

Thomas Browne
Britse auteur (1605 - 1682)

CHAPTER 4



CHAPTER 4

Effect of therapeutic hypothermia on renal and myocardial function in asphyxiated (near) term neonates:

A systematic review and meta-analysis

Maureen van Wincoop, Karen de Bijl-Marcus, Marc Lilien, Agnes van den Hoogen, Floris Groenendaal

PLOS ONE

4.1 ABSTRACT

Background: Therapeutic hypothermia (TH) is a well-established neuroprotective therapy applied in (near) term asphyxiated infants. However, little is known regarding the effects of TH on renal and/or myocardial function.

Aim: To describe the short- and long-term effects of TH on renal and myocardial function in asphyxiated (near) term neonates.

Methods: An electronic search strategy incorporating MeSH terms and keywords was performed in October 2019 and updated in June 2020 using PubMed and Cochrane databases. Inclusion criteria consisted of a RCT or observational cohort design, intervention with TH in a setting of perinatal asphyxia and available long-term results on renal and myocardial function. We performed a meta-analysis and heterogeneity and sensitivity analyses using a random effects model. Subgroup analysis was performed on the method of cooling.

Results: Of the 107 studies identified on renal function, 9 were included. None of the studies investigated the effects of TH on long-term renal function after perinatal asphyxia. The nine included studies described the effect of TH on the incidence of acute kidney injury (AKI) after perinatal asphyxia. Meta-analysis showed a significant difference between the incidence of AKI in neonates treated with TH compared to the control group (RR = 0.81; 95% CI 0.67–0.98; p = 0.03). No studies were found investigating the long-term effects of TH on cardial function after neonatal asphyxia. Possible short-term beneficial effects were presented in 4 out of 5 identified studies, as observed by significant reductions in cardiac biomarkers and less findings of myocardial dysfunction on ECG and cardiac ultrasound.

Conclusion: TH in asphyxiated neonates reduces the incidence of AKI, an important risk factor for chronic kidney damage, and thus is potentially renoprotective. No studies were found on the long-term effects of TH on myocardial function. Short-term outcome studies suggest a cardioprotective effect.

4.2 BACKGROUND

Perinatal asphyxia poses harmful consequences for all fetal organs including brain, heart and kidney. The incidence of hypoxic-ischemic encephalopathy (HIE) in developed countries is 1 to 2 per 1000 term live births. HIE accounts for 23% of neonatal deaths worldwide. Moreover, 30% of the neonates with moderate HIE and 90% of the neonates with severe HIE develop severe long-term disabilities, including seizures, mental retardation and cerebral palsy [1–4].

Previous studies have demonstrated that whole-body therapeutic hypothermia (TH) is associated with long-term neuroprotection in full term neonates. Subsequently, this therapy is now the standard of care in developed countries [4].

The neuroprotective effect of TH is achieved as a result of a decrease in cerebral metabolism, reducing the accumulation of excitotoxic neurotransmitters, slowing down cell depolarization and suppressing oxygen free radical release and lipid peroxidation of cell membranes. Furthermore, this treatment also has a role in the suppression of apoptotic processes in the brain by inhibition of caspase enzymes. TH also reduces the release of pro-inflammatory interleukins and cytokines, resulting in suppression of microglial activation and thereby reducing direct neurotoxicity [4]. As it is suggested that the main pathogenic processes of brain damage and other organ damage are partly similar after asphyxia, there appears to be an equally sound rationale for the use of hypothermic treatment to protect other organs than the brain [5].

Perinatal asphyxia is associated with a decreased organ perfusion, and may result in multi-organ failure [2]. Multi-organ damage in the surviving neonates poses a high risk of severe chronic morbidities, such as chronic kidney disease (CKD), resulting in 42 million disability adjusted life years (DALY's) from perinatal asphyxia [6]. In this review, we will focus on the kidney and the heart, as both of these organ systems are known to be affected by perinatal asphyxia with potential long-term sequelae. The objective of this review is to determine the possible short-term and long-term beneficial effects of TH on renal and myocardial function in asphyxiated (near) term neonates.

4.3 MATERIAL and METHODS

4.3.1 Search strategy

We report this systematic review in accordance with the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. No review protocol exists for this review. We conducted a literature search on PubMed and The Cochrane Library for studies examining the effects of TH in (near) term asphyxiated neonates on the heart and kidney. We also performed manual searches of reference lists of studies and reviews. The search was performed in October 2019 and last updated on 28 June 2020. Search term keywords included: hypothermia, cooling, neonate, infant, newborn, asphyxia, hypoxic ischemic encephalopathy, hypoxia, ischemia, chronic kidney failure, chronic kidney disease, renal insufficiency, heart failure, myocardial dysfunction, long-term, prognosis, follow-up, development, outcome. Both Medical Subject Heading (MeSH) terms and text words were used. Two different searches on the effect of TH in asphyxiated neonates on both renal and myocardial function were performed, one on long-term effects and one on short-term effects to possibly identify studies on outcomes that indicated predictors of long-term outcome in case the "long-term" search term did not identify sufficient relevant studies. For short-term effects, we searched for studies performed in the first period of life. For long-term effects, we searched for studies performed after the first year of life. The search on long-term effects included keywords regarding 'long-term' and these were left out in the search on short-term effects. If sufficient relevant articles on perinatal asphyxia could not be found, we expanded our search to include other indications for TH, including near-drowning and aortic arch surgery. No restrictions were used on language and date of publication. The exact search strategy is included in Appendix 3.1. The literature search was performed by one reviewer (M.W.) and when any doubt occurred assessed by a second researcher.

4.3.2 Study selection and data extraction

Included studies met the following criteria: (1) RCT or observational cohort design, (2) intervention with TH, (3) evaluation of patients in a setting of perinatal asphyxia (or in a setting of near-drowning or aortic arch surgery if not sufficient articles on perinatal asphyxia can be found), (4) studies that provided outcome data on heart and kidney function, (5) long-term outcome or a valid marker of long-term outcome must be reported. Information was extracted from each included study on: (1) study characteristics (including authors, study period, study design, location

of study, number of participants), (2) patient characteristics (including severity of HIE), (3) the study's inclusion and exclusion criteria, (4) type of intervention (including cooling type, target temperature and period) and (5) outcome (including definition used/parameters assessed and time of measurement). The study selection and data extraction were performed by one researcher (M.W.) and when any doubt occurred assessed by a second researcher (A.H.).

4.3.3 Quality assessment

Two researchers (M.W., A.H.) assessed methodological quality of the identified RCT's using Cochrane's risk of bias [7]. Because it was impossible to achieve blinding in these studies, we did not include this criterion in the quality assessment. Each item of the risk of bias scored minus 1 point for high risk of bias, 0 points for unclear risk of bias and 1 point for low risk of bias, so that each article would get a total score ranging between -6 and 6 points. A score of 3 or lower was labelled high risk of bias and therefore 'low' quality, a score of 4 was labelled 'moderate' risk of bias and moderate quality and a score of 5 or 6 was labelled as low risk of bias and thus of 'high' quality. The National Institute of Health Quality Assessment Tool (NIHQAT), consisting of 14 items, was used to assess methodological quality for observational cohort. The tenth item was not applicable in these studies, therefore only 13 of the 14 items were included. A score of 11–13 was labelled 'high' quality, a score of 7–10 was labelled 'moderate' quality and a score ≤ 7 as 'low' quality [8]. 'Low' quality studies were not included in the meta-analysis. Rigour and trustworthiness were secured by assessing the included studies independently by two researchers (M.W., A.H.). Any discrepancies in risk assessment were resolved by discussion until agreement was reached.

4.3.4 Statistical analysis

If possible, a meta-analysis on the studies was performed. The statistical analysis was performed using Review Manager software (RevMan 5.3) [9], supplied by The Cochrane Collaboration. We calculated the risk ratio (RR) and risk difference (RD) for dichotomous data and the mean difference (MD) for continuous data, with 95% confidence intervals (CI) for all analyses. Subgroup analysis on the method of cooling was performed if relevant. As heterogeneity between the studies is likely due to small differences in e.g., study population, sample size, study quality and method, we used a DerSimonian and Laird random effects model. Heterogeneity of effects was measured with the statistic I 2 and the confidence intervals for I 2 were calculated [10]. A *p*-value of 10 studies is included [7]. Sensitivity analysis will

be performed using the leave-one-out method to assess how each individual study affects the overall estimate of the rest of the studies.

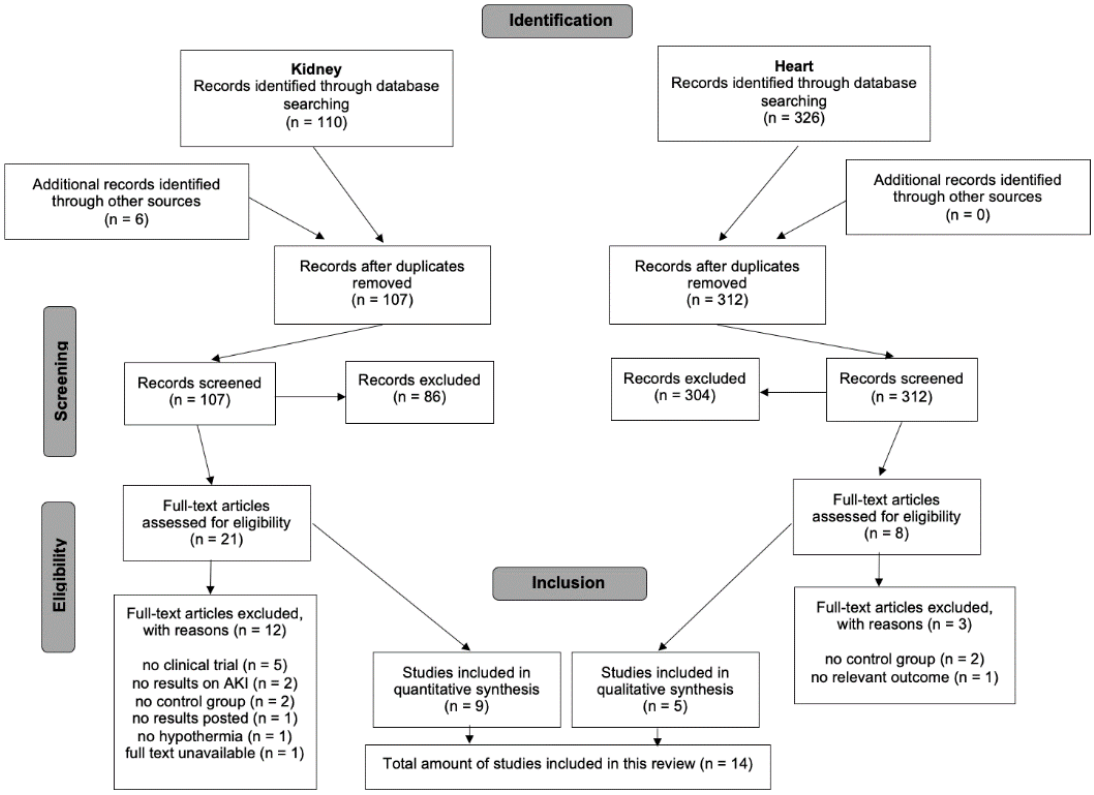
4.4 RESULTS

4.4.1 RENAL DYSFUNCTION

4.4.1.1 Systematic search

Database searching on long-term effects identified 69 citations. Five citations were duplicates and 64 studies were included for analysis. However, no relevant studies regarding the long-term effects of TH on the incidence and risk of developing CKD, defined as structural or functional abnormalities of the kidneys or a GFR < 60mL/min/1.73m^2 for ≥ 3 months, after neonatal asphyxia were found [11]. Follow-up articles of the CoolCap, NICHD and TOBY trials did not include renal parameters [12-14]. Including keywords on other indications for TH in our search identified 13 more studies, but none of these were relevant. A total of 107 citations were excluded because they were duplicates or the titles and abstracts or full texts were not relevant for this review. Overall, there were 9 studies included in this systematic review. A flow diagram is presented in figure 4.1.

Figure 4.1 Prisma chart of the indentification and selection of studies regarding short-term renal and myocardial function.



4.4.1.2 Patient characteristics

The nine included studies were carried out between 1996 and 2015. All 9 trials were randomized controlled trials and reported the effect of TH on the incidence of AKI after perinatal asphyxia [5, 16–23]. Table 4.1 shows the summary of study characteristics of these studies. Clinical baseline characteristics were similar *(p* < 0.05) in TH and control groups in 7 studies. In the study by Simbruner et al., the only differences were the temperature at admission and age at randomization, which were both lower in the control group. In the study by Gluckman et al., 5- and 10-minute Apgar scores and background aEEG amplitude were lower in the TH group. Inclusion and exclusion criteria of the included studies are presented in Table 4.2. Gestational age of the included neonates varied from > 35–37 weeks between the studies. Some studies included a minimum birth weight. All studies included several clinical parameters of hypoxic-ischemic injury in their inclusion criteria, including cord gas (range pH 10–16 mmol/L), 1- (≤ 3) and 5 - (range ≤ 5 - ≤ 6) and 10-minute (≤ 5) Apgar scores, need for resuscitation, heart rate, oxygen desaturation or arterial oxygen pressure. Exact cut-off values varied slightly between studies. Neurologic findings of neonatal encephalopathy, including abnormalities of tone, reflexes, state of consciousness, seizures, posturing and autonomic dysfunction, were also included in most studies. The Sarnat and Sarnat staging was used to assess encephalopathy. An abnormal aEEG was included in two studies. Four studies included only cases with moderate or severe HIE, of which two studies did not further specify on the ratio between moderate and severe HIE. Four studies also included neonates with mild encephalopathy. One study did not describe the ratio of the different stages of HIE. Table 4.2 shows the ratios of the severity of HIE.

Table 4.1 Summary of study characteristics of included studies on renal function

Author [ref], study period, country	Study design	Intervention	Number of patients	AKI definition / renal parameters assessed	Time of measurement	Incidence AKI		Quality assessment
						Cooled	Control	
Akisu et al. [16], **2000–2001, Turkey**	Single centre; randomized controlled trial	Head cooling	11 cooled vs 10 control	ND	ND	5 of 11	5 of 10	Moderate
Eicher et al. [17], **ND, Canada; USA**	Multicentre; randomized controlled trial	Whole body cooling	32 cooled vs 33 control	Urine output <1 mL/kg/h, hematuria, creatinine >150 µmol/L	Any time during hospitalization	2 of 31	3 of 31	Moderate
Gluckman et al. [18], **1999–2002, USA; Canada; UK; New Zealand**	Cool Cap study; multicentre; randomized controlled trial	Head cooling	116 cooled vs. 118 control	Urine output <0.5 ml/kg/h for at least 24 h or maximum serum creatinine >90 µmol/L	In first 7 days of life	73 of 112	83 of 118	Moderate
Gunn et al. [19], **1996–1997, New Zealand**	Single centre; randomized controlled trial	Head cooling plus either minimal or mild systemic cooling	12 cooled vs 10 control	Urine output <0.5 ml/kg/h for at least 24 h, proteinuria, hematuria, maximum serum creatinine levels	ND	12 of 12	10 of 10	High
Roka et al. [5], **2005–2006, Hungary**	Part of TOBY trial; single centre; randomized controlled trial	Whole body cooling	12 cooled vs. 9 control	Rate of diuresis and serum creatinine levels	6h, 24h, 48h, 72h (after birth)	3 of 12	7 of 9	High
Shankaran et al. [20], **2000–2003, USA**	NICHD study; multicentre; randomized controlled trial	Whole-body cooling	102 cooled vs. 106 control	Oliguria or anuria	During hospital course	16 of 102	23 of 106	High
Simbruner et al. [21], **2001–2006, Austria; Germany**	Neo.nEURO. network; multicentre; randomized controlled trial	Whole body cooling	64 cooled vs. 65 control	Urine output <0.5 ml/kg/hour for at least 24h and maximal serum creatinine levels of >90 µmol/L	During intervention period	16 of 62	26 of 63	High
Tanigasalam et al. [22], **2013–2015, India**	Single centre; randomized controlled trial	Whole body cooling	60 cooled vs. 60 control	AKIN criteria: stage 1 (increase in serum creatinine >26.5 µmol/L or serum creatinine >150–200% from baseline), stage 2 (increase in serum creatinine >200–300% from baseline), stage 3 (increase in serum creatinine >300% from baseline or serum creatinine >353.6 µmol/L with an acute rise of >44.2 µmol/L)	6h, 36h, 72h (after birth)	19 of 60	36 of 60	High
Zhou et al. [23], **2003–2005, China**	Multicentre; randomized controlled trial	Head cooling	100 cooled vs. 94 control	Creatinine >120 µmol/L, blood urea nitrogen >8 mmol/L or urine output <1 mL/kg/h	12h, 24h, 48h, 72h (after treatment)	21 of 100	19 of 94	High

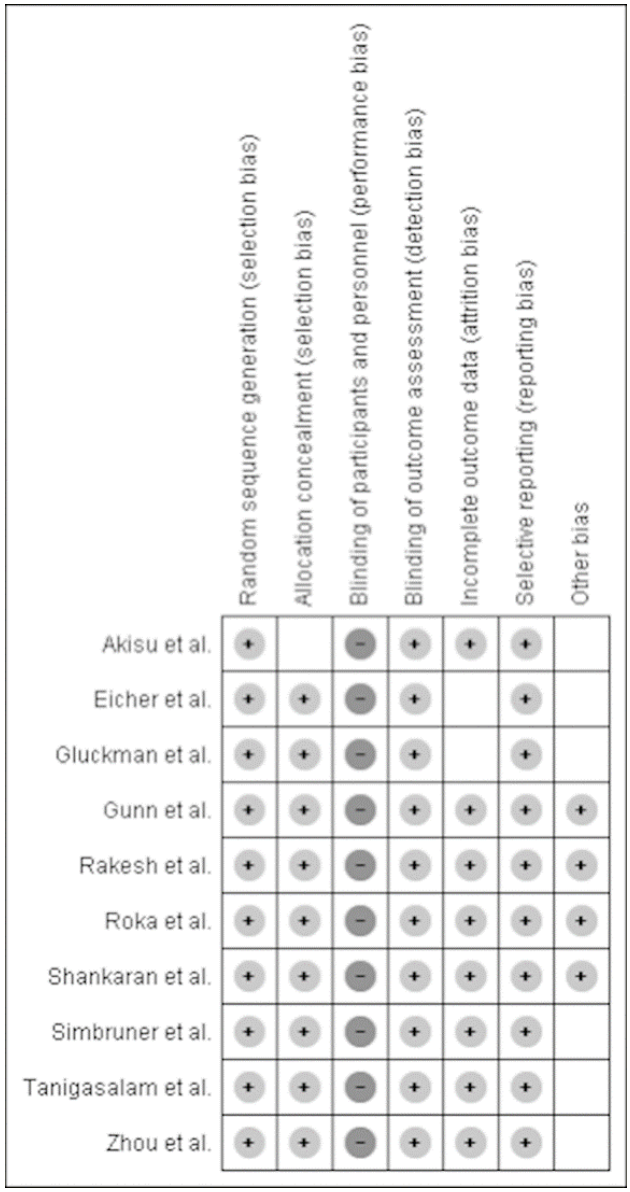
ND = not described.

Table 4.2 Inclusion and exclusion criteria and used intervention in studies on renal function.

Study	Inclusion criteria	Exclusion criteria	Severity of HIE in participants (n, %)			Intervention				Control
			Mild	Moderate	Severe	N	Cooling type	Target temperature (°C)	Period	N
Akisu et al. [16]	5-min Apgar score ≤6; severe acidosis; neurologic findings of encephalopathy	Metabolic disorders; congenital malformations; chromosomal abnormalities; congenital infection; transitory drug depression	3 (14%)	12 (57%)	6 (29%)	11	Head plus minimal systemic	Ear 33.5–33 Rectal 36.5–36	72 h	10
Eicher et al. [17]	Birthweight >2000g; one clinical indication of hypoxic-ischemic injury; two neurologic findings of neonatal encephalopathy	Maternal chorioamnionitis; sepsis at birth; birth weight or head circumference <10%; presumed chromosomal abnormality	2 (3%)	10 (16%)	50 (81%)	32	Whole body	Rectal 33.5	48 h	33
Gluckman et al. [18]	10-minute Apgar score ≤5; continued need for resuscitation; severe acidosis; moderate to severe encephalopathy	Use of anticonvulsants; major congenital abnormalities; head trauma causing major intracranial hemorrhage; severe growth restriction; birthweight <1800g; head circumference <-2 SD; critically ill infants	0	ND	ND	116	Head plus mild systemic	Rectal 34–35	72 h	118
Gunn et al. [19]	Severe acidosis; 5-minute Apgar score ≤6; evidence of encephalopathy	Obvious major congenital abnormalities; metabolic diseases	0	ND	ND	12	Head plus either minimal systemic (n = 6) or mild systemic (n = 6)	Minimal: rectal 36.3 Mild: rectal 35.7	72 h	10
Roka et al. [5]	10-minute Apgar score ≤5; continued need for resuscitation at 10min; severe acidosis; moderate to severe encephalopathy; abnormal aEEG	Congenital malformations; suspected metabolic disorders	ND	ND	ND	12	Whole body	Rectal 33–34	72 h	9
Shankaran et al. [20]	Either severe acidosis or acute perinatal event and 10-minute Apgar score ≤5 or assisted ventilation; moderate or severe encephalopathy	Major congenital abnormality; birth weight of ≤1800 g; moribund infants	0	135 (65%)	72 (35%)	102	Whole body	Esophageal 33.5	72 h	106
Simbruner et al. [21]	10-minute Apgar score <5, continued need for resuscitation, severe acidosis; clinical evidence of encephalopathy; abnormal standard EEG	Use of high-dose anticonvulsant therapy; birth weight <1800 g; head circumference of 3rd percentile; major congenital malformations; imperforate anus; gross hemorrhage; infant "in extremis"	0	41 (33%)	84 (67%)	64	Whole body	Rectal 33.5	72 h	65
Tanigasalam et al. [22]	Encephalopathy; severe acidosis; any two of: 10-min Apgar score of ≤5, evidence of fetal distress, assisted ventilation for at least 10 min after birth, evidence of any organ dysfunction	Extramural neonates; major congenital abnormalities; absence of spontaneous respiratory efforts by 20 min after birth; history of maternal renal failure	5 (4%)	83 (69%)	32 (27%)	60	Whole body	Rectal 33–34	72 h	60
Zhou et al. [23]	Birth weight >2500 g; Apgar score ≤3 at 1 minute and ≤5 at 5 minutes; severe acidosis; need for resuscitation or ventilation at 5 minutes of age	Major congenital abnormalities; infection; other encephalopathy; severe anemia (hemoglobin <120g/L)	39 (21%)	82 (42%)	73 (37%)	100	Head plus mild systemic	Nasopharyngeal 34 Rectal 34.5–35	72 h	94

ND = not described.

Figure 4.2 Risk of bias assessed in the included randomized controlled trials.



Plus-sign represents 'low risk', minus-sign represents 'high risk', empty represents 'unclear risk'.

4.4.1.3 Therapeutic hypothermia

The characteristics of the application of TH for each study are presented in Table 4.2. All studies initiated the TH within the first 6 hours of life. Four of the included studies applied head cooling with mild or minimal systemic hypothermia and five studies applied whole body cooling.

4.4.1.4 Quality assessment

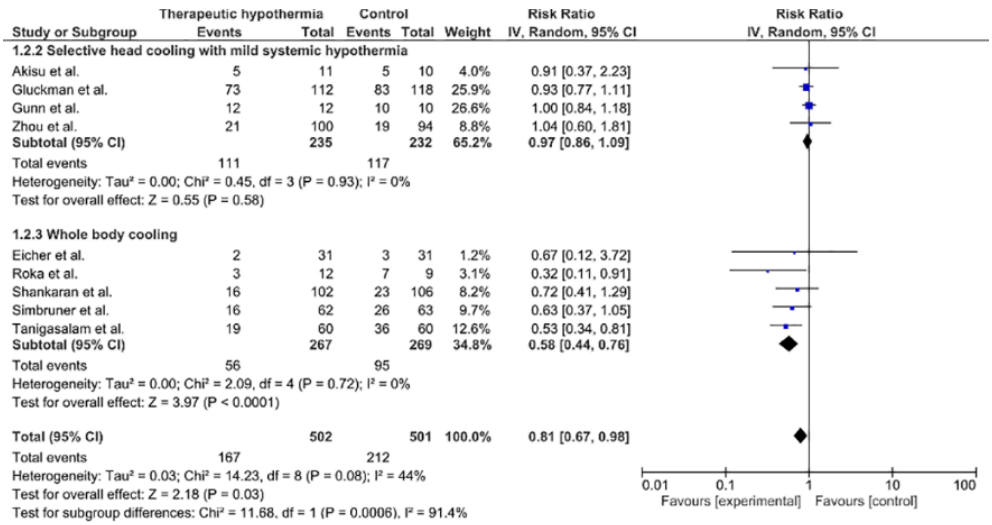
All studies performed proper randomization and allocation concealment, except for one study in which the mode of allocation concealment was not specified. Because of the impossibility to achieve blinding in these studies, we did not include this criterion in the quality assessment. The assessors of outcome were also not blinded. However, as the outcome is objective, we believe there is still low risk of detection bias. Complete outcome data were reported in seven of the nine trials. Two trials missed data of a few participants. There was no selective reporting. We found possible presence of other bias in six of the nine trials and graded this as 'unclear risk'. In two of these studies this was due to baseline imbalance. In the four other studies this was due to overly wide inclusion criteria for participants as they included all neonates with HIE, including those with mild HIE who may not have benefited from TH. The risk of bias assessment is summarized in Figure 4.2. Of the nine trials, four were labelled as 'high' quality and five as 'moderate' quality.

4.4.1.5 Association between TH and AKI

All studies examined the incidence of AKI in patients. However, considerable heterogeneity was noted in the definitions used. AKI was defined differently among each of the reported studies. Both serum creatinine and urine output were included in 7 of the studies. One study did not describe the definition used. Table 4.1 presents the AKI definition used in each study, the time of measurement and the incidence of AKI in the cooled and control groups. Eicher et al., Shankaran et al. and Zhou et al. reported on several renal parameters separately. To calculate the incidence of AKI for this review, serum creatinine was used from the studies by Eicher et al. and Zhou et al. and oliguria from Shankaran et al., as these criteria were most comparable with the other studies. A total of 504 (range 11–112) neonates were treated with TH in the 9 trials, of whom 167 (33.3%) developed AKI. The control groups consisted of a total of 501 neonates, of whom 212 (42.3%) developed AKI.

The nine trials were included in meta-analysis, presented in figure 3.3. There was statistically significant heterogeneity (p = 0.08; I 2 = 44%; 95% CI 0–74%). A significant difference between the rate of AKI was observed in cooled infants when compared to the control group (RR = 0.81; 95% CI 0.67–0.98; p = 0.03) with a RD of -0.09 (95% CI -0.16 –-0.01; p = 0.02). Subgroup analysis of the trials that used selective head cooling with mild systemic hypothermia (RR = 0.97; 95% CI 0.86–1.09; p = 0.58) and the trials that used whole-body cooling (RR = 0.58; 95% CI 0.44–0.76; p < 0.0001) demonstrated that the significant effect only applies for the studies using whole-body cooling. The 95% CI of I 2 was 0–12% in the subgroup that used head cooling with mild systemic hypothermia and 0–61% in the subgroup that used whole-body cooling. Egger's test was not appropriate to conduct as only nine trials were included. Using the leave-one-out method for the sensitivity analysis, we noticed that leaving out Gluckman et al., Roka et al., Shankaran et al., Simbruner et al. or Tanigasalam et al. separately results in an insignificant result. However, regarding only the subgroup of whole-body cooling, leaving out one of the five trials did not affect significance.

Figure 4.3. Forest plot of the effect of hypothermia on the incidence of AKI in asphyxiated neonates, expressed in risk ratios.



Subgroup selective head cooling with mild systemic hypothermia: there is no significant difference between cooled and non-cooled neonates. Subgroup whole body cooling: there is a significant difference between cooled and non-cooled neonates.

4.4.2 MYOCARDIAL DYSFUNCTION

4.4.2.1 Systematic search

Database searching on long-term effects identified 149 citations. Twelve citations were duplicates and 137 studies were included for analysis. However, no relevant studies regarding the long-term effects of TH on the incidence and risk of developing myocardial dysfunction after neonatal asphyxia or other indications for TH were found. Follow-up articles of the CoolCap, NICHD and TOBY trials did not include cardiac parameters [12–14]. Including keywords on other indications for TH in our search identified 109 more studies, but none of these were relevant. Database searching on short-term effects identified 326 citations. A total of 321 citations were excluded because they were duplicates or the titles and abstracts or full texts were not relevant for this review. Overall, there were 5 studies included in this systematic review [17, 24– 27]. A flow diagram is presented in Fig 4.1. Studies on the cardioprotective effect of TH in asphyxiated human neonates are limited to the assessment of myocardial function up till 4 days after birth. Five studies were found on these short-term effects. The study of Eicher et al. was included in both the analysis on renal function and myocardial function. An overview of the study characteristics of these studies is presented in Table 4.3. Two of the studies were an RCT, two were prospective cohort studies and one was a retrospective cohort study.

Table 4.3 Summary of study characteristics and results of included studies on myocardial function.

Author [ref], study period, country	Study design	Intervention	Number of patients	Myocardial parameters assessed	Time of measurement	Results	Quality assessment
Eicher et al. [17], **ND, Canada; USA**	Multicentre; randomized controlled trial	Whole body cooling	31 cooled vs. 31 non-cooled	cTnI, CK-MB	48h	No significant reduction in cTnI; significant increase in CK-MB in hypothermia group	Moderate
Liu et al. [24], **ND, UK**	Retrospective cohort study	Whole body cooling (n = 58), head cooling (n = 4)	61 cooled vs. 14 non-cooled	cTnI	First 3 days	Significant reduction in peak level and AUC of cTnI within 24h in hypothermia group	Moderate
Nestaas et al. [25], **2010–2011, Norway**	Single centre; prospective cohort study	Whole body cooling	44 cooled vs. 20 non-cooled	Tissue doppler measurements, peak cTnT	Day 1, 3, 4	Similar impairment during days 1–3, significant improvement in myocardial function in hypothermia group at day 4 (after rewarming) with a better myocardial function than at day 3 in the non-cooled group; higher median peak cTnT in hypothermia group	High
Rakesh et al. [26], **2014–2016, India**	Single centre; randomized controlled trial	Whole body cooling	60 cooled vs. 60 non-cooled	CK-MB, cTnI, ECG, ECHO	0, 24 and 72h	Significant increase in median of difference of CK-MB and cTnI in hypothermia group; less findings of myocardial dysfunction on ECG and ECHO at 72h in hypothermia group	High
Vijlbrief et al. [27], **2006–2008, The Netherlands**	Single centre; prospective cohort study	Whole body cooling	20 cooled vs. 28 non-cooled	cTnI, BNP	0, 24, 48 and 84h	Significant reduction in BNP at 48 and 84h in hypothermia group; no difference in cTnI between the two groups	Moderate

ND = not described; cTnI = cardiac troponin I; BNP = brain natriuretic peptide; CK-MB = creatinekinase MB; ECG = electrocardiography; ECHO = echocardiography; AUC = area under the curve; cTnT = cardiac troponin T.

4.4.2.2 Therapeutic hypothermia

All studies applied TH for 72 hours, except for the study by Eicher et al, which used a period of 48 hours. Inclusion criteria were comparable among the studies.

4.4.2.3 Quality assessment

One of the RCT's was labelled as 'moderate' quality and the other as 'high' quality, summarized in figure 4.2. Two of the three observational studies were labelled as 'moderate' quality and one as 'high' quality, presented in Table 4.4. The third item of the NIHQAT was not applicable for retrospective studies, therefore the needed score for each level of quality was lowered by one. There were significant differences in one or more baseline characteristics between the TH group compared to the control group in the studies by Vijlbrief et al., Liu et al. and Nestaas et al.

Table 4.4 Quality assessment using the National Institute of Health Quality Assessment Tool for observational cohort studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total
Vijlbrief et al.	Y	Y	CD	Y	N	Y	Y	N	Y	NA	Y	N	Y	Y	9/13Y
Liu et al.	Y	N	NA	CD	N	Y	Y	N	Y	NA	Y	N	Y	Y	7/12Y
Nestaas et al.	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	N	Y	Y	11/13Y

Q = question; CD = cannot be determined; NA = not applicable; N: = no; Y = yes.

4.4.2.4 Association between TH and myocardial (dys)function

Possible short-term beneficial effects were presented in 4 out of 5 identified studies, assessed by the level of BNP, cTnI and CK-MB and findings of myocardial dysfunction on ECG, ECHO and tissue doppler measurements. An overview of the results of these studies is presented in Table 3.3. Four of the five studies presented results on the effect of TH on the level of cTnI. Because of the different times of measurements applied in these four studies, no meta-analysis could be performed on the effect of TH on the level of cTnI.

4.5 DISCUSSION

In addition to the brain, perinatal asphyxia exerts a profound harmful effect on the function of major organ systems. The temporary lack of oxygen delivery leading to hypoxic-ischaemic damage can result in multiorgan failure, including cardiovascular and renal dysfunction [5,28]. In this systematic review we tested the hypothesis that TH, which is used as a neuroprotective strategy, has an additional protective effect on the heart and kidney

4.5.1 RENAL DYSFUNCTION

To evaluate the effect of TH on renal function, we performed two searches on trials that assessed the short-term and long-term effects of TH on the kidneys. However, no long-term follow-up trials on asphyxiated neonates treated with TH that included renal parameters in their outcome were found. Therefore, we performed a review and meta-analysis of studies on the incidence of AKI, assessed during the hospital course in the first period of life, after treatment with TH in comparison to control groups treated without TH. Our meta-analysis showed a significant difference between the rate of AKI in cooled infants and the control group. Furthermore, subgroup analysis showed that the significant effect was only present

in the trials that used whole-body cooling. This is likely due to the fact that the renal temperature during head cooling with mild systemic TH did not decrease sufficiently to exert a beneficial effect. At present whole-body cooling is more commonly used, but the superiority of either whole-body cooling or selective head cooling for neuroprotection has not yet been established [29,30]. Based on the results of this review, whole-body cooling could be more effective than selective head cooling in preventing damage to other organs than the brain, such as the kidneys.

The results of our meta-analysis were slightly different from a Cochrane review on cooling for newborns with HIE including six studies, in which a risk ratio of 0.87 (95% CI 0.74 -1.02; P = 0.077) was calculated for renal impairment [31]. This Cochrane review showed a superior effect of whole-body cooling over selective head cooling as well.

With the redistribution of cardiac output as a reaction to asphyxia, blood is directed preferentially to the brain and the heart, thereby limiting oxygen delivery to the kidneys. Renal cells only have a limited capacity for anaerobic respiration, as the tubular cells already live in an environment of low oxygen tension, and are highly susceptible to reperfusion injury [2,6]. As a result, AKI is frequently seen in asphyxiated neonates. With an incidence of 40-50%, renal injury is a common organ dysfunction after perinatal asphyxia [22]. AKI is characterized by a period of impairment in the kidney's excretory function. The AWAKEN study found an overall incidence of 36.7% of AKI in neonates, including those with HIE, born at a gestational age of ≥36 weeks. This study also determined that AKI is an independent risk factor for mortality and longer hospital stay [32]. Previous studies have shown an incidence of 36.1%-72% of AKI after perinatal asphyxia, which is comparable to the incidence we found in the pooled control groups (42.3%) [33–40]. Furthermore, studies have found that AKI correlates with the severity of asphyxia, mortality and neurological outcome [33,41]. A possible long-term consequence is nephron loss, causing hypertension and proteinuria, which in turn leads to progressive renal damage. Hyperfiltration in the remaining nephrons, together with an impairment in renal oxygenation due to capillary rarefaction, proteinuria as a result of glomerular damage, chronic overactivity of the renin-angiotensin-aldosteron system (RAAS) and interstitial inflammation all contribute to the progression of CKD [42,43]. Multiple animal studies have shown that ischemia can cause permanent kidney damage as a result of fibrosis, inflammation and loss of peritubular capillaries [44–46].

A systematic review and meta-analysis by Greenberg et al. evaluated the long-term risk of CKD and mortality after an episode of AKI in children [47]. Ten cohort studies evaluating long-term renal outcomes were selected. Included in these studies were a total of 346 patients with a mean follow-up of 6.5 years (range 2-16). They determined the cumulative incidence rate of hypertension, proteinuria, GFR <90 ml/min/1.73m^2, GFR <60 ml/min/1.73m^2, end stage renal disease and mortality per 100 patient-years, which respectively were 1.4, 3.1, 6.3, 0.8, 0.9 and 3.7. However, these studies used a total of six different definitions of AKI and were of variable quality. There was a considerable difference in outcome between the studies, presumably as a result of discordant outcome measures, study size and differences in methodology. There was no control group without AKI included in any of these studies. However, studies in adults did include control groups and hereby demonstrated that AKI acts as an independent risk factor for CKD [48].

Overall, it is likely that neonates who suffered from AKI are at higher risk of developing CKD later in life. Consequently, reducing the incidence of AKI in asphyxiated neonates is of great importance in preventing the progression to CKD. Therefore, as TH resulted in a significantly lower risk of developing AKI in our meta-analysis, we argue that this treatment yields a protective effect on the long-term function of the kidneys. Furthermore, as AKI is a risk factor for developing CKD and early treatment of risk factors for rapid progression like hypertension and proteinuria protect renal function, we recommend screening on the development of CKD throughout life in children with a history of AKI in the neonatal period, which is currently not performed [55].

4.5.2 MYOCARDIAL DYSFUNCTION

To evaluate the effect of TH on myocardial function, we performed a search on trials that assessed the long-term effect of TH on the heart. However, no long-term follow-up trials were found on asphyxiated neonates treated with TH that included cardiac parameters in their outcome. Results from short-term studies suggest a trend towards a decrease in cardiac biomarkers and myocardial dysfunction assessed by ECG, ultrasound and tissue-Doppler in asphyxiated neonates treated with TH compared to normothermia. Whether this short-term cardioprotective effect also implies a positive effect on the long-term must be explored in further research. Furthermore, animal studies also suggest a cardioprotective effect of TH.

Treatment with TH in hypoxic-ischaemic newborn pigs significantly reduced pathological cardiac lesions and the cardiac biomarker troponin I [56]. Another animal study on embryonic rat hearts after oxidative stress has shown a cardioprotective role of TH by reducing cardiomyocyte injury [57]. The possible positive effect of TH on myocardial dysfunction is likely a result of a reduction in cardiac metabolism, cardiac output and oxygen demand during TH [26].

The five studies included different cardiac parameters and the time of measurement of these parameters also differed between the studies. BNP levels correlate well with echocardiographic measurements of myocardial dysfunction [27]. The sensitivity and specificity of CK-MB is lower than that of cTnI and cTnT as it is influenced by other factors, like kidney injury, gestational age, mode of delivery and birth weight [58] cTnI levels correlate well with the degree of myocardial damage in asphyxiated neonates and might be an appropriate marker of the anticipated severity of myocardial dysfunction [59]. A systematic review by Teixeira et al. investigating the use of cardiac biomarkers in neonates found that cTnI and cTnT levels are useful tools for assessing myocardial dysfunction in asphyxiated neonates, with a higher sensitivity and specificity than echocardiography and other biomarkers. However, cTnI and cTnT can also be elevated in congenital heart defects (only cTnT), patent ductus arteriosus (only cTnT) and respiratory distress [58].
Changes in ECG, performed after the first 24 hours of life, and echocardiography including Doppler tissue imaging have also been proven to be reliable markers [25,60]. Approximately 30% to 50% of asphyxiated neonates show indications of ventricular dysfunction on echocardiography [61].
cTnI and cTnT appear to be the most reliable biochemical markers for myocardial dysfunction.

Studies on the effect of TH after myocardial infarction in adults showed a trend towards a reduction in infarct size (IS) [62–70]. However, this reduction was only statistically significant in the IS normalized to myocardium at risk in two of the nine trials, which were the only two trials in which all patients reached a temperature of <35°C before reperfusion. An absolute reduction in IS of 5% is currently accepted as a clinically meaningful result for cardioprotective trials [67]. This reduction was achieved in four of the nine trials. The cardioprotective effect of TH appeared to be very dependent on reaching a temperature of <35°C before reperfusion took place. However, it is not clear how well these results from studies on myocardial

infarction may be extrapolated to asphyxiated neonates because of the marked differences in clinical picture. In myocardial infarction, the cardiac damage is focal, due to ischemia and often a result from pre-existing coronary artery disease. Furthermore, adult hearts and neonatal hearts might react differently to damage and it is possible that neonatal hearts are more resilient and salvageable.

Myocardial function and its markers can be influenced by several factors. Nestaas et al. could not assess the impact from the use of inotropic medication on myocardial function as this is probably more often used in infants in an impaired hemodynamic state. Liu et al. investigated the effect of cardiovascular confounders on the peak level of cTnI before initiation of cooling. Receiving cardiac compressions was the only near significant variable (p = 0.06). Receiving adrenaline had no effect on the level of cTnI shortly after resuscitation. Vijlbrief et al. found no significant correlations between cTnI and BNP levels and possible confounders, such as epinephrine use at resuscitation, changes in heart rate, pulmonary hypertension (PPHN) or hypotension treatment.

4.6 STUDY LIMITATIONS

An important limitation of our review is the difference in definitions of AKI used in the included studies, therefore caution before interpreting these findings is advised. The KDIGO guideline uses a definition of an increase in serum creatinine of ≥26.5 µmol/L or ≥50% within 48 hours or urine output of <0.5 mL/kg/hour for >6 hours.[49] However, in newborns the serum creatinine concentration normally decreases over the first days of life, urine production is notoriously difficult to determine accurately and because of limited renal concentration capacity, renal osmolar excretion can already be insufficient at urine production rates below 1.5mL/kg/hour [43]. For this review, presence of oliguria was used in the definitions of five of the included studies and increased creatinine levels in seven studies. In the study by Gunn et al., neonates with proteinuria or hematuria were also considered to suffer from AKI. This study reported signs of AKI in all participating neonates, which is likely a result from the use of a too broad definition. We believe the difference in results between the studies can presumably be partially explained by these discrepant definitions. A universal definition of neonatal AKI is important to enable reliable comparison of different trials. Several studies have proposed neonatal AKI definitions using modifications to the KDIGO definition and RIFLE criteria [43,50].

Other limitations are small study sizes in some studies (<100 participants in 4 studies) and different proportions of the severity of HIE between the studies. Four studies did also include neonates with mild HIE, who may not have benefited from TH, while other studies only included moderate and severe HIE. Thus far, neither the safety nor efficacy of TH for mild HIE has been demonstrated [51]. However, for the development of AKI, no subgroup analysis on the severity of HIE was performed in these studies. More severe HIE might also imply more severe damage in other organs. Included studies in this review found that a more severe stage of HIE results in a higher rate of mortality and severe disability. Gluckman et al. found no apparent improvement on mortality and severe disability with TH in neonates with the most severe or most advanced aEEG changes after birth. Regarding the effect of TH on the incidence of AKI in infants with mild HIE, the two studies with respectively 14% and 21% neonates with mild HIE used head cooling, so the fact that these studies did not show a superior effect is likely due to the method of cooling. The two other studies, that used whole body cooling, only included respectively 3% and 4% neonates with mild HIE, which is too little to draw any conclusions on the effect of TH on AKI in case of mild HIE.

Another limitation is the fact that the presence of publication bias can only be reliably assessed when there are at least 10 studies included in the meta-analysis [7,52]. With only nine trials we can therefore not rule out the presence of publication bias in our meta-analysis. Furthermore, included studies were performed between 1996 and 2015. More recent studies are potentially more relevant, since there is lower risk of publication bias and adjustments in clinical practice over time could have affected the outcomes [53]. However, as TH has been the standard of care in developed countries for the treatment of neonates with moderate to severe HIE, relatively recent studies comparing this intervention to a control group without TH are rare [4].

In our review, we found an I^2 value of 44%. According to the Cochrane Handbook, a I^2 value of 0-40% might not be important, a value of 30-60% may represent moderate heterogeneity, a value of 50-90% may represent substantial heterogeneity and a value of 75-100% may represent considerable heterogeneity [7]. The I^2 value we found in our meta-analysis may represent moderate heterogeneity. This is most likely due to differences in method used, as the heterogeneity in the two subgroups were both 0%. However, the I^2 statistic is underpowered to detect heterogeneity with a small number of studies, so the presence of heterogeneity in these subgroups cannot be ruled out [54]. The

calculated confidence intervals also show that some heterogeneity might be present in the subgroups.

It is important to also keep in mind other risk factors that could influence renal function and increase the risk for developing AKI other than HIE. Six of the nine studies provided data on the incidence of hypotension and in all these studies hypotension was equally present in the hypothermia groups and control groups. Other risk factors for AKI were not part of the exclusion criteria and were not adjusted for, which is another possible limitation of this review.

4.7 FUTURE RESEARCH

There appears to be an important gap in literature concerning the long-term effect of TH on renal and myocardial function in asphyxiated neonates. This review showed a renoprotective effect to be very likely. However, additional research will be needed to confirm the positive effect of TH on long-term renal function. Research should evaluate the risk of developing CKD and heart failure later in life in children with a history of perinatal asphyxia treated with or without TH. Determining whether neonatal hypothermia reduces chronic organ dysfunction will require long-term follow-up of the children in RCT's. However, as TH is now the standard of care in perinatal asphyxia, it will be difficult to compare the effect of TH to a control group in new studies outside of historic controls. Therefore, follow-up studies of large trials on the effect of TH in perinatal asphyxia, e.g., NICHD and TOBY, should also assess renal and cardiac parameters, like creatinine, proteinuria, blood pressure and echocardiography. Furthermore, a sizeable proportion of neonates with asphyxia still develops AKI even after cooling. This supports research into the development of other therapeutic options to further decrease renal injury. For example, treatment with theophylline was found to reduce the incidence of AKI in term neonates with severe asphyxia at birth by 60%. However, the effect of this treatment has not been evaluated in neonates receiving TH [71]. For clinical reasons, follow-up of asphyxiated neonates with renal or cardiac involvement should include assessment of renal and cardiac parameters. In general, the focus of follow-up visits of these children is on neurodevelopment. Future studies should also assess the best methods to assess renal and cardiac function in these children. During follow-up, renal function can be assessed with parameters like creatinine, proteinuria and blood pressure and cardiac function with echocardiography including Doppler tissue imaging. This is both relatively

inexpensive and easy and the development of CKD and heart failure can be prevented or timely treated to avoid further costs and minimize the burden of disease for these patients.

4.8 CONCLUSION

In conclusion, systemic TH had definite protective effects on renal and probably also myocardial function in the days following perinatal asphyxia in (near) term infants. Further studies are needed to describe the long-term effects of systemic TH on renal and myocardial function.

4.9 APPENDIX

Full search strategy.

The exact search for kidney failure used in PubMed was:

("hypothermia, induced"(mesh) OR hypothermia OR cooling) AND ("infant, newborn"(mesh) OR infant OR newborn OR neonate) AND (“kidney failure, chronic”(mesh) OR “renal insufficiency, chronic”(mesh) OR “acute kidney injury”(mesh) OR “acute kidney” OR “kidney” OR "dialysis" OR “renal”) AND (“asphyxia”(mesh) OR “hypoxia”(mesh) OR “hypoxia-ischemia, brain”(mesh) OR “hypoxia, brain”(mesh) OR “ischemia”(mesh) OR “hypoxic ischemic encephalopathy” OR “asphyxia” OR “hypoxia” OR “ischemia” OR “aortic arch” OR “shock” OR “ near-drowning” OR drown*) AND (“long-term” OR “long term” OR “chronic” OR “follow up” OR “follow-up” OR “development” OR “outcome” OR “prognosis”)

No limitation in search field was used in this search.

The exact search for cardiac injury used in Pubmed was:

("hypothermia, induced"(mesh) OR hypothermia OR cooling) AND ("infant, newborn"(mesh) OR infant OR newborn OR neonate) AND ("asphyxia"(mesh) OR asphyxia OR "hypoxia"(mesh) OR "hypoxia-Ischemia, brain"(mesh) OR "hypoxia, brain"(mesh) OR “hypoxic ischemic encephalopathy” OR hypoxia OR “ischemia”(mesh) OR “ischemia” OR “aortic arch” OR “shock” OR “ near-drowning” OR drown*) AND (“heart failure”(mesh) OR “heart”(mesh) OR “heart failure” OR myocard* OR cardiac OR heart OR troponin OR “CPK-MB” OR “CK-MB”) AND (“long-term” OR “long term” OR “chronic” OR “follow up” OR “follow-up” OR “development” OR “outcome” OR “prognosis”)

No limitation in search field was used in this search.

REFERENCES

1. Groenendaal F, Casaer A, Dijkman KP, Gavilanes AWD, de Haan TR, ter Horst HJ, et al. Introduction of hypothermia for neonates with perinatal asphyxia in the Netherlands and Flanders. Neonatology. 2013;104(1):15–21.
2. Polglase GR, Ong T, Hillman NH. Cardiovascular Alterations and Multiorgan Dysfunction After Birth Asphyxia. Clin Perinatol. 2016 Sep;43(3):469–83.
3. Giannakis S, Ruhfus M, Rüdiger M, Sabir H, Network TGNH. Hospital survey showed wide variations in therapeutic hypothermia for neonates in Germany. Acta Paediatr. 2019 Aug;109(1):200-201
4. Cornette L. Therapeutic hypothermia in neonatal asphyxia. Facts Views Vis ObGyn. 2012;4(2):133–9
5. Roka A, Vasarhelyi B, Bodrogi E, Machay T, Szabo M. Changes in laboratory parameters indicating cell necrosis and organ dysfunction in asphyxiated neonates on moderate systemic hypothermia. Acta Paediatr. 2007 Aug;96(8):1118–21
6. LaRosa DA, Ellery SJ, Walker DW, Dickinson H. Understanding the Full Spectrum of Organ Injury Following Intrapartum Asphyxia. Front Pediatr. 2017;5:16.
7. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from: www.training.cochrane.org/handbook
8. National Heart, Lung, and Blood Institute. Study Quality Assessment Tools. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. [Internet]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
9. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
10. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. Identifying and Quantifying Heterogeneity. Introduction to Meta-Analysis. 2009. p. 107–25
11. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005 Jun;67(6):2089–100.
12. Guillet R, Edwards AD, Thoresen M, Ferriero DM, Gluckman PD, Whitelaw A, et al. Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. Pediatr Res. 2012 Feb;71(2):205–9.
13. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med. 2012 May;366(22):2085–92.
14. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. N Engl J Med. 2014

Jul;371(2):140–9.
15. Bindroo S, Quintanilla Rodriguez BS, Challa HJ. Renal Failure. In Treasure Island (FL); 2020.
16. Akisu M, Huseyinov A, Yalaz M, Cetin H, Kultursay N. Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. Prostaglandins Leukot Essent Fatty Acids. 2003 Jul;69(1):45-50l
17. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: safety outcomes. Pediatr Neurol. 2005 Jan;32(1):18-24
18. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005 Feb;365(9460):663–70
19. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics. 1998 Oct;102(4 Pt 1):885-892
20. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy. N Engl J Med. 2005 Oct;353(15):1574–84
21. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic Hypothermia After Neonatal Encephalopathy: Outcomes of neo.nEURO.network RCT. Pediatrics. 2010 Oct;126(4):771-778
22. Tanigasalam V, Bhat V, Adhisivam B, Sridhar MG. Does therapeutic hypothermia reduce acute kidney injury among term neonates with perinatal asphyxia?--a randomized controlled trial. J Matern Fetal Neonatal Med. 2016;29(15):2545-2548
23. Zhou W, Cheng G, Shao X, Liu X, Shan R, Zhuang D, et al. Selective Head Cooling with Mild Systemic Hypothermia after Neonatal Hypoxic-Ischemic Encephalopathy: A Multicenter Randomized Controlled Trial in China. J Pediatr. 2010 Sep 1;157(3):367-372
24. Liu X, Chakkarapani E, Stone J, Thoresen M. Effect of cardiac compressions and hypothermia treatment on cardiac troponin I in newborns with perinatal asphyxia. Resuscitation. 2013 Nov;84(11):1562–7
25. Nestaas E, Skranes JH, Støylen A, Brunvand L, Fugelseth D. The myocardial function during and after whole-body therapeutic hypothermia for hypoxic–ischemic encephalopathy, a cohort study. Early Hum Dev. 2014 May;90(5):247–52
26. Rakesh K, Vishnu Bhat B, Adhisivam B, Ajith P. Effect of therapeutic hypothermia on myocardial dysfunction in term neonates with perinatal asphyxia - a randomized controlled trial. J Matern Neonatal Med. 2018 Sep;31(18):2418-2423
27. Vijlbrief DC, Benders MJNL, Kemperman H, van Bel F, de Vries WB. Cardiac Biomarkers as Indicators of Hemodynamic Adaptation during Postasphyxial Hypothermia Treatment. Neonatology. 2012;102(4):243–8
28. Diederen CMJ, van Bel F, Groenendaal F. Complications During Therapeutic

Hypothermia After Perinatal Asphyxia: A Comparison with Trial Data. Ther Hypothermia Temp Manag. 2018 Dec;8(4):211-215

29. Gulczynska E, Gadzinowski J, Kesiak M, Sobolewska B, Caputa J, Maczko A, et al. Therapeutic hypothermia in asphyxiated newborns: selective head cooling vs. whole body cooling — comparison of short term outcomes. Ginekol Pol. 2019;90(7):403–10
30. Peliowski-Davidovich A, Canadian Paediatric Society F and NC. Hypothermia for newborns with hypoxic ischemic encephalopathy. Paediatr Child Health. 2012 Jan;17(1):41–6
31. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan;(1):CD003311
32. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Heal. 2017 Nov;1(3):184–94.
33. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of Renal Functions in Asphyxiated Newborns. J Trop Pediatr. 2005 Oct;51(5):295–9
34. Kaur S, Jain S, Saha A, Chawla D, Parmar VR, Basu S, et al. Evaluation of glomerular and tubular renal function in neonates with birth asphyxia. Ann Trop Paediatr. 2011 May;31(2):129–34
35. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol. 1995 Dec;9(6):718–22
36. Hankins GD V, Koen S, Gei AF, Lopez SM, Van Hook JW, Anderson GD. Neonatal organ system injury in acute birth asphyxia sufficient to result in neonatal encephalopathy. Obstet Gynecol. 2002 May;99(5, Pt 1):688–91
37. Jayashree G, Dutta A, Sarna M, Saili A. Acute renal failure in asphyxiated newborns. Indian Pediatr. 1991 Feb 1;28:19–23.
38. Gupta B, Sharma P, J B, Parakh M, Soni J. Renal failure in asphyxiated neonates. Indian Pediatr. 2005 Oct 1;42:928–34.
39. Martín-Ancel A, García-Alix A, Gayá Moreno F, Cabañas F, Burgueros M, Quero J. Multiple organ involvement in perinatal asphyxia. J Pediatr. 1995 Dec 1;127:786–93.
40. Ahmed N, Chowdhary J, Saif R. Acute renal failure: Nephrosonographic findings in asphyxiated neonates. Saudi J Kidney Dis Transplant. 2011 Dec;22(6):1187–92
41. Sarkar S, Askenazi DJ, Jordan BK, Bhagat I, Bapuraj JR, Dechert RE, et al. Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. Pediatr Res. 2014 Mar;75(3):431-5
42. Chou Y-H, Huang T-M, Chu T-S. Novel insights into acute kidney injury-chronic kidney disease continuum and the role of renin-angiotensin system. J Formos Med Assoc. 2017 Sep;116(9):652—659.

43. Chaturvedi S, Ng KH, Mammen C. The path to chronic kidney disease following acute kidney injury: a neonatal perspective. Pediatr Nephrol. 2017 Feb;32(2):227–41.
44. Basile DP: Rarefaction of peritubular capillaries following ischemic acute renal failure: a potential factor predisposing to progressive nephropathy. Curr Opin Nephrol Hypertens. 2004 Jan;13(1):1–7
45. Basile DP, Donohoe DL, Roethe K, Mattson DL. Chronic renal hypoxia after acute ischemic injury: effects of l-arginine on hypoxia and secondary damage. Am J Physiol. 2003 Feb ;284(2):F338–48
46. Yang L, Besschetnova TY, Brooks CR, Shah J V, Bonventre J V. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med. 2010 May;16(5):535–43
47. Greenberg JH, Coca S, Parikh CR. Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. BMC Nephrol. 2014 Nov;15(1):184
48. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney Int. 2019 Jan;95(1):160–72.
49. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012 Mar;2(1):1-138
50. Zappitelli M, Ambalavanan N, Askenazi DJ, Moxey-Mims MM, Kimmel PL, Star RA, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017;82(4):569–73.
51. Saw CL, Rakshasbhuvankar A, Rao S, Bulsara M, Patole S. Current Practice of Therapeutic Hypothermia for Mild Hypoxic Ischemic Encephalopathy. J Child Neurol. 2019 Jun;34(7):402–9.
52. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000 Nov;53(11):1119–29.
53. Kicinski M, Springate DA, Kontopantelis E. Publication bias in meta-analyses from the Cochrane Database of Systematic Reviews. Stat Med. 2015 Sep;34(20):2781–93.
54. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One. 2013;8(7):e69930.
55. van den Belt SM, Heerspink HJL, Gracchi V, de Zeeuw D, Wuhl E, Schaefer F. Early Proteinuria Lowering by Angiotensin-Converting Enzyme Inhibition Predicts Renal Survival in Children with CKD. J Am Soc Nephrol. 2018 Aug;29(8):2225–33.

56. Liu X, Tooley J, Løberg EM, Suleiman MS, Thoresen M. Immediate Hypothermia Reduces Cardiac Troponin I After Hypoxic-Ischemic Encephalopathy in Newborn Pigs. Pediatr Res. 2011 Oct;70(4):352–6
57. Huang C-H, Chen H-W, Tsai M-S, Hsu C-Y, Peng R-H, Wang T-D, et al. Antiapoptotic Cardioprotective Effect of Hypothermia Treatment Against Oxidative Stress Injuries. Acad Emerg Med. 2009 Sep;16(9):872–80
58. Teixeira RP, Neves AL, Guimarães H. Cardiac biomarkers in neonatology: BNP/NTproBNP, troponin I/T, CK-MB and myoglobin – a systematic review. J Pediatr Neonatal Individ Med. 2017 Aug 23;6(2 SE-):e060219
59. Shastri AT, Samarasekara S, Muniraman H, Clarke P. Cardiac troponin I concentrations in neonates with hypoxic-ischaemic encephalopathy. Acta Paediatr. 2012 Jan;101(1):26–9.
60. Jedeikin R, Primhak A, Shennan AT, Swyer PR, Rowe RD. Serial electrocardiographic changes in healthy and stressed neonates. Arch Dis Child. 1983 Aug;58(8):605—611
61. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, et al. Targeted Neonatal Echocardiography in the Neonatal Intensive Care Unit: practice guidelines and recommendations for training. Writing Group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiograp. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2011 Oct;24(10):1057–78.
62. Testori C, Beitzke D, Mangold A, Sterz F, Loewe C, Weiser C, et al. Out-of-hospital initiation of hypothermia in ST-segment elevation myocardial infarction: a randomised trial. Heart. 2019 Apr;105(7):531-537
63. Nichol G, Strickland W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, et al. Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment- elevation myocardial infarction. Circ Cardiovasc Interv. 2015 Mar;8(3):e001965.
64. Erlinge D, Gotberg M, Lang I, Holzer M, Noc M, Clemmensen P, et al. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous cathet. J Am Coll Cardiol. 2014 May;63(18):1857–65.
65. Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv. 2010 Oct;3(5):400-407
66. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol. 2002 Dec;40(11):1928–34.

67. Wang Y-S, Zhang J, Li Y-F, Chen B-R, Khurwolah MR, Tian Y-F, et al. A pilot clinical study of adjunctive therapy with selective intracoronary hypothermia in patients with ST-segment elevation myocardial infarction. Catheter Cardiovasc Interv. 2018 Dec;92(7):E433-E440
68. Grines C. Intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction; The ICE-IT trial. Presented at: 16th Annual Transcatheter Cardiovascular Therapeutics. 27 October 2004; Washington DC, USA.
69. O'Neill W. A prospective randomized trial of mild systemic hypothermia during PCI treatment of ST elevation MI; the COOL MI trial. Presented at: 15th Annual Transcatheter Cardiovascular Therapeutics; 16 September 2003; Washington DC, USA.
70. Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, et al. COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. EuroIntervention J Eur Collab with Work Gr Interv Cardiol Eur Soc Cardiol. 2017 Aug;13(5):e531–9.
71. Bhatt GC, Gogia P, Bitzan M, Das RR. Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review. Arch Dis Child. 2019 Jul;104(7):670 LP – 679.

Save 1 life and you are a hero
Save 100 lives and you are a nurse

Unknown

CHAPTER 5

CHAPTER 5

The effect of head positioning and head tilting on the incidence of intraventricular hemorrhage in very preterm infants:

a systematic review

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Neonatology

5.1 ABSTRACT

Background: Despite advances in neonatal intensive care, germinal matrix-intraventricular hemorrhage (GMH-IVH) remains a frequent, serious complication of premature birth. Neutral head position and head tilting have been suggested to reduce the risk of GMH-IVH in preterm infants during the first 72 hours of life.

Aim: The aim of this study was to provide a systematic review of the effect of neutral head positioning and head tilting on the incidence of GMH-IVH in very preterm infants (gestational age ≤ 30 weeks). In addition, we reviewed their effect on cerebral hemodynamics and oxygenation.

Methods: Literature was searched (June 2016) in the following electronic databases: CINAHL, Embase, Medline, SCOPUS, and several trial registers.

Results: One underpowered trial studied the effect of head positioning on the incidence of GMH-IVH. This randomized controlled trial enrolled 48 preterm infants and found no effect on the occurrence of GMH-IVH. Three observational studies investigated the effect of head rotation and/or tilting on cerebral oxygenation in 68 preterm infants in total. Their results suggest that cerebral oxygenation is not significantly affected by changes in head positioning. The effect of head positioning and/or tilting on cerebral hemodynamics was described in 2 observational studies of 28 preterm infants and found no significant effect.

Conclusion: There is insufficient evidence regarding the effect of head positioning and tilting on the incidence of GMH-IVH and cerebral hemodynamics and oxygenation in preterm infants. We recommend further research in this field, especially in extremely preterm and clinically unstable infants during the first postnatal days.

5.2 BACKGROUND

Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a major, frequently occurring complication of preterm birth. Of the extremely premature infants (gestational age [GA] < 28 weeks), 20–25% will develop a GMH-IVH, with the incidence being inversely proportional to GA [1]. Typically, GMH-IVH originates from the germinal matrix, a highly vascularized collection of neuronal-glial precursor cells in the developing brain that involutes from about 26 weeks of gestation onwards [2]. The etiology of GMH-IVH in preterm infants is multifactorial. One key factor is the intrinsic fragility of the germinal matrix vasculature [2]. The delicate blood vessels easily rupture when rapid changes in cerebral perfusion occur. This may subsequently lead to bleeding into the ventricles (intraventricular hemorrhage). A second contributing factor is the vessel pattern of the venous system in this area. Due to the U-shaped alignment, the veins are prone to venous congestion, which can cause vessel damage and bleeding [3]. Thirdly, disturbances and fluctuations in cerebral blood flow (CBF) are common in preterm infants. Especially in sick or extremely preterm neonates, autoregulation of cerebral perfusion is impaired [4–7]. Preterm infants are thus less able to maintain a relatively constant blood flow to the brain when changes in cerebral perfusion pressure occur. Consequently, fluctuations in systemic blood pressure as well as postural changes could lead to alterations in CBF. Once a GMH-IVH has occurred, this may result in serious complications such as posthemorrhagic ventricular dilatation and periventricular hemorrhagic infarction. A large and/or complicated GMH-IVH is strongly associated with an adverse outcome, including disabilities and death [1, 3, 8–10]. Despite numerous efforts to prevent GMH-IVH in premature infants, the incidence of severe GMH-IVH has remained stable during the last few decades [11, 12].

Though seemingly harmless, routine caregiving events may affect cerebral perfusion and oxygenation in the preterm neonate [13]. In an attempt to avoid (rapid) fluctuations in CBF as well as intracranial pressure during routine care, several nursing interventions have been proposed. These nursing interventions are especially important during the first 72 hours after birth, since GMH-IVH mostly develops during this time window [3, 14].
The first of these interventions consists of positioning the head of the infant in a neutral (i.e., midline) position, enabling optimal cerebral venous drainage through the internal jugular veins. The jugular veins are the major outflow paths for cranial

blood. Head rotation to either side may lead to occlusion or obstruction of the jugular venous-drainage system at the ipsilateral side. Indeed, jugular phlebograms and catheterization studies in term infants and children have shown that rotating the head 90° to one side may result in torsion and complete compression of the internal jugular vein on the same side [15–17]. As a consequence, hampered venous drainage could lead to venous congestion, subsequent increase in intracranial pressure, altered cerebral oxygenation, and ultimately bleeding [18–21].
The second proposed intervention consists of elevating the head of the incubator 15–30° upwards (i.e., tilting) in order to facilitate venous outflow from the brain by promoting hydrostatic cerebral venous drainage [22].
A multidisciplinary focus group has identified maintaining a neutral head position together with 30° tilting as 1 of 10 potential practices for the prevention of GMH-IVH. The rationale behind this recommendation was the finding that the benchmark site with the lowest rate of GMH- IVH used this practice [23, 24].

Our aim was to provide a systematic review of studies assessing the influence of head positioning and tilting on the incidence of GMH-IVH, as well as on cerebral hemodynamics and cerebral oxygenation in preterm neonates. The latter two being important factors in the etiology of GMH-IVH. Near-infrared spectroscopy (NIRS)-monitored cerebral oxygenation, oxygen extraction, and cerebral hemodynamics are correlated to the risk of GMH- IVH [7, 25].

5.3 MATERIAL and METHODS

5.3.1 Design

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26].

5.3.2 Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials, as well as observational studies were eligible for inclusion. Reviews, poster presentations, conference papers, or single-case studies were excluded. Studies were eligible for inclusion if they reported an objective clinical outcome measure such as the incidence and severity of GMH-IVH, cerebral oxygenation, or cerebral hemodynamic parameters. Availability of the full text was imperative.

Types of study population

The target population of this review consisted of preterm neonates (GA ≤ 30 weeks).

Types of interventions

Studies evaluating at least 1 of the following 2 interventions for preventing GMH-IVH were included:

- Neutral head positioning
- Head tilting

Types of outcome measures

Primary outcome:

- Incidence of GMH-IVH diagnosed by cranial ultrasonography

Secondary outcomes:

- Cerebral perfusion
- Cerebral oxygenation

5.3.3 Data collection and analysis

Electronic searches

The following electronic databases were searched: Medline, Embase, CINAHL, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The search strategies are outlined in Appendix 5A. To avoid missing studies, we did not use a search filter to differentiate between study types. There was neither restriction on the basis of publication date nor on publication status. We restricted our search to articles written in English, Dutch, German, and French. We performed the searches on June 6, 2016.

Searching other resources

To identify potential additional studies, reference lists from relevant reviews and papers were hand searched.

Selection of studies

Titles and abstracts of the search results were independently assessed by 2 review authors (K.A.d.B.-M. and A.J.B.). Full copies of all potentially relevant studies were obtained. Decision on final inclusion after retrieval of full papers was made by 2 authors independently (K.A.d.B.-M. and A.J.B.). Disagreements were resolved by discussion with a 3rd review author (G.v.W.-M.).

Data extraction

Two review authors extracted details of the included studies independently using a data extraction form. Any disagreements about data were resolved by consensus; if necessary, a 3rd reviewer was consulted. The following data were extracted from each study: study design, setting, patient characteristics, data collection, results, conclusion, and quality assessment.

Quality appraisal of individual studies

Two authors (K.A.d.B.-M. and A.J.B.) independently evaluated the methodological quality. Discrepancies in ratings were discussed between the reviewers until consensus was reached. The methodological quality of the RCT was rated according to the "Jadad scale" (Appendix 5B) and the risk of bias by the "Cochrane Collaboration tool" [27]. The Jadad scale is used to independently assess the methodological quality of an RCT, with emphasis on the quality of randomization and blinding. It consists of a questionnaire composed of three questions resulting in a score ranging from 0 to 5 points. The Cochrane Collaboration risk of bias tool assesses the risk of various forms of bias (e.g., selection bias, performance bias, attrition bias, and reporting bias). Each of the items can be classified as low-risk, unclear-risk, or high-risk bias. For the quality appraisal of observational studies, the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement was used [28]. The STROBE checklist is detailed in Appendix 5C. Each item was rated as positive, plus/ minus, or negative. To provide a final judgment about the article, scores were categorized. If less than 33% of the total score of 22 points was achieved an article was classified as "weak." If an article achieved between 34 and 66% of the total score, it was classified as "moderate." An article was classified as "strong" if the total score was higher than 66%.

Grading quality of a body of evidence

The quality of evidence for each of the outcome parameters was evaluated using the GRADE approach. The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome specifying four levels of quality. The highest quality rating is assigned to evidence from RCTs. However, the evidence from RCTs can be downgraded depending on 5 factors. Observational studies are generally graded as "low quality", but 3 factors may increase the quality level of a body of evidence (Appendix 5D) [29].

5.4 RESULTS

5.4.1 Study selection

The electronic database search yielded 864 articles. One additional article was identified through hand searching. The initial selection, based on title and abstract, included 29 records that seemed to fulfill the predefined criteria. After reading the full-text articles, 24 of these 29 articles did not meet the inclusion criteria and were therefore excluded (12 reports on children/infants with a GA > 30 weeks, 7 described no relevant outcome parameters, 1 letter to the editor, 1 case report, and 3 poster abstracts). Finally, 5 studies were included in this systematic review [30–34]. Figure 5.1 provides a flowchart of the study selection.

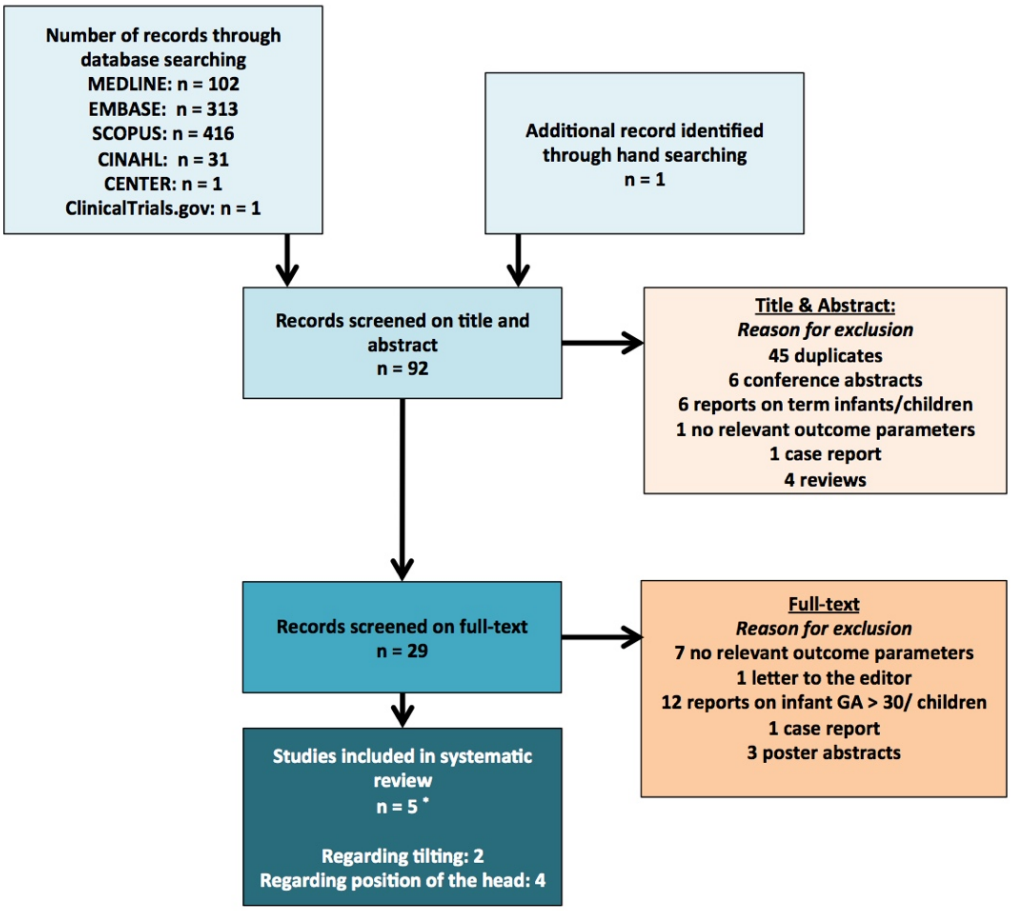

Figure 5.1 Flowchart study selection

5.4.2 Study characteristics

The 5 included studies involved a total of 120 preterm infants undergoing positional interventions. The number of subjects ranged from 4 to 48 for each study. Three reports included only neonates with a GA < 30 weeks [30, 33, 34]. Due to a wider variation in GA in 2 other studies, the range of GA at birth in all studies combined varied between 24 and 33 weeks. Two studies included infants with a postnatal age ≤ 72 hours [30, 33]. Postnatal age in the other three studies varied considerably within, as well as between studies, ranging from 1 hour to 3 weeks [31, 32, 34]. The designs of the included studies were predominantly prospective observational; there was 1 RCT. Table 5.1 gives an overview of the outcome parameters measured in the included studies. Table 5.2A-C provides an overview about the characteristics and results of the included studies.

Table 5.1: Overview of measured outcome parameter(s) per study

ARTICLES REGARDING HEAD POSITION			
Author, Journal, year	**Incidence of GMH-IVH**	**Cerebral hemodynamics**	**Cerebral oxygenation**
Al-Abdi Saudi Med J, 2011	✓	✗	✗
Ancora, Neonatology, 2010	✗	✓	✓
Elser, Adv Neonatal Care, 2012	✗	✗	✓
Liao, Am J Perinatol, 2015	✗	✗	✓
ARTICLES REGARDING HEAD TILTING			
Author, Journal, year	**Incidence of GMH-IVH**	**Cerebral hemodynamics**	**Cerebral oxygenation**
Ancora, Neonatology, 2010	✗	✓	✓
Buckley, Opt Express, 2009	✗	✓	✗

Table 5.2: Table of evidence

A

ARTICLES REGARDING INCIDENCE GM-IVH					
Author, year, country	**Design & Method**	**Participants**	**Results**	**Quality of the RCT**	**Classification of evidence according to GRADE**
Al-Abdi, 2011, Saudi Arabia (ref. 30)	Pilot RCT NICU Ultrasound Incidence IVH	n = 48 Mean GA 27 weeks (± 1.3 SD) Intervention started < 2 hours after birth; duration first 7 days of life 90% on mechanical ventilation	Incidence all IVH in midline (neutral) head position: 6/23 (26%) Incidence all IVH in lateral head position (90° rotation): 5/25 (20%) *RR 1.30; 95% CI 0.46-3.70; p=0.62* Incidence IVH grade III-IV in midline head position: 2/23 (9%) Incidence IVH grade III-IV in lateral head position: 4/25 (12%) *RR 1.40; 95% CI 0.61-3.37; p=0.94* *Results inconclusive due to small sample size (underpowered)*	(1) Jadad score: 4/5 (2) Risk of bias: - Random sequence: ✓ - Allocation concealment: ✓ - Performance bias: ✗ - Detection bias: ✓ - Attrition bias: ✓ - Reporting bias: ✓	*Moderate evidence* (minus 1 point due to sparse data)

✓: no/minimal risk of bias; ✗: risk of bias

B

ARTICLES REGARDING CEREBRAL OXYGENATION					
Author, year, country	**Design & Method**	**Participants**	**Results**	**Quality of study**	**Level of evidence (GRADE)**
Ancora, 2010, Italy (ref. 31)	Obser-vational Cross-over NICU NIRS (TOI)	n = 24 Mean GA at birth: 27.5 weeks (± 2.8 SD) Mean postnatal age at time study: 10.3 days (± 7.9 SD) No mechanical ventilation	<u>MIDLINE (NEUTRAL) VERSUS LATERAL</u> Horizontal midline (neutral) head position: TOI 66.7% (SD 2.2) Horizontal lateral (90° rotation) head position: 5-10 minutes after rotation: TOI 68.1% (SD 2.1) *No significant change* Elevated (30°) midline (neutral) head position: 5-10 minutes after rotation: TOI 68.5% (SD 2.0) Elevated (30°) lateral (90° rotation) head position: TOI 67.2% (SD 1.9) *No significant change* <u>HORIZONTAL VERSUS HEAD TILTING</u> Horizontal midline (neutral) head position: TOI 66.7% (SD 2.2) Elevated (30°) midline (neutral) head position: 5-10 min after elevation: TOI 68.5% (SD 2.0) *No significant change* Horizontal lateral (90° rotation) head position: TOI 68.1% (SD 2.1) Elevated (30°) lateral (90° rotation) head position: 5-10 min after elevation: TOI 67.2% (SD 1.9) *No significant change*	STROBE 16 / 22 (73%) Strong obser-vational study	***Low evidence*** (well-performed observational studies)
Elser, 2012, USA (ref. 32)	Obser-vational Cross-over NICU NIRS ($rScO_2$)	n = 24 GA at time of inclusion: < 32 weeks (mean/SD not given) Repeated measures (day 2, day 5, day 7, weekly thereafter) No information on respiratory support	Horizontal, head midline (neutral) position (101 observations): mean $rScO_2$ 72.9% (SD 9.6) Horizontal, head 45° rotated to the right (19 observations): 10-20 minutes after rotation: mean $rScO_2$ 76,0% (SD 8.5) *No significant change* *Differences in cerebral oxygenation after positional change became smaller as post-menstrual age increased (data not specified)*	STROBE 16 / 22 (73%) Strong obser-vational study	
Liao, 2015, USA (ref. 33)	Obser-vational Cross-over NICU NIRS ($rScO_2$)	n = 20 Mean GA at birth: 26.5 weeks (± 1.7 SD) Mean postnatal age at the time of study: 2 days (range: 1-3 d) 35% mechanical ventilation	Elevated (30°) midline (neutral) head position: $rScO_2$: 72.7% (SD 6.4) Elevated (30°) 45° rotated the left side head position: $rScO_2$: 71.7% (SD 4.8) (measured with sensor positioned on left side of the head after 10-20 min after rotation) $p < 0.05$ *No statistically significant differences measured on the right side of the brain and/or after rotation to the right side*	STROBE 20 / 22 (91%) Strong obser-vational study	

C

ARTICLES REGARDING CEREBRAL HEMODYNAMICS					
Author, year, country	**Design & Method**	**Participants**	**Results**	**Quality of study**	**Level of evidence (GRADE)**
Buckley, 2009, USA (ref. 34)	Observational, Cross-over NICU Diffuse correlation spectro-scopy and Doppler ultrasound	n = 4 Mean GA at birth 26.3 weeks (range: 25-27 weeks) Mean corrected GA at time study: 29.2 weeks (range: 26-34 weeks) No inform-ation on respiratory status	In each infant nine days of data sets *No significant change in cerebral blood flow during first 5 minutes after tilting (12° elevation)* *Small sample size*	STROBE 12 / 22 (55%) Moderate obser-vational study	***(Very) low evidence*** (Moderately-performed obser-vational study)
Ancora, 2010, Italy (ref. 31)	Observational, Cross-over NICU NIRS (nTHI)	n = 24 Mean GA at birth: 27.5 weeks (± 2.8 SD) Mean postnatal age at time study: 10.3 days (± 7.9 SD) No mechanical ventilation	**MIDLINE (NEUTRAL) VERSUS LATERAL** Horizontal midline (neutral) head position: nTHI 1.04 (SD 0.06) Horizontal lateral (90° rotation) head position: 5-10 minutes after rotation: nTHI 0.93 (SD 0.08) *No significant change* Elevated (30°) midline (neutral) head position: 5-10 minutes after rotation: nTHI 1.09 (SD 0.09) Elevated (30°) lateral (90° rotation) head position: nTHI 0.89 (SD 0.07) *No significant change* *Subgroup analysis: in all newborns with GA ≤ 26 weeks nTHI was significantly higher in the midline (neutral) head position compared to the 90° rotated position (p <0.05) (data not specified)* **HORIZONTAL VERSUS HEAD TILTING** Horizontal midline (neutral) head position: nTHI 1.04 (SD 0.06) Elevated (30°) midline (neutral) head position: 5-10 min after elevation: nTHI 1.09 (SD 0.09) *No significant change* Horizontal lateral (90° rotation) head position: nTHI 0.93 (SD 0.08) Elevated (30°) lateral (90° rotation) head position: 5-10 min after elevation: nTHI 0.89 (SD 0.07) *No significant change*	STROBE 16 / 22 (73%) Strong obser-vational study	

5.4.3 Methodological quality

The quality of the single RCT is presented in Table 5.2. The Jadad score was 4/5, indicating adequate randomization and blinding. Evaluation of the quality of the RCT using the Cochrane Collaboration risk of bias tool indicated a low risk of bias. The results of the quality appraisal of the observational studies are presented in Table 5.3. The quality of the studies varied between moderate and strong. None of the studies fulfilled all 22 STROBE quality criteria. Frequently observed weaknesses were a lack of power analysis and strategies to prevent any type of bias.

Table 5.3 Overview of methodological quality of observational studies regarding head position and tilting

Author / year	Ancora	Elser	Liao	Buckley
Title/ abstract	(+)	(+)	(+)	(±)
Background	(+)	(+)	(+)	(+)
Objectives	(+)	(+)	(+)	(+)
Study design	(+)	(+)	(+)	(+)
Setting	(+)	(+)	(+)	(-)
Participants	(+)	(+)	(+)	(-)
Variables	(+)	(+)	(+)	(-)
Data sources	(+)	(+)	(+)	(+)
Bias	(-)	(+)	(+)	(-)
Study size	(-)	(-)	(-)	(-)
Quantitative variables	(+)	(+)	(+)	(+)
Statistical methods	(+)	(-)	(+)	(+)
Participants	(-)	(-)	(+)	(-)
Descriptive data	(+)	(-)	(+)	(±)
Outcome data	(+)	(-)	(+)	(-)
Main results	(-)	(-)	(-)	(-)
Other analyzes	(-)	(-)	(+)	(+)
Key results	(+)	(+)	(+)	(+)
Limitations	(-)	(+)	(+)	(+)
Interpretation	(+)	(+)	(+)	(+)
Generalizability	(+)	(+)	(+)	(+)
Funding	(+)	(+)	(+)	(+)
Total	**16 / 22**	**15 / 22**	**20 / 22**	**13 / 22**
Category	**Strong**	**Strong**	**Strong**	**Moderate**

5.4.4 Study description

The results of the included studies are described according to the primary and secondary outcome measures:
incidence of GMH-IVH, cerebral oxygenation, and cerebral hemodynamics.

Incidence of GMH-IVH

Only 1 report studied the effect of head position (neutral versus 90° rotation) on the incidence of GMH-IVH. In this RCT, premature infants (mean GA 27 weeks) were randomized to maintain either a neutral (midline) head position or a lateral head position during the first 7 days of life. Their results were inconclusive due to the small sample size (underpowered) [30]. GMH-IVH developed in 26% (6/23) of the infants with a neutral head position versus 20% (5/25) of the infants with a lateral head position (risk ratio 1.30; 95% confidence interval 0.46–3.70; $p = 0.62$).

Cerebral oxygenation

Three observational reports investigated the effect of head rotation on NIRS parameters. These 3 studies, including a total of 68 infants, collected the NIRS measurements at different time points following head rotation, ranging from 5 to 20 min after rotation. Ancora et al. [31] did not find any significant changes in the cerebral tissue oxygenation index (TOI) 5–10 min after head rotation from midline to the side. All infants were stable and none was mechanically ventilated. Elser et al. [32] found no statistically significant difference in cerebral regional oxygen saturation ($rScO_2$) 10–20 min after head rotation. Their results did however indicate that $rScO_2$ changes following head rotation were smaller with increasing GA (no quantitative data presented). In a study performed by Liao et al. [33], a small but statistically significant decrease in $rScO_2$ of 1% was found 10–20 min after head rotation from the midline (neutral position) to the left side. Rotation to the right side did not result in a significant change [33]. The effect of tilting on cerebral oxygenation in premature infants was investigated in the study performed by Ancora et al. [31], who did not find a significant change in the cerebral TOI 5–10 min after 30° elevation of the head of the incubator.

Cerebral hemodynamics

Two observational reports on a total of 28 infants investigated the effect of head position on parameters reflecting cerebral hemodynamics. First, Ancora et al. [31] did not find any significant changes in the cerebral normalized total hemoglobin index (nTHI) 5–10 min after head rotation from the midline to the side. A sub-

group analysis was conducted in infants with a GA ≤ 26 weeks, which revealed that nTHI was significantly higher if the head was in the midline position as compared to 90° rotation. No quantitative data were presented on the number of neonates in this subgroup analysis or their clinical characteristics [31]. Their study also investigated the effect of tilting on cerebral hemodynamics and found no significant change in cerebral nTHI after 30° elevation of the head of the incubator [31]. Buckley et al. [34] repeatedly studied the effect of a small elevation of the head (12° tilting) in a small group of 4 infants. They did not find a significant alteration in microvascular blood flow (assessed by means of diffuse correlation spectroscopy) or macrovascular blood flow velocity in the middle cerebral artery (assessed by transcranial Doppler ultrasound).

5.4.5 Grading the quality of a body of evidence

Incidence of GMH-IVH

The evidence regarding the effect of head rotation on the incidence of GMH-IVH was qualified as being "moderate". Although the magnitude of the effect was investigated by a well-performed RCT, the sample size was considered too small and underpowered. Therefore, there is insufficient evidence that head rotation affects the incidence of GMH-IVH in premature infants with a GA ≤ 30 weeks. None of the studies investigated the effect of tilting on the incidence of GMH-IVH in premature infants. Therefore, there is insufficient evidence supporting a relationship between head elevation and the occurrence of GMH-IVH.

Cerebral oxygenation

Three well-performed observational studies provided information about changes in cerebral oxygenation after head rotation [31–33]. One of these studies also provided information on the effect of tilting on cerebral oxygenation [31]. Combined the previous studies provide low quality of evidence that head rotation and/or head tilting in premature infants (GA ≤ 30 weeks) does not (importantly) affect cerebral oxygenation 5–20 min after rotation/elevation.

Cerebral Hemodynamics

Together the 2 observational studies represent (very) low quality of evidence that head rotation and/or tilting does not influence cerebral hemodynamics [31, 34].

5.5 DISCUSSION

Our aim was to provide a systematic review of studies assessing the influence of maintaining a neutral head position and of head tilting on the incidence of GMH-IVH in very preterm neonates (GA ≤ 30 weeks). In addition, we reviewed the effect of these postural changes on cerebral hemodynamics and oxygenation in this subset of patients, since these factors are closely related to the development of GMH-IVH [7, 25]. We found moderate quality of evidence that the *incidence of GMH-IVH* is not influenced by maintaining a neutral head position in very preterm infants. Al Abdi et al. [30] conducted the first and only study investigating the effect of head position on the occurrence of GMH-IVH in preterm infants with a GA < 30 weeks during the first 7 days after birth. The results of this pilot study were inconclusive due to its small sample size.

Low-quality evidence indicated that there is no significant effect on *cerebral oxygenation* by head rotation and/ or head tilting in preterm infants [31–33]. One study performed by Liao et al. [33] revealed a small statistically significant one-sided decrease in $rScO_2$ after head rotation to the left side. However, this decline of only 1% is unlikely to be of clinical significance.

Regarding *cerebral hemodynamics,* (very) low-quality of evidence showed no effect on cerebral hemodynamics after head rotation and/or head tilting [31, 34].

The studies included in this systematic review were heterogeneous, especially with regard to the characteristics of the participants (e.g., variation in respiratory support), type of intervention (e.g., degree of tilting and/or rotation), and type of data collected (e.g., NIRS or ultrasound). All studies were performed in small groups of clinically stable infants. Postnatal age of most infants was more than 1 week, which is important since autoregulation of cerebral perfusion improves with postnatal age, whereas the risk of developing a GMH-IVH declines after the first postnatal days.

None of the studies reported information on the occurrence of side effects of the postural changes such as respiratory distress or increased rate of apnea. Maintaining a neutral head position hampers a prone position. Since prone position is thought to facilitate breathing it is possible that maintaining a neutral head position might predispose infants to respiratory complications [35–37].

Implications for clinical practice

Presently, there is insufficient evidence regarding the effect of a neutral head position and/or head tilting on the incidence of GMH-IVH in preterm infants. We therefore can neither recommend nor refute the use of a neutral head position and/or head tilting in order to prevent GMH-IVH.

Implications for research

Further research (preferably an RCT) is needed in larger groups of preterm infants, focusing on the effect of neutral head positioning and head tilting on the incidence of GMH-IVH as well as cerebral hemodynamics and oxygenation. Special attention should be given to unstable, ill, preterm infants during the first 72 hours after birth, since these are at greatest risk of developing a GMH-IVH. In addition, GA may influence the vulnerability to the unfavorable effects of head rotation and/or horizontal head position [19, 22, 31, 32]. Therefore, extremely premature infants should be included in future research. Importantly, these future studies should include information on possible negative side effects such as increased work of breathing.

5.6 STUDY LIMITATIONS and STRENGTHS

This review has several limitations. First, literature bias may be possible because only original, published studies were included. Results published in journals may differ systematically from those in reports, poster presentations, dissertations, or conference papers. Second, due to the lack of homogeneity among the study designs, types of measurement, and statistical analyses, it was not possible to pool the data for meta-analysis. Third, selec tion based on language could possibly have led to some degree of selection bias. Strengths of this review are the detailed transparent and structured data collection procedure according to the GRADE system. Second, there were no limitations set on publication date. Furthermore, two reviewers performed the selection process and the analysis of the methodological quality.

5.7 CONCLUSION

There is insufficient evidence regarding the effect of head positioning and/or tilting on the incidence of GMH-IVH and on cerebral oxygenation and/or hemodynamics in very preterm infants. Further research is recommended with special focus on the clinically unstable, extremely preterm infant during the first 72 hours after birth.

5.8 APPENDIX

APPENDIX 5A ELECTRONIC SEARCH

MEDLINE SEARCH:

(head position [tiab] OR prone [tiab] OR supine [tiab] OR head rotat* [tiab] OR neck rotat* [tiab] OR nursing [tiab] OR handling [tiab] OR positional [tiab] OR posture [tiab] OR postural [tiab] OR tilting [tiab])

AND

("intracranial hemorrhages"[Mesh] OR "cerebral hemorrhage"[Mesh] OR intracranial hemorrhage [tiab] OR cerebral hemorrhage [tiab] OR intraventricular hemorrhage [tiab] OR intraventricular haemorrhage [tiab] OR periventricular hemorrhage [tiab] OR subependymal hemorrhage [tiab] OR intracranial bleed* [tiab] OR intraventricular bleed* [tiab] OR subependymal bleed* [tiab] OR brain hemorrhage [tiab] OR brain bleed* [tiab] OR "intracranial pressure"[Mesh] OR intracranial pressure [tiab] OR cerebral perfusion [tiab] OR brain perfusion [tiab] OR cerebral oxygen* [tiab] OR cerebral saturation [tiab] OR cerebral hemodynamic* [tiab] OR cerebral haemodynamic* [tiab] OR brain hemodynamic* [tiab] OR cerebral blood flow [tiab])

AND

("infant, premature"[Mesh] OR "infant, extremely premature"[Mesh] OR premature infant [tiab] OR neonate [tiab] OR infant [tiab] OR newborn [tiab] OR preterm [tiab]) OR neonat* [tiab])

Restriction: newborn: birth – 1 month. Restriction: language: English, Dutch, German and French.

EMBASE SEARCH:

(prematurity/exp OR premature: ab,ti OR preterm :ab,ti OR neonatal :ab,ti OR neonate :ab,ti OR low birthweight/exp OR low birthweight :ab,ti OR infant :ab,ti OR newborn)

AND

('intracranial hemorrhage'/exp OR intracranial hemorrhage :ab,ti OR cerebral hemorrhage :ab,ti OR intraventricular hemorrhage :ab,ti OR 'brain hemorrhage'/exp OR brain hemorrhage :ab,ti OR periventricular hemorrhage :ab,ti OR subependymal hemorrhage :ab,ti OR intracranial bleeding :ab,ti OR intraventricular bleeding :ab,ti OR subependymal bleeding :ab,ti OR brain bleeding :ab,ti OR 'intracranial pressure'/exp OR intracranial pressure :ab,ti OR cerebral perfusion :ab,ti OR brain perfusion :ab,ti OR cerebral oxygenation :ab,ti OR cerebral saturation :ab,ti OR cerebral hemodynamics :ab,ti OR cerebral haemodynamics :ab,ti OR brain hemodynamics :ab,ti OR cerebral blood flow :ab,ti)

AND

(head position :ab,ti OR prone :ab,ti OR supine :ab,ti OR head rotation :ab,ti OR neck rotation :ab,ti OR head movement :ab,ti OR elevating :ab,ti OR elevation :ab,ti OR nursing :ab,ti OR handling :ab,ti OR positional :ab,ti OR posture :ab,ti OR postural :ab,ti OR tilting :ab,ti)

CINAHL SEARCH:

("infant, premature" (AB) OR premature (AB) OR preterm (AB) OR neonatal (AB) OR neonate (AB) OR "infant, low birth weight" (AB) OR low-birth-weight (AB) OR baby (AB))

AND

(intracranial hemorrhage (AB) OR cerebral hemorrhage (AB) OR intraventricular hemorrhage (AB) OR brain hemorrhage (AB) OR intraventricular bleeding (AB) OR intracranial pressure (AB) OR cerebral perfusion (AB) OR brain perfusion (AB) OR cerebral oxygenation (AB) OR cerebral saturation (AB) OR cerebral hemodynamics (AB) OR cerebral blood flow (AB))

AND

(head position (AB) OR prone (AB) OR supine (AB) OR head rotation (AB) OR neck rotation (AB) OR head movement (AB) OR OR handling (AB) OR positional (AB) OR posture (AB) OR postural (AB) OR tilting (AB) OR elevating (AB) OR nursing (AB))

SCOPUS SEARCH:

TITLE-ABS (prematurity) OR TITLE-ABS (premature) OR TITLE-ABS (preterm) OR TITLE-ABS (neonatal) OR TITLE-ABS (neonate) OR TITLE-ABS (low birth weight) OR TITLE-ABS (infant) OR TITLE-ABS (newborn)

AND

TITLE-ABS (intracranial hemorrhage) OR TITLE-ABS (cerebral hemorrhage) OR TITLE-ABS (intraventricular hemorrhage) OR TITLE-ABS (periventricular hemorrhage) OR TITLE-ABS (subependymal hemorrhage) OR TITLE-ABS (intracranial bleeding) OR TITLE-ABS (intraventricular bleeding) OR TITLE-ABS (subependymal bleeding) OR TITLE-ABS (brain bleeding) OR TITLE-ABS (intracranial pressure) OR TITLE-ABS (cerebral perfusion) OR TITLE-ABS (brain perfusion) OR TITLE-ABS (cerebral oxygenation) OR TITLE-ABS (cerebral saturation) OR TITLE-ABS (cerebral hemodynamics) OR TITLE-ABS (brain hemodynamics) OR TITLE-ABS (cerebral blood flow)

AND

TITLE-ABS (head position) OR TITLE-ABS (prone) OR TITLE-ABS (supine) OR TITLE-ABS (head rotation) OR TITLE-ABS (neck rotation) OR TITLE-ABS (head movement) OR TITLE-ABS (positional) OR TITLE-ABS (posture) OR TITLE-ABS (postural) OR TITLE-ABS (tilting)

APPENDIX 5B SCORING OF JADAD SCALE

Score: Assign a score of 1 point for each "yes" or 0 points for each "no".

Question 1: Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?

Question 2: Was the study described as double-blind (blinding of patients and evaluators, not necessarily therapists)?

Question 3: Was there a description of withdrawals and dropouts (explicit statement that all included patients were analyzed or the number and reasons for dropouts in all groups are given separately)?

Give 1 additional point if:

For question 1: The method to generate the randomization sequence was described and appropriate (table of random numbers, computer generated).

For question 2: The method of double blinding was described and appropriate (independent blinded assessors used, identical placebo or active placebo treatment, neither the person doing the assessment nor the study participant could identify the intervention being assessed.

Deduct 1 point if:

For question 1: The method to generate the randomization sequence was described and *inappropriate* (e.g., alternate allocation to groups, according to date of birth, hospital number, etc).

For question 2: The method of double blinding was described and *inappropriate* (the person doing the assessment and/or the study participant could identify the intervention being assessed).

APPENDIX 5C STROBE

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract *(b)* Provide in the abstract an informative and balanced summary of what was done and what was found
INTRODUCTION		
Background	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
METHODS		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	*(a) Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding *(b)* Describe any methods used to examine subgroups and interactions *(c)* Explain how missing data were addressed *(d) Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy *(e)* Describe any sensitivity analyses

RESULTS		
Participants	13*	*(a)* Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed *(b)* Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram
Descriptive data	14*	*(a)* Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders *(b)* Indicate number of participants with missing data for each variable of interest *(c) Cohort study*—Summarize follow-up time (e.g., average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study* Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* Report numbers of outcome events or summary measures
Main results	16	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included *(b)* Report category boundaries when continuous variables were categorized *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses
DISCUSSION		
Key results	18	Summarize key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
I*nterpretation*	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
OTHER INFORMATION		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. Freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

APPENDIX 5D GRADE SYSTEM

LEVELS OF QUALITY OF BODY OF EVIDENCE	QUALITY RATING
RCT's or double-upgraded observational studies	HIGH
Downgraded RCT's or upgraded observational studies	MODERATE
Double-downgraded RCT's or observational studies	LOW
Triple-downgraded RCT's, downgraded observational studies or case series/reports	VERY LOW

FACTORS THAT MAY DECREASE THE QUALITY LEVEL OF A BODY OF EVIDENCE
1. Limitations in the design and implementation of available studies suggesting a high likelihood of bias *(minus one or two level depending on degree of limitations)*
2. Indirectness of evidence *(minus one or two level depending on degree of uncertainty about directness)*
3. Unexplained heterogeneity or inconsistency of results *(minus one level)*
4. Imprecision of results (wide confidence intervals) or sparse data *(minus one level)*
5. High probability of publication bias *(minus one level)*

FACTORS THAT MAY INCREASE THE QUALITY LEVEL OF A BODY OF EVIDENCE
1. Large magnitude of effect *(plus one level)*
2. All plausible confounders would have reduced a demonstrated effect or suggest spurious effect when results show no effect *(plus one level)*
3. Dose-response gradient *(plus one level)*

DEFINITIONS GRADE OF EVIDENCE	
HIGH	Further research is unlikely to change the confidence in the estimate of effect
MODERATE	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
LOW	Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
VERY LOW	Any estimate of effect is very uncertain

REFERENCES

1. McCrea HJ and Ment LR. The diagnosis, management and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol 2008;35(4):777–92.
2. Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol 2014;41(1):47–67.
3. Volpe JJ. Intracranial hemorrhage. In: Saunders Elsevier., editor. Neurology of the newborn. 5 th. Philadelphia, PA.; 2008. p. 481588.
4. Perlman JM. The Relationship Between Systemic Hemodynamic Perturbations and Periventricular-Intraventricular Hemorrhage-A Historical Perspective. Semin Pediatr Neurol 2009;16(4):191–9
5. Wong FY, Silas R, Hew S, Samarasinghe T, Walker AM. Cerebral oxygenation is highly sensitive to blood pressure variability in sick preterm infants. PLoS One 2012;7(8):e43165.
6. Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, Walker AM. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. Pediatrics 2008;121(3):e604–11.
7. Alderliesten T, Lemmers PM, Smarius JJM, Van De Vosse RE, Baerts W, Van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. J Pediatr 2013;162(4):698–704.
8. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. J Perinatol 2002;22(1):31–6.
9. Pinto-Martin J, Whitaker A, Feldman J, Cnaan A, Zhao H, Rosen-Bloch J, McCulloch D, Panet N. Special education services and school performance in a regional cohort of low-birthweight infants at age nine. Paediatr Perinat Epid 2004;18(2):120–9.
10. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133(1):55–62.
11. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, Bauer CR, Donovan EF, Korones SB, Laptook AR, Lemons JA, Oh W, Papile LA, Shankaran S, Stevenson DK, Tyson JE, Poole WK, NICHD Neonatal research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196(2):147.e1-8.
12. Jain NJ, Kruse LK, Demissie K, Khandelwal M. Impact of mode of delivery on neonatal complications: trends between 1997 and 2005. J Matern Fetal Neonatal Med 2009;22(6):491–500.
13. Limperopoulos C, Gauvreau KK, O'Leary H, Moore M, Bassan H, Eichenwald EC, Soul JS,Ringer SA,DiSalvo DN, du Plessis AJ. Cerebral hemodynamic changes during intensive care of preterm infants. Pediatrics 2008;122:e1006–13.
14. Perlman J, Volpe J. Intraventricular hemorrhage in premature infants. Am J Dis Child 1986;140(11):1122–4.

15. Watson GH. Effect of head rotation on jugular vein blood flow. Arch Dis Child 1974;49(3):237–9
16. Gooding CA, Stimac GK. Jugular vein obstruction caused by turning of the head. AJR Am J Roentgenol 1984;142(2):403–6.
17. Cowan F, Thorensen M. Changes in superior sagittal sinus blood velocities due to postural alterations and pressure on the head of the newborn infant. Pediatrics 1985;75(6):1038-47.
18. Goldberg RN, Joshi A, Moscoso P, Castillo T. The effect of head position on intracranial pressure in the neonate. Crit Care Med 1983;11(6):428-30.
19. Pellicer A, Gaya F, Madero R, Quero J, Cabanas F. Noninvasive continuous monitoring of the effects of head position on brain hemodynamics in ventilated infants. Pediatrics 2002; 109(3):434-40.
20. Emery R, Peabody JL. Head position affects intracranial pressure in newborn infants. J Pediatr 1983;103(6):950-3.
21. Urlesberger B, Müller W, Ritschl E, Reiterer F. The influence of head position on the intracranial pressure in preterm infants with posthemorrhagic hydrocephalus. Child's Nerv Syst 1991;7(2):85-7.
22. Pichler G, Boetzelar MC, Müller W, Urlesberger B. Effect of tilting on cerebral hemodynamics in preterm and term infants. Biol Neonate 2001;80(3):179-85.
23. Carteaux P, Cohen H, Check J, George J, McKinley P, Lewis W, Hegwood P, Whitfield JM, McLendon D, Okuno-Jones S, Kleins S, Moehring J, McConnell C. Evaluation and development of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. Pediatrics 2003;111(4 Pt 2):e489-96.
24. Kling P. Nursing interventions to decrease the risk of periventricular-intraventricular hemorrhage. J Obstet Gynecol Neonatal Nurs 1989;18(6):457-64.
25. Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr 2014;164(2):264-70.
26. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ (OPEN ACCESS) 2009;339:b2535.
27. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.
28. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. PLoS Med 2007;16;4(10):1628–54.
29. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J,

Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490-4.

30. Al-Abdi SY, Nojoom MS, Aishaaian HM, Al-Aamri MA. Pilot-randomized study on intraventricular hemorrhage with midline versus lateral head positions. Saudi Med J 2011;32(4):420-1.
31. Ancora G, Maranella E, Actei A, Pierantoni L, Grandi S, Corvaglia L, Faldella G. Effect of posture on brain hemodynamics in preterm newborns not mechanically ventilated. Neonatology 2010;97(3):212-7.
32. Elser HE, Holditch-Davis D, Levy J, Brandon DH. The effects of environmental noise and infant position on cerebral oxygenation. Adv Neonatal Care 2012;12(Suppl 5):S18-27.
33. Liao SM, Rao R, Mathur AM. Head position change is not associated with acute changes in bilateral cerebral oxygenation in stable preterm infants during the first 3 days of life. Am J Perinatol 2015;32:645-52.
34. Buckley EM, Cook NM, Durduran T, Kim MN, Zhu C, Choe R, Yu G, Schultz S, Sehgal CM, Licht DJ, Arger PH, Putt ME, Hurt H, Yodh AG. Cerebral hemodynamics in preterm infants during positional intervention measured with diffuse correlation spectroscopy and transcranial Doppler ultrasound. Opt Expr 2009;17(15):12571-81.
35. van der Burg PS, Miedema M, de Jongh FH, Frerichs I, van Kaam AH. Changes in lung volume and ventilation following transition from invasive to noninvasive respiratory support and prone positioning in preterm infants. Pediatr Res 2015;77(3):484-8.
36. Balaguer A, Escribano J, Roqué M, Rivas-Fernandez M. Infant position in neonates receiving mechanical ventilation. Cochrane Database Syst Rev 2013;28(3):CD003668.
37. Gouna G1, Rakza T, Kuissi E, Pennaforte T, Mur S, Storme L. Positioning effects on lung function and breathing pattern in premature newborns. J Pediatr 2013;162(6):1133-7.

5

It is much more important to know what sort of patient has a disease than what sort of disease a patient has

William Osler (1849 - 1919)
Canadese arts, één van de vier oprichters van het John Hopkins Hospital

CHAPTER 6

CHAPTER 6

Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants:

a multicentre cohort study

Karen de Bijl-Marcus, Annemieke Johanna Brouwer, Linda S De Vries, Floris Groenendaal, Gerda van Wezel-Meijler

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6.1 ABSTRACT

Aim: To investigate the effect of a nursing intervention bundle (NIB) during the first 72 hours of life aimed at maintaining a more stable cerebral blood flow and decreasing cerebral venous congestion, and thus reducing the incidence of GMH-IVH in preterm infants.

Design: Multicenter cohort study.

Setting: Two Dutch tertiary neonatal intensive care units participated in this study.

Patients: The intervention group consisted of 140 neonates per center, whereas 140 infants per center served as historical controls (gestational age for both groups <30 weeks).

Interventions: After a training period, the NIB was implemented and applied during the first 72 hours after birth. The NIB consisted of maintaining the head in the midline, tilting the head of the incubator and avoidance of flushing/rapid withdrawal of blood and sudden elevation of the legs.
Main outcome measures: The incidence of a GMH-IVH occurring after the first ultrasound (but within 72 hours), progressive GMH-IVH, cystic periventricular leukomalacia (cPVL) and/or in-hospital death was the primary composite outcome measure. Logistic regression analysis was used to explore statistically significant differences between groups.

Results: The NIB was associated with a lower risk of developing a GMH-IVH (any degree), cPVL and/or mortality (OR 0.42, 95%CI 0.28-0.65). In the group receiving the NIB, severe GMH-IVH, cPVL and/or death were less often observed (OR 0.55, 95% CI 0.33-0.91).

Conclusions: The application of a bundle of nursing interventions reduces the risk of a new/progressive (severe) GMH-IVH, cPVL and/or mortality in preterm infants when applied during the first 72 hours after birth.

6.2 BACKGROUND

Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a major, frequently occurring complication of preterm birth associated with serious complications such as periventricular hemorrhagic infarction (PVHI) and post-hemorrhagic ventricular dilatation (PHVD).[1-5] Complicated GMH-IVH is strongly associated with adverse outcome, including disabilities and death.[1,6–8] Unfortunately, the incidence of moderate to severe GMH-IVH in premature infants has not declined during the last few decades.[2,9,10] Seemingly insignificant, routine caregiving events may affect cerebral perfusion and oxygenation in preterm neonates and hereby increase the risk of a GMH-IVH.[11–15] To avoid (rapid) fluctuations in cerebral blood flow (CBF) during routine care, nursing interventions have been proposed. These nursing interventions are especially important during the first 72 postnatal, since GMH-IVH mostly develops during this time window.[6,16] The first of four interventions under current investigation is positioning the head in a midline position, enabling optimal cerebral venous drainage. Head rotation to either side may lead to complete occlusion or obstruction of the jugular venous-drainage system at the ipsilateral side.[17–19] In preterm neonates hampered venous drainage due to head rotation could lead to venous congestion, altered cerebral oxygenation and ultimately GMH-IVH.[20,21] The second proposed intervention is elevating the head of the incubator 15-30° upwards to facilitate cerebral venous outflow by promoting hydrostatic cerebral venous drainage.[22] A focus group has identified maintaining a midline head position together with tilting as one of ten potential better practices for the prevention of GMH-IVH. Rationale behind this recommendation was the finding that the benchmark site with the lowest rate of GMH-IVH used this practice.[23, 24] The third intervention is avoidance of elevation of the legs during diaper change that may result in abrupt increased venous return and cardiac preload which may alter cerebral perfusion.[11] The last intervention is slow arterial/intravenous flushing and slow arterial blood withdrawal. Rapidly withdrawing blood from an arterial line has been associated with a temporary, significant decrease in cerebral oxygenation through a rapid steal of blood. Prolonging sampling time can prevent this phenomenon.[25]

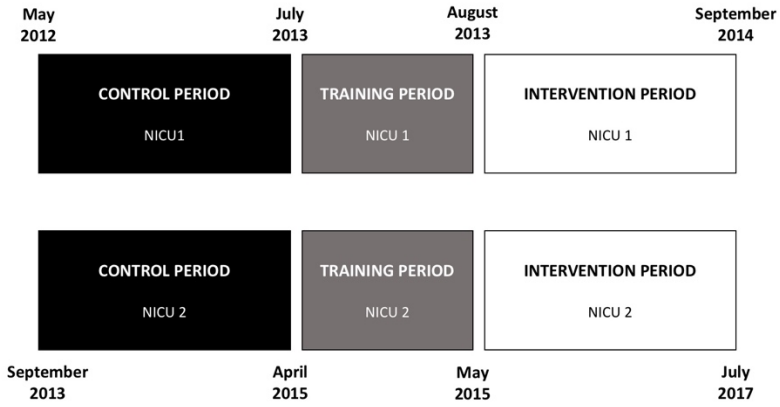
The aim of our study was to investigate the effect of a nursing intervention bundle (NIB), aimed at maintaining a more stable CBF and less cerebral venous congestion on the incidence of GMH-IVH in preterm neonates.

6.3 MATERIAL and METHODS

6.3.1 Design

This is an intervention cohort study conducted in two Dutch tertiary neonatal intensive care units (NICUs): (NICU1) Wilhelmina Children's Hospital, University Medical Center Utrecht; (NICU2) Isala Women and Children's Hospital, Zwolle. The Medical Ethical Committees of both hospitals considered the study an evaluation of an adaptation in nursing care. Since anonymized data were analyzed, a waiver of informed consent was granted according to Dutch/European legislation. The study had a stepwise design (Figure 6.1). In both centers two patient groups were. The first group corresponded to the pre-intervention period when patients received standard care (control group). After this first period nursing staff received a one-month training period how to apply the NIB. Afterwards, NIB was applied to all patients who fulfilled the inclusion criteria and were admitted to one of both NICUs. The time periods for NICU2 were longer than for NICU1, as NICU2 is smaller than NICU 1.

Figure 6.1 Stepwise study design



6.3.2 Study population and intervention

The study population included all preterm neonates with a gestational age (GA) <30 weeks, consecutively admitted to one of the NICUs. Outborn infants, infants who died in the delivery room and/or infants with major congenital anomalies were excluded from the study.

Control group

The control group received standard, routine care. Blood product transfusion protocols, sedation protocols and ventilation strategies were similar for both units.

Intervention group

The NIB was applied during the first 72 postnatal hours and consisted of:

1. Posture:
   a. Maintaining midline head position
   b. Incubator tilted 15-30 degrees
   c. Avoidance of head down position and sudden elevation of the legs
2. Avoiding rapid intravenous/arterial flushes and rapid arterial blood withdrawal (< 30 sec)

6.3.3 Neuro-imaging

In all infants, cranial ultrasound scanning (cUS) was performed within six hours after admission and additionally two to three times during the first 72 postnatal hours. Thereafter, cUS was performed at least once a week until discharge. GMH-IVH was classified according to Volpe.[6] Severe GMH-IVH was defined as IVH grade 3, hemorrhages complicated by PVHI, and/or PHVD with need for intervention. Ultrasound images were analyzed offline by two experts in neuro-imaging (LdV and GvW-M) blinded for the type of nursing care the patients received.

6.3.4 Outcome

The primary outcome was a composite of in-hospital death, GMH-IVH occurring and/or increasing after the first cUS scan but within the first 72 postnatal hours or cystic periventricular leukomalacia (cPVL).

6.3.5 Statisical analyis

Interobserver and intra-observer reliability of presence and classification of GMH-IVH was assessed, using respectively the multiple rater kappa k and Cohen's kappa statistic method. The cUS examinations of fifteen patients were analyzed by both experts blinded for previous interpretations. Intra-observer reliability was assessed by repeating the analysis of the same fifteen exams by GvW-M three months after the first. Statistical analysis was performed using binary logistic regression analysis of the primary outcome, with the NIB as intervention, and GA and the clinical risk index for baby's (CRIB) score[26], gender, birthweight and center as covariates. Statistical Package for Social Sciences for Windows, version 21 (SPSS, Chicago, IL)

was used. Statistical significance is set at a *p* value of .05. We estimated that the proportion of patients/infants with the primary outcome would be around 30%. With a sample size of 240 patients receiving standard care and 240 patients treated with the NIB we were able to detect a reduction of more than 33% of the primary outcome with a power of 0.80 and alpha of 0.05.

6.4 RESULTS

6.4.1 Patient characteristics

Patient characteristics are described in Table 6.1. Characteristics of the control and intervention groups of the two NICUs were comparable except for the number and percentage of infants receiving minimal invasive surfactant replacement therapy. All infants underwent serial cUS examinations. Five infants were excluded prior to inclusion (outborn). In 53 patients a GMH-IVH was diagnosed on the first cUS (25 patients in the control group vs 28 in the NIB group).

Table 6.1 Patient characteristics of both control groups and intervention groups in NICU1 and NICU2

CHARACTERISTICS	Control group NICU1 (n = 140)	NIB Intervention group NICU1 (n = 140)	Control group NICU2 (n = 140)	NIB Intervention group NICU2 (n = 141)
Gestational age in weeks mean ± SD	27.3 ± 1.7	27.6 ± 1.5	27.8 ± 1.6	27.4 ± 1.5
Gender number (%)	72 male (51)	75 male (54)	80 male (57)	66 male (47)
Birthweight Z score mean ± SD	- 0.8 ± 1.3	- 1.0 ± 1.4	- 0.8 ± 1.4	- 0.9 ± 1.4
Apgar score at 5 minutes median (IQR)	8 (2)	8 (2)	8 (2)	8 (2)
Antenatal corticosteroids % of cases	69%	70%	74%	76%
CRIB score* median (IQR)	3 (5)	3 (3)	2 (4)	3 (5)
Intubation rate % of infants intubated at least once in first 72 hours after birth	62%	61%	56%	70%
Duration of endo-tracheal mechanical ventilation in hours median (IQR) during first 72 hours after birth	31 (70)	25 (70)	29 (66)	35 (70)
Surfactant therapy % of cases Of which: using minimal invasive surfactant replacement therapy	66% 0%	70% 2% (3 infants)	52% 16% (22 infants)	66% 18% (25 infants)
Necrotizing enterocolitis Number of infants (%)	9 (6%)	8 (6%)	3 (2%)	6 (4%)
Sepsis Number of infants (%)	29 (21%)	31 (22%)	26 (19%)	24 (17%)
Post hemorrhagic ventricular dilatation with need of intervention Number of infants (%)	3 (2%)	1 (1%)	4 (3%)	1 (1%)

* CRIB score: clinical risk index for babies score.[27]

TABLE 6.2: Outcome parameters of control group and intervention group in both NICUs

OUTCOME			
	CONTROL GROUP 280 infants: NICU1 + NICU2)	NIB INTERVENTION GROUP 281 infants: NICU1 + NICU2	Sign.
Primary composite outcome: **New or progressive GMH-IVH within first 72 hours, in-hospital death or cPVL** Number of patients (%)	**86 (31%)** 45 NICU1 41 NICU2	**49 (17%)** 18 NICU1 31 NICU2	< 0.001
New or progressive GMH-IVH within first 72 hours after birth Number of patients (%)	**65 (23%)** 33 NICU1 32 NICU2	**27 (10%)** 7 NICU1 20 NICU2	< 0.001
c-PVL Number of patients (%)	**3 (1%)** 2 NICU1 1 NICU2	**2 (1%)** 1 NICU1 1 NICU2	N. S.
In-hospital death Number of patients (%)	**28 (10%)** 14 NICU1 14 NICU2	**29 (10%)** 13 NICU1 16 NICU2	N.S.
Composite outcome: **New or progressive *severe** GMH-IVH within first 72 hours, in-hospital death or cPVL** Number of patients (%)	**54 (19%)** 29 NICU1 25 NICU2	**35 (12%)** 15 NICU1 20 NICU2	0.01
	CONTROL GROUP Survivors 252 infants: NICU1 + NICU2	NIB INTERVENTION GROUP Survivors 252 infants: NICU1 + NICU2	
New or progressive *severe GMH-IVH within first 72 hours after birth** Number of patients (%)	**26 (9%)** 15 NICU1 11 NICU2	**6 (2%)** 2 NICU1 4 NICU2	0.01

* Severe GMH-IVH defined as a grade III hemorrhage, hemorrhages accompanied by periventricular hemorrhagic infarction and/or resulting in ventricular dilatation with need of intervention

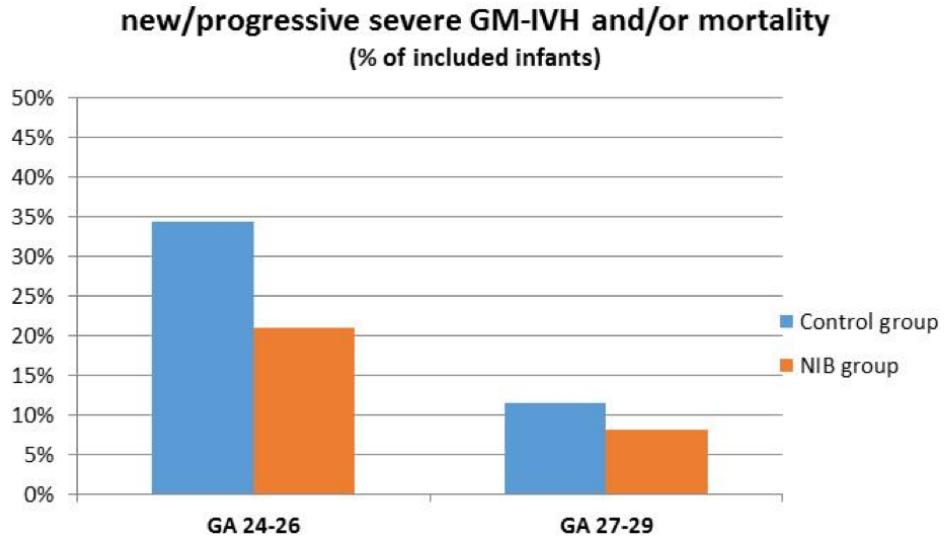
6.4.2 Outcome parameters

The outcome parameters are shown in Table 6.2. Mortality rate was equal in both patient groups. The primary outcome (composite of in-hospital death, new/progressive GMH-IVH or cPVL) was less frequently observed in the NIB group (OR 0.42; 95CI 0.28–0.65, *p* <0.001). The difference was slightly, but not significantly more pronounced in NICU1 as compared to NICU2 (*p* 0.07) when all grades of GMH-IVH were included, however the effect of NIB on the incidence of *severe* GMH-IVH was equal in both NICUs (*p* 0.51). The composite outcome of the development of a new/progressive *severe* GMH-IVH, cPVL or mortality was also less frequent in the NIB group (OR 0.55, 95CI 0.33–0.91, *p* 0.02). The effect of the intervention was more outspoken in the subgroup of infants born after a GA of less than 27 weeks (Figure 6.2). No undesirable effects of the NIB were observed. In 27 patients a new GMH-IVH or progression of a known bleed **after** the first 72 hours (median day 8; range 4-56) was observed (15 NICU1 vs 12 NICU2; 11 control group vs 16 intervention group; five patients with a severe GMH-IVH). All five patients who developed a late severe GMH-IVH suffered from serious, acute illness at that time (sepsis, necrotizing enterocolitis and/or surgery). In three patients a newly formed GMH-IVH was diagnosed more than one month after birth (33, 37 and 56 days). All three had extremely low birth weights and/or were born extremely prematurely. All three suffered from severe illness at time of onset of the hemorrhage.

6.4.3 Intra- and interobserver reliability

For the assessment of the presence of a hemorrhage (yes vs no) we found excellent reliability with a Cohen's kappa's of 0.86 (intra-observer) and 0.76 (interobserver). The average intra-observer agreement of the grade of the GMH-IVH was 60% (moderate). The average interobserver agreement of the grade of the GMH-IVH was also 60% (moderate). For the assessment of the presence of a severe hemorrhage (yes or no) we found excellent reliability with kappa's of 1.0 (intra-observer) and 0.91 (interobserver).

Figure 6.2 Percentage of infants who died or developed a new/ progressive severe germinal matrix-intraventricular haemorrhage (GMH- IVH) or cystic periventricular leukomalacia (c-PVL) (control group vs nursing intervention bundle group)



Stratified by gestational age (GA)

6.4.3 Logistic regression

Binary logistic regression analysis demonstrated that NIB strongly reduced the risk of adverse primary outcome after adjustment for GA, Apgar score at 5 min (AS5) and CRIB, although the R^2 of the model was not high (R^2 0.20). For the composite outcome of new/progressive **severe** hemorrhage, cPVL or in-hospital death the best model also consisted of NIB, GA, AS5 and CRIB score with a R^2 of 0.27. According to the model for an infant with a GA of 24 weeks and a CRIB score of 3 the NIB reduces the risk of developing a new/progressive severe GMH-IVH or mortality from 25% to 15%. For an infant with a GA of 24 weeks and a CRIB score of 6 this risk reduced from 36% to 23%, while for an infant with a GA of 29 weeks and a CRIB score of 3 the risk reduced from 8% to 4%.

6.5 DISCUSSION

We have shown that the NIB applied during the first 72 postnatal hours decreased the risk of (severe) GMH-IVH in preterm infants (GA < 30 weeks). We postulate that the NIB contributes to a more stable perfusion of the vulnerable preterm brain and decreases the risk of venous congestion. One key factor in the etiology of GMH-IVH is the intrinsic fragility of the germinal matrix vasculature which causes the delicate blood vessels to easily rupture when rapid changes in cerebral perfusion occur.[27] Autoregulation of cerebral perfusion is impaired in preterm infants, especially when they are ill.[28,29] Preterm infants are thus less able to maintain a relatively constant blood flow to the brain when changes in cerebral perfusion pressure occur. A second contributing factor to GMH-IVH is the U-shaped alignment of the venous vessels that are hereby prone to venous congestion and stasis, which can cause vessel damage and bleeding.[6,30] The NIB in the current study aimed at a more stable cerebral perfusion and preventing cerebral venous congestion. Maintaining a midline head position during the early transition period has been included in GMH-IVH prevention bundles at several institutions. However, so far strong data to support the practice are lacking.[23,31-33] Two RCTs have been performed by the same group.[34,35] Their first pilot study analyzed the effect of head position on the incidence of GMH-IVH and mortality of preterm infants and found no difference between different head positions. However, no cUS examinations were conducted prior to inclusion. It is therefore likely that in some infants, hemorrhages were already present before inclusion.[34] The second study was a multicenter RCT.[35] Infants who were diagnosed with a GMH-IVH within the first 12 postnatal hours were excluded. The intervention was identical to their previous study. However, the study was terminated prematurely owing to low accretion rate. They found no difference in risk of GMH-IVH or mortality between the groups. Unfortunately, both RCTs are characterized by small sample sizes, few events and wide confidence intervals. A recent retrospective cohort study investigated differences of incidence of GMH-IVH when comparing two NICUs that had established a protocol to maintain a midline head position during the first 72 postnatal hours with two NICUs that provided routine care. They included a total of 1226 preterm infants and did not find a difference in the incidence of GMH-IVH. However, there were significant differences between groups regarding AS5, patent ductus arteriosus, mode of delivery, and inborn/outborn which may have influenced the results. No information was given regarding whether or not the GMH-IVH was already present at time of the first cUS.[36] A study performed by

Ancora et al. did not show significant changes in either the tissue hemoglobin index (which reflects changes in cerebral blood volume) or cerebral oxygenation after rotation of the head. Only the most immature infants (GA < 26 weeks) showed a reduction in cerebral blood volume with head rotation.[37] As the latter group represents the infants with the greatest risk of developing a GMH-IVH, this reduction may therefore be of clinical importance. Our findings also indicate that extremely premature infants (GA < 27 weeks) benefit most from the NIB intervention. One RCT investigated the effect of tilting on the incidence of GMH-IVH and mortality. They found significantly fewer grade 4 hemorrhages and lower mortality rates in the group with tilted heads.[38] To the best of our knowledge there are no previous studies that analyzed the combined effect and/or the other components of the NIB under investigation in the present study (avoidance of rapid flushes/blood withdrawal, avoidance of elevating legs/head down position) on the incidence of GMH-IVH, cPVL and/or mortality in preterm infants. We have shown that the application of a NIB during the first 72 postnatal hours reduces the risk of developing a (severe) GMH-IVH in very preterm infants. Our results show a more pronounced effect on the incidence of severe GMH-IVH compared to low grade hemorrhages. This is clinically relevant as especially severe GMH-IVH is associated with an unfavorable prognosis.[4,6–8] The effect of NIB on the incidence of low grade hemorrhages differed between both NICUs. In NICU1 a larger reduction of the incidence of low grade GMH-IVH was observed when compared to NICU2. A possible explanation for this difference could be the quality of cUS (in NICU1 the quality of cUS was more often hampered by the bonnets used to secure CPAP systems).

6.6 STUDY LIMITATIONS

Our study has several limitations. The first being the study design as it is a cohort study and not a RCT. The implementation of two simultaneous nursing protocols was considered not feasible in our units. Due to the nature of the intervention blinding was only feasible for the outcome assessors. The second limitation is the study period (NICU1 two years, NICU2 four years). It is possible that improvements in overall neonatal care contributed to a reduction in GMH-IVH. However, previous studies have indicated that the incidence of GMH-IVH has remained stable for the last few decades.[2,9,10] There was no difference in mortality between the control and NIB groups. Third, our intervention consists of a bundle of interventions. The individual contribution of each of the interventions remains therefore unclear in

the current study. Fourth, the intra- and interobserver agreement of the assessment of the grade of the GM-IVH was moderate despite the fact that cUS were evaluated by experts. These findings are consistent with previous studies.[39] However, intra- and interobserver agreement for the presence of a bleed (any grade), as well as the diagnosis of a severe GMH-IVH were excellent.

6.7 CONCLUSION

In conclusion, a reduction in the composite outcome of in-hospital death, GMH-IVH or cPVL was found using a NIB. Since it is relatively easy and cheap to apply and no disadvantages of the NIB were observed, we advise the routine use of this NIB in all preterm neonates during the first 72 postnatal hours, especially in those born extremely prematurely.

REFERENCES

1. McCrea, HJ, Ment, LR. The Diagnosis, Management, and Postnatal Prevention of Intraventricular Hemorrhage in the Preterm Neonate. *Clinics in Perinatology* 2008; 35(4): 777–92.
2. Fanaroff, A. Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, Bauer CR, Donovan EF, Korones SB, Laptook AR, Lemons JA, Oh W, Papile LA, Shankaran S, Stevenson DK, Tyson JE, Poole WK; NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am. J. Obstet. Gynecol* 2007; 196(2):147e1-8.
3. V. O. N. Vermont Oxford Network. Database of very low birth weight infants born in 2012 Nightingale Internet Reporting System. *http://public.vtoxford.org*
4. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K; New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection. Intraventricular Hemorrhage and Neurodevelopmental Outcomes in Extreme Preterm Infants. *Pediatrics* 2014; 133(1): 55–62.
5. Mukerji A, Shah V, Shah PS. Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis. *Pediatrics* 2015; 136(6): 1132-43.
6. Volpe JJ. Intracranial hemorrhage. in *Neurology of the newborn.* (ed. Saunders Elsevier.) 481–588 (2008).
7. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. *J. Perinatol* 2002(1); 22: 31–6.
8. Pinto-Martin J, Whitaker A, Feldman J, Cnaan A, Zhao H, Bloch JR, McCulloch D, Paneth N. Special education services and school performance in a regional cohort of low-birthweight infants at age nine. *Paediatr Perinat Epidemiol* 2004;18(2): 120–9.
9. Jain NJ, Kruse LK, Demissie K, Khandelwal M. Impact of mode of delivery on neonatal complications: trends between 1997 and 2005. *J. Matern. Fetal. Neonatal Med* 2009; 22(6): 491–500.
10. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015; 314(10): 1039–51.
11. Limperopoulos C, Gauvreau KK, O'Leary H, Moore M, Bassan H, Eichenwald EC, Soul JS, Ringer SA, Di Salvo DN, du Plessis AJ. Cerebral hemodynamic changes during intensive care of preterm infants. *Pediatrics* 2008; 122(5): e1006–13.

12. Tsuji M, duPlessis A, Taylor G, Crocker R, Volpe JJ. Near infrared spectroscopy detects cerebral ischemia during hypotension in piglets. *Pediatr Res* 1998; 44(4): 591–5.
13. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. *N Engl J Med* 1983; 309(4): 204–9.
14. Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in Intraventricular Hemorrhage by Elimination of Fluctuating Cerebral Blood-Flow Velocity in Preterm Infants with Respiratory Distress Syndrome. *N Engl J Med* 1985; 312(21): 1353–7.
15. Van Bel F, Van de Bor M, Stijnen T, Baan J, Ruys JH. Aetiological Rôle Of Cerebral Blood-Flow Alterations In Development And Extension Of Peri-Intraventricular Haemorrhage. *Dev Med Child Neurol* 1987;29(5): 601–14.
16. Perlman J, Volpe JJ. Intraventricular hemorrhage in premature infants. *Am J Dis Child* 1986; 140(11):, 1122–4.
17. Watson GH. Effect of head rotation on jugular vein blood flow. *Arch Dis Child* 1974; 49(3): 237–9.
18. Gooding CA, Stimac GK. Jugular vein obstruction caused by turning of the head. *Am J Roentgenol 1984;* 142(2): 403–6.
19. Cowan F, Thoresen M. Changes in Superior Sagittal Sinus Blood Velocities Due to Postural Alterations and Pressure on the Head of the Newborn Infant. *Pediatrics* 1985; 75(6): 1038-47.
20. Goldberg RN, Joshi A, Moscoso P, Castillo T. The effect of head position on intracranial pressure in the neonate. *Crit Care Med* 1983; 11(6): 428-30.
21. Pellicer A, Gayá F, Madero R, Quero J, Cabañas F. Noninvasive continuous monitoring of the effects of head position on brain hemodynamics in ventilated infants. *Pediatrics* 2002; 109(3): 434–40.
22. Pichler G, Van Boetzelar MC, Müller W, Urlesberger B. Effect of tilting on cerebral hemodynamics in preterm and term infants. *Biol. Neonate* 2001; 80(3): 179–85.
23. McLendon D, Check J, Carteaux P, Michael L, Moehring J, Secrest JW, Clark SE, Cohen H, Klein SA, Boyle D, George JA, Okuno-Jones S, Buchanan DS, McKinley P, Whitfield JM. Implementation of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics* 2003; 111(4Pt2): e497–e503.
24. KLING P. Nursing Interventions to Decrease the Risk of Periventricular-Intraventricular Hemorrhage. *J. Obstet. Gynecol. Neonatal Nurs.* 1989; 18(6): 457–64.
25. Schulz G, Keller E, Haensse D, Arlettaz R, Bucher HU, Fauchère JC. Slow blood sampling from an umbilical artery catheter prevents a decrease in cerebral oxygenation in the preterm newborn. *Pediatrics* 2003; 111(1): e73–6.
26. Network, I. N. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing preformance of neonatal intensive care units.

Lancet 1993; 342(8865): 193–8.
27. Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. *Clin Perinatol* 2014; 41(1): 47–67.
28. Perlman JM. The Relationship Between Systemic Hemodynamic Perturbations and Periventricular-Intraventricular Hemorrhage-A Historical Perspective. *Semin. Pediatr Neurol* 2009; 16(4): 191–9.
29. Alderliesten T, Lemmers PM, Smarius JJ, van de Vosse RE, Baerts W, van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr* 2013; 162(4): 698–704.
30. Tortora D, Severino M, Malova M, Parodi A, Morana G, Sedlacik J, Govaert P, Volpe JJ, Rossi A, Ramenghi LA. Differences in subependymal vein anatomy may predispose preterm infants to GMH-IVH. *Arch Dis Child Fetal Neonatal* 2018; 103(1): F59-65.
31. Romantsik O, Calevo MG, Bruschettini M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants. *Cochrane Database Syst Rev* 2017; CD012362.
32. De Bijl-Marcus KA, Brouwer AJ, De Vries LS, van Wezel-Meijler G. The Effect of Head Positioning and Head Tilting on the Incidence of Intraventricular Hemorrhage in Very Preterm Infants: A Systematic Review. *Neonatology* 2017; 111(3): 267–79.
33. Malusky S, Donze A. Neutral Head Positioning in Premature Infants for Intraventricular Hemorrhage Prevention: An Evidence-Based Review. *Neonatal Netw J Neonatal Nurs* 2011; 30(6): 381–96.
34. Al-Abdi SY, Nojoom MS, Alshaalan HM, Al-Aamri MA. Pilot-randomized study on intraventricular hemorrhage with midline versus lateral head positions. *Saudi Med J* 2011; 32(4): 420–1.
35. Al-Abdi S, Allah J, Al Omran, Al Alwan Q, Al Hashimi H, H. S. The risk of intraventricular hemorrhage with flat midline versus flat right lateral head positions: a prematurely terminated multicenter randomized clinical trial. *The Pediatric Academic Societies (PAS)* https://clinicaltrials.gov/ct2/show/NCT01584375?id (2015).
36. Carroll K, Praveen K, Prazad P, Mohammad K, Raghavan A, Wang H. Midline Head Positioning for Prevention of Intraventricular Hemorrhage (IVH) in Infants Born at 23-28 weeks gestation: a multicenter retrospective cohort study. Poster presentation UICOMP Research Day april 2018 (not yet published)
37. Ancora G, Maranella E, Aceti A, Pierantoni L, Grandi S, Corvaglia L, Faldella G. Effect of posture on brain hemodynamics in preterm newborns not mechanically ventilated. *Neonatology* 2010; 97(3): 212–7.
38. Kochan M, Leonardi B, Firestine A, McPadden J, Cobb D, Shah TA, Vazifedan T, Bass WT. Elevated midline head position of extremely low birth weight infants: effects on cardiopulmonary function and the incidence of periventricular-intraventricular hemorrhage. J Perinatol 2018; Epub ahead of print.

39. Hintz SR, Slovis T, Bulas D, van Meurs KP, Perritt R, Stevenson DK, Poole K, Das A, Higgins RD. Interobserver reliability and accuracy of cranial ultrasound interpretation in premature infants. J Pediatr 2007; 150(6):592-6.

SECTION THREE

Perception of quality of care from the view of parents and care professionals

Experience is the teacher of all things

Julius Caesar
Romeinse generaal en staatsman (100 – 44 a.C.)

CHAPTER 7

CHAPTER 7

The perception of safety regarding the transfer of infants from the neonatal intensive care unit to a level II neonatology department:

a cohort study using a safety-II approach

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Submitted

7.1 ABSTRACT

Aim: This study aimed to investigate the perceived safety during the transfer process of infants from a Neonatal Intensive Care Unit (NICU) to a regional level II department. It sought to identify areas of agreement and divergence among the perspectives on safety of stakeholders and to determine the facilitators and barriers to achieving a high level of perceived safety.

Design: This study employed a mixed-method cohort design and action research approach grounded in Safety-II principles.

Setting: The study focused on transfers from a single Dutch university hospital NICU to multiple regional level II neonatology departments.

Methods: Surveys were administered to parents and care professionals, including NICU staff, level II department staff, and ambulance personnel. The surveys consisted of both quantitative and open-ended questions. Data were analysed using quantitative and qualitative methods, considering Safety-I and Safety-II perspectives, to assess the perceived safety and identify facilitators and barriers.

Results: A total of 46 transfers were evaluated by 239 stakeholders. The overall perception of safety was positive among all stakeholder groups. There were no significant differences in the overall level of perceived safety between parents and care professionals. However, significant variations between stakeholder groups were observed during specific transfer phases. Qualitative analysis revealed facilitators and barriers related to timing, parental participation and information exchange.

Conclusion: This study indicated a consistent positive perception of safety among parents and care professionals. Effective communication, parental participation and optimal timing were identified as crucial for enhancing safety perceptions during transfers.

7.2 BACKGROUND

The prevalence of preterm birth is increasing, with approximately 15 million preterm infants born worldwide each year. Preterm birth is the leading cause of death in children under the age of five years [1,2]. To improve short- and long-term outcomes for high-risk infants, many countries have implemented regionalized and specialized neonatal care systems [3,4]. However, this has led to neonatal intensive care units (NICUs) operating at full capacity due to improved survival rates and the treatment of even more complex and immature infants, combined with staffing challenges [5–11]. As a result, in the Netherlands infants who no longer require highly specialized care are often transferred to regional level II neonatology departments to ensure optimal utilization of NICU resources and access to appropriate levels of care (see APPENDIX 1 for neonatal care levels) [12–16]. Furthermore, transferring stable infants to a regional level II hospital brings them closer to home, facilitating parents and local care professionals to become acquainted with each other prior to discharge.

However, transferring infants from a NICU to a level II neonatology department is not without risks. In 38% of cases there is a transient physical decline following the interhospital transfer of infants [17]. Moreover, the transfer adds complexity to the care process for these still vulnerable, recovering infants and may disrupt continuity of care, potentially negatively influencing (the perceived) patient safety and satisfaction [18]. Previous studies have primarily focused on parental perceptions of the safety of the transfer process. Their results indicated that parents often experience distress related to the interhospital transfer and identified three major sources of parental distress during the transfer process: (1) lack of communication between the NICU staff and parents, (2) the transfer process itself, and (3) the level of care and differences in practice during and shortly after the transfer process [19–32].

Little is known about the perceived safety of the transfer process from the perspective of care professionals and how it relates to parental perceptions. Only two previous studies have investigated the perceived safety and quality of care during the transfer process from the perspective of care professionals. Hanrahan et al. conducted focus group meetings with parents, physicians, nurse practitioners, and nurses from the NICU and level II departments to explore their experiences with the transfer process [25]. Many of the issues mentioned by participants of this study centered around (stimulating) optimal communication. Helder et al. conducted a qualitative explorative study by interviewing parents and

nurses from NICU and level II neonatology departments [32]. Their interviews focused on the positive and negative experiences of parents during the transfer process and the recognition of those parental experiences by nurses. Trust emerged as a central theme for parents in their study: gaining trust, betrayal of trust, and rebuilding confidence following the transfer. Both studies provided us with valuable information regarding the degree of safety experienced by parents and the role of care professionals in the improvement of those experiences. However, there is a gap in knowledge regarding how care professionals themselves perceive the safety of transferring these vulnerable infants to a lower level of care in a high workload environment and how their perspective aligns with parental experiences. Studies in other patient groups have shown differences in safety perceptions between patients/families and care professionals, as well as variation among care professionals [33–37]. Investigating the perspective on safety of all care professionals involved, not exclusively the physicians and nurses working at the hospital, could provide valuable insights.

In recent years, there has been a notable shift in the field of safety evaluation from the traditional "Safety-I" approach to the emerging "Safety-II" approach [38]. Safety-I primarily focuses on preventing failures and incidents by identifying and eliminating risks. It follows a reactive and retrospective model, emphasizing compliance with safety regulations and procedures. On the other hand, Safety-II recognizes that organizations and systems are complex and adaptive. It acknowledges that incidents and failures are not the only indicators of safety, and that studying successful outcomes and normal operations can provide valuable insights as well. It aims to understand how systems function effectively under normal circumstances. Safety-II takes into consideration the reality of the workplace (e.g., complex, dynamic, full interactions and affected by human factors), which mandates flexibility and resilience within work processes and among all different stakeholders to build on what goes right and prevent adverse outcomes [38,39]. Evaluating and learning from normal, routine transfers of infants from the perspectives of all relevant stakeholders, while focusing on how these complex processes usually go right, matches well with the Safety-II principles.

The aims of the present study were:
(1) To investigate the perceived degree of safety regarding the transfer process from the perspective of all stakeholders involved (parents, physicians, physician assistants (PA's), nurses, secretary personnel and ambulance personnel). We will identify areas of agreement and divergence in the perspective of different stakeholder.
(2) To identify facilitators and barriers to achieving a high level of perceived safety during the transfer process. A detailed analysis of transfers perceived as safe will provide valuable insights on how to enhance the safety.

7.3 MATERIAL and METHODS

7.3.1 Study design

This mixed method cohort study presents the diagnostic phase of an action research that aimed at the understanding and improving (the perception of) safety during the transfer process. Action research is a research approach in which transformative change is pursued through the simultaneous process of taking action and gaining knowledge by means of critical reflection with all those who participate in the action research. The participative, reflective nature of action research matches well with the complexity of the transfer process, where multiple stakeholders are involved (aim 1) and where a Safety-II perspective can encourage a safe transfer process (aim 2) [40–44].

7.3.2 Period

The evaluations of transfers were conducted from 1-1-2022 to 1-6-2022, reflecting the period prior to improvement actions.

7.3.3 Setting

The present study focused on the transfer of infants from a NICU department to a regional level II department. The NICU of the Wilhelmina Children's Hospital is part of a Dutch university hospital with 24 level NICU beds and a full range of pediatric medical subspecialists. The NICU is located in a highly regionalized area with four regional post-NICU/High care (HC) departments and three non-HC units. A high percentage (>90%) of infants are transferred to regional level II hospitals for convalescent care. Five regional level II neonatology departments participated in this study. Transportation occurred by ambulance. Parents were encouraged to

familiarize with the receiving hospital through a physical/online tour prior to the transfer.

7.3.4 Participants

All consecutive infants who were transferred from the NICU to a regional level II neonatology department were eligible for inclusion in our study when at least one of the parents could speak Dutch or English. There were no other inclusion or exclusion criteria. Care professionals involved in the transfer process of included infants were asked consent to participate in the study. This included:

- Nurses, physicians, PA's, and secretary personnel working at the NICU.
- Nurses, physicians, PA's/nurse practitioners working in level II departments of hospitals participating in the present study.
- Ambulance personnel that conducted the transfer of the infant.

7.3.5 Surveys

For each enrolled infant that was transferred, we invited the aforementioned care professionals (see: 'participants') to complete an online survey to describe their experiences with the transfer process of this specific infant. Each transfer was given a unique identification number. Content validity of this survey was established and confirmed by interviews with parents (n=3) and care professionals (n=15, including all stakeholders), and by reviewing the pre-existing literature to ensure that all aspects of the transfer experience for parents and care professionals were considered. The survey consisted of quantitative (Likert scale or grading) and open-ended written questions (see APPENDIX 2).

NICU professionals, secretary, and ambulance personnel completed a written or online survey directly after the transfer of the infant from the NICU to the level II neonatology department. Level II care professionals completed an online survey one week after the transfer. Parents completed a survey via an interview setting by telephone approximately one week after the transfer, conducted by a research nurse not involved in the care process and not involved in the data analysis process.

7.3.6 Quantitative analysis (1st & 2nd aim)

Quantitative data regarding the perception of safety were analyzed using SPSS version 26. Significant differences between medians (Mann-Whitney U test) and mean ranks (Kruskal-Wallis test) was set at $p<0.05$. Parents were not included as a stakeholder group in all comparisons analyses due to differences in response

category for some questions: a Likert scale for care professionals versus a dummy response category for parents.

7.3.7 Qualitative analysis (2nd aim)

Constant comparative qualitative methods were used to analyze open-ended questions. Content analysis was performed by four investigators independently for identifying the thematic content. The investigators then agreed on overarching themes regarding facilitators and barriers to a safe transfer perception using a method comparable to the "Colaizzi's descriptive phenomenological method" described by Morrow et al. [45]. This descriptive phenomenological method is a step-by-step approach in which texts are read and re-read, themes are coded and after clustering of these themes, the investigated phenomena 'light up'. These phenomena are then articulated in simple terms and mirrored to the participants, as in this case through focus groups. Five focus group meetings were conducted in which participated: parents (n=3), representatives of infant association (n=2), ambulance personnel (n=1), physicians NICU (n=4), nurses NICU (n=4), physicians level II department (n=6), nurses level II department (n=7), secretary employees (n=2), (action)researchers (n=5). The focus groups were intended to present and interpret the collected results. This led to a deeper understanding of the factors that play a role in the experience of the participants.

7.3.8 Ethics approval

The study was exempted from formal approval under the Dutch Medical Research Involving Human Subjects Act by the Medical Research Ethics Committee of the Erasmus School of Health Policy & Management, Erasmus University Rotterdam (ETH2021-0098) and of the Medical Research Ethics Committee of the University Medical Centre Utrecht. Additionally, a substantive test of the integrity of the research plan was carried out by the Ethical Review Committee of the University of Humanistic Studies (2022-03). Participants provided written informed consent. Data were analyzed anonymously.

7.4 RESULTS

7.4.1 Inclusion

During the study period 70 infants matched the inclusion criteria. Of those infants, 19 were transferred before parents were informed and/or gave their consent for inclusion in the study. Five parents refused participation. The

remaining 46 were included in the study. These 46 transfers were evaluated by 239 stakeholders (see Table 7.1). Although all stakeholders were invited for each eligible transfer, the response varied between two and ten surveys per individual transfers.

TABLE 7.1 Descriptive sample

Stakeholder	n	%	Survey topic		
			Preparation	Transfer	Admission Level II
NICU: Physician/PA	44	18	✓	✓	NA
NICU: Nurse	44	18	✓	✓	NA
NICU: Secretary	45	19	✓	NA	NA
Ambulance personnel	31	13	✓	✓	NA
Level II: Physician/PA	16	7	✓	✓	✓
Level II: Nurse	20	9	✓	✓	✓
Parents	39	16	✓	✓	✓
Total	**239**		**231 of 239**	**173 of 194**	**63 of 75**

NA = not applicable; PA = physician assistant

7.4.2 Perceived safety regarding the transfer process by stakeholders: *1st aim*

Perception of safety: similarities and differences

Table 7.2 describes the overall perception of safety reported by the various stakeholders. Median scores indicated a *uniform positive perception* regarding the degree of safety of the overall transfer process perceived by parents and care professionals. All parents perceived the overall transfer process as safe. There were *no statistically significant differences* between stakeholder groups (Kruskal-Wallis H (4)= 1.02, p>0.05). Table 7.3 presents the degree of perceived safety by the different stakeholders for three important phases in the transfer process. Again, the degree of *perceived safety was high among all stakeholder groups during all three phases of the transfer process*, with a median score varying between: 8 and 9 The Kruskal-Wallis test revealed *significant differences between stakeholder groups* regarding perceived safety during the transfer (Kruskal-Wallis H (5)= 12.39, p=0.03) and the admission phase (Kruskal-Wallis H (2)= 9.24, p=0.01), but not regarding the preparation phase (Kruskal-Wallis H (6)= 9.02, p=0.17). Pairwise comparison showed that parents significantly perceived a higher safety of the

transfer compared to care professionals working at the level II or NICU department. This was also seen regarding the admission to the level II department: parents perceived a significantly higher level of safety when compared to the care professionals working at the level II department. Ambulance personnel significantly perceived a lower safety of the transfer compared to care professionals working at the level II departments.

TABLE 7.2 Evaluation of perceived overall safety (scale 1 – 5) categorized into different stakeholder groups

	Stakeholder	N	Median	1 Strongly disagree %	2 Disagree %	3 Neutral %	4 Agree %	5 Strongly agree %	N.O.
Overall safety of the transfer	Physician/PA NICU	44	4	5	0	0	50	36	9
	Nurse NICU	41	4	2	2	2	39	44	10
	Ambulance personnel	30	5	13	3	0	23	60	0
	Physician/PA (II)	16	4	0	0	0	56	44	0
	Nurse (II)	20	4	0	0	0	55	45	0

N.O. = no opinion; PA = physician assistant; II: Care professional from a level II department

* Significant differences between mean ranks $p<.05$ (Kruskal-Wallis test)

TABLE 7.3 **Degree of perceived safety by the different stakeholders for three phases in the transfer process: preparation, the actual transfer and admission**

Stakeholder / Perceived safety (grade) during 3 transfer phases		NICU			Ambulance personnel	Level II department		Parents
		Physician / PA	Nurse	Secretary personnel		Physician / PA	Nurse	
1. Preparation of transfer	Median	8	8	8	8	8	8	8
	Mean Rank	106.99	112.70	134.99	126.35	92.28	101.30	177.37
	N = 231	43	43	44	31	16	20	34
2. Transfer *	Median	8	8	NA	8	8	8	9
	Mean Rank	80.81	81.63	NA	101.52	72.94	73.08	107.94
	N = 173	43	38	NA	31	16	20	25
3. Admission level II hospital*	Median	NA	NA	NA	NA	8.0	8.0	8.5
	Mean Rank	NA	NA	NA	NA	27.97	25.80	38.98
	N = 63	NA	NA	NA	NA	16	20	27

Grade 1 – 10: 1 least optimal, 10 most optimal; NA = not applicable; PA = physician assistant
* Significant differences between groups are based on mean ranks $p<.05$ (Kruskal-Wallis test)

7.4.3 Facilitators and barriers of a high degree of perceived safety: *2nd aim*

To investigate which aspects, facilitate or hamper the level of perceived safety, stakeholder groups were asked several questions (see Table 7.4AB).

TABLE 7.4AB Evaluation of the timing of the transfer & information exchange (grade 1 – 5)

TABLE 4A: TIMING OF TRANSFER	Stakeholder	N	Median	Mean rank	1 Strongly disagree %	2 Disagree %	3 Neutral %	4 Agree %	5 Strongly agree %	N.O.
Optimal timing transfer **Q: the timing of the transfer was optimal**	Physician/ PA NICU	44	4	74.93	0	9	16	43	23	9
	Nurse NICU	44	4	70.86	14	11	14	23	36	2
	Ambulance personnel	30	4.5	84.83	0	10	10	13	33	33
	Physician/ PA (II)	16	4	49.84	6	38	0	56	0	0
	Nurse (II)	20	4	60.05	0	25	10	60	5	0
TABLE 4B: INFOR-MATION EXCHANGE	**Stakeholder**	**N**	**Median**	**Mean rank**	**1 Strongly disagree %**	**2 Disagree %**	**3 Neutral %**	**4 Agree %**	**5 Strongly agree %**	
Receiving sufficient & timely information from the NICU professionals	Secretary personnel NICU	43	4	59.69	5	9	0	67	19	
	Ambulance personnel	31	4	52.05	3	19	7	55	16	
	Physician/ PA (II)	16	4	50.06	0	13	6	81	0	
	Nurse (II)	20	4	56.20	0	10	5	75	10	
	Parents	38	NA	NA	No %	Yes %				
					24%	76%				
Providing sufficient & timely information to level II	Physician/ PA NICU	44	4	40.48	0	7	9	59	25	
	Nurse NICU	43	4	47.60	5	5	2	46	42	
Providing sufficient & timely information to parents	Physician/PA NICU	43	4	44.28	0	5	14	60	21	
	Nurse NICU	43	4	42.72	5	12	12	44	28	

PA = physician assistant; N.O. = no opinion;
II: Care professional from a level II department
* Significant differences between mean ranks p<.05 (Kruskal-Wallis test)

Timing of the transfer

TABLE 4A presents the perception of the timing of the transfer as one of the facilitators/barriers. The Kruskal-Wallis test revealed overall no significant differences between stakeholder groups (Kruskal-Wallis H (4)= 8.83, p=0.066). Pairwise comparison showed that the perception of ambulance personnel regarding the timing of the transfer was significantly more positive when compared to the perspective of NICU professionals (p <0.05).

In addition, respondents were asked to select a reason why the timing of transfer was not optimal. Of the respondents, (63%) claimed that another moment during the day would have been better, (9%) believed that the preparation for transfer was not complete. None of the respondents believed that the timing was inadequate based on the care needs of the patient. The remaining respondents did not select one of the predefined categories. Level II care professionals perceived the transfer as safe more often when the transfer was conducted during the day shift. When patients were transferred during the late afternoon/evening, level II care professionals felt that they could not deliver the best possible care since less personnel was working at the department, which negatively influenced their perception of safety. In one quarter of cases (26%) parents evaluated the timing of the transfer of their infants as suboptimal, often related to uncertainties and lack of information regarding the exact timing of the transfer. Preparing parents for the uncertainties regarding the exact timing and explaining the reasons behind those uncertainties facilitated parents and endorsed the feeling of trust.

Information exchange

The exchange of information was evaluated as one of the facilitators/barriers (see TABLE 4B). The Kruskal-Wallis test revealed no overall significant differences between stakeholder groups regarding receiving information. Regarding providing information, Mann-Whitney U-test showed no differences between physicians/PAs and nurses (NICU). In addition, comparing the evaluation of receiving and giving information among stakeholder groups showed overall significant differences (Kruskal-Wallis H (5)= 12.52, p=0.03). Pairwise comparison showed that NICU nurses were more positive than physicians/PAs and nurses from the receiving hospital, but also than secretary and ambulance personnel. These findings indicate that the care professionals receiving information were less satisfied with the information exchange than care professionals providing information. Parents indicated that they were informed by NICU staff sufficiently and timely in 76% of cases. In addition, in the perception of parents, level II care

professionals were well informed by the NICU professionals in 84% of cases. This is in line with the perception of NICU professionals.

The qualitative analyses signal that discrepancies between (the interpretation of) discharge criteria or type of care that can be delivered in specific level II departments increased the feeling of unsafety perceived by parents and/or level II care professionals. Both care professionals (NICU and level II) and parents expressed the need for more (adherence to) uniform and clear discharge criteria, that are shared with parents. Parents appreciated repeated information provision starting soon after admission at the NICU, preferably using multiple modalities (written, oral and visual information). Personal contact between parents and level II / ambulance care professionals prior to the transfer facilitated the safety perception of parents. Furthermore, involving parents in the exchange of information between parties (NICU, ambulance, level II) stimulates the parental empowerment and feeling of being in control. For instance, in some cases parents were asked to document specific aspects that care professionals should be aware of from the parents' perspective. This written parental handover was subsequently given to the level II care professionals, facilitating them to deliver optimal care and meeting the expectations of parents. In complex cases, the level II care professionals received a discharge letter and radiological images prior to the transfer of the infant in addition to a handover conversation in which parents, referring and receiving care professionals participated through an online meeting. These examples of Safety-II behavior, were highly valued by both parents as well as level II care professionals and endorsed the perception of safety.

(Attention for) concerns

The Kruskal-Wallis test revealed no overall significant differences between stakeholder groups regarding having concerns during the transfer process. Pairwise comparison also did not reveal differences between groups. Prior to the transfer 20-25% of the care professionals working at the NICU had concerns regarding the transfer. One third of the parents experienced concerns regarding the transfer. These concerns were mainly related to the fear of the unknown and worries concerning the comfort of their infant during the transfer process. Most parents had a great deal of confidence in the knowledge, skills, and expertise of the health care providers. When a familiar care professional accompanied their infant during the transfer or when parents could accompany their infant themselves this facilitated the safety perception. Most parents felt reluctant to share their concerns with the care professionals. They felt that they experienced "normal"

concerns and they did not want to "burden care professionals with them". When care professionals actively asked parents about concerns it reduced the fears and uncertainties experienced by parents. When a care professional, despite the high workload, exuded calmness and took the time to provide personal attention to parents and their thoughts, it fostered trust among parents.

TABLE 7.5: Summary of facilitators and barriers to a high level of perceived safety

	FACILITATOR
TIMING OF TRANSFER	Transfer in the morning/early afternoon
	Complete preparation
	Preparing parents for the uncertainties regarding the exact timing of the transfer and explaining the reasons behind those uncertainties
INFORMATION EXCHANGE	Adherence to uniform discharge criteria and share these discharge criteria with parents
	Sharing discharge criteria with parents soon after admission to the NICU
	Knowledge regarding which care can and cannot be delivered by specific level II facilities
	Informing parents soon after admission to the NICU regarding the transfer
	Providing parents with transparent, consistent, repeated information using multiple modalities (oral, written, visual)
	Knowing which information, the receiving care professionals need to deliver optimal care
	Sharing written handovers and diagnostic images prior to the transfer with care professionals of the level II department
PARENTAL PARTICIPATION & CONCERNS	Involving parents in the preparation, transfer and handover conversation For complex cases an online meeting can be scheduled involving parents, referring and receiving care professionals
	A parent or familiar care professionals accompanying the infant during the transfer
	Asking parents if they have concerns or fears regarding the transfer
	Asking parents to write down what, in their opinion, is important for the receiving care professionals to know regarding the optimal care for their child. This written parental handover facilitates level II care professionals in providing optimal care

7.5 DISCUSSION

The results of our study provide valuable insights into the perception of safety during the transfer process of infants from a NICU to a level II neonatology department from multiple perspectives. Overall, both parents and all different care professionals involved in this study expressed *a uniform positive perception* regarding the degree of safety throughout the transfer process. This is a significant finding as it indicates that all stakeholders have confidence in the care process and safety measures implemented during the transfer. Importantly, there were no statistically significant differences between stakeholder groups regarding the overall degree of safety, suggesting a consistent perception of safety across the board. This finding is particularly noteworthy considering previous reports that have indicated that parents often experience stress and feelings of anxiety regarding the transfer [19–32]. The positive perception of parents in our study may be attributed to various factors, such as effective communication, a sense of trust in the healthcare team, and the overall stability of the infant's condition at the time of transfer. It could indicate that efforts to enhance safety measures and collaboration among stakeholders have been effective in mitigating parental concerns and instilling confidence in the care provided during the transfer. This unexpected finding highlights the potential impact of interventions aimed at improving the transfer experience and ensuring the well-being of infants and their families. Reflecting on these positive findings from the appreciative Safety-II perspective, we can conclude that our research provides valuable insight in the facilitators of a positively experienced transfer process. Parents witnessed and valued the knowledge, skills, and expertise of the health care providers, which endorsed feelings of trust and safety. When parents were actively involved in the transfer process or when care professionals took the time to pay attention to parents and their thoughts, it was associated with a high degree of safety perception by parents. The same applied to care professionals. When care professionals proactively made the effort to take interest in the abilities and concerns of other care professionals, it stimulated the feeling of safety.

These findings underscore the value of promoting effective, open communication channels between parents and care professionals, as well as among care professionals. The involvement of parents in decision-making and encouraging collaborative decision-making among care professionals can facilitate problem-solving and ensure a safe transfer process. Based on these findings we currently are currently exploring opportunities to further involve parents in the transfer

process and strengthen the dialogue among care professionals. The impact of these interventions will be evaluated in future research.

Zooming in on different *phases of the transfer process*, again our results indicate that all stakeholder groups reported high levels of perceived safety. Median scores consistently ranged between 8.0 and 9.0, indicating a robust perception of safety across all phases. However, there were significant differences in the perceived safety during the transfer and admission phases among different stakeholders, with parents together with ambulance personnel being the most positive in their perception. Furthermore, *parents perceived a significantly higher level of safety* during admission compared to the level II care professionals. There are several potential explanations for this finding.

First, parents often develop a strong bond, feeling of gratitude, and trust with the healthcare professionals, which can contribute to their positive perception of safety during the transfer process [32]. They may feel reassured by the expertise and information provided by the professionals and the knowledge that the transfer is being conducted under their professional guidance. In contrast, care professionals may be more aware of potential risks and complexities involved. They may have a deeper understanding of the challenges, limitations, and potential complications that can arise during the transfer of these vulnerable infants. Their professional knowledge and experience may lead to a more cautious perception of safety compared to parents. Furthermore, care professionals may experience a feeling of accountability and responsibility for the care provided. They may be more attuned to potential risks and may have a greater awareness of adverse events that can occur during transfers. This heightened awareness and responsibility may influence their perception of safety, leading to a more critical assessment.

The *differences in perceptions among care professionals* may stem from various factors, including variations in experience, training, and exposure to transfer cases. It is crucial to address these differences and foster a shared understanding of the transfer process among all care professionals involved. This can be achieved through effective communication, collaboration, education, and the establishment of clear guidelines and protocols to ensure consistent and standardized care during transfers. Our finding that level II healthcare professionals who receive information were less satisfied with the completeness and accuracy of the information compared to the NICU professionals providing the information raises important considerations regarding communication and information exchange within the transfer process. Effective communication is crucial for ensuring a

smooth and safe transfer of patients. In this study, it appears that there may be a discrepancy between the expectations and perspectives of healthcare professionals providing and receiving information. The providers of information may have a better understanding of the context, patient history, and specific details relevant to the transfer. They may assume that certain information is already known or overlook elements they consider less significant. On the other hand, the receiving healthcare professionals may have different expectations and requirements regarding the information they need to provide optimal care. These differing perspectives and expectations can contribute to discrepancies in perceived completeness and accuracy, potentially leading to misunderstandings, delays, and a decreased overall perception of safety. To bridge this gap, referring healthcare professionals should have an optimal understanding of the context, nuances, and specific needs of the receiving healthcare professionals. This would allow them to tailor the information to meet those needs more effectively. When written handovers and/or diagnostic images were shared with the receiving care professionals prior to the transfer, it stimulated the perception of safety. The same applied to a handover conversation in which parents, referring, and receiving care professional participated through an online meeting. These examples of Safety-II behavior, where care professionals learned from previous successful transfers, facilitated the receiving care professionals and parents in adequately preparing for the transition of care. These exemplary actions simultaneously addressed the healthcare needs of the patient, the expectations of the parents, and facilitated level II care professionals in the delivery of optimal care.

Overall, difference in perception regarding the safety of care delivered can be attributed to a combination of personal involvement/emotional attachment, professional knowledge, and differing perspectives on what constitutes safety. Different individuals may have varying thresholds for what they consider safe or unsafe and may prioritize aspects of safety differently. Understanding these variations in perception can help healthcare professionals optimize their communication and care. The difference in perception of safety between stakeholders underscores the need for effective communication and shared decision-making throughout the transfer process. Using those different perspectives to increase knowledge regarding (improving) safety could enhance the quality of the transfer process.

We have identified several facilitators and barriers to the perception of a high degree of safety.
The most important *facilitators* were related to (1) the optimal timing of the transfer, (2) early, consistent, transparent information exchange, (3) knowing and meeting each other's expectations and limitations, (4) parental participation and (5) attention for concerns. *Barriers* to experiencing a high level of safety mainly revolved around two themes: 1. communication (e.g., too little, too late, inconsistent) and 2. planning/organizing (e.g., incomplete preparation). Although parents perceived the transfer as safe, many parents did experience *concerns* regarding the transfer. These concerns were predominantly related to the fear of the unknown and concerns about the comfort of their infant. Interestingly, most parents felt reluctant to share their concerns with care professionals. However, actively addressing parents' concerns by care professionals alleviated fears and uncertainties, emphasizing the importance stimulating open communication and support. Our study demonstrates that we can increase our understanding of safety by reflecting on daily practice from the perspective of all major stakeholders, even when safety has already been achieved and perceived. This finding aligns with Safety-II principles.

7.6 STUDY LIMITATIONS

It is possible that parents as well as care professionals rated the degree of safety of care more positively due to the survey investigating safety itself and the attention given to safety by the department. This phenomenon is known as the Hawthorne effect, where individuals modify their behavior or perception when they know they are being observed or studied [46]. When respondents are aware that their opinions and perceptions of safety are being assessed through a survey, it can create a sense of importance and attention to the topic of safety. This heightened awareness can lead parents/care professionals to pay closer attention to safety measures, be more cautious, and potentially have a more positive perception of safety during their care. Furthermore, the survey itself can serve as a reminder for healthcare professionals to prioritize safety and implement safety measures more diligently. The knowledge that safety is being assessed may lead to increased vigilance and efforts to enhance safety protocols and communication, which can contribute to a more positive perception of safety among patients. It is important to acknowledge that our study's findings may be context-specific and influenced by various factors, such as the specific healthcare setting and the

effectiveness of local protocols and guidelines. Our NICU transfers a high percentage of infants to level II hospitals for convalescent care. Transfer of infants from a NICU to a level II department is therefore a frequent occurring event. Nonetheless, the consistent perception of safety among stakeholders provides valuable insights into the effectiveness of current practices and highlights the potential for further improvements in the transfer process.

7.7 CONCLUSION

In conclusion, our study highlights the positive perception of safety regarding the transfer of infants from a NICU to a level II neonatology department among parents and care professionals. Despite some variations in perceptions among stakeholder groups, overall high levels of perceived safety were observed. The difference in perception of safety between stakeholders underscores the need for effective communication, reflection and shared decision-making throughout the transfer process. Understanding the factors that influence safety perception, could facilitate healthcare professionals to optimize the transfer process and ensure the well-being of infants and their families. Further research and implementation of targeted interventions based on these findings can contribute to ongoing efforts to improve the safety and quality of care during transfers in neonatal settings.

REFERENCES

1 Kinney M V., Lawn JE, Howson CP, *et al.* 15 million preterm births annually: What has changed this year? Reprod Health. 2012;9.

2 Perin J, Mulick A, Yeung D, *et al.* Global, regional, and national causes of under-5 mortality in 2000–19: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet Child Adolesc Health* 2022;6:106–15.

3 Marie Lasswell S, Wanda Denise Barfield M, Roger William Rochat M, *et al.* Perinatal Regionalization for Very Low-Birth-Weight and Very Preterm Infants A Meta-analysis. 2010. www.jama.com

4 Bode MM, O'Shea TM, Metzguer KR, *et al.* Perinatal regionalization and neonatal mortality in North Carolina, 1968-1994. *Am J Obstet Gynecol* 2001;184:1302–7.

5 Saigal S, Doyle LW. Preterm Birth 3 An overview of mortality and sequelae of preterm birth from infancy to adulthood. www.thelancet.com

6 Horbar J, Badger G, Carpenter J, *et al.* Trends in Mortality and Morbidity for Very Low Birth Weight Infants, 1991–1999. *Pediatrics* 2022;110:143–51.

7 Capaciteitsorgaan. Capaciteitsplan 2020-2023. Utrecht: 2020. https://capaciteitsorgaan.nl/app/uploads/2020/11/20200119_Capaciteitsplan-FZO-AVP-2020_DEF-WEB.pdf (accessed 15 Mar 2023).

8 Wise J. Neonatal units in Wales are understaffed and under-resourced, says report. *BMJ* Published Online First: July 2016.

9 Rogowski JA, Staiger D, Patrick T, *et al.* Nurse staffing and nicu infection rates. *JAMA Pediatr* 2013;167:444–50.

10 Rogowski JA, Staiger DO, Patrick TE, *et al.* Nurse Staffing in Neonatal Intensive Care Units in the United States. *Res Nurs Health* 2015;38:333–41.

11 Sherenian M, Profit J, Schmidt B, *et al.* Nurse-to-patient ratios and neonatal outcomes: A brief systematic review. Neonatology. 2013;104:179–83.

12 Phibbs C, Mortensen L. Back transporting infants from neonatal intensive care units to community hospitals for recovery care: effect on total hospital charges. *Pediatrics* 1992;90:22–6.

13 Phibbs CS, Baker LC, Caughey AB, *et al.* Level and Volume of Neonatal Intensive Care and Mortality in Very-Low-Birth-Weight Infants A BS T R AC T. 2007. www.nejm.org

14 Chung JH, Phibbs CS, Boscardin § W John, *et al.* The Effect of Neonatal Intensive Care Level and Hospital Volume on Mortality of Very Low Birth Weight Infants. 2010. www.lww-medicalcare.coml

15 Blackmon L, Batton DG, Bell EF, *et al.* Levels of neonatal care. Pediatrics. 2004;114:1341–7.

16 Zein H, Yusuf K, Paul R, *et al.* Elective transfers of preterm neonates to regional centres on non-invasive respiratory support is cost effective and increases tertiary

care bed capacity. *Acta Paediatrica, International Journal of Paediatrics* 2018;107:52–6.

17 De Nieuport SMDPHDH, Van Beek R, Kornelisse RF, *et al.* Interhospital transfer of premature neonates from intensive to lower care settings: Impact on the clinical condition. Arch Dis Child Fetal Neonatal Ed. 2017;102:F560–1.

18 Donohue PK, Hussey-Gardner B, Sulpar LJ, *et al.* Convalescent care of infants in the neonatal intensive care unit in community hospitals: Risk or benefit? *Pediatrics* 2009;124:105–11.

19 Kuhnly J, Freston M. Back transport: exploration of parents' feelings regarding the transition. *Neonatal Netw* 1993;12:57–8.

20 Page J, Lunyk-Child O. Parental perceptions of infant transfer from an NICU to a community nursery: implications for research and practice. *Neonatal Network* 1995;14:69–71.

21 Slattery M, Flanagan V, Cronenwett LR, *et al.* Mothers' Perceptions of the Quality of Their Infants' Back Transfer. 1998.

22 Cagan J. Weaning parents from intensive care unit care. *MCN Am J Matern Child Nurs* 1988;13:275–7.

23 Aagaard H, Hall EOC, Ludvigsen MS, *et al.* Parents' experiences of neonatal transfer. A meta-study of qualitative research 2000–2017. Nurs Inq. 2018;25.

24 Aagaard H, Uhrenfeldt L, Spliid M, *et al.* Parents' experiences of transition when their infants are discharged from the Neonatal Intensive Care Unit: a systematic review protocol. JBI Database System Rev Implement Rep. 2015;13:123–32.

25 Hanrahan K, Gates M, Attar M, *et al.* Neonatal Back Transport: Perspectives from Parents of Medicaid-Insured Infants and Providers. *Neonatal network* 2007;26:301–11.

26 Dosani A, Murthy P, Kassam S, *et al.* Parental perception of neonatal transfers from level 3 to level 2 neonatal intensive care units in Calgary, Alberta: qualitative findings. *BMC Health Serv Res* 2021;21.

27 Murthy P, Dosani A, Sikdar KC, *et al.* Parental perception of neonatal retro-transfers from level 3 to level 2 neonatal intensive care units. *Journal of Maternal-Fetal and Neonatal Medicine* 2022;35:5546–54.

28 Donohue PK, Hussey-Gardner B, Sulpar LJ, *et al.* Parents' perception of the back-transport of very-low-birth-weight infants to community hospitals. *Journal of Perinatology* 2009;29:575–81.

29 Ballantyne M, Orava T, Bernardo S, *et al.* Parents' early healthcare transition experiences with preterm and acutely ill infants: a scoping review. Child Care Health Dev. 2017;43:783–96.

30 Van Manen M. Carrying: Parental experience of the hospital transfer of their baby. *Qual Health Res* 2012;22:199–211.

31 Meyer C, Mahan C, Schreiner R. Retransfer of newborns to community hospitals: questionaire survey of parents' feelings. . *Perinatology & Neonatology* 1982;6:75–8.

32 Helder OK, Verweij JCM, Van Staa A. Transition from neonatal intensive care unit to special care nurseries: Experiences of parents and nurses. *Pediatric Critical Care Medicine* 2012;13:305–11.
33 De Grood C, Leigh JP, Bagshaw SM, *et al*. Patient, family and provider experiences with transfers from intensive care unit to hospital ward: A multicentre qualitative study. *CMAJ* 2018;190:E669–76.
34 Cheyne A, Tomás JM, Cox S, *et al*. Perceptions of safety climate at different employment levels. *Work Stress* 2003;17:21–37.
35 Listyowardojo TA, Nap RE, Johnson A. Variations in hospital worker perceptions of safety culture. *International Journal for Quality in Health Care* 2012;24:9–15.
36 Pluut B. Differences that matter: developing critical insights into discourses of patient-centeredness. *Med Health Care Philos* 2016;19:501–15.
37 noord IV van, Wagner C, dyck C Van, *et al*. Is culture associated with patient safety in the emergency department? A study of staff perspectives. *International Journal for Quality in Health Care* 2014;26:64–70.
38 Hollnagel E, Leonhardt J, Licu T, *et al*. From Safety-I to Safety-II: a white paper. Brussels (Belgium): 2013.
39 Damen NL, De Vos MS, Moesker MJ, *et al*. Preoperative Anticoagulation Management in Everyday Clinical Practice: An International Comparative Analysis of Work-as-Done Using the Functional Resonance Analysis Method. 2018. www.journalpatientsafety.com
40 Brydon-Miller M, Greenwood D, Maguire P. Why action research? *Action Research* 2003;1:9–28.www.sagepublications.co.uk
41 de Brún T, O'Reilly-De Brún M, Van Weel-Baumgarten E, *et al*. Using participatory learning & action (PLA) research techniques for inter-stakeholder dialogue in primary healthcare: An analysis of stakeholders' experiences. *Res Involv Engagem* 2017;3.
42 Gordon C, Ellis-Hill C, Dewar B, *et al*. Knowing-in-action that centres humanising relationships on stroke units: An appreciative action research study. *Brain Impairment* 2022;23:60–75.
43 Langley J, Wolstenholme D, Cooke J. 'Collective making' as knowledge mobilisation: The contribution of participatory design in the co-creation of knowledge in healthcare. BMC Health Serv Res. 2018;18.
44 Coughlan P, Coghlan D. Action research for operations management. *International Journal of Operations and Production Management* 2002;22:220–40.
45 Morrow R, Rodriguez S, King N. Colaizzi's descriptive phenomenological method. *The psychologist* 2015;28:643–4.
46 Sedgwick P, Greenwood N. Understanding the hawthorne effect. BMJ (Online). 2015;351.

CHAPTER 8

CHAPTER 8

Summary, discussion and future perspectives

SUMMARY & GENERAL DISCUSSION

What is value?

Imagine closing your eyes and reflecting on how you personally define "value."

What aspects of life and abilities are most important to you and could potentially be threatened during illness? The notion of value is not fixed: it's a dynamic concept that is shaped by individual experiences, beliefs, and circumstances [1,2]. What carries immense value for one person might carry differing weight for another. Even at an individual level, value can change over time due to experiences and altering conditions. This disparity in viewpoints leads to important, thought-provoking questions:

- What truly constitutes value?
- How do we go about quantifying it?
- Do various stakeholders in healthcare, including healthcare professionals, insurance companies, parents, and patients, share a common understanding of value?

It is paramount for healthcare providers to comprehend what is of value to individual patients, as this knowledge can significantly influence diagnostic and therapeutic choices. Within the context of adult care, this entails healthcare professionals actively listening to patients' needs, thereby enabling the delivery of the most suitable and efficacious care for each individual patient through shared decision making [3,4]. In the domain of neonatal intensive care, where the fragility of life intersects with the profound implications of medical interventions, the concept of value becomes layered in complexity. Does providing intensive, costly, and sometimes painful care to an extremely premature infant who may not survive hold value? What if parents find solace in the time spent with their child, despite the tragic outcome? These questions underscore the need to consider value from multiple angles and emphasize the importance of adopting a value-based approach within neonatal care.

Defining Value in Neonatal Care

Value, within the context of contemporary Western healthcare, commonly entails achieving the best possible long-term outcomes for NICU patients while ensuring efficient resource utilization. This concept recognizes that medical care extends beyond clinical interventions; it encompasses the holistic impact on patients' lives, their families, and society at large. In the domain of neonatal intensive care, characterized by the vulnerability of young lives and the potential for enduring consequences, the concept of 'value' extends beyond immediate medical outcomes to encompass the long-term aspects of quality of life and the broader societal implications of medical interventions. It is imperative to acknowledge that significance lies not solely in medical outcomes, but also in patient-reported outcomes and experiences. In essence, what truly matters to patients are the values they attach to their care and its profound influence on their overall well-being.

Measuring Neonatal Outcomes (section one)

Evaluating outcomes serves as a fundamental cornerstone in assessing the value of healthcare interventions. As eloquently expressed by H. James Harrington: *"If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it" [5].*

The act of measuring outcomes not only provides a roadmap for progress, but also knowledge, understanding, purpose, and the motivation to strive for excellence. Delving into outcomes grants us the opportunity to reflect on our actions, compare results through benchmarking, and gain invaluable insights. From these insights, we uncover a wealth of knowledge about the effectiveness of our interventions. We decipher what works, what falls short, and where improvements can be made. From a Value Based HealthCare (VBHC) perspective discovering that a specific intervention does not improve a patient outcome is an important finding. By avoiding subjecting the patient to the risks or burdens of unnecessary interventions, while simultaneously lowering costs, we can create value through a strategy of doing less. On an individual level, measuring outcomes is a compass guiding patient-centered care, ensuring that each decision benefits the patient. Zooming out, measuring and learning from outcomes hold the potential to transform healthcare systems. They support resource allocation, refine treatment

protocols, and optimize service delivery. And yet, the potential impact goes even further. Societal implications emerge, as healthier individuals mean more productive communities. In short, learning begins with measuring, and it is through this learning that we sculpt a healthcare landscape of continuous enhancement. This upward spiral of continuous improvement is depicted in Figure 8.1.

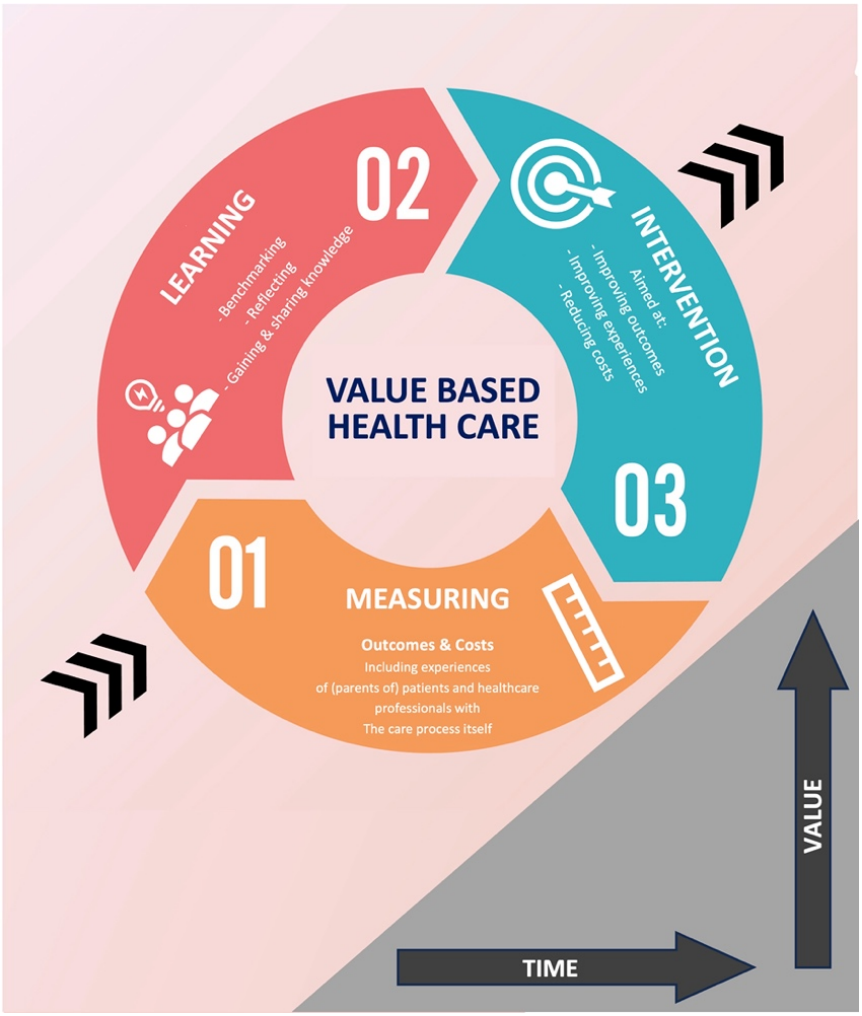

Figure 8.1

The **first section** of this thesis presents two studies that explore different aspects of neonatal outcomes, in particular renal function and length of stay in the hospital. The study described in **chapter two** investigates the occurrence and outcomes of Acute Kidney Injury (AKI) in neonates admitted to a level III Neonatal Intensive Care Unit (NICU). Out of the 9,376 infants who were admitted during the study

period, 1.5% experienced AKI within the initial week after birth. However, it is worth noting that this percentage might underestimate the actual occurrence, given that not every infant underwent an assessment of renal function. The causes of AKI varied, with 14% being attributed to congenital renal anomalies, 81% to acquired conditions, and 5% to congenital heart disease. Notably, AKI was associated with high morbidity and mortality, especially in severely ill neonates. The management of AKI was exclusively conservative, and while most infants' renal function improved, those with severe AKI showed increased risks of renal complications. However, long-term follow-up was lacking. In the context of VBHC, these findings hold significance. The study's identification of AKI risk factors and its demonstration of associated morbidity and mortality underscore the potential for improving patient outcomes through early detection and intervention. It can be used for the implementation of a screening protocol for AKI in neonates, helping healthcare providers manage this condition and potentially prevent severe complications. Furthermore, the study's insights into the varying causes and outcomes of AKI in neonates contribute to the understanding of personalized care and the importance of tailoring interventions based on individual patient characteristics. The application of this new knowledge can enhance VBHC by minimizing adverse outcomes and identifying patients at risk for chronic kidney disease. Detecting infants at risk of chronic kidney disease offers the opportunity for secondary prevention measures, such as implementing a diet and monitoring blood pressure and renal function. The costs of these diagnostic procedures in the current market are low (creatinine measurements costs less than € 2 per sample, urine protein tests cost € 2-6 per sample), making them interesting tools for the potential enhancement of outcomes from a VBHC perspective. However, future research is necessary to investigate if and how such a screening of infants at risk for chronic kidney disease would increase value for the patient and/or society.

Chapter three of the thesis describes the analysis of trends in morbidity and the length of stay (LoS) among patients admitted to both NICU and level II neonatal care units. LoS serves as a crucial indicator of healthcare quality, offering insights into care efficiency, complication rates, treatment effectiveness, and resource utilization. The importance of LoS lies in its dual role as both an outcome measure and a potential avenue for cost reduction. Our study reveals a significant increase in the overall LoS of infants born with a gestational age below 32.0 weeks between 2008 and 2021. The treatment of severe complications are the primary factors driving this increment. This prolonged length of stay presents ramifications for healthcare systems, families, and the infants themselves, underscoring the

importance of holistic approaches to care delivery, resource management, and quality enhancement. Embracing the principles of VBHC, we recognize that by prioritizing the reduction of severe complications linked to preterm birth, healthcare systems can exert a positive influence on both NICU-specific and overall length of stay. This strategy will lead to improved patient outcomes, judicious resource utilization, and the mitigation of healthcare expenditures.

Strategies for Improving Neonatal Outcomes (section two)

In the **second section** of the thesis, a variety of interventions aimed at improving outcomes for NICU patients is discussed. These strategies highlight the potential for medical innovation to positively influence neonatal care quality and value. **Chapter four** consists of a systematic review exploring the impact of therapeutic hypothermia (TH) on renal and myocardial function in neonates suffering from perinatal asphyxia. Perinatal asphyxia leading to hypoxic-ischemic encephalopathy (HIE) presents risks to multiple fetal organs, including the brain, heart, and kidneys. This review focuses on the effects of TH on the heart and kidney, considering their susceptibility to the consequences of perinatal asphyxia and potential long-term complications. TH has demonstrated efficacy in mitigating mortality and neurocognitive disability risk for neonates with moderate to severe HIE. The study aimed to assess the potential short-term (tier one) and long-term (tier three) benefits of TH on renal and myocardial function in (near) term asphyxiated neonates. The acquired knowledge underscores that TH is a valuable intervention. The study highlights TH's capacity to provide additional safeguarding effects on renal and myocardial function. Notably, TH has been identified as a potential means to decrease acute kidney injury (AKI) in neonates affected by perinatal asphyxia, especially through whole-body cooling. This reduction in AKI risk holds substantial significance due to the association between renal health and long-term well-being. By mitigating AKI, TH not only enhances patient outcomes but also fosters more efficient utilization of healthcare resources and ultimately lowers healthcare costs. Moreover, TH's short-term evidence of cardioprotective effects underscores its potential to improve myocardial function among asphyxiated neonates, promising even more substantial benefits for their long-term health prospects. While these findings are promising, further research is needed to unravel the comprehensive long-term effects of TH on both renal and myocardial function.

Chapters five and six of the thesis focus on interventions to reduce the incidence of germinal matrix and intraventricular hemorrhage (GMH-IVH) in preterm neonates admitted to the NICU. GMH-IVH is a significant neonatal outcome measurement, linked to long-term consequences. Approximately 20-25% of extremely premature infants develop GMH-IVH, with the risk decreasing as gestational age increases. Severe GMH-IVH is associated with adverse outcomes including disabilities and mortality. Despite efforts to reduce GMH-IVH, the incidence of severe GMH-IVH remains unchanged. Because cerebral blood flow is assumed to be pressure dependent in extremely preterm neonates shortly after birth, nursing interventions aiming to maintain stable cerebral blood flow during routine care are proposed to prevent GMH-IVH.

Chapter five presents a systematic review assessing the influence of head positioning and tilting on GMH-IVH incidence and cerebral oxygenation in preterm neonates. Based on the studies included in the review, there is insufficient evidence regarding the effect of a neutral head position and/or head tilting on the incidence of GMH-IVH in preterm infants. However, due to heterogeneity among studies and limitations in sample sizes, no conclusive recommendations can be made regarding the effect of head positioning on GMH-IVH prevention This served as the rationale for conducting a prospective cohort study described in chapter six, focusing on a nursing intervention bundle (NIB) aimed at stabilizing cerebral blood flow to reduce GMH-IVH incidence in preterm neonates. The NIB decreased the risk of GMH-IVH, particularly for extremely premature infants. The intervention's effect was more pronounced for those born before 27 weeks of gestation. Kangaroo care was possible by placing infants in a lateral position. A large multicenter randomized controlled trial is recommended to further investigate the NIB's effect on GMH-IVH incidence. However, from a VBHC perspective, the implications of these findings are profound. The direct correlation between the incidence of GMH-IVH, a tier one neonatal outcome (achieved health status), and its long-term tier three sequelae (sustainability of health) underscores the critical importance of targeted interventions. By concentrating efforts on interventions aimed at reducing GMH-IVH, healthcare systems can achieve a threefold benefit: improved patient outcomes, optimized resource utilization, and diminished long-term healthcare costs. The significance of evidence-based practices in neonatal care, highlighted by both the systematic review and the cohort study, aligns perfectly with the core principles of VBHC. This alignment ensures that interventions are finely tuned to provide maximum value to patients. Furthermore, this research underscores that solutions need not always be complex

or high-tech. We advocate the potential impact of nursing interventions to achieve improved patient outcomes. Nurses are crucial actors in the care process, and their involvement in interventions, such as the NIB, illustrates how practice changes can lead to significant value creation. Seeking opportunities in everyday practices can yield remarkable value gains applicable across various healthcare systems. This lesson is particularly pertinent for environments under high work pressure or constrained resources, as it emphasizes that valuable improvements are attainable without a significant financial burden.

Perception of Safety and Quality of Care from multiple perspectives (section three)

The **third section** of the thesis examines the perception of safety and quality of care from the viewpoints of healthcare professionals, parents, and patients. In **chapter seven** we present an analysis of safety perception regarding the transfer of infants from the level III NICU to level II neonatology departments from multiple viewpoints. In this prospective cohort study, we employed a Safety-II approach, which views safety as more than just incident prevention but also as the study of successful outcomes and normal operations. Our results reveal that while there might be disparities in perspectives during certain phases of care, the overall perception of safety remains positive. Effective communication, parental participation, and optimal timing are identified as crucial components of enhancing safety perceptions during patient transfers. This highlights the significance of holistic, patient-centered care, and effective communication in ensuring positive outcomes and experiences. The study's insights align with the triple aim and quadruple aim, striving for better patient experience, improved health outcomes, reduced costs, and enhanced provider satisfaction [6,7].

FUTURE PERSPECTIVES

Challenges & Recommendations for Future Research

Balancing Perspectives

One of the fundamental challenges in healthcare is achieving a balance between the perspectives of healthcare professionals, parents, and patients. The diverse perceptions of value held by these stakeholders necessitate a collaborative approach to decision-making. While healthcare professionals bear the

responsibility of assessing medical viability, parents and patients bring insights into the emotional and personal dimensions of care. This balance is intricate, as it requires medical professionals to ask the right questions, actively listen to patients and families, and incorporate their preferences into treatment plans. Moreover, within the field of neonatal care, an additional layer of complexity arises due to the fact that the patients themselves, infants, have no voice and cannot articulate their perception of value. Parents speak on behalf of these patients by proxy. Parents and care professionals are compelled to make challenging decisions regarding what they believe is essential for the future well-being of the infant. These choices are complex given the uncertainties surrounding the long-term consequences of neonatal illness and medical interventions, as well as the evolving perspectives on what holds value over time.

Determining an infant's best interests is typically done by considering the potential benefits and burdens of the available treatment options [8,9]. However, many of these assessments are subjective and related to perceptions of quality of life and potential burdens of disability. Research indicates that parents and individuals with disabilities are often more accepting of severe disability than many health professionals [10,11]. Consequently, the 'harm principle,' which assesses whether the infant will be harmed by a decision, has gained recent support among ethicists [12,13]. It provides a broader scope for parental discretion. In such scenarios, the principles of shared decision-making remain crucial [9]. The challenge of accurately representing the patient's voice highlights the need for open communication and an empathetic approach in understanding the patient's needs and preferences through the lens of their parents. More long-term follow-up studies are paramount to comprehensively assess the impact of neonatal illness, interventions, and care processes. These follow-up studies should not only focus on medical outcomes but also delve into the quality of life experienced by both the infants and their families over time. Investigating the long-term effects on various aspects of quality of life, including physical, cognitive, and emotional well-being, will provide a more holistic understanding of the outcomes of neonatal care. Involving parents and former patients in discussions about these results can play a vital role in shared decision-making, as they bring unique insights into their (children's) experiences and needs. By incorporating these insights, healthcare providers can tailor interventions to maximize value and promote the overall well-being of infants and their families in the long term.

Organizational, Financial & Societal Implications

The pursuit of value does not end with patient-centered care. It must also consider the organizational, financial, and societal implications. Neonatal illness and neonatal intensive care often come with high costs, putting pressure on healthcare systems, families, and society. In addition to the initial hospitalization costs, these infants often need continuous medical assistance, which can also affect parental employment, the patient's future employment prospects, and the demand for non-medical social support services. Given the inherent limitation of resources within healthcare systems, the imperative lies in the strategic allocation of these finite resources to yield optimal patient outcomes. The failure to effectively manage these resources jeopardizes the principle of equal access to care, potentially leaving vulnerable populations underserved. These aspects are captured in the six fundamental domains of quality in healthcare: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity [14]. Each domain encapsulates essential dimensions of care delivery that collectively shape the healthcare experience. By addressing these domains within the context of the neonatal setting, healthcare systems can strive for comprehensive improvements that benefit both patients and providers. This includes making difficult decisions about costs while striving for optimal patient care. However, an important obstacle to achieving this goal is that most care professionals and policymakers do not possess a clear, evidence-based overview of the organizational, financial, and societal implications of interventions and/or choices. It is difficult to see the complete picture. For instance: although the scarcity of NICU bed availability and personnel can be felt in everyday practice, as well as the resulting high workload, evidence-based studies regarding the extent of scarcity within neonatal care departments are lacking. In addition, the consequences of scarcity for patient safety and (unequal) access to care are not well studied. Information regarding these aspects is crucial for the future. As healthcare systems seek to enhance the value they provide, a comprehensive understanding of the organizational, financial, and societal aspects is essential to make decisions that ultimately optimize patient outcomes, resource utilization and provide a safe, healthy working environment for the care professionals themselves.

Financial Reimbursement

To foster previously mentioned changes, it is imperative that the financial structure of healthcare aligns with the principles of value-based healthcare. This involves shifting away from traditional fee-for-service models to models prioritizing value

over volume. Healthcare organizations should consider transition to payment models that reward quality and outcomes rather than the quantity of services provided [15]. Pay-for-performance arrangements motivate healthcare providers to efficiently deliver value. [16] This, in turn, necessitates the implementation of robust systems for measuring patient outcomes and experiences, including benchmarking against standards and best practices. These metrics should drive reimbursement, enabling providers who consistently achieve better outcomes to receive higher payments. In addition, benchmarking enables health care providers to assess their performance, learn from others, and make data-driven improvements. This can lead to enhanced quality, increased efficiency, and greater overall value for the patient and other stakeholders.

In conclusion, this thesis's exploration of VBHC principles in the context of neonatal care presents a comprehensive understanding of challenges, strategies, and implications. The intricate balance of perspectives, the need for effective resource allocation, and the pursuit of optimal patient outcomes underscore the complexity of neonatal care. This thesis describes small **(baby) steps on the pathway towards improvement of neonatal care**. Small actions or contributions can lead to significant and positive changes. We encourage the power of collective effort and advocate that progress doesn't always require giant leaps. Incremental improvements achieved through teamwork can accumulate and create substantial impact over time in the achievement of a common goal: **adding value**. By measuring, enhancing, and incorporating outcomes, healthcare professionals can tailor interventions to the unique needs of neonatal patients. Through this multifaceted approach, neonatal care can navigate challenges, improve outcomes, and provide high-quality, patient-centered care that aligns with the principles of value-based healthcare.

In summary, let us continue to add value by measuring, reflecting, benchmarking, improving, and, above all, listening to the needs of (the family of) patients while keeping the bigger picture in mind.

As a final thought, I'd like to ask you personally:

How will YOU contribute to enhancing the VALUE for the next patient you encounter TODAY?

REFERENCES

1. Osborne H. Definition of value. Philosophy 1931;6(24):433-45.
2. Prada G. Value-based procurement: Canada's healthcare imperative. Healthcare Management Forum 2016;29(4):162-4.
3. Cossio-Gli Y, Omara M, Watson C, Casey J, Chakhunashvili A, Gutiérrez-San Miguel M, Kahlem P, Keuchkerian S, Kirchberger V, Luce-Garnier V, Michiels D, Moro M, Philipp-Jaschek B, Sanchini S, Hazelzet J, Stamm T. The roadmap for implementing Value-Based Healthcare in European University Hospitals-consensus report and recommendations. Value Health 2022;25(7):1148-56.
4. Steinmann G, Delnoij D, van de Bovenkamp H, Groote R, Ahaus K. Expert consensus on moving towards a value-based healthcare system in the Netherlands: a Delphi study. BMJ Open 2021;11(4):e043367.
5. Harrington HJ, Harrington JS. Total improvement management: the next generation in performance improvement. New York: McGraw-Hill (1994).
6. Berwick DM, Noal TW, Whittington J. The triple aim: care, health, and cost. Health Aff 2008;27(3):759-69.
7. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. Ann Fam Med 2014;12(6):573-6.
8. Beauchamp TL, Childress JF. Principles of Bioethics. 7th ed. New York, NY: Oxford University Press; 2009.
9. Partridge JC, Dickey BJ. Decision-making in Neonatal Intensive Care: interventions on Behalf of Preterm infants. NeoReviews 2009;10(6):e270-9.
10. Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, Rosenbaum PL, Hoult L. Differences in preferences for neonatal outcomes among health care professionals, parents, and adolescents. JAMA 1999;281(21):1991–7.
11. Lam HS, Wong SP, Liu FYB, Wong HL, Fok TF, Ng PC. Attitudes toward neonatal intensive care treatment of preterm infants with a high risk of developing long-term disabilities. Pediatrics 2009;123(6):1501-8.
12. Gillam L. The zone of parental discretion: an ethical tool for dealing with disagreement between parents and doctors about medical treatment for a child. Clin Ethics 2016;11(1):1–8.
13. Rhodes R, Holzman IR. Is the best interest standard good for pediatrics? Pediatrics 2014;134(suppl 2):S121–S129.
14. Institute of Medicine (IOM). Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C: National Academy Press; 2001.
15. Porter ME, Lee TH. The strategy that will fix health care. Harvard Business Review 2013; 91(10): 50-70.
16. Porter ME, Kaplan RS. How to pay for health care. Harvard Bus Rev 2016; 94(7-8):88-98.

Science is always wrong
It never answers a question without creating ten more

George Bernard Shaw
Ierse toneelschrijver en mede-oprichter van the London School of Economics
(1856 - 1950)

CHAPTER 9

CHAPTER 9

Nederlandse samenvatting

(summary in Dutch)

Wijsheid is de samenvatting van het verleden
Schoonheid is de belofte van de toekomst

Oliver Wendell Holmes
Amerikaanse schrijver (1809 – 1894)

SAMENVATTING & DISCUSSIE

Wat is waarde?

Sluit je ogen eens en denk na over hoe jij persoonlijk "waarde" definieert.

Welke aspecten van het leven zijn voor jou het meest belangrijk en kunnen mogelijk bedreigd worden tijdens een periode van ziekte? Het begrip waarde is niet vaststaand: het is een dynamisch concept dat wordt gevormd door individuele ervaringen, overtuigingen en omstandigheden [1,2]. Wat voor de ene persoon van immense waarde is, kan door een ander verschillend gewogen worden. Zelfs op individueel niveau kan waarde in de loop van de tijd evolueren door opgedane levenslessen en veranderende omstandigheden. Dit roept belangrijke vragen op:

- Wat vormt werkelijk waarde?
- Kun je dat kwantificeren en hoe?
- Hebben verschillende belanghebbenden binnen de zorg, waaronder zorgprofessionals, patiënten, de familie van patiënten en zorgverzekeraars, een gemeenschappelijk begrip van waarde?

Het is essentieel voor zorgverleners om te begrijpen wat voor individuele patiënten van waarde is, aangezien deze kennis diagnostische en therapeutische keuzes aanzienlijk kan beïnvloeden. In de context van volwassenenzorg houdt dit in dat zorgprofessionals actief luisteren naar de behoeften van patiënten, waardoor het mogelijk wordt om de meest geschikte en doeltreffende zorg te bieden aan elke individuele patiënt door middel van gedeelde besluitvorming ("shared decision making") [3,4]. Binnen de neonatale intensive care zorg is het beschrijven van waarde nog ingewikkelder en raakt het vrijwel direct aan ethische dilemma's. Is het bieden van intensieve, kostbare en soms pijnlijke zorg aan een extreem vroeggeboren kind dat mogelijk niet zal overleven, waardevol? Misschien niet als je naar de kosten kijkt, maar wat als ouders troost vinden in de tijd die ze met hun kind doorbrengen, ondanks het tragische resultaat? En wat als het medisch team op basis van kennis en ervaring een kleine, maar niet afwezige kans op overleving zonder ernstige handicaps ziet? Deze vragen onderstrepen de noodzaak om waarde vanuit meerdere invalshoeken te bekijken en benadrukken het belang van het aannemen van een waardegedreven benadering binnen de neonatale zorg.

Definitie van Waarde in Neonatale Zorg

De betekenis van 'waarde' binnen de moderne Westerse gezondheidszorg is het bereiken van de best mogelijke resultaten voor patiënten, terwijl er tegelijkertijd efficiënt gebruik wordt gemaakt van middelen. Dit concept erkent dat medische zorg verder gaat dan klinische interventies; het omvat de holistische impact op het leven van patiënten, hun families en de samenleving als geheel. Dit geldt zeker voor neonatale intensieve zorg, die wordt gekenmerkt door de kwetsbaarheid van jonge levens en het risico op langdurige nadelige effecten van zowel de ziekten als de behandelingen. Dit zorgt ervoor dat het concept van 'waarde' zich uitstrekt voorbij de directe medische resultaten en ook de lange termijn aspecten van de kwaliteit van leven en de bredere maatschappelijke implicaties van medische ingrepen omvat. Het is van essentieel belang om te erkennen dat waarde niet alleen wordt weerspiegeld in medische resultaten, maar ook in door patiënten gerapporteerde uitkomsten en ervaringen. In wezen draait het voor patiënten om de waarden die zij toekennen aan hun zorg en de impact ervan op hun algehele welzijn.

Meten van Resultaten (sectie één)

Het evalueren van resultaten vormt een fundamentele pijler bij het beoordelen van de waarde van gezondheidszorginterventies. Zoals prachtig verwoord door H. James Harrington [5]:

"Als je iets niet kunt meten, kun je het niet begrijpen. Als je het niet begrijpt, kun je het niet beheersen. Als je het niet kunt beheersen, kun je het niet verbeteren."

Het meten van resultaten biedt niet alleen een routebeschrijving voor vooruitgang, maar ook kennis, begrip, doel en de motivatie om te streven naar excellentie. Het meten van resultaten geeft ons de kans om te begrijpen, vergelijken en leren van waardevolle inzichten. Uit deze inzichten halen we een schat aan kennis over de effectiviteit van onze interventies. Zo is vanuit het perspectief van Value-Based HealthCare (VBHC) het ontdekken dat een specifieke interventie géén verbetering oplevert in een uitkomst die belangrijk is voor de patiënt een belangrijke bevinding. Door de patiënt op basis van die verkregen kennis niet bloot te stellen aan de risico's of lasten van onnodige interventies, worden tegelijkertijd de kosten verlaagd, en kunnen we waarde creëren door minder te doen. Op individueel

niveau fungeert het meten van resultaten als een kompas voor patiëntgerichte zorg, waarbij elke beslissing ten goede komt aan de patiënt en diens familie. Vanuit een bredere visie kunnen meten en leren van resultaten bijdragen aan het transformeren van zorgsystemen. Ze ondersteunen de toewijzing van middelen, verfijnen behandelprotocollen en optimaliseren de dienstverlening. De maatschappelijke impact daarvan kan groot zijn aangezien een goede gezondheid veelal een randvoorwaarde is voor arbeidsproductiviteit. Deze opwaartse spiraal van continue verbetering is weergegeven in figuur 9.1.

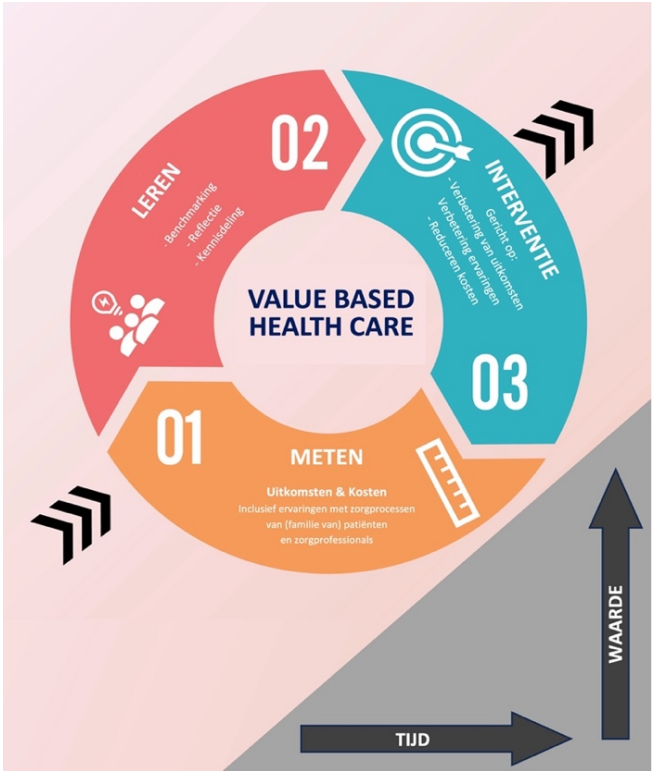

Figure 9.1

De **eerste sectie** van dit proefschrift presenteert twee studies die verschillende aspecten van neonatale resultaten onderzoeken, zoals nierfunctie en verblijfsduur in het ziekenhuis. De studie beschreven in **hoofdstuk twee** onderzoekt de incidentie en de uitkomsten van acute nierbeschadiging bij neonaten die zijn opgenomen op een level III Neonatale Intensive Care Unit (NICU). Van de 9.376 kinderen die gedurende de onderzoeksperiode werden opgenomen, ervoer 1,5% acute nierbeschadiging binnen de eerste week na de geboorte. Dit percentage is

mogelijk een onderschatting van het werkelijke aantal patiënten, omdat niet bij elke pasgeborene standaard de nierfunctie werd bepaald. De oorzaken van acute nierbeschadiging varieerden, waarbij 14% werd toegeschreven aan aangeboren nierafwijkingen, 81% aan verworven aandoeningen en 5% aan aangeboren hartafwijkingen. Opmerkelijk is dat acute nierbeschadiging gepaard ging met een hoge morbiditeit en mortaliteit, vooral bij ernstig zieke neonaten. De behandeling van acute nierbeschadiging was uitsluitend conservatief, en hoewel de nierfunctie van de meeste kinderen verbeterde, vertoonden degenen met ernstige acute nierbeschadiging een verhoogd risico op niercomplicaties. Er ontbrak echter een structurele lange termijn follow up van de nierfunctie. In het kader van VBHC zijn deze bevindingen van belang. De identificatie van risicofactoren voor acute nierbeschadiging en het aantonen van de geassocieerde morbiditeit en mortaliteit benadrukken het potentieel om patiëntresultaten te verbeteren door vroegtijdige detectie en interventie. De resultaten sporen de implementatie aan van een screeningsprotocol voor acute nierbeschadiging bij neonaten, waardoor zorgverleners deze aandoening kunnen behandelen en ernstige complicaties mogelijk kunnen voorkomen. Bovendien dragen de inzichten in de uiteenlopende oorzaken en resultaten van acute nierbeschadiging bij neonaten bij aan het begrip van gepersonaliseerde zorg en het belang van het afstemmen van interventies op individuele patiëntkenmerken. Conform VBHC kan de toepassing van deze nieuwe kennis waarde toevoegen door ongunstige resultaten te minimaliseren en patiënten met een risico op chronische nierziekte te identificeren. Dit biedt de mogelijkheid voor secundaire preventiemaatregelen, zoals het voorschrijven van een zoutarm dieet en het monitoren van bloeddruk en nierfunctie. De kosten hiervan zijn laag (creatinine-meting in bloed kost minder dan 2 euro per monster, eiwitbepaling in de urine kost 2-6 euro per monster), waardoor het interessante hulpmiddelen zouden kunnen zijn voor de potentiële verbetering van resultaten vanuit een VBHC-perspectief. Daarom wordt toekomstig onderzoek aanbevolen om te onderzoeken of en hoe een dergelijke screening van zuigelingen met een risico op chronische nierziekte de waarde voor de patiënt en/of de samenleving zou kunnen verhogen.

Hoofdstuk drie beschrijft de analyse van trends in morbiditeit en verblijfsduur (LoS) bij patiënten die zijn opgenomen op zowel NICU- als level II-neonatologie afdelingen. LoS dient als een belangrijke indicator van de kwaliteit van de gezondheidszorg, en biedt inzicht in efficiëntie van zorg, het voorkomen van complicaties, behandelingseffectiviteit en het gebruik van middelen. De relevantie

van LoS ligt in de dubbele rol ervan: het is zowel een uitkomstmaat en tegelijkertijd ook een potentieel middel voor kostenverlaging en capaciteitsmanagement. Deze studie onthult een significante toename van de totale LoS van baby's geboren met een zwangerschapsduur onder de 32.0 weken tussen 2008 en 2021, toegeschreven aan de behandeling van in toenemende mate extreem vroeggeboren baby's en diegenen die ernstige complicaties ondervonden. Deze verlengde verblijfsduur heeft gevolgen voor gezondheidszorgsystemen, families en de patiënten zelf. Door de principes van VBHC toe te passen wordt zichtbaar dat door de vermindering van ernstige complicaties van vroeggeboorte, gezondheidszorgsystemen een positieve invloed kunnen uitoefenen op zowel de specifieke verblijfsduur op de NICU als de totale verblijfsduur. Deze strategie leidt tot verbeterde patiëntresultaten, doelmatig middelengebruik en het beperken van zorgkosten.

Strategieën voor het Verbeteren van Resultaten (sectie twee)

In de **tweede sectie** wordt gesproken over verschillende interventies die gericht zijn op het verbeteren van resultaten voor NICU-patiënten. Deze strategieën benadrukken het potentieel van medische innovatie om een positieve invloed te hebben op de kwaliteit en waarde van neonatale zorg. **Hoofdstuk vier** bestaat uit een systematische review die de impact van therapeutische hypothermie (TH) op nier- en hartfunctie bij neonaten met perinatale asfyxie onderzoekt. Perinatale asfyxie die leidt tot hypoxisch-ischemische encefalopathie (HIE) brengt risico's met zich mee voor meerdere foetale organen, waaronder de hersenen, het hart en de nieren. Deze review richt zich op de effecten van TH op het hart en de nieren, gezien hun vatbaarheid voor de gevolgen van perinatale asfyxie en mogelijke lange termijn complicaties. TH heeft zijn effectiviteit bewezen bij het verminderen van het risico op sterfte en neurocognitieve handicaps bij neonaten met matige tot ernstige HIE. De studie beschreven in hoofdstuk 4 beoogde de potentiële korte termijn (tier één) en lange termijn (tier drie) voordelen van TH op nier- en hartfunctie bij (bijna) voldragen kinderen met asfyxie te beoordelen. De studie benadrukt het vermogen van TH om extra beschermende effecten op nier- en hartfunctie te bieden, naast het beschermende effect op de hersenen. Met name is TH geïdentificeerd als een mogelijke manier om het optreden van acute nierbeschadiging bij neonaten die worden getroffen door perinatale asfyxie te verminderen, vooral door toepassing van de koeling van het volledige lichaam (i.t.t. koeling van enkel het hoofd). Deze vermindering van het risico op acute

nierbeschadiging is van groot belang vanwege de relatie tussen de integriteit van de nieren en lange termijn gezondheidsrisico's. Bovendien onderstreept het korte termijn bewijs van hart-beschermende effecten van TH het potentieel om de hartfunctie bij asfyxie-neonaten te verbeteren, wat nog meer voordelen belooft voor hun lange termijn gezondheidsperspectieven. Hoewel deze bevindingen veelbelovend zijn, is verder onderzoek nodig om de uitgebreide langetermijneffecten van TH op zowel nier- als hartfunctie volledig te doorgronden.

Hoofdstukken vijf en zes richten zich op interventies om de incidentie van germinale laag- en intraventriculaire bloedingen (GMH-IVH) bij prematuur geboren neonaten op de NICU te verminderen. GMH-IVH is een significante neonatale uitkomstmaat, gekoppeld aan langetermijngevolgen. Ongeveer 20-25% van de extreem vroeggeboren baby's ontwikkelt een GMH-IVH, waarbij het risico afneemt naarmate de zwangerschapsduur toeneemt. Ernstige GMH-IVH wordt geassocieerd met ongunstige lange termijn uitkomsten, waaronder handicaps en sterfte. Ondanks inspanningen blijft de incidentie van ernstige GMH-IVH stabiel. Omdat wordt aangenomen dat de cerebrale bloedstroom drukafhankelijk is bij zeer premature neonaten kort na de geboorte, worden verpleeginterventies die tot doel hebben om een stabiele hersendoorbloeding te handhaven, voorgesteld om GMH-IVH te voorkomen.
Hoofdstuk vijf presenteert een systematische review die de invloed van hoofdpositie en kanteling van het hoofdeinde van de couveuse op de incidentie van GMH-IVH en cerebrale oxygenatie bij premature neonaten onderzoekt. Op basis van de opgenomen studies in de review is er onvoldoende bewijs over het effect van een neutrale hoofdpositie en/of kanteling op de incidentie van GMH-IVH bij prematuur geboren baby's. Vanwege de heterogeniteit tussen studies en beperkte omvang van de studiepopulaties kunnen geen conclusieve aanbevelingen worden gedaan met betrekking tot het effect van hoofdpositie en kanteling op het voorkomen van GMH-IVH. Dit diende als aanleiding en rechtvaardiging van het uitvoeren van een prospectieve cohortstudie beschreven in **hoofdstuk zes**, waarin een verpleeginterventiepakket (VIP) werd onderzocht om de cerebrale bloedstroom te stabiliseren en daarmee de incidentie van GMH-IVH te verminderen bij prematuur geboren neonaten. Het VIP verminderde het risico op GMH-IVH, vooral bij extreem vroeggeboren baby's. Het effect van de interventie was sterker bij diegenen die vóór 27 weken zwangerschapsduur waren geboren. Een grootschalige multicenter gerandomiseerde gecontroleerde studie

wordt aanbevolen om verder het effect van een (soortgelijke) VIP op de incidentie van GMH-IVH te onderzoeken. Vanuit een VBHC-perspectief zijn de implicaties van deze bevindingen diepgaand. De directe correlatie tussen de incidentie van GMH-IVH, een "tier één neonatale uitkomst" (behaalde gezondheidsstatus), en de lange termijn-sequentie ervan in "tier drie" (lange termijneffect) benadrukt het kritieke belang van gerichte interventies. Door inspanningen te concentreren op interventies die gericht zijn op het verminderen van GMH-IVH, kunnen gezondheidszorgsystemen een drievoudig voordeel behalen: verbeterde patiëntresultaten, verminderde langetermijngevolgen en kostenbesparingen. Bovendien onderstreept deze bevinding de potentiële impact van verpleeginterventies op het bereiken van deze voordelen. Verpleegkundigen zijn cruciale actoren in het zorgproces, en hun betrokkenheid bij interventies zoals het VIP illustreert hoe praktijkveranderingen kunnen leiden tot aanzienlijke verbeteringen in waarde creatie. Het zoeken naar kansen in de dagelijkse praktijk kan substantieel bijdragen aan het toevoegen van waarde en is toepasbaar in alle gezondheidszorgsystemen. Dit is vooral interessant voor zorgsystemen met een hoge werkdruk en/of beperkte middelen, omdat waarde verhogende verbeteringen te realiseren zijn zonder dat daarvoor omvangrijke investeringen benodigd zijn.

Perceptie van Veiligheid en Kwaliteit van zorg vanuit meerdere perspectieven (sectie drie)

Het **derde deel** van het proefschrift onderzoekt de perceptie van veiligheid en kwaliteit van zorg vanuit het standpunt van gezondheidszorgprofessionals, ouders en patiënten. In **hoofdstuk zeven** presenteren we vanuit meerdere gezichtspunten een analyse van de veiligheidsperceptie met betrekking tot de overplaatsing van pasgeborenen van een derdelijns NICU naar tweedelijns neonatologie afdelingen. In deze prospectieve cohortstudie hebben we een Safety-II-aanpak toegepast, waarbij veiligheid niet alleen gaat om het voorkómen van incidenten, maar ook het bestuderen van succesvolle resultaten en normale zorgprocessen. Uit onze resultaten blijkt dat, hoewel er tijdens bepaalde fasen van de zorg verschillen in perspectieven kunnen bestaan, de algehele perceptie van veiligheid positief blijft. Effectieve communicatie, ouderparticipatie en optimale timing worden geïdentificeerd als cruciale componenten voor het verbeteren van de veiligheidspercepties tijdens patiënttransfers. Dit benadrukt het belang van holistische, patiëntgerichte zorg en effectieve communicatie bij het garanderen

van positieve resultaten en ervaringen. De inzichten van het onderzoek sluiten aan bij de "Triple Aim" beschreven door Berwick en het "Quadruple Aim" beschreven door Bodenheimer: het streven naar een betere patiëntervaring, betere gezondheidsresultaten, lagere kosten en grotere tevredenheid van zorgverleners [6,7].

VISIE OP DE TOEKOMST

Balanceren tussen Perspectieven

Eén van de fundamentele uitdagingen in gezondheidszorg is het bereiken van een balans tussen de perspectieven van zorgprofessionals, ouders en patiënten. De diverse percepties van waarde die deze belanghebbenden hebben, vereisen een samenwerkingsgerichte benadering van besluitvorming. Terwijl zorgprofessionals verantwoordelijk zijn voor het beoordelen van medische inhoudelijke vraagstukken, brengen ouders en patiënten inzichten in de emotionele en persoonlijke dimensies van zorg met zich mee. Deze balans is gecompliceerd, omdat het van medische professionals vereist dat ze de juiste vragen stellen, actief luisteren naar patiënten en families, en hun voorkeuren meewegen in behandelplannen. Bovendien ontstaat binnen het vakgebied van neonatale zorg een complicerende factor, namelijk het feit dat de patiënten zelf, de pasgeborenen, geen stem hebben en hun perceptie van waarde nog niet kunnen verwoorden. Ouders spreken namens deze patiënten bij volmacht. Ouders en zorgprofessionals worden gedwongen om uitdagende beslissingen te nemen met betrekking tot wat zij essentieel achten voor het toekomstige welzijn van de patiënt. Deze keuzes zijn complex gezien de onzekerheden rondom de langetermijngevolgen van neonatale ziekten en medische ingrepen, evenals de zich ontwikkelende perspectieven op wat in de loop van de tijd waarde heeft. Het bepalen van het beste belang van de patiënt wordt doorgaans gedaan door de mogelijke voordelen en lasten van de beschikbare behandelingsopties te overwegen [8,9]. Veel van deze beoordelingen zijn echter subjectief en gerelateerd aan percepties van kwaliteit van leven en mogelijke lasten van handicap. Studies laten zien dat ouders en mensen met een handicap vaak een ruimere acceptatie hebben van ernstige handicaps dan veel gezondheidsprofessionals [10,11]. Daarom heeft het 'schadebeginsel', dat beoordeelt of de zuigeling schade zal ondervinden door een beslissing, recentelijk steun gekregen van ethici [12,13]. Het biedt een breder kader voor de discretie

van ouders. In dergelijke situaties blijven de principes van gedeelde besluitvorming van cruciaal belang [9]. De uitdaging om de stem van de patiënt nauwkeurig te vertegenwoordigen, benadrukt de noodzaak van open communicatie en een empathische benadering om de behoeften en voorkeuren van de patiënt te begrijpen vanuit het perspectief van diens ouders. Meer lange termijn follow up studies zijn cruciaal om de impact van neonatale ziekte, ingrepen en zorgprocessen grondig te leren en begrijpen. Deze vervolgstudies zouden zich niet alleen moeten richten op medische resultaten, maar ook op de kwaliteit van leven die zowel de pasgeborenen als hun families in de loop van de tijd ervaren. Het onderzoeken van langetermijneffecten op verschillende aspecten van levenskwaliteit, waaronder fysiek, cognitief en emotioneel welzijn, zal een meer holistisch begrip bieden van de resultaten van neonatale zorg. Het betrekken van ouders en patiënten (die in het verleden opgenomen zijn geweest op de NICU) bij discussies over deze resultaten kan een cruciale rol spelen in gedeelde besluitvorming, omdat zij unieke inzichten bieden in de ervaringen en behoeften van hun kinderen. Door deze inzichten kunnen zorgverleners interventies aanpassen om de waarde te maximaliseren en het algehele welzijn van pasgeborenen en hun families op de lange termijn te bevorderen.

Organisatorische, Financiële en Maatschappelijke Gevolgen

Het streven naar waarde eindigt niet bij zorg die op de patiënt is gericht. Er moet ook rekening worden gehouden met de organisatorische, financiële en maatschappelijke gevolgen. Neonatale ziekte en neonatale intensieve zorg gaan vaak gepaard met hoge kosten, wat druk legt op gezondheidssystemen, gezinnen en de samenleving. Naast de initiële ziekenhuisopnamekosten hebben deze zuigelingen vaak voortdurende medische hulp nodig, wat ook van invloed kan zijn op de werkgelegenheid van de ouders, de toekomstige arbeidsvooruitzichten van de patiënt zelf en de vraag naar/behoefte aan uitkeringen en sociale voorzieningen. Gezien de inherente beperkingen van middelen binnen de zorg, ligt de nadruk op de strategische toewijzing van deze beperkte middelen om optimale patiëntresultaten te behalen. Het niet effectief beheren van deze middelen brengt het principe van gelijke toegang tot zorg in gevaar, wat mogelijk kwetsbare bevolkingsgroepen raakt. De complexiteit van deze uitdaging resoneert in de zes fundamentele domeinen van kwaliteit in de gezondheidszorg: veiligheid, doeltreffendheid, patiëntgerichtheid, tijdigheid, efficiëntie en gelijkheid [14]. Elk van deze domeinen omvat essentiële dimensies van zorgverlening die gezamenlijk de zorgervaring vormgeven. Door deze domeinen

binnen de context van de neonatale setting aan te pakken, kunnen gezondheidssystemen streven naar algehele verbeteringen die zowel patiënten als zorgverleners ten goede komen. Dit omvat ook het nemen van moeilijke beslissingen over kosten terwijl gestreefd wordt naar optimale patiëntenzorg.
Een belangrijk obstakel is echter dat de meeste zorgprofessionals en beleidsmakers geen duidelijk, op bewijs gebaseerd overzicht hebben van de organisatorische, financiële en maatschappelijke gevolgen van interventies. Het is moeilijk om het complete plaatje te overzien. Een concreet voorbeeld is de beperkte NICU-capaciteit. Hoewel het tekort aan beschikbare NICU-bedden en personeel op de NICU dagelijks merkbaar en voelbaar is, evenals de resulterende hoge werkdruk, ontbreken objectieve studies over de omvang en effecten van schaarste binnen neonatologie afdelingen. Bovendien zijn de gevolgen voor de veiligheid van patiënten en (ongelijke) toegang tot zorg niet goed bestudeerd. Informatie over deze aspecten is cruciaal voor de toekomst. Hoe anders kunnen gefundeerde keuzes gemaakt worden met betrekking tot interventies?

Financiële Vergoedingen

Verder is het van essentieel belang dat de financiële structuur van de gezondheidszorg in lijn is met de principes van waardegedreven gezondheidszorg. Dit omvat een verschuiving weg van traditionele vergoedingsmodellen op basis van verrichtingen naar modellen die waarde boven volume stellen. Zorgorganisaties zouden moeten overgaan naar betalingsmodellen die kwaliteit en resultaten belonen in plaats van de hoeveelheid geleverde diensten [15]. Betaling-op-basis-van-prestaties motiveert zorgverleners om efficiënt hoogwaardige zorg te leveren [16]. Dit vereist op zijn beurt de implementatie van robuuste systemen voor het meten van patiëntresultaten en -ervaringen, inclusief benchmarking tegen standaarden en best practices. Deze metingen zouden de vergoeding moeten sturen, waardoor zorgverleners die consistent betere resultaten behalen, hogere betalingen kunnen ontvangen. Bovendien stelt benchmarking zorgverleners in staat hun prestaties te beoordelen, te leren van anderen en op gegevens gebaseerde verbeteringen door te voeren. Dit kan leiden tot verbeterde kwaliteit, verhoogde efficiëntie en over het algemeen meer waarde voor de patiënt en andere belanghebbenden.
Concluderend biedt dit proefschrift inzicht in VBHC-principes binnen de context van neonatale zorg en een algeheel begrip van uitdagingen, strategieën en gevolgen. De complexe balans van perspectieven, de noodzaak van effectieve middelenallocatie en het streven naar optimale patiëntresultaten benadrukken de

complexiteit van neonatale zorg. Het beschrijft kleine (baby) stapjes op weg naar verbetering van de zorg voor neonaten. Kleine kosteneffectieve acties of interventies kunnen leiden tot significante en waardevolle veranderingen. We moedigen de kracht van collectieve inspanning aan en betogen dat vooruitgang niet altijd gigantische sprongen vereist. Multipele kleine verbeteringen die worden bereikt door teamwork kunnen in de loop van de tijd een aanzienlijke impact creëren op weg naar een gemeenschappelijk doel: **waarde toevoegen** voor de patiënt, het zorgsysteem en de maatschappij. Door resultaten te meten en te verbeteren, kunnen zorgprofessionals interventies aanpassen aan de unieke behoeften van patiënten en diens familie. Via deze veelzijdige aanpak kan neonatale zorg uitdagingen aangaan en uitkomsten verbeteren.

Laten we doorgaan met waarde toevoegen door te meten, te reflecteren, te benchmarken, te verbeteren en vooral te luisteren naar de behoeften van de patiënten en hun ouders, terwijl we het grotere plaatje in het vizier houden. Dat is een collectieve opdracht, maar ook een individuele plicht.

Daarom zou ik u willen vragen:

Hoe gaat U VANDAAG bijdragen aan het verhogen van de WAARDE voor de eerstvolgende patiënt die u tegenkomt?

REFERENTIES

1. Osborne H. Definition of value. Philosophy 1931;6(24):433-45.
2. Prada G. Value-based procurement: Canada's healthcare imperative. Healthcare Management Forum 2016;29(4):162-4.
3. Cossio-Gli Y, Omara M, Watson C, Casey J, Chakhunashvili A, Gutiérrez-San Miguel M, Kahlem P, Keuchkerian S, Kirchberger V, Luce-Garnier V, Michiels D, Moro M, Philipp-Jaschek B, Sanchini S, Hazelzet J, Stamm T. The roadmap for implementing Value-Based Healthcare in European University Hospitals-consensus report and recommendations. Value Health 2022;25(7):1148-56.
4. Steinmann G, Delnoij D, van de Bovenkamp H, Groote R, Ahaus K. Expert consensus on moving towards a value-based healthcare system in the Netherlands: a Delphi study. BMJ Open 2021;11(4):e043367.
5. Harrington HJ, Harrington JS. Total improvement management: the next generation in performance improvement. New York: McGraw-Hill (1994).
6. Berwick DM, Noal TW, Whittington J. The triple aim: care, health, and cost. Health Aff 2008;27(3):759-69.
7. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. Ann Fam Med 2014;12(6):573-6.
8. Beauchamp TL, Childress JF. Principles of Bioethics. 7th ed. New York, NY: Oxford University Press; 2009.
9. Partridge JC, Dickey BJ. Decision-making in Neonatal Intensive Care: interventions on Behalf of Preterm infants. NeoReviews 2009;10(6):e270-9.
10. Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, Rosenbaum PL, Hoult L. Differences in preferences for neonatal outcomes among health care professionals, parents, and adolescents. JAMA 1999;281(21):1991–7.
11. Lam HS, Wong SP, Liu FYB, Wong HL, Fok TF, Ng PC. Attitudes toward neonatal intensive care treatment of preterm infants with a high risk of developing long-term disabilities. Pediatrics 2009;123(6):1501-8.
12. Gillam L. The zone of parental discretion: an ethical tool for dealing with disagreement between parents and doctors about medical treatment for a child. Clin Ethics 2016;11(1):1–8.
13. Rhodes R, Holzman IR. Is the best interest standard good for pediatrics? Pediatrics 2014;134(suppl 2):S121–S129.
14. Institute of Medicine (IOM). Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, D.C: National Academy Press; 2001.
15. Porter ME, Lee TH. The strategy that will fix health care. Harvard Business Review 2013; 91(10): 50-70.
16. Porter ME, Kaplan RS. How to pay for health care. Harvard Bus Rev 2016; 94(7-8):88-98.

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
GA	Gestational Age
GMH-IVH	Germinal Matrix Hemorrhage- Intraventricular Hemorrhage
HIE	Hypoxic-Ischemic Encephalopathy
LoS	Length Of Stay (hospitalization)
NIB	Nursing Intervention Bundle
NICU	Neonatal Intensive Care Unit
TH	Therapeutic Hypothermia
VBHC	Value Based Health Care

Waarom moeilijk doen
als het samen kan?

Loesje

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LIST OF PUBLICATIONS

Van Wincoop M, de Bijl-Marcus K, Lilien M, van den Hoogen A, Groenendaal F.
Effect of therapeutic hypothermia on renal and myocardial function in asphyxiated (near) term neonates: A systemaic review and meta-analysis.
PLoS One 2021; 16(2):e0247403.

Gallo D, de Bijl-Marcus KA, Alderliesten T, Llien M, Groenendaal F.
Early acute kidney injury in preterm and term neonates: incidence, outcome and associated clinical features.
Neonatology 2021;118(2):174-9.

de Bijl-Marcus K, Brouwer AJ, De Vries LS, Groenendaal F, Wezel-Meijler GV.
Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study.
Arch Dis Child Fetal Neonatal Ed. 2020;105(4):419-24.

de Bijl-Marcus KA, Brouwer AJ, de Vries LS, van Wezel-Meijler G.
The Effect of Head Positioning and Head Tilting on the Incidence of Intraventricular Hemorrhage in Very Preterm Infants: A Systematic Review.
Neonatology 2017;111(3):267-79.

de Bijl-Marcus K, Benders M, Dudink J, Ahaus K, Kahlmann M, Groenendaal F
Morbidity and trends in length of hospitalization of very preterm infants born Between 2008 – 2021: a cohort study.
Under review

de Bijl-Marcus KA, Mossel F, Ahaus K, Pluut B, Benders M, Bruintjes A, Buljac-Samardzic M
The perception of safety regarding the transfer of infants from the neonatal intensive care unit to a level II neonatology department: a cohort study using a safety-II approach
Under review

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Feeling gratitude and not expressing it, is like wrapping a present and not giving it

William Arthur Ward
Amerikaanse auteur (1921 - 1994)

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Confucius
Chinese filosoof (551 a.C. - 479 a.C.)