# Prognostication in Neonatal Hypoxic Ischemic Encephalopathy: A Qualitative Research Study

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**Abstract**

**Background**

Hypoxic ischemic encephalopathy is the most frequent cause of neonatal encephalopathy, and results in significant morbidity and mortality. From an ethical and clinical standpoint, neurological prognosis is fundamental in the care of neonates with hypoxic ischemic encephalopathy. However, accurately predicting neurodevelopmental outcomes for neonatal hypoxic ischemic encephalopathy is particular difficult, and fraught with challenges. At present, focused research in this area is limited.

**Objectives**

This thesis aims to present a review of the current literature on prognosis and the practice of prognostication in neonatal hypoxic ischemic encephalopathy, focusing on the integral challenges posed by this vulnerable group of neonates. Furthermore, this thesis incorporates an original qualitative study that explores physician perspectives about prognostication in neonatal hypoxic ischemic encephalopathy. The main objective of this thesis is to advance the current understanding of the practice of prognostication in neonatal hypoxic ischemic encephalopathy, in hopes of opening up dialogue and encouraging modifications in clinical practice to improve patient care.

**Methods**

The introduction and background section of this thesis presents a review of the literature on prognosis, prognostication, and neonatal hypoxic ischemic encephalopathy. Focus is placed on selected articles in an attempt to introduce the reader to the subject mater. The research publication included in this thesis is based on a Canadian qualitative study of neonatologists and pediatric neurologists, which focuses on exploring physician perspectives on prognosis and prognostication in neonatal hypoxic ischemic encephalopathy. For the purpose of this thesis, only data pertaining to the practice of prognostication will be presented, though there were other themes explored in the larger research study including uncertainty, communication, and shared-decision-making.

**Results**

There are two chapters presenting the results in this thesis. The first consists of a published manuscript that reports on data regarding physician perspectives on prognostication in neonatal hypoxic ischemic encephalopathy, and the second presents unpublished data exploring the challenges of prognostication in neonatal hypoxic ischemic encephalopathy.

**Conclusions**

Although this thesis offers some practical changes for the improvement of clinical care in neonatal HIE, its true contribution is to serve as a launching point for further research. Focused research is needed to explore both the parental perspective and, prospectively, the impact of different clinical approaches and styles to prognostication for neonatal hypoxic ischemic encephalopathy.

**Abstract**

**Introduction**

L'encéphalopathie ischémique hypoxique est la cause la plus fréquente d'encéphalopathie néonatale, et entraîne une morbidité ainsi qu'une mortalité significative. D'un point de vue éthique et clinique, le pronostic neurologique est fondamental dans les soins apportés aux nouveau-nés atteints d'une encéphalopathie ischémique hypoxique. Toutefois, la prédiction précise des conséquences neurodéveloppementales de l'encéphalopathie ischémique hypoxique est particulièrement difficile, et remplie de défis. Présentement, la recherche dans ce domaine ciblé est limitée.

**Objectifs**

Cette thèse vise à présenter une revue de la littérature actuelle sur le pronostic et la pratique du pronostic de l'encéphalopathie ischémique hypoxique néonatale, en se concentrant sur les défis globaux posés par ce groupe vulnérable de nouveau-nés. De plus, cette thèse incorpore une étude qualitative originale qui explore la perspective des physiciens à propos de la pratique du pronostic dans l'encéphalopathie ischémique hypoxique néonatale. L'objectif principal de cette thèse est d'avancer la compréhension actuelle de la pratique du pronostic dans le contexte de l'encéphalopathie ischémique hypoxique néonatale, en espérant ouvrir le dialogue et encourager les modifications dans la pratique clinique pour améliorer les soins aux patients.

**Méthode**

La section de l'introduction et de la problématique de cette thèse présente une revue de la littérature sur le pronostic, la pratique du pronostic et sur l'encéphalopathie ischémique hypoxique néonatale. L'accent est mis sur des articles précis en vue d'introduire le lecteur à l'importance de ce sujet. La publication de recherche incluse dans cette thèse repose sur une étude qualitative canadienne de néonatologistes et de neurologues pédiatriques, qui met l'accent sur l'exploration de la perspective des médecins sur le pronostic et la pratique du pronostic dans l'encéphalopathie ischémique hypoxique néonatale. Aux fins de cette thèse, seulement les données se rapportant à la pratique du pronostic seront présentées, bien qu'il y avait d'autres

thèmes explorés dans la recherche plus globale incluant l'incertitude, la communication et la prise de décisions partagée.

**Résultats**

Il y a deux chapitres présentant les résultats dans cette thèse. Le premier consiste en un manuscrit publié qui rapporte les données se rapportant à la perspective des médecins à l'égard de la pratique du pronostic dans le contexte de l'encéphalopathie ischémique hypoxique néonatale. Le second présente des données non publiées qui explorent les défis de la pratique du pronostic dans le contexte de l'encéphalopathie ischémique hypoxique néonatale.

**Conclusions (Conclusion)**

Même si cette thèse recommande des changements pratiques pour l'amélioration des soins cliniques dans l'encéphalopathie ischémique hypoxique néonatale, sa plus grande contribution est de servir de tremplin pour de plus amples recherches. Des recherches ciblées sont requises pour explorer à la fois la perspective parentale et prospectivement, l'impact de différentes approches et de styles cliniques dans la pratique du pronostic de l'encéphalopathie ischémique hypoxique néonatale.

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To my dear friend Vaso, thank you for all your support and for encouraging me to "write one word every day." To Alex, Katie, and Kirsten, thank you for believing in me. Thank you for your unconditional love and your never-ending support. To my husband Todd, thank you for your love, your patience, and for listening to all my thesis ramblings. To my Farmor, who told me to 'quit going school and have a baby,' your advice was the best I ever received. And finally to my son Felix Naveen, thank you for opening my eyes and my heart to the experience of being a mother, and for allowing me to know more fully the true value of this research. All my love.

**Preface and Contribution of Authors**

This study was part of a larger study funded by the Kids Brain Health Network, entitled "Ethical challenges of magnetic resonance imaging for prognostication in neonatal hypoxic-anoxic brain injury". The aim of the broader study was to better define the challenges related to prognostication and the contribution of information derived from MRI to prognostication and decision-making for the infant with hypoxic-anoxic injury.

For the published manuscript submitted as part of this thesis Lisa Anne Rasmussen, Emily Bell, and Eric Racine developed the interview grid. Lisa Anne Rasmussen performed the interviews. Data was analyzed and coded by Lisa Anne Rasmussen, and reviewed by Eric Racine and Emily Bell. Lisa Anne Rasmussen wrote the manuscript, with Emily Bell and Eric Racine reviewing and contributing commentary and suggestions prior to submission. This manuscript was published in the Journal of Child Neurology in 2016 (Rasmussen LA, Bell E, Racine E. A Qualitative Study of Physician Perspectives on Prognostication in Neonatal Hypoxic Ischemic Encephalopathy. J Child Neurol. 2016 Oct;31(11):1312-9).

This thesis and all chapters was developed and written in full by Lisa Anne Rasmussen, with Eric Racine acting as supervisor, reviewing and providing commentary and suggestions as necessary.

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**List of Abbreviations**

| | |
|---|---|
| ADC | Apparent diffusion coefficient |
| aEEG | Amplitude integrated electrocephalogram |
| CT | Computed tomography |
| DTI | Diffusion tensor imaging |
| DWI | Diffusion weighted imaging |
| EEG | Electrocephalogram |
| FA | Fractional anisotropy |
| HIE | Hypoxic ischemic encephalopathy |
| ICU | Intensive care unit |
| MRI | Magnetic resonance imaging |
| MRS | Magnetic resonance spectroscopy |
| NICU | Neonatal intensive care unit |
| PICU | Pediatric intensive care unit |
| PLIC | Posterior limb of the internal capsule |
| QOL | Quality-of-life |
| TH | Therapeutic hypothermia |
| US | Ultrasound |

**Forward**

*Nothing in its essence is one way or the other.*
-Pema Chodron; Comfortable with Uncertainty

Neurological prognosis in neonatal hypoxic ischemic encephalopathy (HIE) poses a perpetual challenge to physicians and parents. Forming prognostic predictions at such an early age is a practice fraught with many logistical difficulties and is often incomplete, or worse yet, incorrect. Despite these challenges neurological prognosis remains integral to the care of neonates with HIE, required for in-the-moment decision-making and future planning.

This thesis presents the work of a qualitative study aimed, through semi-structured interviews with neonatologists and pediatric neurologists, to understand the practice of prognostication in neonatal HIE. For the purpose of this thesis we focus primarily on the prognostication data and report two main findings: 1) neurological prognosis remains fundamental to quality-of-life predictions and considerations of best interest, and 2) magnetic resonance imaging (MRI) is presented to parents with a greater degree of certainty than actually exists.

The thesis starts with a clinical vignette, summarizing a common scenario experienced during my time working as a pediatric neurologist. Its aim is to focus the reader to the importance of this research and furthering our understanding of prognostication in neonatal HIE.

The first chapter offers an introduction to neonatal HIE, and the rationale for developing this thesis. The first section focuses on a brief overview of neonatal HIE, including the approach to diagnosis and currently available therapy. Although brief comments are made on the prognosis of neonatal HIE, this will be the distinct focus of chapter 3. The second section outlines the reasoning behind the developmental of this thesis, and the third section focuses on the thesis objectives. The final section of this chapter outlines the limitations of this thesis.

The second chapter presents a focused overview of the literature on prognosis. The first section introduces the concept of prognosis. The second section briefly discusses the growing clinical

and research interest in prognosis. The third section focuses on uncertainty as an integral component of prognosis. The final section discusses the challenges to prognostication, considering in turn general medicine, neurology, and the pediatric/neonatal setting. Emphasis is placed on selected articles in an attempt to introduce the reader to the notion of prognostic challenges, but an in-depth systematic review of this literature was not preformed. For the sections on prognostic challenges in general medicine and neurological prognosis, the majority of the literature originates from adult studies. The focus is placed on adult studies because this represents the largest and most studied population in the literature. Furthermore, whenever possible, focus was placed on Canadian literature because of the context of the study.

The third and fourth chapters present a focused overview of the literature that is most relevant to the published manuscript and supplementary results presented in this thesis. Specifically, the third chapter presents the current understanding of the prognosis for neonatal HIE and gives an overview of the practice of prognostication in neonatal HIE, including the indicators and investigations used. Again, emphasis is placed on selected articles to introduce the reader to the prognosis for neonatal HIE and the practice of prognostication, rather than on performing an in-depth systematic review of this literature.

The fourth chapter introduces challenges specific to prognostication in neonatal HIE. The first section focuses on challenges stemming from the neonatal HIE research literature, whereas the second section considered challenges from clinical practice.

The fifth chapter outlines the approach and methodology for this thesis, specifically focusing on the qualitative study that it is based on.

The results are presented in the sixth and seventh chapters, which focus on the published results from the Journals of Child Neurology October 2016, and unpublished results on challenges to prognostication in neonatal HIE respectively.

The eighth, and final, chapter presents the summation of the thesis, practical implications for clinical practice, and some thoughts on future research directions.

# Chapter 1: Introduction

## 1.1 Neonatal Hypoxic Ischemic Encephalopathy: An Introduction

### 1.1-1 What is Neonatal Hypoxic Ischemic Encephalopathy?

#### Description

Neonatal encephalopathy (NE) is a common occurrence in the NICU and refers to central nervous system dysfunction in the neonatal period (birth through 28 days-of-life), in a neonate born at or beyond 35 weeks gestation (1-2). NE is a clinical syndrome characterized by an abnormal level of consciousness, abnormal neurological examination, possible seizures, and frequent respiratory difficulties (1-2). The underlying etiology of NE is heterogeneous, one such cause being hypoxic ischemic brain injury. In situations where NE is due to hypoxic ischemic brain injury, the term used is neonatal HIE.

There are currently no universally accepted definitions for neither NE nor neonatal HIE, making research in this area confusing and difficult to interpret (3-4). There are several terms often used interchangeably for neonatal HIE, including NE, post-asphyxial encephalopathy, birth asphyxia, and perinatal asphyxia (4). For this thesis I will use the term neonatal HIE, but it is important to understand that the literature review comes from a broader search of all possible terms for a hypoxic-ischemic injury in neonates.

#### Incidence

HIE is the most frequent cause of NE, responsible for about 50-80% of cases (5). The published data approximate 1-6 per 1000 live births in developed countries (2, 6-8). Rates as high as 26 per 1000 live births have been reported in developing countries (4). Neonatal HIE is graded as mild, moderate, or severe according to the clinical presentation, and outcomes are very much tied to the grade of severity (2). In a 2010 meta-analysis study of NE associated with a hypoxic-ischemic event, the approximate breakdown of neonatal HIE was mild 37.8% (31.0–44.6%),

moderate 37.7% (32.9– 42.5%), and severe 23.4% (19.9–27.0%) (9).

**Basic Pathophysiology**

The pathophysiology of hypoxic-ischemic brain injury is complex and incompletely understood. An in depth review of the science behind neonatal HIE is beyond the scope of this thesis, but in general neonatal HIE results from maternal, placental and fetal factors either in isolation or combination (2, 10). Regardless of the underlying factors involved, ultimately damage results from insufficient oxygenation (hypoxia) and/or insufficient blood flow (ischemia) to the neonatal brain (2, 10). This hypoxic-ischemic environmental, combined with reduction in cerebral glucose ultimately leads to energy failure, and cellular death (2, 10).

**Biphasic and Evolving Injury**

The damage of neonatal HIE occurs in a biphasic manner. There is an initial acute phase of reduced blood flow, oxygen and glucose, and then a secondary phase of deterioration, which occurs within 6-15 hours of the injury (10). This 6-hour delay prior to the onset of secondary phase injury creates a therapeutic window in which treatments can be offered in order to prevent further brain injury. Beyond this basic conception of a biphasic injury pattern, it is important for the reader to understand that neonatal HIE is a dynamic process that develops and evolves not only over hours, but over days, weeks, and even months (2, 10). Understanding of the ever evolving nature of neonatal HIE is important not only for potential therapeutic interventions, but also for the consideration of prognosis.

**Multisystem Organ Injury**

Neonatal HIE also causes injury to other organs, specifically the liver, lungs, kidneys and heart (2). Although multisystem organ injury typically accompanies brain injury, there have been reports of isolated systemic organ injury in neonatal HIE (2). Presumably the systemic organ injury is related to hypoxia and/or ischemia, and involvement of systemic organs is particularly likely after severe insults that also produce severe brain injury (2). Although multisystem organ injury is important, this thesis focuses on neonatal brain injury and neurological prognosis in

neonatal HIE. The diagnosis and prognosis of multisystem organ injury will not be discussed.

### 1.1-2 How is Neonatal Hypoxic Ischemic Encephalopathy Diagnosed?

#### Basic Approach

There is currently no single test available to dependably diagnose neonatal HIE. Rather, physicians base their diagnosis on the presence of NE in combination with specific supportive features and the absence of another clear etiology to explain the diagnosis. When etiology is unclear, a thorough diagnostic evaluation is compulsory. A full differential diagnosis must be considered, and alternative etiologies including, congenital infections, trauma, cerebral dysgenesis, inborn error of metabolism, or other genetic abnormality must be excluded (3, 5, 11). Furthermore, it is important to consider concurrent condition that may predispose a neonate to HIE. Such etiologies may include genetic abnormalities, cerebral malformations, or neuromuscular syndromes (3). Preforming a full and extensive work-up in HIE, although essential, can be difficult given the considerable time limitation. Specifically, TH (the primary therapy for neonatal HIE) must be initiated within 6-hours of birth. Thus, physicians are limited by what they are able to accomplish in this tight time window.

The general approach to diagnosis in medicine, regardless of the etiology, starts with a thorough history. When it comes to neonatal HIE, the history focuses on understanding the maternal and prenatal history, particularly focusing on identifying possible risk factors for neonatal HIE. The identification of risk factors for neonatal HIE is clearly helpful for suggesting the diagnosis of neonatal HIE, but also for more fully understanding the pathophysiology, and developing appropriate therapies and preventative strategies. The currently available research on this front is limited and often confusing, in so far as data for neonatal HIE and the more general NE are often pooled (4). There are a number of risk factors known to increase the risk of NE (4). Given neonatal HIE is the most common underlying etiology for NE, we can use the risk factors for NE as proxy risk factors or HIE, at least in the sense that the presence of these risk factors should heightened a physicians suspicion that an hypoxic-ischemic event might be at play.

Kurinczuk et al. 2010 tabulated the statistically significant risk factors for NE and identified factors existing pre-conception, during pregnancy (antenatal), and surrounding the delivery (peripartum) (4). Pre-conception risks may include advance maternal age and parity, maternal height, and socio-economic status (as measured by maternal education, employment, and health insurance) (4). Risk factors during pregnancy include maternal thyroid disease, twin pregnancy and intrauterine growth restriction, among others (3). Finally, aspects of labour management (induction, need for emergency cesarean section) and the presence of meconium stained-amniotic fluids at birth were also identified as significant risk factors (4). Other research on risk factors for neonatal HIE identified features suggestive of fetal distress including, decreased fetal movements, nonreactive stress tests, fetal heart rate decelerations, and the need for resuscitation (3). These factors are commonly used in clinical practice, with the knowledge that none of these factors are specific for neonatal HIE (3). Despite the lack of specificity, these risk factors all inform the clinical history which is a fundamental step in the formation of an accurate diagnosis. As outlined by Volpe, when considering neonatal HIE it is important to recognize: fetal distress, depression at birth, and neonatal encephalopathy (2).

Following the clinical history, the next step in forming a diagnosis is the physical examination. In the neonatal setting, the physical examination starts at birth with Apgar scores. In fact, the first identifying clue for NE after birth is fetal depression noted by low Apgar scores (12). According to Volpe JJ. 2012, low Apgar scores are a required feature of neonatal HIE (12). Apgar scores are derived from a clinical scoring system based on five key clinical features including heart rate, respiratory rate, muscle tone, reflex irritability and color (13). Each clinical feature is given a score of 0-2 and then combination of results gives the overall Apgar score. A normal reassuring Agar score ranges from 7-10, whereas scores at or below 6 are considered evidence of newborn distress (13). Apgar scores are routinely done at 1 minute of life and 5 minutes of life, and if the 2 minute Apgar is abnormal again every 5 minutes until 20 minutes of life (13). Although useful to identify newborns at risk, low Apgar scores are not specific to neonatal HIE. Beyond the initial Apgar scores, the clinical examination (specifically the neurological examination) is essential to diagnosis. In the setting of NE, the clinical examination often focuses on assessing treatable and reversible etiologies, and then assessing the severity of NE by Sarnat staging, which will be discussed below under classification.

The next step in diagnosis generally involves ancillary exams and investigations, which are dual focused to eliminate the differential diagnosis, and also identify findings consistent with neonatal HIE. Laboratory investigations are routine following birth, and can be performed easily within the time constraints. Metabolic acidosis (identified in umbilical cord blood and/or fetal blood) must be present for neonatal HIE to be considered, but in itself is not diagnostic (10, 12). Evidence of multi-organ injury including specific abnormalities of the liver, lungs, kidneys, and/or heart further support the diagnosis of neonatal HIE (10, 12). Further investigations such as neurophysiology and neuroimaging can be beneficial to the diagnosis of neonatal HIE, yet very difficult to obtain in the 6-hour time limit.

Neuroimaging can play a key role in the diagnosis of neonatal HIE, through providing patterns of brain injury that are unique to neonatal HIE and help to indicate the severity and duration of the insult (11, 14) Furthermore, neuroimaging can provide valuable information regarding alternative etiologies that might mimic neonatal HIE (11). Neuroimaging may consist of cerebral ultrasound (US), computed-tomography (CT) scan, and/or MRI. Cerebral US is widely available and easily provided at the bedside in the NICU (3, 11). Although cerebral US can provide valuable information regarding alternative etiologies, it provides limited information in the term neonate presenting with NE (3, 11). In fact, the cerebral US is often normal, even in cases of severe neonatal HIE (14). On the other hand, early CT is able to detect brain injury consistent with neonatal HIE, as well as identify other possible etiologies including hemorrhage, stroke, and possibly severe forms of cerebral dysgenesis or inborn errors of metabolism (11, 15). However the information about neonatal HIE provided by CT is limited in both sensitivity and specificity, and many suggest avoiding the ionizing radiation of CT on the developing brain by resorting to MRI as the primary neuroimaging technique (14, 16-17). That said CT still holds value in the setting where a neonate is too systemically unstable to withstand an MRI, which is a longer procedure (11). As far as imaging, MRI is considered the best imaging modality for identifying neonatal HIE, and ruling out other etiologies (11). The information provided by MRI is also integral to prognostication, which is discussed further in Chapter 3. It is important to recognize that the brain injury associated with neonatal HIE develops over time, accordingly there is also an evolution of the changes seen on MRI (11, 14, 17). Furthermore, performing an MRI in neonates, especially sick neonates, is not without risk and, therefore, it is important to

ensure optimal timing of the MRI, such that the most useful information can be obtained (11). Typically, two MRIs are performed in neonates with HIE, an early and a later scan. Given the changes on MRI require time to develop, the general recommendation is that the first MRI should be preformed between days 2 and 8 in neonates presenting with NE (18). In fact, many advocate for a tighter time window with the first MRI optimally occurring between 3 and 5 days of life (14). The timing of the second MRI is more debated; with the time range being 3-180 days of life in a recent survey study of Canadian physicians (19). Despite the guidelines outlined in the literature, in practice the timing of MRI varies depending on the center and physicians involved (19). Nonetheless, irrespective of the center and physician involved it is unlikely (outside of a research setting) that MRI is performed within the 6-hour time window needed for the initiation of TH. Thus, although cerebral MRI can be used to confirm the presence of damage consistent with neonatal HIE, at present MRI does not typically contribute to the initial diagnosis of neonatal HIE.

Overall, given the 6-hour time frame in which treatment decisions need to be made for neonates with HIE, decisions are often made on the basis of suspected neonatal HIE, rather than a confirmed diagnosis. Confirmation of neonatal HIE comes with observation over time, the exclusion of other etiologies, considering the response to treatment, and accumulating further confirmatory evidence from additional investigations (principally MRI).

**Diagnostic Criteria**

There are no universally accepted diagnostic criteria for neonatal HIE. Perhaps the best proxy available is the treatment criteria, as outlined by the Canadian Pediatric Society (7). The current practice parameters suggest that all term and late preterm infants (≥36 weeks gestation) who meet criteria A and B (Table 1) should be considered for TH and, thus, are considered to have neonatal HIE (7).

**Table 1: Canadian Pediatric Society Criteria for Therapeutic Hypothermia**

| Criteria A | Criteria B |
|---|---|
| Any two of the following<br>• Apgar score <5 at 10 min of age.<br>• Continued resuscitation and need for ventilation at 10 min of age.<br>• Metabolic acidosis (pH <7 or base deficit >16 mmol/L) measured in cord or arterial blood gases within 1 hour of birth. | • Sarnat stage II or III (moderate or severe) encephalopathy demonstrated by the presence of seizures or at least one sign in at least three of the following six categories: level of consciousness, spontaneous activity, neuromuscular control, primary reflexes, autonomic system, seizure activity, and degree of depression on electroencephalogram. |

Adapted from the Canadian Pediatric Society publication (7)

**Classification**

Neonates with HIE are classified according to severity of their encephalopathy by a clinical scoring system called Sarnat staging (10). Like the Apgar scores, Sarnat staging also relies on the assessment of defined clinical features including level of consciousness, level of activity, neuromuscular function (posture and muscle tone), reflexes (tendon and primitive), autonomic functions (pupils and heart rate), and the presence of seizures (20). The Sarnat stage classifies neonatal HIE as mild (stage I), moderate (stage II), and severe (stage III) based on the combination of these clinical parameters (20).

### 1.1-3 Therapies in Neonatal HIE

There have been a number of medical advancements in the care asphyxiated neonates receive in the NICU, including improved intensive care support (i.e. respiratory and cardiovascular support), improved management of fluids and electrolytes, and improved treatment of seizures (10). Although systemic support continues to be the basis of care for neonates with HIE, the majority of these supportive measures do little for the underlying process of hypoxic-ischemic

injury itself. Rather, these supportive measures are aimed at preventing further deterioration and the possibility of further brain injury due to systemic failure (10). For over a decade now, the research focus has shifted to the development of neuro-protective treatments, one being TH.

At the present time TH is considered to be the only therapeutic intervention with proven benefit, and is thus standard of care for neonatal HIE in Canada (and elsewhere) (8, 10). This intervention is indicated in neonates with the moderate to severe form of HIE, based on a clinical grading score (8). TH aims to reduce the temperature of the vulnerable brain structures to $32^{\circ C}$ - $34^{\circ C}$ through either total body cooling or selective head cooling (8). TH is time sensitive and must be initiated within 6 hours of birth, or ideally sooner (8). This is due to the biphasic injury pattern of neonatal HIE discussed previously, the 6 hour time window aims to reduce damage amassed during the secondary stage of HIE (10). When used according to these guidelines, TH has been shown to reduce death and severe disability, without increasing disability in survivors (8).

Although TH has given hope of improved developmental outcomes, many of the neonates still endure important health and developmental sequelae.

### 1.1-4 Brief Introduction to Outcome Data for Neonatal Hypoxic Ischemic Encephalopathy

Neonatal HIE has a high rate of mortality; it is estimated that up to one-fifth of neonates afflicted by HIE will die in the newborn period (21-22). Perhaps even more important is the significant morbidity that follows neonatal HIE. In general, approximately 25% of all newborns with neonatal HIE will have permanent neurological deficits, in the form of cerebral palsy with or without associated mental retardation, learning disability, and epilepsy (22). The prognosis for neonatal HIE will be expanded on in chapter 3.

## 1.2 Rationale for this Thesis and Significance Regarding Ethics

Despite the aforementioned medical advancements, neonatal HIE remains to be an important cause of both mortality and neurological morbidity with subsequent long-term neuro-developmental disabilities. In fact, the incidence of neonatal HIE in Canada has remained fairly static over the last two decades (23). The potentially devastating outcomes of neonatal HIE are lifelong, yielding significant burden for the patient, the family, the health care system, and

society at large (3). Thus, an effective neuro-protective treatment to decrease brain injury and improve outcomes in neonatal HIE would be of major benefit.

Until recently there were no specific treatments for neonatal HIE; TH has demonstrated that neuro-protective therapy is possible. However, the therapeutic benefit of hypothermia is not absolute, and the development of further neuro-protective therapies is needed. Furthermore, TH is a time sensitive intervention, requiring initiation within 6 hours or ideally sooner (5). Given that brain injury in neonatal HIE evolves over time, it is likely that all potential neuro-protective therapies will be constrained by time. Thus, prompt identification of HIE affected neonates is essential, as well as the ability to predict the severity of injury (5). Furthering our understanding and ability to both identify and prognosticate in neonatal HIE is dire, leading many experts in the field to search for an appropriate biomarker.

From an ethical and clinical standpoint providing accurate neurological prognosis is fundamental in the care of neonates with HIE, as the neurological prognosis helps guide treatment plans, including neuro-protective interventions and, in some cases, decisions regarding transition to palliative care (3). The importance of prognostication relative to clinical and ethical decisions partly explains the continued interest in biomarker research for revealing more accurate prognostic tools (19, 24). The neurological prognosis is also fundamental for informed parental counseling, and guiding parental decision-making (3, 25). Moreover neurological prognosis is pivotal in end-of-life decision making, especially considering that death in intensive care units (including the NICU) is routinely preceded by withdrawal or withholding of life-supporting treatments (26-33). In fact, evidence suggests that most newborn deaths following neonatal HIE are preceded by end-of-life decisions and withdrawal of life-supporting therapies, typically within the first 3 days of life (33).

It is well recognized that prognostication in medicine is fraught with difficulties, and further that prognostication is particularly challenging in the context of neonatal HIE (3). In the face of these challenges, the clinical request and need for prognostication remains. Thus, prognostication in this group of neonates is an important topic for research, as it will likely continue to challenge health care providers for generations to come.

Currently there are no Canadian guidelines for prognostication in neonatal HIE, nor have American or other international guidelines been identified. Specifically there are no guidelines as to which investigations and tests should be utilized. Clinically there is great discrepancy in practice and much debate on the topic (19). Furthermore, the currently available predictive tests appear to assist in prognostication for the extreme cases, but are less helpful in prognosticating for moderate cases (19). Thus, advancements in our understanding of the practice of neurological prognostication in neonatal HIE are essential.

### 1.3 Objectives of this Thesis

The aim of this thesis is to explore the current practice of prognostication in neonatal HIE and focus on a new qualitative research study in hopes of providing some insights into both clinical and ethical challenges associated with clinical practice. This thesis is developed out of a broader Canadian national mixed quantitative and qualitative study that explores physician perspectives about neurological prognosis in neonatal HIE. Support for this work comes from NeuroDevNet (Racine) and the Fonds de recherché du Québec – Santé for a career award (Racine).

The study aimed, through semi-structured interviews with neonatologists and pediatric neurologists, to develop a better understanding of the practice of prognostication in neonatal HIE in the Canadian context.

### 1.4 Scope of this Thesis

This thesis is limited in that it will not provide an in-depth systematic review of the literature, but rather gives a focused overview of the literature that is most relevant to the published manuscript and supplementary results presented in this thesis. Furthermore, this thesis will not discuss all the results of the qualitative research study. The data on uncertainty, communication, and shared decision-making will not be presented because of lack of space. Instead, this thesis will focus on the data specifically relating to prognostication in neonatal HIE, which is one of five results sections from the broader study. There are also limitations specific to the research paper submitted, which are outlined in the paper itself in Chapter 6.

## Chapter 2: Background; Prognosis

### 2.1 What is Prognosis?

Prognostication is an integral aspect of medical practice, and is present in nearly every clinical encounter. Although the importance of prognostication seems most relevant for patients with a significant chance of mortality, or severe morbidity, providing a prognostication may be as simple as providing an expected course for a common seasonal respiratory virus. Generally, patients (their families or surrogates) want to know what to expect for their future, meaning they seek to know their prognosis. In medicine prognosis is defined as a physician's opinion or prediction about a patient's recovery potential and their likely future outcome. According to the Merriam-Webster Dictionary, prognosis is defined as "the prospect of recovery as anticipated from the usual course of disease or peculiarities of the case" (34). To *prognosticate* designates the act of making these predictions, "to foretell from signs or symptoms" (35). Typically patients are interested in knowing information about "how long" and "how well," two aspects that makeup a complete prognosis (36).

Prognosis in medicine is founded on the published literature on specific populations at-risk or specific disease entities; thus, the act of prognostication typically involves applying the population-based research on outcome to an individual patient (25). That said, the process of prognostication is tailored to the individual, in that a patient's prognosis is typically based on a combination of clinical and non-clinical variables; for example their specific disease profile, their non-modifiable factors such as age, sex, and genetic determinates, and their modifiable lifestyle factors such as diet and exercise (37). Furthermore, a patient's foretold prognosis is affected by their social circumstances, including socioeconomic status, social support and their personal beliefs or religion (38). Prognostication typically considers specific outcomes, such as complications or death, but also relays information on factors such as disease progression, symptom burden, and predicted quality of life (36).

Although prognostication typically assumes that the predicted outcome is unavoidable, previous authors have highlighted the importance of both intrinsic and extrinsic factors, which can modify outcome (3, 25, 38). Previously identified intrinsic factors include individual resiliency and personal motivation, while extrinsic factors include social supports, socioeconomic status, and

access to rehabilitation services (3, 25, 38). In considering these factors, the complexity of prognosis and the practice of prognostication are highlighted.

### 2.2 Prognosis as a Topic of Interest in Research and Clinical Medicine

Prognosis is a topic of growing significance in the medical literature and clinical practice (38-40). This resurgence of attention stems in part from an increasing awareness that prognostic information is fundamental to ethical medical decision-making, practices of informed consent, patient counselling, end-of-life decision-making and aspects of life planning (e.g. financial planning) for patients themselves and their families (38-40). Furthermore previous authors have identified wider contextual factors encouraging this revival of attention to prognosis including, but not limited to, the increasing prevalence of chronic diseases, increasing government oversight of health care funding and delivery, and increasing demand from patients for direct and accurate information (38).

### 2.3 Uncertainty in Prognosis

Uncertainty afflicts all aspects of medicine from the interpretation of test results, to determining a diagnosis, to planning an appropriate treatment course (41). Perhaps the area of medicine where uncertainty it most prominent and troubling is the prediction of prognosis. Despite mounting focus, the identification of robust prognostic factors eludes medical research and there continues to be a considerable degree of outcome variability in individuals with similar health conditions and prognostic indicators (39).

Fundamentally, prognosis is a probability of a possible outcome and, thus, uncertainty is an inherent aspect of prognostication. This prognostic uncertainty stems from a number of previously identified issues within research and identification of prognostic factors, including limited sample sizes, lack of testing in heterogeneous clinical settings, and extrapolation from population-based data to make predictions for individual patients (39).

Uncertainty, including prognostic uncertainty, is knowingly stressful for physicians (41). Furthermore, prognostic uncertainty undoubtedly leads to anxiety for patients and families (39,

41), thus advancement in our ability to provide accurate prognosis, and in doing so minimize uncertainty, is essential.

## 2.4 Challenges in Prognostication

### 2.4-1 Prognostic Challenges in General Medicine

It is well recognized that the practice of prognostication in medicine is itself fraught with difficulties (40, 42-45). Although physicians frequently communicate prognosis to patients and families, most feel anxiety, and even dread in doing so (38, 40,44). Lack of emphasis on prognosis in medical textbooks and published literature is well documented (38, 42, 46). This lack of emphasis combined with poor mentorship in medical training creates a medical culture where prognostication is a poorly acquired skill (38, 40). Thus, prognostic error is common and widespread (38, 44). A prospective cohort study of physicians' prognostic accuracy in terminally ill patients verified unfailing prognostic inaccuracy, which tended to sway to the optimistic (44). This tendency towards optimistic prognosis has been demonstrated in several studies (47-52). Furthermore, there is also considerable variation in the communication of prognosis and again the majority of physicians are most comfortable providing prognostic information that is either vague or optimistically oriented. (39-40)

Research focusing on physician perspective on prognostication is emerging and unveiling many practice challenges. A national study of internists working in the USA surveyed physicians about their perspectives on prognostication (40). The results focused on four aspects of prognostication; the practice, training, attitudes, and tolerance. The practice of prognostication varied according to physician specialty; meaning how and how often physicians were asked to determine prognosis depended on speciality. For example, oncologists (as compared to general internists) were more frequently asked about prognosis by patients, were more likely to be giving prognostication in a situation of withdrawing life supporting therapies, and were also more likely to be giving prognostication in a hospice referral situation (40). Lack of effective training was also a key finding, with 56.8% of physicians reporting inadequate training in prognostication (as compared to 7% and 6% reporting inadequate training in diagnosis and treatment). As for attitude, the majority of physicians surveyed described the practice of prognostication as

stressful; and moreover that providing accurate prognosis was often more difficult than providing an accurate diagnosis (40). There was also considerable physician distress when faced with giving prognosis in situations of medical uncertainty. Of interest providing prognosis was stressful regardless of physician experience, meaning the notion of practice makes perfect (and less difficult) does not hold true in this situation (40). Finally, Christakis et al. 1998 revealed that physicians felt a substantial intolerance of prognostic errors, from both patients and colleagues (40).

Given that the majority of deaths in the ICU setting follow withholding or withdrawing of life-supporting therapies (53-63), we can identify additional challenges in the practice of prognostication through the lens of end-of-life care and decision-making.

There are both patient-level and physicians-level (or healthcare worker-level) factors that have been shown to influence end-of-life care in the adult ICU (56, 60, 63-76). A cross-sectional survey study of Canadian ICU staff investigating the factors at play when determining withdrawal from life-supporting therapies, revealed independent patient factors including age, premorbid cognitive function, premorbid physical function, likelihood of surviving the current illness deterioration, and likelihood of long-term survival (64). Advance directives and familial directives also weighed significantly (64). This same study identified variability in determining withdrawal of life-supporting therapy, which was associated with respondent (ICU attending staff, ICU house staff, and ICU nursing staff) characteristics (64). Respondent factors included age, years of practice, profession (physician, nurse or trainee), the size of the ICU, and the city and province of the hospital (64). Furthermore, another Canadian study showed that practice setting (community hospital versus university affiliated teaching hospital) affected end-of-life decision making; withholding of life-supporting therapy being more common in community hospitals (63). These physician-level factors of age, profession, experience, geography, and practice setting have been reported widely in the literature. In fact, several other physician-level factors have been reported, including personal life support preferences, specialty, surgical investment, medical errors, and familiarity with life support (65-73). Religious beliefs and ethnic-cultural factors have also been shown to influence end-of-life decision making, for patients and physicians alike (74-75). Additionally, the use of technology in ICU settings has also been shown to influence end of life practices (76). The majority of the studies references

above are constructed through survey-based methods, whereas Wilson ME et al. 2013, used a qualitative approach of semi-structured interviews with physicians and nurses (with 10 years and 3 years of ICU experience respectively) (77). This study identified 4 categories of factors that influence end-of-life decision-making including, work environment, experience, attitudes and relationship with patient and family (77). Several interesting factors were highlighted in this study, specifically within the work environment, experience and relationship category. Considering the work environment there were several institutional factors or practices at play including, workload and competing priorities, shift changes with the associated hand-over of patient care between physicians, and also how nursing information was incorporated into decision-making (77). Experience in this study went beyond a simple numerical estimation of years or numbers of patients seen, and focused on specific physician experiences that can impact end-of-life practices such as, previous experiences of unexpected patient survival, and of personal family experiences of limiting life supporting therapies (77). Finally, this study highlights that the relationship between the physician and the patient (and family) is key, specifically firsthand communication of patient wishes and engagement of family preferences (77). This highlights that physician-level factors, in addition to patient (and family) preferences and beliefs, may contribute to the variation in end-of-life practices.

### 2.4-2 Prognostic Challenges in Neurological Injury

Neurological illness threatens core features of an individual's identity, including cognition, communication, and often the ability to live independently. Given the unique nature of neurological injury, there are specific challenges to providing accurate prognosis in patients presenting with neurological injury. Neurological injury is tremendously diverse, with some etiologies being acute (such as acute stroke, severe traumatic brain injury, and hypoxic-ischemic encephalopathy after resuscitation from cardiac arrest), and others being chronic or degenerative (such as multiple sclerosis, ALS, or other common neurological diseases). Here the focus will be on literature from acute neurological injury, as this most closely mirrors the situation in neonatal HIE.

Given the abrupt nature of these injuries, life-sustaining interventions are often initiated at the level of emergency care, and while many of the injuries are neurologically devastating, they are

often systemically survivable (78). Despite the survivability of these injuries, patients admitted to the neurological and neurosurgical ICU (neuro-ICU) have a high risk of death. As in the general ICU setting, death in the neuro-ICU typically follows withdrawal of life-supporting therapies, even in patients who are not deemed brain-dead (78-80). Even in the general ICU, patients with neurological injury are more likely to die after life-supporting therapies are withheld or withdrawn (81). Typically the decision to withhold or withdraw life-supporting therapies occurs within the 2-3 days of the injury, typically following a catastrophic prognosis is given with a bleak outlook for future neuro-disability and poor quality-of-life (82-84). However, there is considerable variability in both the practice of withholding/withdrawing life-supporting therapy, and mortality (83). Thus, we can again identify challenges in the practice of prognostication through the analysis of end-of-life care and decision-making around life-supporting therapies.

As in the general medicine/ICU setting, there are both patient-level and physicians-level (or healthcare worker-level) factors that have been shown to influence end-of-life care in the neuro-ICU. However, these challenges related to prognostication are less well documented and defined in the literature for patients with acute neurological injury.

Patient age (particularly advance age), probability of death, race, pre-existing comorbidities (cardiovascular, endocrine (diabetes), and renal), and the occurrence of surgery are identified patient-level factors (78, 82). That said the most important patient-level factor seems to be the severity of the neurological injury itself (78, 82). Devastating neurological injury occurs suddenly, and often in otherwise healthy individuals making chronic debilitating comorbidities less common in this population (78). Therefore, decisions to withhold or withdraw life-supporting therapies tend to be based solely on the severity of the neurological injury and the associated prediction of neurological morbidity and its effect on quality-of-life (78, 82).

This focus on neurological prognosis is troublesome due to a number of nonstandard patient factors which may ultimately influence the eventual outcome, including neuro-genetic influences on individual neuroplasticity and recovery potential, patient access to and participation in rehabilitation programs, and the socio-economic and social support systems in place to help a patient during their recovery and in life after the injury (3, 25, 38). Furthermore, the meaning of

a patient's prognosis depends greatly on the value system of the patient, as QOL is a very subjective outcome. QOL is a complex notion and may be defined in different ways to capture the ability of an individual to have meaningful functioning and achieve personal fulfillment in their life (85). It is clear that predictions of QOL are not standard. In one clinical vignette based study of neurological prognostication by ICU physicians, attitudes towards QOL varied with older and more experienced physicians tending to more objective and negative in their predictions (86). Furthermore, we know that predictions of QOL given by physicians are generally not in keeping with the true experience of caregivers and/or patients (87-90). In neurological disease, the pediatric and adult literature reveals that physicians are poor at predicting QOL, often by focusing primarily on physical and motor manifestations (87, 91-94). Furthermore, the literature confirms our finding that prognosis and predictions of QOL are used to determine a patient's best interest and, therefore, affect significantly medical decision-making (87-89, 95-96). Junod Perron et al. (2002) looked at the effect of QOL evaluations on a group of adults with critical illness and showed that QOL influenced 70% of resuscitation orders (88). This study again exposed that the majority of physicians underestimate the QOL that patients actually experienced.

Despite the clear importance of patient perspective, patients admitted to the neuro-ICU often have severe physical and cognitive impairments preventing them from participating in medical decision making, thus emphasis is placed on familial and physician input. End-of-life decisions are typically made by physicians in consultation with a spouse or first-degree relative, and advance directives are uncommon (84). The key issue here being that concepts of QOL are known to be divergent between physicians, family and patients themselves.

With so much weight given to the physician provided prognostic information, it is important to consider the physicians-level (or healthcare worker-level) factors that have been shown to influence end-of-life care in the neuro-ICU. Providing a neurological prognosis is a task met with much unease. In one study looking at moderate-severe traumatic brain injury, only 8 % of all respondents (including attending, ICU fellows, ICU nursing staff, and affiliated health care workers) where comfortable providing neurological prognosis (82). This discomfort was only minimally abated with clinical experience, as only 18% of attending physicians reported ease with providing neurological prognosis in the same study (82). Furthermore, we know there is

significant variation in provided neurological prognosis both between and within centers, thus, highlighting the significance of physician-level factors (82, 86). In one clinical vignette based study of neurological prognostication by ICU physicians, variability was documented in the predicted long-term functional outcomes, as well as in the confidence level with which the physicians' made these predictions (86). In this study more experience physicians tended to be more pessimistic in their predictions (86). The relative frequency of optimism versus pessimism is debated in the literature, with some suggesting that physicians tend to be overly pessimistic in prognosticating functional outcomes, and other studies alluding to a culture of optimism within neurological prognosis (84, 86, 97).

Beyond the variability in predicted functional outcomes, there is also variability in the aggressiveness of care provided to patients with neurological injury (86). Given the reliance on prognostic information for end-of-life decision-making in neurological injury, there is a real risk of clinical nihilism, and subsequent self-fulfilling prophecies. Clinical nihilism occurs when there is a lack of belief in therapy, due to its perceived futility for the patient (98). In acute neurological injury the concept of futility is heavily relied upon for determining the course and aggressiveness of medical intervention, despite the fact that futility is a poorly defined and controversial concept (84). Hemphill et al. (2010) explored the presence of clinical nihilism in acute neurological injury, and concluded that nihilism was not an effective therapeutic approach (98). Hemphill et al. (2010) suggested that early limitations of life-supporting therapy in acute neurological injury must be considered within the context that clinical nihilism may lead to self-fulfilling prophecy of poor outcomes (98). Additional authors have also suggested that prognostication of outcomes for severely ill neurological patients may be biased by a self-fulfilling prophecy; meaning that the decision to withhold or withdrawal life-supporting therapy may influence outcomes and, thus, predictive models (84).

The existence of significant variability in the care of individuals with acute neurological injury brings attention to the necessity for a deeper understanding of prognostic practices, in hope of creating more uniform of practices and predictions. Especially given that the divergence of physician opinion and prognostication practices may influence end-of-life decision-making in critical situations.

### 2.4-3 Prognostic Challenges in Paediatrics and the Neonatal Intensive Care Unit

Over the last several decades momentous advancements in diagnostic, therapeutic, and supportive medicine has transformed not only the sophistication of care provided in pediatric and neonatal intensive care, but also the outcome of this care (99). Illnesses that were unvaryingly fatal in years past are now managed successfully leading to greater survivorship (99). The other consideration of survivorship is the degree of medical complexity with which the patients survive; indeed medical success have resulted in a growing frequency of complex childhood disease and disability (100). There is also rising need for medical care, nursing care, medical technology and overall coordination of these services (100). Given that more infants and children are surviving with complex medical conditions, improved prognostic predictions are essential for medical decision-making and future planning.

One key challenge to prognosis in paediatrics in that 'children are not just little adults,' a maxim commonly uttered by those in paediatric clinical practice. In fact, research has shown that children are more likely than adults to survive episodes of significant physiological compromise, such as multi-organ system failure (101-102). This significant difference between adults and children may indeed be one reason for variation in mortality risk assessments in pediatrics, specifically in physicians of less experience. A comparative prospective study of mortality risk estimates in the PICU has shown that critical care attending physicians were both more accurate and more certain of their predictions, when compared to critical care fellows, residents, and nurses (103). Another study showed that clinical experience is an important factor affecting mortality predictions in critically-ill children (104).

Similar to the adult ICU setting, the majority of deaths in the PICU and NICU are preceded by withholding or withdrawing of life-supporting therapies (26-33). Practices in end-of-life care in the PICU and NICU have been shown to be variable and inconsistent (105-106). In the pediatric and neonatal settings, similar physician characteristics (specialty training, healthcare discipline, age, experience, and practice setting) have been shown to influence end-of-life care in the intensive care setting (103-104,106-108). Religious affiliation and gender also influences physicians' attitudes towards end-of-life decision-making in the NICU (107).

# Chapter 3: Focused Background; Prognosis in Neonatal Hypoxic Ischemic Encephalopathy

## 3.1 Prognosis in Neonatal Hypoxic Ischemic Encephalopathy

### 3.1-1 Mortality & Morbidity in the Era of Therapeutic Hypothermia

The prognostic literature is complicated by the fact that TH has created some concern about the usefulness of the available prognostic tests, and the potential that outcomes may ultimately be different than expected. That said TH is effective in reducing mortality, without increasing major disability in survivors (8). TH also reduces morbidity (8), though severe motor and cognitive deficits still occur in as many as 40% of survivors (109). Although there are short-term complications and adverse effects associated with hypothermia, the benefits on survival and neurodevelopment outweigh these concerns (109).

### 3.1-2 Mortality

As stated in the introduction, neonatal HIE has a high rate of mortality and it is a major source of neonatal death globally (9, 33, 110). The death rate in neonatal HIE depends largely on access to tertiary level neonatal care (9). Studies estimating mortality rates likely underestimate the true global burden, as most data comes from developed countries and populations with access to resuscitative care and the NICU (9). That said, approximately 20% of neonates with HIE die during the newborn period, and nearly all of these deaths occur in neonates who have severe neonatal HIE (21-22, 33). In fact, looking at severe encephalopathy alone, deaths rates climb significantly (9). The majority of these deaths, at least in developed countries, routinely follow early end-of-life decisions to withdraw or withhold life-supporting therapies (33). Although most deaths occur with in the first week of life, some survivors with severe neurological disabilities will die in infancy or early childhood most often from overwhelming systemic infection or aspiration pneumonia.

In the Canadian context, the Canadian Neonatal Network reported 496 cases of neonatal HIE in 2015, and although the published mortality data was limited to neonates treated with hypothermia (n=328), there were 31 deaths in neonates treated with hypothermia, making the group mortality at least 9% (111). This figure is slightly lower than the average over the

previous years with mortality rates of 14% in 2014 (n=313, deaths=45), 9% in 2013 (n=277, deaths=24), 15% in 2012 (n=233, deaths=35), 16% in 2011 (n=238, deaths=38), and 23% in 2010 (n=159, deaths=36) (112-116).

### 3.1-3 Morbidity; Long-Term Neurodevelopmental Outcome

Neonatal HIE also results in significant morbidity; depending on the study cited, upwards of 25% - 40% of all newborns with neonatal HIE will have permanent neurological deficits (22, 109). Cerebral palsy is a common outcome of neonatal HIE, cerebral palsy referring to a non-progressive, yet permanent, disorder of abnormal movement and posture (117). Dyskinetic CP and spastic quadriplegia are the most common CP subtypes attributable to neonatal HIE (118). Following neonatal HIE, cerebral palsy may present with or without associated cognitive deficits, learning disability, language problems, executive or social skills impairment and epilepsy (22, 109, 119). Beyond the major outcomes of death, cerebral palsy, or severe cognitive impairment, survivors of neonatal HIE are at increased risk for more subtle outcomes, such as specific learning or intellectual impairments, verbal deficits, behavioural problems, and difficulties with social competence (120).

There is a cohort of neonates who suffer a hypoxic-ischemic insult, yet never develop neonatal HIE. This represents the neonates who require significant resuscitation at birth, then recover quickly and do not require NICU admission. Generally this cohort of neonates is said to have a completely normal outcome, however recent studies have suggested the possibility of more subtle disability, specifically the increased risk of low IQ at school age and in early adulthood (121-122). This risk of low IQ seems to be an isolated outcome. In a follow up study, other aspect of neuropsychological functioning (attention, memory, language skills, and/or the need for educational support at school) seemed to be normal in children who required significant resuscitation at birth in the absence of neonatal HIE (123).

When considering neonates who developed clinical encephalopathy and are classified as neonatal HIE, the long-term neurodevelopmental outcome varies considerably according to the severity of encephalopathy (mild, moderate or severe). It is apparent in the literature that at

either end of the HIE spectrum outcomes are clearer (124). Neonates with mild encephalopathy usually survive with normal outcomes (124), however early subtle motor impairment has been reported (125-127). At the other end of the spectrum, neonates with severe encephalopathy either die in the neonatal period or survive with severe neurological disability associated with premature death (119, 124, 128). Neonates with moderate encephalopathy have more variable outcomes, ranging from normal to severe disability (127). According to the literature, there is a 30-50% risk of major permanent motor disability, such as cerebral palsy (119,129), and more subtle motor impairment is common in children without cerebral palsy (127). A much greater number of survivors (50-80%) have cognitive difficulties (124). Behavioural problems have also been separately considered in a few studies, with rates around 24% (127). Specifically, children with moderate and severe enchepalopathy have been reported to increased risk of hyperactivity, autism spectrum disorders, and psychotic symptoms (130-133).

### 3.1-4 Morbidity; Seizures & Epilepsy

Seizures are considered to be a significant short-term, and potentially long-term, complication of neonatal HIE. Long-term seizures are termed epilepsy.

Neonatal HIE is the most frequent cause of neonatal seizures, accounting for 38-60% of neonatal seizures, depending on the study (2, 134-135). Furthermore, seizures in the context of neonatal HIE tend to be recurrent, refractory to treatment, and status epilepticus is common (134).

By classification seizures occur in cases of moderate and severe HIE, meaning that once seizures are detected mild HIE is no longer a diagnostic possibility. Seizures associated with neonatal HIE tend to be subtle and difficult to diagnose, in fact electrographic seizures (those detectable only on electrocephalogram (EEG) monitoring) are common (2,136). Studies suggest that up to 80% of neonatal seizures are not detectable clinically, and require EEG (136). In the context of neonatal HIE, seizures typically develop within the first 48 hours, although delayed seizures can occur (2,5). Seizures incidence in neonates with moderate or severe HIE is estimated at 22% to 90% depending on the study sited (5, 136-139).

Although several studies suggest that hypothermia reduces the burden of seizures in neonatal

HIE (137, 140-142), electrographic seizures are still present in up to 30-65% of neonates receiving TH (136-140). Furthermore neonatal HIE continues to be the most frequent cause of neonatal seizures, despite the advancement of TH (134). In fact, the literature is quite conflicting with regards to the impact of TH on seizures in neonatal HIE.

The incidence of epilepsy following neonatal HIE in the literature varies from 9% to 33% (142). Although epilepsy has been seen following both moderate and severe neonatal HIE, the incidence of epilepsy seems to correlate with the severity of encephalopathy (143-144). The incidence of epilepsy also correlates with the severity and pattern of MRI injury (142, 144-145). Furthermore, there is an increased risk of infantile spasms (a very severe form of infantile epilepsy) following neonatal HIE (146). Again, the occurrence of infantile spasm seems to be associated with specific abnormalities on the MRI (147).

**3.1-5 Morbidity; Neuro-Sensory Outcomes**

Sensory deficits are also common following neonatal HIE, specifically hearing loss and cortical visual impairment (148-156).

Hearing loss following neonatal HIE is possible, but the prevalence is debated with some authors reporting no correlation (148) and others clearly showing neonatal HIE to be a significant risk factor (149). Jiang ZD, found that hearing loss, although not common, tended to be more frequent in children who had long-term neurodevelopmental disability (17.1%) as compared to those with normal outcome (6.3%). It should be noted that this trend did not meet statistical significance (150).

Cortical visual impairment is vision loss caused by damage to the central nervous system, and now represents the primary cause of acquired childhood visual impairment in developed countries (151-152). Neonatal HIE is the most common aetiology of cortical visual impairment, accounting for up to one third of cases in various studies (152-154). Although the majority of neonates with cortical visual impairment show improvement over time, more than 90% continue to have significant visual impairment in childhood (151). Cortical visual impairment often remains in combination with neurodevelopmental disabilities, including (but not limited to)

cerebral palsy, motor impartment, epilepsy, global developmental delay, and behavioural problems (151-152). In fact, there is correlation between the severity of early CVI and long-term neurodevelopmental outcome (155). The proportion of patients with CVI who have neurodevelopmental impairments ranges from 65-100% depending on the study sited (152,156).

## 3.2 The Practice of Prognostication in Neonatal Hypoxic Ischemic Encephalopathy; a Brief Review of Prognostic Indicators & Investigations

Currently, there are no Canadian guidelines or practice parameters for investigation or prognostication in neonatal HIE. Generally speaking, investigations such as clinical examination (including Sarnat Staging; a clinical staging system), cord blood pH, EEG, evoked potentials and MRI (including spectroscopy) are available and utilized according to the specific physician and/or hospital involved.

### 3.2-1 A Brief Comment on Sensitivity and Specificity

Throughout this section on the practice of prognostication, whenever possible focus will be placed on the sensitivity and specificity of prognostic indicators and investigations. In medicine, sensitivity is a measure of how good a test is at correctly identifying people with disease and specificity is a measure of how good a test is at correctly identifying people without the disease (157). In the context of neonatal HIE, sensitivity refers to the probability that an investigation identifies poor outcome in neonates who are truly destined have poor outcomes. Conversely, specificity refers to the probability that an investigation identifies neonates who are destined to have good outcomes.

### 3.2-2 Apgar Scores, Sarnat Staging & Clinical Examination

Apgar scores have long been considered in determining prognosis in neonatal HIE. That said the use of Apgar scores is fraught with difficulties, due in part to the subjectivity of scoring by different observers (2, 5), and in part to poor sensitivity and poor specificity (5). Despite these limitations, poor Apgar scores at 1 and 5 minutes are generally considered to be a predictor of neurological injury and poor long-term outcome (5, 158). That said, it is not a perfect correlation in that many children with low Apgar scores at 1 and 5 minutes (score <7) have normal

outcomes (159) and, in fact, some children with abysmal Apgar scores at 10 minutes (score 0), still survive without major morbidity (160). Some recommend using delayed Apgar scores, at 10, 15 or even 20 minutes to help clarify the outcome, as lower scores at these extended times tend to correlate with worsening prognosis (2).

Clinical examination and neurological dysfunction have long been regarded as fundamental predictors of prognosis (2, 20, 161-162). That said, given the subjective nature of the clinical examination and the considerable inter-observer variability in performing them, the clinical examination is fraught with inaccuracies and variability. Furthermore, the clinical examination may be hampered or the results altered due to various NICU interventions, including intubation, sedative medications, anticonvulsant medications, and hypothermia (5). TH has also been shown to reduce the accuracy of the early clinical examination (163). These factors will be discussed further in the section on prognostic challenges in neonatal HIE. The specificity of clinical examination has also been questioned. A recent meta-analysis by van Laerhoven et al. 2013, found that although clinical examination has good sensitivity, the specificity is poor enough that the usefulness is debatable (164). With such poor specificity the risk is incorrectly predicting poorer outcomes, leading to a significant number of false positives (164). Some authors have suggested that discharge examinations may be somewhat helpful (5), as compared to the early clinical examinations that have proven unhelpful in predicting long-term outcomes, even when standardized approach is used (165).

Despite the criticisms of the neurological examination, it is generally agreed upon that the severity of neurological dysfunction is one of the most important prognostic indicators (2-3). As part of the clinical examination, Sarnat staging is used to identify the severity of encephalopathy (20). Like the Apgar scores, Sarnat staging also relies on the assessment of defined clinical features and is affected by subjectivity of the observer. The Sarnat stage classifies neonatal HIE as mild (stage I), moderate (stage II), and severe (stage III) based on a combination of clinical features (20). Long-term neuro-developmental outcomes clearly differ according to the severity of encephalopathy (mild, moderate or severe), but as discussed in the previous section on prognosis in neonatal HIE, there is significant variability in outcomes and outliers do exist (119, 124-129). Furthermore, the duration of neurological dysfunction seems to be a good indicator of outcome, thus making serial examinations and/or discharge examinations essential (2).

### 3.2-3 Seizures as Prognostic Indicators

Neonatal seizures in general are associated with a significant risk of mortality and long-term neurodevelopmental disabilities, including cerebral palsy, intellectual disability, poor social/academic performance, and/or epilepsy (166-169). In fact, even isolated electrographic seizures are known to carry a significant risk for mortality and long-term morbidity (170-171). The burden of long-term neurodevelopmental disability is significant, with upwards of 50% of neonates with seizures being affected (134). Furthermore, neonatal seizures are associated with an increased risk of early death, and generally the greater the seizure burden the greater the risk of adverse outcome (134).

In the context of neonatal HIE, the occurrence of seizures is an important prognostic factor to consider. Seizures in neonatal HIE are an ominous sign, associated with increased mortality and long-term neurodevelopmental disability (2, 141-142, 170-173). In fact seizure burden in neonatal HIE is independently associated with severity of neurodevelopmental outcome, impartial of the severity of hypoxic-ischemic brain injury (172).

Beyond poor neurodevelopmental outcomes, there is also a risk of epilepsy following both neonatal seizures (166-169) and neonatal HIE (142-144). Specifically there seems to be an association between neonatal HIE and the development of infantile spasms, a severe infantile epilepsy syndrome (146-147).

Finally, the potential implications that short-term (early) seizures carry for management are important to consider. Garfinkle et al. 2011, proposed that TH was likely less beneficial in neonates who suffered seizures related to neonatal HIE (173).

### 3.2-4 Laboratory Investigations

Laboratory investigations of systemic involvement, including serum electrolyte levels, renal function studies, cardiac and liver enzymes, and coagulation studies are often done during the initial evaluation, or diagnostic phase, of neonatal HIE (10, 12). However, the majority of these investigations provide little to no prognostic value. One exception to this may be oliguria, which

has been associated with more severe grades of neonatal HIE and suggests an increased risk of long-term neurodevelopmental impairment (174). Another exception may be elevated blood glucose in the first 12 hours of life, which was shown in one study to be correlated with poor motor outcomes (175).

Another common laboratory investigation is assessment of acid-base balance at birth. Abnormal acid-base balance is an early and strong indicator of fetal distress, typically measured by an umbilical artery blood sample (5). Umbilical artery blood samples (called cord blood samples) are considered routine care, especially in high-risk or complicated deliveries, and can offer some important information for both the diagnosis of and prognostication for neonatal HIE (176). The main value of cord blood samples is to provide information on the neonates' acid-base balance at the time of delivery, specifically providing values for the pH, base access, and lactate (5, 176). It is important to recognize that cord blood values are affected by several factors beyond the presence hypoxia-ischemia (176). For example, caesarean section, twin pregnancies, and the use of regional anaesthesia during delivery are all factors known to affect the cord blood values (176). Despite these variables, cord blood values are typically used as indicators of fetal distress that is hypoxic-ischemic in nature (5, 176). Neonates with a cord blood pH greater than 7.0 tend to have normal outcomes; whereas a cord blood pH below 7.0 is typically considered pathological (5, 176). That said, most infants with isolated cord blood pH below 7.0 have normal outcomes as well, suggesting that cord blood pH alone is a poor predictor of hypoxic-ischemic injury and outcome (159, 176). When combined with other clinical features, particularly low Apgar scores, the predictive value of cord blood pH increases dramatically (176). In non-vigorous neonates with low Apgar scores, a cord blood pH below 7.0 is strongly predictive of an abnormal and poor outcome (176). Beyond cord blood pH, base excess and lactate levels are also assessed, with abnormal values being considered above 12 mmol/L and above 4.1 mmol/L respectively (176). Although these cord blood values closely correlated with pathological pH, their individual predictive value and use for prognostication in neonatal HIE remains non-uniform and controversial (5, 176). For example, lactate seems to correlate closely to abnormal pH and base excess values, and is useful in predicting low Apgars, however its ability to predict long-term outcomes correctly, such as abnormal development and death, is poor (176).

In general, many reviews of prognostic tests for neonatal HIE do not even consider cord blood values or other laboratory investigations in their analysis (3, 5, 164, 177), suggesting that at present laboratory investigations do not add much weight to the practice of prognostication in neonatal HIE.

There is developing interest in systemic biomarkers for neonatal HIE, identified by various laboratory investigations of the blood, urine and cerebrospinal fluid (178).
A systemic review by Ramsaway et al., 2009 looked at the usefulness of these biomarkers and concluded that although they may provide important information for prognostication, further research was needed (178). At present these biomarkers are of no clinical relevance to the practice of prognostication in neonatal HIE (164).

### 3.2-5 Neurophysiology; Electrocephalogram and Evoked Potentials

Neurophysiological investigations include EEG and evoked potentials.

EEG examinations can take the form of conventional EEG and amplitude-integrated EEG (aEEG). EEG undoubtedly provides information on the occurrence and evolution of seizures (specifically those that are electrographic). However, the focus for this section will be on the neuro-monitoring aspects of EEG, specifically how evaluation of brain activity and background informs prognosis. To start it is important to understand that the implementation of EEG techniques is non-standard, and varies depending on each center's preference and resources (179).

Conventional EEG is considered routine care in neonatal NICU (179), and a recent meta-analysis by van Laerhoven et al. 2013, found conventional EEG to be an extremely valuable prognostic indicator during the first week of life (164). Early conventional EEG has been shown to have good sensitivity and specificity in several studies, for both normal and abnormal outcomes, specifically early death or neuro-developmental disability at 12-24 months (180-183). In one prospective observational study, normal EEG background predicted normal outcome at 12-months in all patients with this pattern (180). In the same study an abnormal EEG background (particularity a burst-suppression pattern) predicted death or abnormal neuro-developmental

outcomes at 12-months in 13 of 14 patients (180). A 2016 meta-analysis of 31 previous studies also concluded that an abnormal EEG background (particularity a burst-suppression pattern) was the most accurate predictor of abnormal neuro-developmental outcome (184). Given the clear value of conventional EEG, some studies advocate for serial conventional EEG recordings, which have been shown to be beneficial in predicting long-term outcome in neonatal HIE (179, 185). Conventional EEG may also be used continuously. In fact, continuous EEG with video recording is considered gold standard for neonatal brain monitoring (186). Despite this there are considerable barriers to its wide implementation (expense, access to the equipment, specializes training for interpretation), and currently continuous EEG tends to be used on a case-by-case basis (186). Finally, it is important to recognize that hypothermia does affect the predictive value of the conventional EEG (181). This will be discussed further in the section on challenges to prognostication in neonatal HIE.

aEEG is a bedside method for continuous monitoring of brain activity, which generally records from a limited number of electrodes placed by NICU staff (neonatologists or nurses) (186). aEEG is a technique that allows for interpretation without a neurophysiologist or neurologist, in fact the majority of aEEG is executed and interpreted by neonatologists and other NICU staff member (186). aEEG is becoming more commonplace and widely used in the NICU, given it's bedside application and ease of use (184, 186-187). aEEG has been used widely in European countries for decades, and its use in North America has significantly increased over the last several years (186-187). aEEG provides valuable prognostic information and its use is widely supported (164, 186-191). In fact van Laerhoven et al. 2013, suggested that aEEG is one of the most valuable investigations in the first week of life (164). Prior to the application of TH, abnormal background on early aEEG (within 3-6 hours of birth) was strongly predictive of abnormal outcome, especially when combined with clinical examination (188-190). Even in the setting of TH, aEEG is still a valuable indicator of prognosis (191). Although an abnormal aEEG is slightly less predictive of adverse outcome, a normal aEEG is very reassuring (191). Assessing the aEEG over time is also valuable as the evolution of the background over several days provides further prognostic information (186). Clearly aEEG is a valuable investigation for prognosis in neonatal HIE, but it is not without difficulties. Specifically, several studies have reported on user dependent variability in aEEG interpretation (192-194).

Evoked potentials can either be visual evoked potentials (VEPs) or somatosensory evoked potentials (SEPs). Despite their potential benefit, evoked potentials are not routinely used in the majority of NICUs (164, 195). van Laerhoven et al. 2013, determined that VEPs are amongst the most worthwhile neurophysiological exams during the first week of life (164). Abnormal VEPs are a good indicator of abnormal neuro-developmental outcomes, with strong sensitivity and specificity (164). Abnormal SEPs are also considered to carry significant risk of mortality and poor long-term neurodevelopment outcome (195-199). However, their reliability has been brought into question due to considerable variability in specificity (164). The reliability of SEPs is also be affected by TH (200). This will be discussed further in the section on prognostic challenges in neonatal HIE.

### 3.2-6 Neuroimaging; Ultrasound, Computed-Tomography & Magnetic Resonance Imaging

Neuroimaging for the purpose of prognostication consists primarily of MRI (11, 201). Although cerebral US, and CT may be used during the early diagnostic stage, in current practice neither modality contributes significantly to the practice of prognostication in neonatal HIE (11). MRI is recommended for all neonates with neonatal HIE. For the purpose of prognostication in neonatal HIE, typically two MRIs are preformed. As mentioned previously, the general recommendation is that the first MRI should be preformed between 2 and 8 days of life, with many advocating for a tighter time window of 3 to 5 days of life (11, 14, 18). The occurrence and timing of a second scan is much more variable (19). Overall, MRI practice guidelines are not widely followed, with both the number and the timing of MRIs varying according to the center and physicians involved (19).

For the purpose of prognostication in neonatal HIE, standard MRI protocols include anatomic T1 and T2 sequences (termed conventional MRI) and diffusion-weight imaging (DWI) (14, 201). Conventional MRI identifies the region of injury and extent of injury through variations in signal intensity seen on the MRI images (14). Conventional MRI is interpreted by visual assessment. DWI is a more advance technique that further depicts the region and extent of injury, but also adds to the understanding of onset and progression of injury (11, 14). DWI is based on the movement of free water, with areas of injury showing decreased free water movement and an associated increase in signal intensity on the MRI images (11, 14). A widely discussed weakness

with these standard MRI modalities is the subjectivity of interpretation, which will be discussed further in the section on challenges to prognostication in neonatal HIE (202). Furthermore, great attempts have been made to develop better quantitative measure of brain injury. A few of these advanced imaging techniques will be discussed briefly at the end of this section.

Although an extensive explanation of the pathophysiology of abnormalities seen on conventional MRI and DWI is beyond the scope of this thesis, it is key to highlight the importance of MRI timing. Given the brain injury associated with neonatal HIE evolves over days to weeks, the timing of MRI is crucial (11, 14, 18). Furthermore, the interpretation of MRI results must acknowledge this evolution of injury and avoid underestimating the extent of brain injury in cases of poorly timed MRI (14). For example, DWI in particular is sensitive to the timing of MRI. The reduction in free water movement develops over the several days, such that optimal timing for DWI is 2 to 4 days after injury, and early imaging may underestimate the true injury (14). Similarly, after 7 days the DWI may no longer show injury, an effect called pseudonormalization (14). Important transformations also occur for the anatomic MRI sequences (T1- and T2- weighted imaging).

When interpreting conventional MRI and DWI, two main patterns of injury are distinguishable (14, 201). These patterns of injury are important to identify, as each is associated with particular long-term morbidity predictions. The first pattern of injury is the basal ganglia–thalamus pattern (BGT), in which the primary injury involves the basal ganglia, thalamus, and perirolandic cortex (14, 201). The outcome of the BGT pattern of injury tends to be severe cerebral palsy, hence severe motor disability (14, 201). Learning disability and epilepsy are also prominent, and associated the severity of the motor disability (201). As part of the BGT pattern of injury damage can often be identified in the posterior limb of the internal capsule (termed the PLIC sign), which is highly predictive of severe adverse motor sequelae (14, 201-203). The second pattern of injury is the watershed predominant pattern (WS), in which the primary injury involves the intravascular boundary zones (termed the watershed), affecting mainly the cerebral white matter and extending into the cerebral grey matter (cortex) with more severe injury (14, 201). As opposed the severe motor sequelae of the BGT pattern, the WS pattern of injury tends to relate to severe cognitive and language disabilities, in the absence of motor disability (201-

202). Although severe motor disability is possible, it is not common in this group of infants (14, 201). Given that the early developmental assessment focuses on motor development, many toddlers with the WS pattern are considered normal when seen in early follow-up at 12-18 months (201). However, with time the true outcome is revealed with cognitive deficits, language delays, and behavioral disturbances being common (201, 204-205).

In the pre-TH literature, the prognostic utility of conventional MRI and DWI is debated. A large meta-analysis by Thayyil et al. (2010), tabulated the results of 32 studies of MRI in neonatal HIE not exposed to TH (206). This extensive review reported the sensitivity and specificity of each method in predicting neurodevelopmental outcome in neonates with neonatal HIE. The results of this meta-analysis showed that, for non-cooled neonates with neonatal HIE, conventional MRI had an overall sensitivity of 91% and specificity of 51% when performed between day 1 to 30 of life (206). The study did acknowledge considerable statistical heterogeneity, which decreased when MRI was sub-grouped as early (1 to 7 days) and later (8-30 days) (206). Specifically, late MRI had higher specificity, but lower sensitivity as compared to early MRI (206). Overall, Thayyil et al. (2010) felt that both conventional MRI and DWI had poor discriminatory power for predicting outcomes in neonatal HIE (206). A more recent meta-analysis by van Laerhoven at al. (2013) evaluating 29 studies of prognostic tests in non-cooled cases of neonatal HIE, showed that both conventional MRI and DWI had good sensitivity and specificity (164). Specifically, conventional MRI (performed in the first 2 weeks) had the best imaging sensitivity with a value of 98%, and DWI (performed in the first week) had the best imaging specificity with a value of 89% (164). As mentioned earlier, it has also been shown that injury in the region of the PLIC carries a signification risk of abnormal outcome. Thus, van Laerhoven at al. (2013) concluded that although there was considerable variability in the accuracy of conventional MRI and DWI, both still played a key role in prognostication for neonatal HIE (164). Hayes et al. (2016) also studied conventional MRI and DWI in non-cooled population of neonatal HIE, and showed that all neonates with PLIC injury suffered from developmental sequelae (207). However, acceptance of the PLIC sign is not universal. The earlier meta-analysis by Thayyil et al. (2010) gave the PLIC sign a sensitivity of 71% and specificity of 86%, and concluded that it did not show good prognostic utility (206). Despite the fact that the value of conventional MRI and DWI to prognosticate in neonatal HIE continues to be debated, both modalities are common

in clinical practice and often relied upon.

Given that TH is now considered the standard of care for neonatal HIE, it is important to consider the utility of conventional MRI and DWI in this context. Charon et al. (2016) conducted a retrospective study on all cases of neonatal HIE that were eligible for TH in their center (208). The aim of the study was to compare the prognostic value of early (≤ 6 days) versus late MRIs (≥ 7 days) in relation to neurodevelopmental outcomes at 2 years of age (208). This study concluded that hypothermia did not alter the predictive value of MRI, but that early MRI had better specificity than late MRI (208). The study reported sensitivity and specificity of 96.3% and 83.3% for early MRI, and 89.3% and 70% for late MRI receptivity; results that are similar to the pre-TH literature (208). Charon et al. (2016) also found that the PLIC sign on early MRI was a good predictor of adverse neurodevelopmental outcomes, even in the context of TH (208). Although in this study all neonates with adverse outcome had abnormal MRI findings, there were still those outliers with diffuse abnormal MRI changes that surprisingly had favorable outcomes (208). These outliers exist within both the pre- or post- TH literature. At present, the wider literature seems to support that in the context of TH both conventional MRI and DWI maintain their prognostic value (14). However, there is literature to suggest altered evolution of changes on the MRI, specifically that changes will appear later (14, 209).

Advanced MRI techniques, including diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) are increasingly being used to help fine-tune prognostication (11, 14), but these modalities are still far from standard in clinical practice (19).

DTI measures the amount (apparent diffusion coefficient [ADC]) and the directionality (fractional anisotropy [FA]) of water motion within the brain (210). The aim of DTI is to characterize microstructural changes within the brain, thus identifying distinct areas of injury (210). As opposed to DWI, areas of hypoxic-ischemic brain injury have decreased signal intensity on the ADC (11). Many of the measurements techniques involved in DTI are still used primarily on a research basis, and will not be explored further. However, there is some research to support the use of the ADC value within the region of the PLIC to prognosticate in neonatal HIE. In the context of neonatal HIE, a reduced ADC value in the PLIC is associated with adverse neurodevelopmental outcomes (211). Yet other research has indicated differently, with

ADC showing low sensitivity (66%) and specificity of (64%) to predict neurologic outcome after 12 months of age (206). In fact from these results, Thayyil et al. (2010) concluded that ADC does not sufficiently predict outcomes in neonatal HIE (206).

MRS measures the biochemical makeup of the brain, specifically comparing the biochemical composition of normal brain with areas of brain injury (212). The key metabolites present in healthy brain are choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) (212). Although an extensive review of the alterations of brain metabolites in neonatal HIE is beyond the scope of this thesis, a basic point is that with brain injury NAA levels will decrease, altering the ratios between the other brain metabolites (212). Furthermore, in the context of neonatal HIE brain injury results in elevated lactate (Lac) levels (212). In fact, many belief that reduced NAA and elevated Lac are highly predictive of adverse neurodevelopmental outcome in neonatal HIE. Thayyil et al., 2010 reported that MRS measurement of Lactate/N-acetylaspartate (NAA) ratio offers a sensitivity of 82% and specificity of 95% for later neurodevelopmental outcome (206). As compared to the finding for conventional MRI outlined above (sensitivity of 91% and specificity of only 51%), MRS seemed to be more adept at accurately predicting adverse neurodevelopmental outcomes (206). In fact, Thayyil et al (2010) conclude that MRS (specifically referencing the Lac/NAA ratio and LacCr peak) is the most accurate neuroimaging measurements to predict adverse neurodevelopmental outcome (206). Yet the more recent meta-analysis by van Laerhoven at al. (2013) disagreed with this conclusion, and felt at present there was insufficient evidence to conclude positivity or negatively on the use of MRS in neonatal HIE (164).

# Chapter 4: Focused Background; Prognostic Challenges in Neonatal Hypoxic Ischemic Encephalopathy

As discussed previously (Chapter 2) prognostication in medicine is fraught with difficulties, with neurological prognosis, and the pediatric/neonatal contexts posing further specific challenges. It is also well recognized that prognostication is particularly challenging in the context of neonatal HIE (3, 25). The multiple general challenges to prognostication already discussed (Chapter 2) are pertinent to prognostication in neonatal HIE, but there are also several unique challenges that arise. The direct literature focusing on challenges to prognostication in neonatal HIE is very limited and, therefore, specific challenges must be inferred or extrapolated from the broader neonatal HIE literature. Issues can be divided in to challenges interpreting the research, and clinical challenges.

## 4.1 Research Challenges

Physicians rely upon the outcome data in the literature to inform their prognostication in specific cases (3), thus challenges to the neonatal HIE literature are also challenges to the practice of prognostication.

### 4.1-1 No Universal Definition & Varied Research Terminology

There is currently no universally accepted definition for neonatal HIE, and the research terminology for neonatal HIE is unclear (3-4). The literature for neonatal HIE is often imbedded in the larger literature on NE, and references to neonatal HIE use numerous terms including post-asphyxial encephalopathy, birth asphyxia, and perinatal asphyxia (4). Overall, the research literature in this area is confusing, and difficult to interpret.

### 4.1-2 Research Limitations and Poor Outcome Data

One well-established challenge of prognostication in neonatal HIE is the fact that current understanding of outcome is based on data originating from large population studies and, thus,

offers little certainty with regards to individual cases (3). Shevell et al. (1999) in their paper on neonatal neurological prognostication outlined several other research challenges that complicate the physician's ability to prognosticate accurately. Challenges included: 1) small numbers of cases used to generate long-term data about outcomes; 2) large variability in the length of follow up to assess outcomes; 3) assessment of only severe outcomes such as death or severe disability; and 4) varied medical care (3). Overall, Shevell et al. (1999) emphasized that the interpretation of the outcome literature is quite challenging (3). Awal et al. (2016) also underlined this issue, commenting on the varied selection of neurodevelopmental outcome assessments in studies of neonatal HIE (184). Pointing out that almost every study has a unique approach to neurodevelopmental outcome assessment (184). Furthermore, many authors agree with Shevell et al. (1999) that the neonatal HIE literature focuses on inappropriate outcomes (3). Specifically that there is too much focus placed on the major outcomes of death, sever motor disability, and severe cognitive impairment (1, 120). Conversely, very little attention is paid to the more subtle outcomes such as milder cognitive impairments, as well as social and behavioural difficulties (120, 127). This is particular concerning given that these more subtle outcomes may have an important affect on QOL, which is poorly explored in the literature (127).

## 4.2 Clinical Challenges

### 4.2-1 Imprecise Diagnosis

The first step to generating a prognosis in any situation is to identify the exact diagnosis, this, as outlined in the introduction, can be difficult in neonatal HIE. There are currently no uniformly accepted diagnostic criteria for neonatal HIE. MRI is arguably the test relied upon most, but outside of the research setting it is unlikely that MRI will be performed within the 6-hour time window needed for the initiation of TH. Therefore, much of the decision making in neonatal HIE is done with a presumed diagnosis of neonatal HIE.

### 4.2-2 The Lack of Practice Standards

There are currently no standard practice parameters for prognostication in neonatal HE, and

although there are some general guidelines for specific tools (such as MRI), clinical practice is far from standardized. Thus, the specific tools used to prognosticate vary widely. For example although evoked potentials do contribute to prognosis, they are not routinely used in the majority of NICUs (164). Wilkinson (2010) conducted an exploratory qualitative study with neonatologists in the United Kingdom focusing on prognosis, MRI and treatment withdrawal in neonatal HIE (213). In this study, many of the participants compared the practice of prognostication to a "jigsaw puzzle," piecing together several different sources of information (clinical examination, EEG, MRI, etc.) to form a complete prognosis (213). Wilkinson (2010) found that the specific investigations used and the weight given to their respective results varied amongst physicians and hospital centers (213). A more recent study of Canadian centers revealed variability in the use of MRI for prognostication in neonatal HIE not only between Canadian hospitals, but also amongst individual physicians (19). These clear inconsistencies in approach to prognostication between physicians and centers pose a major challenge in neonatal HIE, especially when it comes to medical education and informing residents in training.

### 4.2-3 Unclear Timing of Outcome Predictions

As discussed in the previous chapters, neonatal HIE is an entity that evolves over days to weeks, and perhaps even longer. Consequently, the timing of prognostic testing and outcome prediction is critical; at present the correct timing is still undecided. One major distinction of relevance here is the difference between motor outcome predictions, versus cognitive and/or behavioral outcome predictions. It is generally accepted that motor outcomes are predictable at an earlier age, the literature typically suggesting a window of 12-24 months. Van schie et al. (2015) showed that for motor disability (CP), an assessment at age 2 reliably predicted outcome at school age (127). The caveat being that there are children with a normal assessment at age 2, who have long-term neurodevelopmental difficulties (127). One reason for this discrepancy is likely that cognitive and behavioral outcomes are often poorly assessed at age 2, in fact most agree that it is not until school age (ranging 5-7 years) when these more subtle outcomes can be properly assessed (128). Cognitive functions continue to develop throughout childhood and subtle abnormalities in function may not present themselves until the child is faced with specific cognitive tasks in school (128). The same is true for behavioral functioning and social

interactions (128). Barnett et al. (2002) demonstrated that a normal outcome at age 2 did not predict a normal outcome at school age (126). In this study of those children with normal outcome at age 2, 15 % had minor neurological dysfunction and/or perceptual-motor difficulties and 2 % had cognitive impairment when assessed at school age (126).

### 4.2-4 Non-Uniform Use of Tools & Subjective Interpretation

MRI, which is considered standard and generally relied upon heavily for prognostication in neonatal HIE is non-uniformly implemented with variability in both timing and the specific MRI techniques used (19). Furthermore, MRI results can very depending on the scanner used, meaning that the same MRI protocol on different scanners may give different results (214). Not only are there no specific practice parameters for prognostication in neonatal HIE, there is also a lack of standards for the interpretation of results. Although some general guidelines exist, MRI results are analyzed by visual assessment relying on the training and experience of the evaluator (214). EEG is also interpreted by visual assessment. Awal et al. (2016) highlighted the fact that there are no universally accepted definitions for many of the EEG abnormalities seen in neonatal HIE (184). Evoked potentials results are also dependent on the interpretation by an evaluator, although it is suggested that SEPs are easier to interpret (215). Overall, the subjectivity of interpretation is a clear challenge for prognostication in neonatal HIE.

### 4.2-5 Difficulty obtaining MRI and/or MRI Results

Wilkinson (2010) identified difficulty in obtaining MRI and/or MRI results as a major theme for the participants (213). MRI facilities were not equivalent across all centers, and performing scans on sick neonates requiring ventilation was particularly challenging (213). Furthermore, obtaining accurate interpretation of the MRI images was identified as challenging due to lack of specialized radiologist across all centers (213).

### 4.2-6 Environmental Factors of the NICU & Management of Neonatal HIE

The NICU is a highly technical and often a very busy environment. This environment can be challenging when performing certain investigations; for example, SEP recordings must be isolated from the background noise of the intensive care environment. Thus, the ambient noise and intensive care equipment can affect the generation and interpretation of SEPs (216). Many neonates will be administered sedating medications and anticonvulsant medications, which can impede or at least influence the clinical examination and the EEG (213, 215). Another aspect for consideration is the substantial advancement made in NICU care, and how this might impede our ability to interpret certain tools and investigation that were developed prior to these advancements. One such example in neonatal HIE is the use of the Sarnat classification for documenting the severity of HIE. Although initially reliable for prognosticative purposes, its usefulness has come in to question given that medical advances like artificial ventilation and medications with sedative effects are much more prominent now than when the Sarnat staging was developed (124). The advancement of TH requires focused attention and will be discussed next.

### 4.2-7 Therapeutic Hypothermia and its Effects on Prognostic Tools

TH is currently the standard of care for neonatal HIE, yet its effect on the various prognostic tools and investigation is still not fully understood. There is concern that TH may alter the usefulness of prognostic testing, and that ultimately outcomes may be different than predicted. Although the literature is limited, there is a suggestion that TH alters the predictive value of the clinical examination (163, 217). In the setting of TH, the initial stage of encephalopathy no longer predicts outcome, specifically meaning the utility of Sarnat staging has diminished (217). TH also alters the utility of the clinical examination and stage of encephalopathy at 4 days of life, upon completion of therapy (163, 200). Gunn et al. (2008) reported that infants with continued moderate encephalopathy following TH have more favorable outcomes than would be expected for their degree of encephalopathy (163). Thus, it has been suggested that in the context of TH, the true value comes from the evolution of the clinical examination and stage of encephalopathy. Specifically, improvement in the stage of encephalopathy during the first several days implies better outcome, whereas a lack of improvement in stage of encephalopathy indicates a higher risk of death and/or poor neurodevelopmental outcome (217). There has been much controversy

on the significance of TH for specific prognostic tools and investigations, with literature suggesting that TH may reduce the utility of early aEEG pattern and EEG background (200). That said, at present the data seems to indicate that TH does not alter the predictive value of aEEG and conventional EEG (14). However, considering the evolution of these results over time is again fundamental (217). Conversely, TH affects the predictive value of evoked potentials, specifically SEPs. Garfinkle et al. (2015) reported that in the setting of TH, abnormal SEPs are much less predictive of abnormal outcomes than in a non-cooled population (200). Normal SEPs, however, continue to be predictors of better outcome even in the setting of TH (200). An intensely debated topic is the effect of TH on MRI images and results. That said, at present the general consensus is that MRI retains it prognostic utility even in the setting of TH (14, 209, 214, 217). One caveat being that TH may affect the evolution of MRI changes, thus the most appropriate time to image is still unclear (14,209).

### 4.2-8 A Wide Spectrum of Disability, Unpredictable Factors, and Variable Meaning

One clear challenge to prognostication in neonatal HIE is the wide spectrum of potential outcomes, from relatively normal, to mild learning delays, to severe motor disability, as well as the possibility of severe cognitive and behavioural difficulties. As highlighted by Shevell et al. (1999) prognostication is fraught with assumptions and predictions are given with a certain amount of certainty that is often not founded (3). To start the core of prognosis is often founded on the published literature and, thus, like in general medicine the act of prognostication in neonatal HIE typically involves applying the population-based research on outcome to an individual neonate (2). One major challenge here is that there are several factors that may influence the ultimate outcome for a neonate; often these factors are unique for each individual and not knowable and controllable. Often these factors are separated into intrinsic and extrinsic factors (2). Examples of intrinsic factors include an individual's functional adaptation to neurological insults (meaning, for example, their motivation to participate in rehabilitation), an individual's resiliency and coping abilities, and finally neuroplasticity, which is particularly relevant to the immature brain (2-3, 213). Extrinsic factors include such things as the accessibility of rehabilitation services (timing, quantity, type), the family's socioeconomic status, and finally the family's aptitude for coping and the richness of their support system (2-3, 213). Given the degree of influence these unpredictable factors hold, offering an accurate prediction on

the wide spectrum of possible outcomes is a sizeable task. Furthermore, even if an accurate appraisal of the future is provided, the meaning that an outcome will eventually hold for a specific child and their family is extremely variable. In fact, the information parents seek from prognosis may range from gauging neuro-developmental disabilities, to more general understating of the likely impact of the disability on their child's psychological, social and physical well-being (218).

### 4.2-9 Unavoidable Uncertainty in Prognosis and its affect on Medical Decision Making

All of the above challenges cumulate and contribute to the overall sense of unavoidable uncertainty present in prognostication for neonatal HIE. This uncertainty is in itself a major challenge. As discussed in the section on prognostication in general medicine, prognostic uncertainty, is knowingly stressful for physicians, as well as patients and their families (39, 41). Wilkinson (2010) specifically addressed the uncertainty as a major challenge for prognosis in neonatal HIE (213). In this study, neonatologists directly referenced occasions when their predictions were wrong; specifically situations when devastating predictions were given, and yet the children had much better outcomes (213). This uncertainty in prognosis for neonatal HIE is not only challenging to the act of prognostication, but also to medical decision making, particularly decisions surrounding end-of-life (213).

In her 1986 paper on the ethics of uncertainty in the case of Baby Doe, Rhoden points out several different approaches to prognostication in the face of uncertainty (219). These same approaches were summarized by Shevell et al. (1999) in a paper specifically looking at prognostication in neonatal HIE (3). It is important to review these basic approaches to prognostication in order to outline where they fall short and, therefore, lead to heightened uncertainty.

The first approach is a variation on the theme "only time will tell" in which clinicians delay giving prognostication until the clinical evolution makes the outcomes better known (3). Meaning the answer to the question "will my child walk?" will have to wait to 12-18 months when children generally begin walking. The obvious shortcoming of this approach is that it lends no information to parents and families during the most crucial phase of decision-making, which is the neonatal period.

The second approach is based on the assumption that "like mimics like" meaning that prognostication can be given based on categorization of neonates into different groups whose outcomes will be similar (3). The issue here is that the generalization of category or population data offers little in the way of certainty when it comes down to an individual case. Shevell et al. (1999) discuss the challenges of generalizing the conclusions gained from previous studies in neonatal HIE to individual newborns (3). These include biases introduced by small sample sizes, outcomes measures weighted towards neurological impairment, varied follow-up time and evolving standards of medical care.

The third approach, and perhaps the most advocated for by Shevell et al. (1999) is based on the uniqueness of each neonate, meaning that every neonate requires individualized prognostication based on the specifics of their medical case and evolution (3). In clinical practice, my experience has been that this is the most commonly invoked approach to prognostication as it pays particular attention to the individual and specific details of each neonate, but it also allows for the giving of timely prognostication, which can be used by the health care team and parents in making difficult medical decisions. The problem is that this individual prognostication, as pointed out by Shevell et al. (1999) is perhaps the approach with the most inherent uncertainty (3).

## Chapter 5: Methodology

### 5.1 Origin and Intention for this Thesis

This thesis was developed from a semi-structured interview project, which was one component of a mixed-methods study at the Institut de recherches cliniques de Montréal. The intent of this thesis is to explore prognostication in neonatal HIE through a qualitative semi-structured interview study with pediatric neurologists and neonatologists. The aim is to better understand the practice of prognostication in neonatal HIE, and the related clinical and ethical challenges. Ultimately, the hope is to make recommendations on approaches to ethical prognostication in neonatal HIE, and to motivate and focus future research on the topic.

## Research Study: A Qualitative Study of Physician Perspectives on Prognostication in Neonatal Hypoxic Ischemic Encephalopathy.

### 5.2 Project Development

The original project entitled "Ethical challenges of magnetic resonance imaging for prognostication in neonatal brain injury" was put forward for funding by Racine E., Bell E., Yager J., and Shevell M through the Institut de recherches cliniques de Montréal. Dr. Michael Shevell originally introduced me to Dr. Eric Racine who was heading up this project, as I was a staff pediatric neurologist at the Montreal Children's Hospital with interest in neonatal work, and concurrently beginning a masters of biomedical ethics.

The project was mixed-methods, and the first portion of the research project was a vignette-based written survey to investigate the perspectives of Canadian neonatologists and pediatric neurologists regarding the contribution and role of MRI for prognostication in neonatal HIE. This work has been previously published in the Journal of Child Neurology (19).

As part of the initial survey and participants were invited to take part in a semi-structured interview that further explored their perspectives on the clinical and ethical implications of prognostication, and the use of MRI for informing prognostication in neonatal HIE.

The interview grid was developed and agreed upon by the three co-authors on the published paper: Dr. Emily Bell, Dr. Eric Racine, and myself. The interview questions were created to be broad and open-ended.

### 5.3 Ethical Considerations

Ethics approval through the Institut de recherches cliniques de Montréal was obtained before commencing the project. Informed consent was obtained prior to each interview by way of a written consent form.

### 5.4 Participant Selection and Contact

Prospective participants were Canadian physicians identified in the following categories: neonatology, neonatal intensive care, child neurology, pediatric neurology and neonatal neurology. They were identified using Scott's Medical Directory Database, a searchable database of Canadian physicians who allow their information to be published (220). Participants willing to take part in the semi-structured interviews self identified themselves in the initial vignette-based survey study.

### 5.5 Sampling

Following principles of qualitative research, the sample size for the semi-structured interviews was determined by the principle of theoretical saturation (221), rather than a strict numerical value or achievement of representation across all centers in Canada. Reaching theoretical saturation entailed continuing interviews until there were no new ideas or commentary provided, at which point recruitment was closed.

### 5.6 Data Collection

I performed all the interviews either in-person or over the phone. The interviews consisted of a series of open-ended questions and participants were encouraged to elaborate on their answers. The duration of the interviews varied from 75-90 minutes and all were performed in English.

There were three main interview sections prompting information about the participants' perspectives on: 1) clinical experience concerning prognostication and outcome in neonatal HIE, 2) the contribution of neuroimaging (MRI, MRS and DWI) as a biomarker in neonatal HIE, and 3) research and development of MRI biomarkers for prognostication in neonatal HIE (Table 2).

**Table 2: Interview Grid- Main Topics Explored**

| **Part 1: Prognosis and outcome in neonatal hypoxic ischemic encephalopathy.** |
|---|
| • The approach to prognostication and the contribution of different tools/investigations.<br>• Challenges in prognosticating in neonatal hypoxic ischemic encephalopathy.<br>• Uncertainty in prognostication and prognosis.<br>• Communication in neonatal hypoxic ischemic encephalopathy.<br>• Decision-making in neonatal hypoxic ischemic encephalopathy.<br>• Ethical issues in the practice of prognostication in neonatal hypoxic ischemic encephalopathy. |
| **Part 2: Neuroimaging (magnetic resonance imaging, magnetic resonance spectroscopy, and diffusion weighted imaging) as a biomarker in neonatal hypoxic ischemic encephalopathy.** |
| • Current use of MRI to prognosticate in neonatal hypoxic ischemic encephalopathy and related decisions.<br>• Current uses evidence-base for MRI in neonatal hypoxic ischemic encephalopathy.<br>• The contribution of MRI as a tool for aiding prognostication in neonatal hypoxic ischemic encephalopathy.<br>• Challenges to the use of MRI for prognostication in neonatal hypoxic ischemic |

| |
|---|
| encephalopathy.<br>• MRI and prediction of future functional outcome.<br>• Decisions informed by MRI results.<br>• Potential negative consequences of using MRI to prognosticate in neonatal hypoxic ischemic encephalopathy.<br>• Ethical considerations of using MRI to prognosticate in neonatal hypoxic ischemic encephalopathy. |
| **Part 3: Research and development of MRI biomarkers for prognostication in hypoxic ischemic encephalopathy.** |
| • Impact of MRI research and development of new technologies.<br>• Potential unintended consequences.<br>• Ethical considerations in developmental of MRI imaging technology.<br>• Challenges in the uptake of MRI research and technology into clinical care.<br>• Access to MRI technology in Canada.<br>• Translation of knowledge to practice. |

### 5.7 Data Analysis

The interviews were digitally recorded and transcribed verbatim by a third party transcribing service. I reviewed transcriptions in detail to ensure accuracy and adjust any content errors. A thematic content analysis was preformed based on themes identified in the data (222). I drafted a coding guide based on an initial analysis of four interviews, where free thematic nodes were generated in an open-coding phase. This open coding was used as a basis for a coding guide containing definitions and rules for the application of each code. During coding, additions and modifications to the coding guide were allowed and all changes were compared to earlier coding to ensure that the material was analyzed with rigor and thoroughness (222). NVivo 8 Software was used as a template for coding. Dr. Eric Racine reviewed all the coding, and Dr. Emily Bell provided a third review in the event of disagreement.

### 5.8 Quality Control

Every effort was made to ensure quality control for this project, specifically by a significant reflexive effort through constant discussion and feedback between myself, Dr. Eric Racine and Dr. Emily Bell.

### 5.9 Manuscript Development

I wrote the manuscript for publication in full, with Dr. Emily Bell and Dr. Eric Racine reviewing, and providing commentary and suggestions prior to submission. This manuscript was published in the Journal of Child Neurology in October 2016 (223).

### 5.10 Thesis Development

I developed and wrote this thesis in full under the supervision of Dr. Eric Racine, who reviewed and provided commentary and suggestions as necessary.

## Chapter 6: Published Results; A Qualitative Study of Physician Perspectives on Prognostication in Neonatal Hypoxic Ischemic Encephalopathy

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**A Qualitative Study of Physician Perspectives on Prognostication in Neonatal Hypoxic Ischemic Encephalopathy.**

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**Abstract**

Hypoxic ischemic encephalopathy is the most frequent cause of neonatal encephalopathy and yields a great degree of morbidity and mortality. From an ethical and clinical standpoint, neurological prognosis is fundamental in the care of neonates with hypoxic ischemic encephalopathy. This qualitative study explores physician perspectives about neurological prognosis in neonatal hypoxic ischemic encephalopathy. Our study aimed, through semi-structured interviews with neonatologists and pediatric neurologists, to understand the practice of prognostication. Qualitative thematic content analysis was used for data analysis. We report two main findings: 1) neurological prognosis remains fundamental to quality-of-life predictions and considerations of best interest, and 2) magnetic resonance imaging is presented to parents with a greater degree of certainty than actually exists. Further research is needed to explore both the parental perspective and, prospectively, the impact of different clinical approaches and styles to prognostication for neonatal hypoxic ischemic encephalopathy.

**Key Words**

Neonatal Hypoxic-Ischemic Encephalopathy, Prognostication, MRI, Ethics.

**Background**

Hypoxic ischemic encephalopathy (HIE) is the most frequent cause of neonatal encephalopathy; the published data approximates 1-6 per 1000 live births in developed countries.[1-4] HIE has a high rate of mortality; it is estimated that up to one fifth of infants with HIE die in the newborn period.[5-6] HIE also leads to significant morbidity with approximately 25% of all neonates having permanent neurological deficits, in the form of cerebral palsy with or without associated cognitive deficits, learning disability, and epilepsy.[5] At the present time therapeutic hypothermia is considered to be the standard of care for these cases in Canada[3], which has been shown to reduce mortality without increasing major disability in survivors.[4]

From an ethical and clinical standpoint neurological prognosis is fundamental in the care of neonates with HIE, specifically for developing treatment plans, informing parental counseling, and guiding decision-making.[7-8] Moreover neurological prognosis is pivotal in end-of-life decision making, especially considering that death in intensive care units (including the neonatal intensive care unit (NICU)) is routinely preceded by withdrawal or withholding of treatment.[9-11] The importance of prognostication relative to clinical and ethical decisions partly explains the continued interest in biomarker research for revealing more accurate prognostic tools.[12-13] Currently, there are no Canadian guidelines for prognostication in neonatal HIE. Generally speaking, investigations such as cord blood pH, clinical exam (including Sarnat Staging), electroencephalogram (EEG), evoked potentials and magnetic resonance imagine (MRI) are available and utilized according to the specific physician and/or hospital involved.

It is well recognized that prognostication in medicine is fraught with difficulties, and further that prognostication is particularly challenging in the context of neonatal HIE.[7-8] The medical literature identifies multiple general challenges to prognostication including lack of emphasis in medical textbooks, poor mentorship, stress and unease in predicting outcomes, and lack of experience.[14-18] Furthermore, several physician factors have been shown to influence end-of-life care in the adult, pediatric, and neonatal intensive care unit (ICU), including specialty and subspecialty, age, experience, religious beliefs, and practice setting.[19-25] One well-established challenge of prognostication in neonatal HIE is the fact that current understanding of outcome is

based on data originating from large population studies and, thus, offers little confidence with regards to individual cases.[7] Other challenges complicate the physician's ability to prognosticate accurately in the clinic or on the ward, including: 1) small numbers of cases used to generate long term data about outcomes; 2) large variability in the length of follow up to assess outcomes; and 3) assessment of only severe outcomes such as death or severe disability.[7] Beyond these challenges, there are many other aspects of prognostication in neonatal HIE which would benefit from further quantitative or qualitative exploration. A previous study conducted with neonatologists in the United Kingdom used an exploratory qualitative approach focusing on prognosis, MRI and treatment withdrawal in neonatal HIE.[26] In this study we focus on the perspectives of neonatologists and pediatric neurologists, within a Canadian context. The objective of this study is to explore the perspectives of physicians on prognostication in HIE, including the importance, the intent, and the practice itself within a qualitative research design.

**Methods**

This semi-structured interview project was one component of a mixed-methods study at the Institut de recherches cliniques de Montréal. A vignette-based survey investigated the perspectives of Canadian neonatologists and pediatric neurologists regarding the contribution and role of MRI for prognostication in neonatal HIE[13] and participants were invited to take part in a semi-structured interview that further explored perspectives on the clinical and ethical implications of prognostication and the use of MRI for informing prognostication in neonatal HIE.

Ethics approval through the Institut de recherches cliniques de Montréal was obtained before commencing the project. Informed consent was obtained prior to each interview by way of a written consent form.

Prospective participants (Canadian physicians identified in the following categories, neonatology, neonatal intensive care, child neurology, pediatric neurology and neonatal neurology) were identified using Scott's Medical Directory Database, a searchable database of Canadian physicians who allow their information to be published.[27] Participants willing to take

part in the semi-structured interviews identified themselves in the initial vignette-based survey study. The sample size for the semi-structured interviews was determined by the principle of theoretical saturation; this means that interviews were continued until there were no new ideas or commentary provided, at which point recruitment was closed. Following principles of qualitative research the sample size was determined by the saturation of ideas communicated, rather than a strict numerical value or achievement of representation across all centers in Canada.[28]

A single interviewer (LAR) performed all the interviews either in-person or over the phone. The interviews consisted of a series of open-ended questions and participants were encouraged to elaborate on their answers. There were three main interview sections prompting information about the participants' perspectives on: 1) clinical experience concerning prognostication and outcome in neonatal HIE, 2) the contribution of neuroimaging (MRI, MRS and DWI) as a biomarker in neonatal HIE, and 3) research and development of MRI biomarkers for prognostication in neonatal HIE (Table 1).

**Table 1: Interview Grid- Main Topics Explored**

| **Part 1: Prognosis and outcome in neonatal hypoxic ischemic encephalopathy.** |
|---|
| • The approach to prognostication and the contribution of different tools/investigations.<br>• Challenges in prognosticating in neonatal hypoxic ischemic encephalopathy.<br>• Uncertainty in prognostication and prognosis.<br>• Communication in neonatal hypoxic ischemic encephalopathy.<br>• Decision-making in neonatal hypoxic ischemic encephalopathy.<br>• Ethical issues in the practice of prognostication in neonatal hypoxic ischemic encephalopathy. |
| **Part 2: Neuroimaging (magnetic resonance imaging, magnetic resonance spectroscopy, and diffusion weighted imaging) as a biomarker in neonatal hypoxic ischemic encephalopathy.** |

| |
|---|
| • Current use of MRI to prognosticate in neonatal hypoxic ischemic encephalopathy and related decisions.<br>• Current uses evidence-base for MRI in neonatal hypoxic ischemic encephalopathy.<br>• The contribution of MRI as a tool for aiding prognostication in neonatal hypoxic ischemic encephalopathy.<br>• Challenges to the use of MRI for prognostication in neonatal hypoxic ischemic encephalopathy.<br>• MRI and prediction of future functional outcome.<br>• Decisions informed by MRI results.<br>• Potential negative consequences of using MRI to prognosticate in neonatal hypoxic ischemic encephalopathy.<br>• Ethical considerations of using MRI to prognosticate in neonatal hypoxic ischemic encephalopathy. |
| **Part 3: Research and development of MRI biomarkers for prognostication in hypoxic ischemic encephalopathy.** |
| • Impact of MRI research and development of new technologies.<br>• Potential unintended consequences.<br>• Ethical considerations in developmental of MRI imaging technology.<br>• Challenges in the uptake of MRI research and technology into clinical care.<br>• Access to MRI technology in Canada.<br>• Translation of knowledge to practice. |

The interviews were digitally recorded and transcribed verbatim by a third party transcribing service. The transcriptions were then reviewed in detail by the interviewer (LAR) to ensure accuracy and adjust any content errors. A thematic content analysis was preformed based on themes identified in the data.[29] The interviewer (LAR) drafted a coding guide based on an initial analysis of four interviews, where free thematic nodes were generated in an open-coding phase. This open coding was used as a basis for a coding guide containing definitions and rules for the application of each code. During coding, additions and modifications to the coding guide were

allowed and all changes were compared to earlier coding to ensure that the material was analyzed with rigor and thoroughness.[29] NVivo 8 Software was used as a template for coding. The coding was then reviewed by one co-author (ER) and a mechanism was in place to review in the event of disagreement by another co-author (EB), but there was no disagreement and consensus was achieved. In this paper, we report data regarding physician perspectives on prognostication; other data (e.g. challenges of prognostication, uncertainty, communication and decision making) will be reported elsewhere.

For each data section, we first present an overview and then illustrate major points using tables featuring examples of qualitative statements made. Omitted words are indicated by '...' and additional words added to clarify meaning are indicated in square brackets.

**Results**

The semi-structured interviews involved twelve participants, five neonatologists (P1-P5) and seven pediatric neurologists (P6-P12). There were participants from six Canadian hospitals, all of which had therapeutic hypothermia as the standard of care for neonatal HIE. There were four female physicians and 8 male physicians, with clinical experiencing ranging from <5 years to >20 years.

During the interviews, participants offered their perspectives as physicians and they also offered a perspective on what parents consider important for the intent and practice of prognostication (Table 3 and Table 5). Although we recognize this data is not from parents themselves, we report it as these assumptions (wrong or right) may affect the physicians' actions in these cases.

***The Importance of Neurological Prognosis***

Neurological prognosis was considered to be more important than prognosis for other organ systems, in part because organs systems tend to recover with more predictability. Furthermore, neurological prognostication was judged to be of fundamental importance for quality-of-life (QOL) given that neurological prognosis is focused on "the whole life consequences" of neonatal

HIE (P8). Participants recognized that the concept of QOL is subjective and affected by both physician and parent "biases," a term used by participants (Table 2).

**Table 2: The Importance of Neurological Prognosis to Physicians and to the Concept of Quality-of-Life.**

| **Neurological Prognosis is Fundamentally Important** |
|---|
| "Brain injury is laden with a lot more emotions and moral concerns for sure… neurologic or neurodevelopmental impairment in the long term is much more associated with a negative outcome compared to compromise of another organ that can be supported with medical therapies in the long term." (P3)<br><br>"Usually it's all about the neurological prognosis and I don't think that is a narrow focus, cause the rest of the body usually recovers." (P8) |
| **Neurological Prognosis Directly Affects Quality-of-Life** |
| "By neurological prognosis I mean that we try to think of the whole life consequence. We talk about, you know, strength and cognitive capacity, but also life and communication and feeing yourself and getting around." (P8) |
| **Physician and Parental Biases are Prominent** |
| "Parents often have their own biases based upon their life experiences, maybe they grew up in a home where someone was severely disabled or maybe they saw someone else's home break up because they had a severely disabled child." (P2)<br><br>"[Related to quality-of-life] I tend to be more on the pessimistic side and that's probably because of a personal bias." (P4) |

### *The Intent of Neurological Prognosis*

For physicians, prognostication is about trying to construct the most truthful estimation of the possible range of outcomes for a particular child, with the intent that neurological prognosis will

aid in medical decision-making. Particularly, prognosis is used to help determine the newborn's best interest.

The participants posit that parents generally want to be given definite information, meaning they do not want uncertainty. The specific information that parents want as part of the prognosis is variable, with some families focused on specific outcomes like walking, talking and school, and others focused on broader questions such as happiness and comfort (Table 3).

**Table 3: The Intent of Neurological Prognosis and the Purpose for Parents.**

| **The intent of neurological prognosis for physicians is providing information and assisting decision-making.** |
|---|
| "The goal of providing [prognosis] to the family is going to be, first, to lay out the best appreciation that we may have of the child's prognosis, then based on whatever we can define as the child's best interest, and then the parent's expectations and values define what is appropriate to be done. So, in the extremes, a child that has a very poor survival or even very poor functional prognosis will certainly influence and dictate recommendations towards an intervention. And then you get all the variations in between." (P4)<br><br>"Prognostication is trying to make the best possible estimation of the range of outcomes that could reasonable be expected based on all the information available. Usually we try to break it down, especially when talking to families about the big picture of good vs. bad." (P8)<br><br>"I see prognosis affecting families medical decisions… they do their best. I mean, it's not easy but they do their best to factor in their values and their lives. And they can't really speak for this individual who's never spoken to them before. But I think they do their best. And it's hard. It's a hard situation to be in." (P12) |
| **The purpose of neurological prognosis for parents is to gather concrete and definite information.** |

| |
|---|
| "Families want prognosis to be definite… and they don't want uncertainty, obviously they want it to be good, but they really want it to be definite, they want it to be cut and dry." (P9)<br><br>"Well, I think they expect that we know exactly what's wrong with the brain and that we'll give them a prediction of the future with a degree of certainty that we probably can't deliver." (P12) |
| **The information that parents seek for prognosis is variable and unique.** |
| "Well, I mean, I think it depends on the particular family. I don't know if you can make a general statement to say that this is what [prognosis] means for all families. I think it's very particular." (P3)<br><br>"[Prognosis] means what it means to them… you certainly hear lots of different questions asked. We usually try to let them start by telling us what they feel like they need to know about the child's future. Usually you hear the basic categories of things, they want to know about walking and talking and going to school and having friends. And sometimes it's even simpler, it's just, you know, can he be happy or is he going to be in pain or is he going to be miserable. So I guess usually it's about real life, it's not too much about the specifics." (P8) |

### *The Practice of Prognostication*

In terms of overall approach, participants highlighted the importance of a detailed history about the pregnancy and delivery, with specific attention given to ruling out other etiologies. Subsequently, the clinical examination must be considered. There was considerable disagreement regarding the usefulness of the clinical examination, however, when physicians endorsed its use the emphasis was placed the evolution of the clinical examination. In addition to the clinical examination, various investigations were highlighted. The most referenced were MRI, electroencephalogram (EEG), and, less prominently, evoked- potentials. Most participants agreed that although the initial cord gas and laboratory investigations were helpful in identifying

neonates with HIE, these investigations were of little value for clarifying long-term prognosis. Participants placed most emphasis on the MRI, whereas the usefulness of the EEG and evoked-potentials was debated with some participants making statements such as, "I don't really care about the EEG or the evoked potentials" (P10). EEG was deemed as difficult to interpret and generally only helpful at the extremes, whereas evoked-potentials were deemed as too often unreliable. MRI was the investigation with the most agreement between participants, they stressed its central and indispensable role in prognostication for neonatal HIE. That said there were still some skeptics. One physician remarked, for instance, "I'm careful with neuroimaging as a prognosticator" (P12). Overall clinical examination, clinical evolution, MRI, EEG and evoked-potentials were all identified as necessary to consider, although their specific contribution to prognosis was subject to diverse opinions (Table 4).

**Table 4: The Practice of Neurological Prognosis – Tools and Investigation Used in Prognostication, Reflections on What is Most Important for Physicians.**

| **The reliability and usability of clinical examination is disputed.** |
|---|
| "The clinical exam is useless… I pay no attention to a clinical exam. I'm being a bit hyperbolic there but the reality is that unless you have a baby who is brain dead, the neurological exam has very limited value." (P6)<br><br>"Honestly I still believe in 2013 that the only truly reliable measure is that of clinical examination." (P12) |
| **If the clinical examination is used for prognostication, the evolution is essential.** |
| "I guess the first tool that I think is helpful is time. So, time. So, the first week, first 14 days." (P4)<br><br>"The first exam [is] helpful, the exam three or four days later is even more helpful, in terms of being able to prognosticate better…" (P9)<br><br>"The best thing to do is to examine the child a few days in a row to see the evolution. I think it informs you a bit more on the prognosis." (P10) |

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| **EEG is generally only helpful at the extremes.** |
| "If the EEG shows a profound burst suppression pattern and shows no evidence of recovery, that I can hang my hat on." (P12) |
| **Evoked-potentials are often used, but generally felt to be unreliable.** |
| "So we usually MRI, EEG and evoked potentials, but we usually the potentials are not reliable." (P10)<br><br>"I think the clinical examination, evoked potentials and MRI are probably the three most important, equally important, for prognostication." (P11) |
| **MRI is central and indispensable role in prognostication.** |
| "I think now with all the studies on the MRI I think it's important to have an MRI done before you do the prognosis." (P10) |
| **Investigations should always be assessed critically, in relation to their individual limitations and the overall clinical picture.** |
| "I find [clinical examination and investigations] all moderately useful, they all have their pitfalls and their advantages. I think each has the potential to give you something useful and then you try to mesh them all together and interpret based upon the best available evidence, with sort of a critical eye to recognizing their limitations. Recognizing that a normal MRI early doesn't mean there's not a horrible injury and that a terribly low blood gas doesn't absolutely mean they're gonna have a big brain injury. So I guess recognizing the limitations is probably most important." (P8) |

With regards to parents, participants emphasized that what matters most is communication with the physicians and health care team. That said, when considering the particular investigations, participants felt that the clinical examination and MRI were the most important and perhaps useful investigation for parents. Multiple references were made to the importance of the visual aspect of MRI and the ability of the parents to see injury. However, participants warned about the importance attributed to MRIs, questioning whether this was in fact secondary to the influence of physicians making comments about the power or absoluteness of the MRI. It was

stressed that physicians need to introduce the MRI to parents in a complete manner, meaning describing both its strengths and limitations (Table 5).

**Table 5: The Practice of Neurological Prognosis- Tools and Investigation Used in Prognostication, Reflections on what is Most Important for Parents.**

| **The central importance of communication.** |
|---|
| "I think that the most important thing is what they hear from the health care providers." (P2) |
| **For parents 'seeing is believing,' so those things they can appreciate with their own eyes (clinical exam, MRI and less so EEG) are the most helpful.** |
| "I think that the most important thing is what they hear from the health care providers. I think the next most important things are what they can see sort of in their own baby [clinically]. The next one would be what they can see visually, a picture of the brain. I think the EEGs are quantitatively less helpful for parents unless they're sort of at the extreme." (P2)<br><br>"I think the MRI is one parents tend to react very much to because they can often see a picture of what the injury looks like. So in that sense it shows you something that becomes very real." (P3) |
| **Overall, MRI is often the most important investigation for parents.** |
| "Usually they like to know what's in the brain [MRI]." (P1)<br><br>"I think intuitively in my experience parents think an MRI carries perhaps some of the best information because it's a big deal and it's a fancy picture and it's, you know, what did the MRI show, what did the MRI show? So I think it rises to the top because they don't really understand what a blood gas is." (P8)<br><br>"It depends on the family of course, but the MRI is most important… because it shows them the brain, and for the family it's something that's a little bit more obvious." (P10) |

| |
|---|
| "I think probably MRI is most important to them beyond what they can see in front of them, because it's probably the only test they understand or have a concept of." (P11) |
| **It is important that physicians introduce the MRI to parents in an honest manner, describing both its strengths and limitations.** |
| "We may bias them into thinking that [MRI is most important]; perhaps, in the way we communicate information. But the MRI certainly has an aura of prediction that's probably very powerful. So, that when you see the nice picture, everybody, including the physicians, tend to be reassured. I'll often tell the parents that it only gives a picture, so you see how the brain looks. It's like looking at a picture of a person. You don't really know how the person is and what their personality is and how they function. It gives you an idea of how the structures are, but you don't necessarily know how the structures are going to function. But I do think the MRI has clearly a very great power. It's the magic wand of neurology." (P4)<br><br>"I think the MRI [is most important]… because they say we say we can see the brain injury. So [parents] always wait for this one… because we also say, oh wait for the brain MRI. So maybe we are influencing them, because they wait these ten days for the MRI and then they all say 'so what did you see?" (P5) |

**Discussion**

Our study identified, based on semi-structured interviews with neonatologists and pediatric neurologists, that neurological prognosis is fundamental to QOL predictions and considerations of best interest for neonates with HIE. This is consistent with a similar finding with respect to the importance of neurological prognosis in the adult literature.[30] Despite there being significant practice challenges, our study suggests that neurological prognosis remains essential in medical decision-making.[31-35] Still there continues to be significant practice variability with no one clear biomarker for prognosis in HIE.[13,36] Our study revealed the presence of considerable variability in the importance physicians placed on clinical examination and other ancillary studies (for example, EEG). Although this is an interesting finding worth further consideration and focus in

future research, we have elected to focus our discussion on MRI, which is undoubtedly a key biomarker for physicians.[13.36] Furthermore, our results suggest that MRI is presented to parents with a greater degree of certainty than actually exists, as found in a companion quantitative study.[13]

We discuss the implications of our findings with regards to; 1) physicians' focus on neurological function for evaluating QOL and its influence on best interests; and 2) the rhetorical use of MRI with parents and its congruence with current evidence given the ongoing discussions about the role of MRI.

***Physician focus on neurological function for predicting and evaluating QOL, and its influence on best interest***

Generally we found evidence that determinations of QOL are central to the goals of prognostication, and play a pivotal role in determining best interest thus influencing medical decision making.

QOL is a complex notion and may be defined in different ways to capture the ability of an individual to have meaningful functioning and achieve personal fulfillment in their life.[37] In the neonatal HIE context, neonatologists have reported being uncomfortable making judgments about QOL because poor neurological outcome does not always guarantee poor QOL.[26] Further complicating the matter, parents and families may differ both in their judgments about QOL and ability to adapt to a disable child.[26] Despite these challenges, parents and families require and are reliant on physicians for information regarding prognosis, specifically on how this prognosis translates into a predicted QOL. Unfortunately, the literature on QOL predictions and QOL assessment in neonatal HIE to support this need is sparse. From the broader literature, we know that predictions of QOL given by physicians are generally not in keeping with the true experience of caregivers and/or patients.[31-33, 38] In neurological disease, the pediatric and adult literature reveals that physicians are poor at predicting QOL, often by focusing primarily on physical and motor manifestations.[31, 39-42] This is not to say that the intellectual impairments are not considered, Wilkinson (2010) found that severe cognitive impairment combined with

physical impairment was deemed worse than physical impairment alone.[26] However, physical impairments continue to be a focus in neurological prognostication. The issue here being that motor outcomes in adolescents with cerebral palsy (a common outcome following neonatal HIE) tend to be poorly correlated to psychosocial well-being and QOL.[39] In fact the literature in cerebral palsy suggests that QOL is less related to the physical motor outcomes and more related to individuals interest and their opportunities to engage in those preference activities in social and peer settings.[40]

Furthermore, the literature confirms our finding that prognosis and predictions of QOL are used to determine a patient's best interest and, therefore, affect significantly medical decision-making.[31-35] Perron et al. (2002) looked at the effect of QOL evaluations on a group of adults with critical illness and showed that QOL influenced 70% of resuscitation orders.[32] This study again exposed that the majority of physicians underestimate the QOL that patients actually experienced.[32] A similar finding was reported in a study involving young children with spinal muscular atrophy type 1, a degenerative neuromuscular disease.[31] This study found that not only did physicians underestimate the child's QOL as compared to their caregivers, but this determination of QOL also influenced decisions in medical management, specifically with regards to ventilator support.[31]

Our results demonstrate a clear preference towards predicted neurological deficits as determinate of future QOL. Given the poor correlation between physician and patient evaluation of QOL previously documented in several areas of medicine, [31-32, 38] this preference could be reinterpreted as a potential source of physician bias toward neurological and motor outcomes that is important to recognize. This sort of bias influencing medical decision-making has been previously suggested in the literature. [31-35] Our study again demonstrates that physicians' predictions about QOL directly inform their perceptions about best interests and, thus, can affect medical decision-making. This association between QOL and best interests needs to be questioned, as there may indeed be hidden implications and consequences. Specifically, this focus on neurological and motor function as the key determinant of QOL may bring with it a lack of consideration of factors important to parents and families and an isolated focus on

developing tools that will give information about neurological function, without considering other factors influencing the clinical picture and future outcome.

***Rhetorical use of MRI (with parents) not congruent with evidence, and the risk of attachment to the image***

MRI remains central to the practice of prognostication in neonatal HIE and is a technology that is heavily relied upon by physicians and parents alike. A recent review of HIE suggested that "brain MRI is the preferred imaging choice in neonates with HIE and is a useful tool to predict long-term outcomes."[43(p399)] This review specifically highlighted the usefulness of diffusion-weighted imaging and the advancements of magnetic resonance spectroscopy.[43] However, previous work has identified variability in prognosis using MRI and in ratings about the usefulness of MRI.[13] Furthermore, there was considerable concern about the reliability of MRI interpretation.[13] Our study confirms these observations (notably the variable appreciation of the clinical examination and ancillary testing) and further highlights a concern about the presentation of MRI results to parents, suggesting that these results may be presented with a greater degree of certainty than is actually provided by MRI technology.

Several studies have suggested that MRI may have a powerful impression on the public's understanding of injury and recovery.[44-45] In the neonatal context MRI remains essential to care of neonates with HIE, although the limitations and ethical concerns are perhaps under recognized by the physicians using the tool.[26]

Joyce (2013) has previously written about the privileged position that MRI holds both in medical practice and in society, suggesting that MRI now signifies authoritative knowledge.[46] She holds that the popularization of MRI in the news media, science exhibits, and popular science "create and reinforce the belief that MRI exams provide definitive knowledge that is more precise than information provided by other methods."[46(p48)] Furthermore, MRI is often held as an entity of knowledge itself, without acknowledging all of the institutional and human factors that influence its actual functioning.[46] This gives further weight to our studies suggestion that MRI is being portrayed to have a greater degree of certainty than actually exist MRI is dependent on multiple

factors including accurate patient history and physical examination, accurate interpretation by the physicians, and institutional practice and policy that shape the quantity and quality of MRI information provided.[46] Each of these factors is affected by variability that is seldom explicitly identified during discussions of MRI, and may serve as a hidden source of uncertainty. The findings of the companion quantitative study to our qualitative investigation confirms the existence of these issues (e.g. hidden source of variability, varying institutional practices) in neonatal hypoxic ischemic encephalopathy.[13]

Our results suggest that in the context of HIE, the rhetorical use of MRI goes one step further in creating attachment to the MRI results. Participants felt that both physicians and parents are at risk of this attachment. This attachment is worrisome in that regardless of the inherent uncertainty of the MRI results, the results may influence or bias the physicians' prognostication and the parents' understanding of the overall clinical picture. In this way clinical decision-making may be influenced. One suggestion of a route forward would be the development of general points to consider when approaching patients and families regarding MRI technology for diagnosis and prognosis; for example, clearly declaring the inherent uncertainty. Similar recommendations have been put forward in the adult literature on the use of neuroimaging in disorders of consciousness.[47]

**Limitations**

This research has a few limitations, first there is a possible selection bias exists in that the participants self-selected for the semi-structured interview. We also acknowledge that the specialty physicians participating in this study had varied degrees of clinical experience and varied experience relative to the practice of prognostication in neonatal hypoxic ischemic encephalopathy. There is a limited clinical environment represented, as all centers included were tertiary care. Finally, the parents' perspective is a critical piece that is missing and needs to be specifically explored with dedicated qualitative research.

**Conclusions**

Given the important role of prognostication following HIE, we embarked on a qualitative study to explore the perspectives of physicians about prognostication in neonatal HIE, including the practice itself, its purpose, and its meaning. Consistent with the adult literature we found that prognostication is fundamental to QOL predictions and also to considerations of best interest for neonates. However, the role played by neurological and motor outcomes, for physicians involved in prognosticating, may be discrepant with the actual assessments of QOL by patients or caregivers. In addition, the crucial role attributed to MRI (and its rhetorical usage described by participants) may further bias decisions toward these outcomes. Further research should explore both the parental perspective and prospectively the real world impact of different clinical approaches and styles to prognostication for HIE.

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**Author contribution**

The interview grid was developed by Lisa Anne Rasmussen, Emily Bell and Eric Racine. The interviews were performed by Lisa Anne Rasmussen. Data was analyzed and coded by Lisa Anne Rasmussen, and reviewed by Eric Racine and Emily Bell. The manuscript was written by Lisa Anne Rasmussen, with Emily Bell and Eric Racine reviewing and contributing commentary and suggestions prior to submission.

**Declaration of Conflicting Interests**

The authors have no conflicting interest or ethical issues to report.

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**Ethical Approval**

Ethics approval through the Institut de recherches cliniques de Montréal was obtained before commencing the project. Informed consent was obtained prior to each interview by way of a written consent form.

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**Linking Statement**

The published results present data concerning physicians' perspectives on prognostication, and the next chapter presents supplementary data on the challenges of prognostication in neonatal HIE. This data was not included in the published manuscript due to the word number limitations set by various scientific journals. However, it seems fitting to present the data as part of this thesis project, to give a more complete representation of the research. The unpublished results are presented similar to the published results, with an overview of the data and major points being illustrated with examples of the qualitative statements made. Omitted words are indicated by '...' and additional words added to clarify meaning are indicated in square brackets.

## Chapter 7: Unpublished Results; Supplementary Data on the Challenges of Prognostication in Neonatal Hypoxic Ischemic Encephalopathy

Prognosticating in neonatal HIE is not an easy task, participants identified multiple challenges faced regularly throughout their practice including unreliable and evolving clinical examinations, unreliable markers, challenges with MRI, poor long-term data and hypothermia. Furthermore, participants indicated that neurological prognosis was made even more challenging given the developing nature of the neonatal brain. In the end, this speaks to the great degree of uncertainty in prognostication in neonatal HIE which stems from "an inability to be completely certain about what the future will hold for a particular child."(P7) The reality is that despite best efforts, when it comes to the neonatal brain the prognosis is often wrong; "the challenge with neurology is that… you find something, you think it's gonna take a turn for the worst, but the baby comes out very nice. Or the opposite, vice versa. So that's the challenging part."(P1) The challenges associated with prognostication in neonatal HIE can be divided into challenges with the research literature and clinical challenges (Table 3).

### Table 3: Challenges Associated with Prognostication in Neonatal HIE

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| **Part 1: Challenges with the Research Literature** |
| **Data originating from large population studies offers little certainty with regards to individual cases.** |
| "The literature [has] a lot of data which concerns the populations as a whole. But the question is always how do you translate that data to an individual patient."(P3) |
| **Part 2: Clinical Challenges** |
| **Lack of specific and sensitive prognostic markers, especially in moderate HIE.** |
| "The overall challenge is a lack of sensitive or specific prognostic markers, either clinically, imaging or otherwise. We need better prognostic markers."(P8)<br><br>"Well, the challenges that I face are that things seem quite clear from a clinical |

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| perspective when it comes to a mild encephalopathy and when it comes to a severe encephalopathy. But there is a lack of clarity, and I would argue a lack of confidence in ancillary tools to provide clarity when it comes to moderate encephalopathy."(P12) |
| **The clinical examination evolves over time, thus early assessment is limited.** |
| "The [clinical examination] can look different from one day to the next."(P11) |
| **Clinical examination is often limited or difficult to interpret due to sedative medications.** |
| "By the time [neurology] is called to examine [the babies] are already cooled, intubated, and sedated. So I think the challenge is to be able to perform prognosis based on physical examination, because it's unreliable."(P10) |
| **Challenges identified with MRI included uncertainty about the best timing for MRIs, difficulty obtaining MRIs, and discrepant interpretation.** |
| "[The timing and number of scans] That's a moving target. Well, as you know, we used to have a protocol in the first three days, and then at ten days, and this is being renegotiated." (P4)<br><br>"Well not surprisingly since MRI interpretation is essentially qualitative, not quantitative. Some measures are quantitative. There will be differences in opinion, sometimes the differences are subtle shades of grey, and sometimes the differences unfortunately can be more substantial."(P7)<br><br>"The first MRI depends on whether you're you know born on Saturday of a long weekend or not."(P9) |
| **Hypothermia affects clinical examination and MRI, making both less reliable.** |
| "The introduction of body cooling made the prognosis a moving target."(P4)<br><br>"If anything I would say because of cooling which has changed our clinical assessment and it also seems to be changing the prognosis, I think we probably get more uncertainty now than we did, you know two years ago. I can tell someone that I think their baby's gonna do well, it's harder now to tell people that I think their baby's gonna do very poorly."(P9) |

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| **Increasing reliance on MRI is not ideal, as it still has many challenges associated with it.** |
| "I think what's one of the biggest issues, is that the MRI is a tool, but it doesn't supplant clinical assessment and reasoning … And that we have prognosticated for many years without the latest MRI and we can still do that… it's just another piece of the puzzle, but it's not 'Well I can't say anything until I get the MRI' and sometimes we get that particularly from our much more junior [staff]."(P9) |
| **Neurodevelopment poses a unique challenge for prognostication in newborns.** |
| "To assess the function of an organ that's still developing is very difficult… And I think we've moved from being very dogmatic… to now being more nuanced and maybe recognizing that we know even less that we thought we knew."(P4) |
| **Neurological prognosis is more than predicting injury; the importance is predicting future function, which is even more challenging.** |
| "Between now and when that final outcome is assessed, so school age or whenever it is, the brain is going to do a bunch of developing. It's going to engage some of its internal mechanisms and plasticity and so on and so forth. But how it does that and how that translates in function is I think a very wide target to try to hit."(P12) |
| **Reliable prognostic information is often too late for time-sensitive decisions regarding transition to palliative care. References made to the concept of "window of opportunity."** |
| "I wish all of our test were their best in the first 12 hours so we could make accurate prognostication early before doing a lot of things. Right now if we're not sure for days and days the babies tend to recover basic functions and sometimes in retrospect you think maybe it would have been better if they didn't survive, you know, the window of decision making was so long and it takes so long to make decisions, sometimes that's not a good thing."(P8)<br><br>"…the second [exam] three or four days later is even more helpful, in terms of being able to prognosticate better, but again you often miss that window to withdraw life-supporting therapies."(P9) |

## Chapter 8: Conclusions, Practical Implications for Clinical Practice, and Future Research Directions

Few phrases have more impact on parents than "I am sorry, but your newborn baby has suffered a brain injury." The power of these words is undeniable. In the face of neonatal HIE many difficult decisions need to be made, including decisions about neuro-protective therapies, and the more difficult decisions surrounding life-supporting therapy and end-of-life. These decisions are never easy, but are even more challenging in situations with great prognostic uncertainty. Given that accurate prognostication in HIE continues to elude medical science "what should or should not be done" is a question, and also a decision that continues to plague health care teams and parents alike. Ultimately there will be a need for decision making in the face of uncertain prognosis, and these decisions will be amongst the most challenging of parents' lives. It is with these patients and parents in mind that further research must be done to clarify the practice of prognostication and prognosis in neonatal HIE, with the aim of reducing uncertainty and improving clinical care.

The aim of this thesis is to explore what is known about the practice of prognostication in the broader medical literature, as well as the more focused lens of neonatal HIE. To better understand the current practice of prognostication, and the inherent challenges is essential to humanizing care. This thesis is developed out of a national qualitative study aimed at surveying the perspectives of physicians about prognostication in neonatal HIE, including the practice itself, its purpose, and its meaning.

The published manuscript considers the practice of prognostication and revels several themes. First, the intent of prognostication varies between physicians and parents. Our research participants suggested that physicians aim to construct the most truthful estimation of the possible range of outcomes for a particular child, where as parents are more focused on the specifics, such as walking, talking, and school. Though, other parents are focused on broader questions such as happiness and comfort. Overall, participants suggested that parents wish to avoid uncertainty. This particular theme is consistent with the findings of Wilkinson (2010), who also reported that parents sought specifics, whereas physicians aimed to provide a range of

possible outcomes (213). Secondly, the importance of neurological prognosis is also highlighted as a main theme, and the published manuscript explores the relation between neurological prognosis and QOL. Consistent with the wider literature, prognostication is fundamental to QOL predictions, and also to considerations of best interest for neonates. However, there is considerable subjectivity in the assessment of QOL, due in part to the inherent biases held by both physician and parents. There are considerable shortcomings of equating neurodevelopmental impairments *w*ith QOL. For example, the role played by neurological and motor outcomes, for physicians involved in prognosticating, may be discrepant with the actual assessments of QOL by patients or caregivers. Lastly, the research publication explores the practice of neurological prognosis, considering the tools and investigation used in prognostication. There is significant variability in the current practice of prognostication Canada, although MRI is held with high value. Furthermore, parents value tools and investigations they can see, such as clinical examination and MRI. The published manuscript highlights the pronounced position attributed to MRI, and raised the concern that the rhetorical use of MRI (with parents) is not congruent with evidence. Thus, there is considerable risk of attachment to the image, which may create bias toward these results.

The unpublished results included as supplementary data in this thesis further describes the challenges associated with prognostication in neonatal HIE. These challenges are divided into those related to the interpretation of the research literature and those faced in clinical practice. Many of the challenges raised by the participants support those extrapolated from the broader neonatal HIE literature in Chapter 4. For example, participants cite the difficulty of using population data to inform prognosis in individual cases. The lack of a specific biomarker, and challenges related to using specific tools and investigations (clinical examination and MRI) are also highlighted. Furthermore, despite a research literature that is increasingly neutral on the effects of hypothermia on prognostication in neonatal HIE, there was considerable concern raised by the participants regarding its effect on the clinical examination and MRI. These unpublished results also hint to an increasing reliance on MRI, and this being a major challenge given the many uncertainties still associated with the use and interpretation of MRI. Perhaps more interesting, is the suggestions that reliable prognostic information is often too late for time-sensitive decisions regarding transition to palliative care. Here the participants' mention the

concept of "window of opportunity," in reference to end-of-life decision-making, a concept that has been written about previously by Wilkinson (2010, 2011) (213, 224). Exploring this concept further is outside of focus of this thesis, but suggests an important focus for future research.

Given the important role of prognostication following HIE, we embarked on a qualitative study to explore the perspectives of physicians about prognostication in neonatal HIE. Although further research and clarification is needed (particularly from the perspective of parents), this research can propose some practical changes for the improvement of clinical care. First and foremost, physicians must be attentive to the limitations of prognostication. In part by acknowledging their own biases and how these biases might affect their practice. Deeply held beliefs, assumptions, and values may all meaningfully affect the determination of prognosis and may ultimately determine how that prognosis is communicated to parents. In this light, it is important for physicians to approach prognostication with humility, being open to uncertainty and allowing for the varied needs of the parents when it comes to communication and decision-making. Second, physicians must reevaluate the importance attributed to neurological prognostication and it's relation to QOL predictions and considerations of best interest for neonates. Third, physicians must remain aware of the limitations of MRI for prognostication in neonatal HIE, through remaining up-to-date on the current literature. Physicians (and the wider health care team) should also be reflective about how they present MRI and the information it provides to parents, avoiding the impulse to present it as the definitive tool for prognosticating in neonatal HIE. Finally, and perhaps most importantly, physicians should remain open to creating conversation and exploring different perspectives on prognostication in neonatal HIE. As it is through unified and collegial focus on this important topic, that we will be able to improve care for future generations. This speaks to the need for further research to explore both the parental perspective, and prospectively the real world impact of different clinical approaches and styles to prognostication for HIE. Attention should be focused on communication and decision-making, allowing input from parents to guide clinical practice.

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