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ARTICLE

The complexity of physicians' understanding and management of prognostic uncertainty in neonatal hypoxic-ischemic encephalopathy

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Abstract

Objective Prognosis of Hypoxic-Ischemic Encephalopathy (HIE) remains challenging and uncertain. This paper investigates how physicians understand and address the ethical challenges of prognostic uncertainty in the case of neonatal HIE, contextualized within the social science literature.

Study design Semi-structured interviews were conducted with 12 Canadian neurologists and neonatologists, addressing their perspectives and clinical experiences concerning neonatal HIE prognostication. Interviews were analyzed using thematic content analysis.

Results Participants unanimously recognized uncertainty in their prognostication. They identified several sources contributing to uncertainty in HIE prognostication, including etiology and underlying pathophysiologic mechanisms, statistical limitations, variable clinical data, the dynamic process of neurodevelopment, or the impact of hypothermia treatment. Unlike in some other literature, some physicians in this study talked about ways to render uncertainty explicit rather than hide it.

Conclusion Results from this study support the call for recognition of the ubiquitous uncertainty surrounding this act in medical education and training.

Introduction

Prognosis is an inherently uncertain process and is especially difficult in the context of neonatal hypoxic-ischemic encephalopathy (HIE). This paper draws on a qualitative interview study and social science literature to investigate how physicians understand and address prognostic uncertainty around neonatal HIE. It reports on the experiences of uncertainty of neonatologists and pediatric neurologists regarding: (1) the balance of certainty and uncertainty; (2) specific sources of uncertainty in prognostication; and (3) tensions caused by uncertainty. Our results highlight the ways in which physicians explicitly engage with uncertainty and doubt.

Uncertainty of prognostication is an important topic within neonatal and perinatal medicine [1, 2], largely with respect to communication about uncertainty [2–4]. While uncertainty affects all aspects of medicine [5], it is perhaps most prominent and troubling in prognostication [6, 7]. Prognostication is fraught with inherent difficulties [8–10]. Deciding what to communicate can be difficult due to physicians' feelings of anxiety and dread [11], leading to reluctance to even discuss prognosis [5, 12].

Prognostic uncertainty stems from a number of issues within research on the identification of prognostic factors and their relationship to particular outcomes, including limited sample sizes, lack of testing in heterogeneous clinical settings, and extrapolating individual outcomes from

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population-based data [13, 14]. Sources of uncertainty arise from these limitations of evidence-based medicine which can impact patients [6], physicians [5], and the patient-physician relationship [15, 16], especially communication. Physicians are faced with two types of challenges when conveying uncertainty in their communication with patients. The first is understanding the fundamental stochastic uncertainty about the probability of a stated prognosis (e.g., having a survival probability of 50% does not reflect if a particular individual patient will either survive or die) [7, 17]. The second is the lack of reliability, credibility, and adequacy of the conveyed risk estimate information [17]. The hesitancy to communicate prognostic information may also arise from the negative psychological effect it could have on the patient [17].

Prognostication is particularly challenging in the case of neonatal HIE [2], the most frequent cause of neonatal encephalopathy. Uncertainty in prognostication for HIE is a major clinical and ethical challenge due to the lack of a universally accepted definition [14], variation in terminology [18], and prognostic tests that are only helpful in extreme, not moderate, cases [19]. Newborns affected by HIE can have serious long-term neurologic impairments such as cerebral palsy, severe developmental delay or an inability to feed or breathe on their own [20]. Functional autonomy life expectancy can be substantially impacted by HIE, although the effect of functional impairments on quality of life are hard to predict and some children may thrive [21], making decisions for these patients particularly high-stakes. In an exploratory qualitative 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 [22].

This uncertainty in prognosis for neonatal HIE is not only challenging to the act of prognostication itself, but also to subsequent decisions surrounding end-of-life. Providing accurate neurological prognosis is fundamental to help guide treatment plans, including neuro-protective interventions [14]. The neurological prognosis is also fundamental for informed parental counselling and decision-making [2]. Moreover, neurological prognosis is pivotal in end-of-life decision-making, especially considering that death in intensive care units is routinely preceded by the withdrawal or withholding of life-supporting treatments and is thus an intentional consequence of treatment decisions [23–25].

While the prognostic accuracy needed for critical decisions in neonatal HIE improves with time as the patient's condition evolves into a chronic state, there is a risk of delaying decision-making in order to attain more certainty in prognostication [26]. In this regard, the prognosis of neonatal HIE is often constrained by time pressures, a situation described by Wilkinson as "the window of opportunity", the clinical conundrum where there is limited time to withdraw artificial respiratory life support to allow death before a HIE newborn becomes no longer respirator-dependent and able to breathe on their own, and therefore survive [27].

Parallel to the literature on prognostic uncertainty, the sociology of medicine has also focused heavily on uncertainty broadly, specifically how physicians learn to address, cope with, or manage it [4, 28]. Although evidence-based medicine is often presumed to reduce uncertainty [29]; social science literature reveals that such new technologies and practices rather just change its focus, often raising new forms of uncertainty [4, 30, 31]. While uncertainty is often described as a threat to be managed, early scholars in the sociology of medicine challenged this notion [32]. Some physicians focus on learning to embrace uncertainty, rather than hide from it [30]. There are calls from within the medical community to move towards a greater tolerance of clinical uncertainty [33] and even highlighting the potential of uncertainty to better inform decision-making [34]. In these ways, literature about and experiences with uncertainty are varied and worth ongoing detailed investigation.

For these reasons, prognostication in the context of HIE is interesting to explore on the topic of physician uncertainty because of its practical importance and its ability to feed back to the more general literature about the social, clinical, and bioethical implications of prognostication in this context [22]. The objective of this study was therefore to understand physicians' experiences with prognostication in the context of HIE. This article presents interview data on the theme of uncertainty.

Participants and methods

This semi-structured interview project was one component of a mixed-methods study conducted at the Institut de recherches cliniques de Montréal from August to December 2013. A vignette-based survey investigated the perspectives of Canadian neonatologists and pediatric neurologists regarding the contribution and role of magnetic resonance imaging (MRI) in prognostication for neonatal HIE. Results of this study have been published elsewhere [19]. Participants in this broader study were invited to take part in a follow-up 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. Some results from this interview-based study have been published elsewhere [31]. The current article presents new data and analyses focused specifically on the theme of uncertainty.

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 and conversation with the interviewer (LAR).

Prospective participants in the categories of 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. Participants willing to take part in the semi-structured interviews identified themselves in the initial vignette-based survey study. Following principles of qualitative research, the sample size for the semi-structured interviews was determined by the principle of theoretical saturation, meaning interviews were continued until there were no new ideas or commentary provided, at which point recruitment was closed [35, 36].

A single interviewer (LAR) performed all the interviews either in-person or over the phone. Interviews were conducted in English, although some participants were bilingual French–English speakers. 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) as a biomarker in neonatal HIE; and (3) research and developmental of MRI biomarkers for prognostication in neonatal HIE.

The interviews were digitally recorded and transcribed verbatim by a third-party transcribing service. The transcriptions were then reviewed in detail by the interviewer to ensure accuracy and adjust any content errors. In this paper, omitted words are indicated by ellipses (i.e., '…') and additional words added to clarify meaning are indicated in square brackets (i.e., [additional word]). The research team examined these transcripts using the method of thematic content analysis [37]. The interviewer 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 [37]. NVivo 8 Software was used to organize codes. The coding was then reviewed by one co-author (ER) and another research team member was available to arbitrate disagreements, although none arose, and consensus was achieved. In this paper, we report data regarding uncertainty in prognostication while other data (e.g., general physician perspectives on prognostication; other data, and uncertainty, communication and decision-making) have been [19] or will be reported elsewhere.

Results

Participant characteristics and themes

Twelve participants (five neonatologists and seven pediatric neurologists, identified as P1-P12) completed semi-structured interviews. Their clinical experience ranged from <5 to >20 years. Participants came from six Canadian hospitals, all of which had therapeutic hypothermia as the standard of care for neonatal HIE. This section reports on participants' discussions of uncertainty, specifically (1) the balance of certainty and uncertainty; (2) specific sources of uncertainty in prognostication; and (3) tensions caused by uncertainty. As will be addressed in the discussion section to follow, these results demonstrate that physicians understood uncertainty as a spectrum, pointed to a range of specific sources of uncertainty, and identified processes for rendering uncertainty explicit.

The balance of uncertainty and certainty

Interview results revealed that the presence of uncertainty is common in neonatal HIE, though experience of uncertainty depends on the clinical circumstances. Participants noted that the degree of certainty in prognostication was variable, but that "the uncertainty outweighs the certainty, still" (P4). Although participants acknowledged the increase in recent certainty brought on by technologies, they nonetheless described uncertainty as an ongoing challenge. "There are still a lot of things we don't know. There is more than before, but you know, still, still not enough" (P5), one participant noted, highlighting the lingering sense of uncertainty despite narratives of progress.

Participants also noted uncertainty was more prominent in some situations than in others. As one participant reflected on the relationship between certainty and severity:

> Well, the challenges that I face are that things seem quite clear from a clinical 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)

This quotation highlights the variation in experiences of clarity and confidence across cases based on severity. This participant described greater certainty at the extreme ends of

severity, but more difficulty in moderate situations. Furthermore, participants mentioned that uncertainty was perhaps most evident with the subtler aspects of prognostication. One participant described these as "harder questions," explaining:

> The really important [questions], which to me is this gonna be horrible or a good chance that it won't be, I think we're slowly getting a little smarter but progress is very slow. Certainly for the much harder questions… is he going to have problems or not, what are they going to look like, is he going to be able to do this or that or, that's so complicated and we're still miles away from that kind of accurate prognostication. (P8)

Despite these prominent narratives of uncertainty, it is important to note that not all participants agreed and some stated that prognosis was more accurate than not. One participant quantified this uncertainty, explaining "I would say they're 85% of the way there. I mean, if I say to families this is what I think's gonna happen. I have an 85% chance of being right" (P6).

Specific sources of uncertainty in prognostication

Against this backdrop of a general feeling of uncertainty, the physicians in this study identified several factors as sources of uncertainty. They reported finding limitations in knowing the etiology and underlying mechanism of HIE, limited usability of the long-term population data, poor acute medical information, variability of the medical information over time, the dynamic process of neurodevelopment, and hypothermia treatment. The following paragraphs address each of these sources in turn.

As described in the introduction, the etiology and underlying mechanisms of HIE are complex and incompletely understood. Lack of knowledge on etiology and underlying mechanisms also impacts communication with parents, as one professional poignantly notes: "So obviously you're facing parents who are asking the question why – why did this happen?" (P1)

Participants also noted the limited usability of long-term population data. Some physicians described this in terms of evidence and the translation of study data into clinical practice, as in the participant who explained; "We can provide evidence for populations, we can not provide evidence for an individual baby. That's where we have the difficulty, is trying to make the link between the two." (P2) Others talked about the difference in tools used for research compared to tools used for prognostication, asserting; "I would say there's still a great deal of uncertainty as far as prognostication. Again, especially most of the tools we have for prognostication are useful in a population basis but for the individual patient, I mean, let's say nothing is that exact." (P3)

In addition to concerns about population-level uncertainty, physicians also spoke of several sources of uncertainty with respect to clinical interactions with specific patients. Poor current clinical information represented a source of uncertainty. Participants expressed difficulty prognosticating based on the clinical data. "So the challenge really," one participant explains, "is that all of the usual data that we collect from clinical examination and just about all laboratory data that we collect have a relatively poor correlation with long term outcome." (P6) This difficulty was also addressed by P12, quoted above, in the case of moderate encephalopathy, who referenced "a lack of confidence in ancillary tools." The data from clinical tools and examinations served to further uncertainty through its poor utility in prognostication.

Similarly, physicians acknowledged the variation in medical information over time, and the difficulties this posed in moving from test results to prognostication. As one physician noted, "So I guess the biggest challenge is change over time, that the kids can look different from 1 day to the next. And their EEGs can look different from 1 day to the next. And early MRI signs can look different on follow up imaging." (P11) Therefore, the uncertainty present in interpreting clinical data applied not only to the relationship between present data and long-term outcomes, but also the relationship between individual points of data.

This concern about change of clinical status over time applies not only to test results, but to human development more broadly. Neurodevelopment is complex and multifaceted, particularly in infancy when there is so much development left to unfold [38]. Because of this, one participant explained, "I think that we can speak in general terms but our precision is not very good. We are better with our precision when things are very bad. We're less able to say that even when things look good, to be sure that they're going to continue to be good because of course, babies have got a tremendous amount of neurological development to occur." (P2) The plasticity of human development provides great opportunity, but that opportunity occurs with uncertainty. In this statement about a good prognosis, the participant frames looming uncertainty in pessimistic terms – as the inability to be sure that things will continue to go well.

Treatment also creates a source of uncertainty. Physicians who used hypothermia treatment, described above, reported both optimism and uncertainty about its impact on prognosis. As one participant summarized, "The introduction of body cooling makes the prognosis a moving target." (P4) Another participant elaborated, explaining "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) In contrast to participant P2 in the preceding paragraph, this participant did link uncertainty with optimism by explaining that although there is more uncertainty now, it is because it is not as certain that a baby will do poorly. Therefore, uncertainty is not always negative.

Tensions caused by uncertainty

Uncertainty leads to various tensions. Tensions specifically referenced by the participants included difficulties in communicating with parents and medical decision-making.

Increasing uncertainty creates challenges when communicating with parents about prognosis. One participant commented: "As the degree of uncertainty becomes wider it becomes more challenging, it is hard to tell parents that it might be fine or they might have lots of problems. That's a pretty hard thing to say." (P8) The degree of uncertainty may change the way parents are counseled and how their viewpoint is considered. One participant reflected:

> I mean, if the prognosis is quite uncertain probably the tendency would be to treat, to continue care and to counsel accordingly with parents. Alternatively, if their prognosis is quite uncertain but there's a high risk of having a severe problem in the long term, then the medical team would much more likely defer and support the parents' decision rather than ever taking an aggressive approach against them. (P3)

Within this process, physicians argued that identifying the uncertainty is extremely important for communication. For example, one participant asserted,

> I think so long as we recognize uncertainty and it's not hidden under the table or is hidden away and you actually recognize it explicitly and you say this is part of the equation, then it's perfectly acceptable to use an uncertain prognostication in trying to formulate your decision-making. But it has to be explicitly recognized. (P7)

Beyond communication with parents and supporting parental decision-making, uncertainty of prognosis impacts the physicians' decision-making in treatment. The degree of uncertainty alters medical decision-making, in the sense that "the more certain we are about a severe outcome the more definitive impact that will have on medical decision-making." (P8) Moreover, the weight of uncertainty depends on the particular medical decision being contemplated, and the input already provided by parents. One participant illustrated the importance of context, saying,

> Oh, I mean if the family's decided and says oh we don't wanna do anything heroic, then obviously you know even uncertain prognosis is huge terms of [decisions for] resuscitation, dialysis, things like that. Most of the time if the family's not at that stage yet, I don't think uncertain prognosis contributes [to medical decision-making]. (P9)

Nonetheless, physicians frequently put forward that when in doubt, the best course of action is to treat. One explained: "So I think that for most physicians, we would err on the side of doing too much and keep treating a baby longer because the baby has a small chance of being normal. We don't want to stop treatment and have a normal baby die." (P2) Another framed this explicitly as an ethical choice, asserting: "So if we're uncertain [about the prognosis] the ethical stance on that is to give the patient the benefit of the doubt." (P6) This participant elaborated that erring on the side of caution – not giving the patient the benefit of the doubt – carries the risk of a devastating outcome.

> Give the patient the benefit of the doubt, and let the patient declare him/herself. And, you know, there are times when you live to regret that. But that's, I can't see another way of doing that. I would have real difficulty going the other way. In other words, I'm not sure, it looks bad so let's, you know, withdraw ventilation. Or withdraw feeding or whatever. I personally would have difficulty with that. (P6)

Discussion

High-stakes decision regarding life and death in neonatal HIE rely on prognostication. Predictions of adverse neurodevelopmental outcomes and projections of future quality of life inform discussions regarding life-sustaining interventions [39]. This study of neonatologists and pediatric neurologists demonstrates how they are confronted with uncertainty when assessing the prognosis of infants with neonatal HIE. The ways these physicians talked about uncertainty revealed that current prognostic, diagnostic, and treatment tools do not eliminate uncertainty. Rather, they

are changing the tenor of the reflection on ethics and uncertainty. This is in line with previous findings on the role of evidence-based medicine in impacting clinical uncertainty [33] and brings support to recent calls for the full integration of prognostic uncertainty in neonatal clinical practices [40].

While uncertainty was unanimously recognized by every physician, the extent and weight of this uncertainty on their prognostication ability varied. Physicians in this study noted that their certainty levels could be influenced by clinical factors such as the severity of the clinical case, or what outcome was predicted, while some saw the recent advances in technologies and knowledge as factors alleviating some types of uncertainty. Other contributing factors included etiology and underlying pathophysiologic mechanisms of HIE, statistical limitations, limited clinical data and the variability of these data, the dynamic process of neurodevelopment and the impact of hypothermia treatment. Physicians also described the challenge of biological variability [41], where every patient is unique in its response to an illness. Specific sources of uncertainty in prognostication have also been described in previous studies [14]. Physicians can be challenged by test variability [31], errors in interpretation (cognitive biases) of those tests [5], an imperfect mastery of knowledge [6], as well as the influence of medical organization, local practice environment, and the physicians' own values [41]. As reported by our participants, there are known limitations in the application of prognostic indices drawn from population-level data to an individual case [14], the non-applicability of research data to clinical situations and challenges in the availability of timely clinical data. Prognostication of neonatal HIE poses additional challenges, such as defining the best interest for a patient population that cannot express their own wishes and opinions [27, 42], the lack of long-term outcome data to reflect recent technological advances or the limitations of clinical and imaging tools specific to HIE [39].

The results of this study are interesting within the broader study of uncertainty in medical training and practice, where the inescapability of uncertainty within medicine is repeatedly stressed. Medicine is uncertain because medical knowledge is incomplete and constantly growing, and because individual patients are unique and complex [43]. Modern medical practice, strives to be an "evidence-based medicine" that is informed by scientific research, and its results; but it is not, nor will it ever be, a straightforward application of scientific knowledge [43]. The participants in this study unpacked some of the disconnections between research and practice in the context of HIE, notably the limited applicability to specific individual patients of population-based research. Our results are therefore in line with previous research on physician uncertainty in the presence of evidence-based medicine which has found that new medical technologies and practices (e.g., evidence-based medicine) did not eliminate uncertainty, but rather served as "a new source of uncertainty to be managed." [30].

However, the results also indicate a more surprising finding: in contrast to much of the previous literature [4, 28, 44, 45], the physicians in this study did not necessarily seek to conceal their uncertainty; rather, they discussed strategies for rendering it more explicit. The sociology of medical education and practice has stressed the importance of physicians coping with uncertainty, and some studies have reported that such strategies lead physicians to "disregard and avoid uncertainty," developing instead and attitude of "overcertainty" with negative consequences for patients [44]. Physician participants in this study took the opposite approach: they in fact discussed the ways in which they faced uncertainty head on and discussed it with their patients.

The physicians interviewed in this study reflected on their own practice and the impact of the underlying uncertainty dominating it. They reported the consequences generated by the ubiquitous uncertainty in HIE: uncertainty led to more complex communication with parents and impacted medical decision-making. Although uncertainty can potentially be useful in clinical decision-making [29], Wilkinson reported on the negative effect of uncertainty affecting neonatologists' ability to make decisions regarding the withdrawal of life support in HIE [22]. Uncertainty has also been associated with a variability in practice patterns [5], decreased patient satisfaction [6], and poor exchange of information [15, 16]. It has even used to exclude parents from decisions about continuing treatment [46].

This finding prompts broader discussion about the way uncertainty is approached in medical literature and education. While uncertainty is inherent to clinical practice, the deep-rooted culture of medicine struggles to acknowledge and embrace it [33]. Physicians are expected to provide answers and can face a harsh rhetoric of shame and possibly blame when their prognostications, inherently uncertain, are wrong [47]. While prognostication has improved precision with the advancement of diagnostic tools and technologies, the data remain imperfect and uncertainty omnipresent. The development of better tools for prognostication is a laudable goal, but evidence in the study of physician uncertainty reveals that it likely will not eliminate uncertainty; medical literature and education must therefore focus on how to address the unavoidable uncertainties of prognostication. Neonatologists have described facing unrealistic parental expectations regarding the prediction of future outcomes [22] and pediatric intensive care unit physicians report having difficulties addressing parental questions about prognostic certainty [48]. The pressures on physicians to "know it all" may

create a sense of vulnerability from the fear of projecting lack of knowledge. Physicians can face a harsh rhetoric of shame and possibly blame when their prognostications, inherently uncertain, are wrong [47]. This makes uncertainty in prognostication a threat [33] that has been found to lead to work-related stress [49]. These findings spark the call for a shift towards more tolerance of uncertainty [33]. In this sense, our results echo the counter-narrative apparent in some studies of physicians, who describe transitioning towards recognition of uncertainty in their practice across all specialties [22, 32, 48] and of decision-making models that encourage increasing uncertainty in clinical discussions [34].

Limitations

This study used a qualitative research design comprised of in-depth semi-structured interviews. This approach has the strength to explore thoroughly a topic and gain rich insight into the lived experiences of practitioners. However, it also has limits with respect to generalizability (the specific population of neonatologists and neurologists in Canada, all working in tertiary care centers, may not reflect all practice settings) and the ability to conduct intra-sample comparisons. Generalizability is further limited by the fact that participants are self-selected to participate, and it is unknown what differences there may be between physicians who chose to participate and those who did not. Studies with larger samples could investigate if these finding are reproducible in all physicians treating HIE patients and could identify variation in physicians' experiences and perspectives.

Conclusion

Uncertainty in clinical practice is a longstanding area of interest in neonatal-perinatal medicine, particularly with respect to prognostication. We examined the nature and role of prognostic uncertainty with respect to a difficult but ever important condition of neonatal encephalopathy caused by hypoxic-ischemic brain injury. We found that physicians readily acknowledged the existence of uncertainty in prognostication and this confirms literature suggesting the existence of pervasive uncertainty in medical practice as well as efforts by physicians to actively embrace and work with it. Uncertainty arises from many factors and cannot be excluded from the practice of prognostication in cases of neonatal HIE. Prognostication has a pivotal influence in the outcome of patients with HIE. Recognition of the ubiquitous uncertainty surrounding this act of prediction is vital and should be emphasized in medical education and training [33]. Further research is warranted to understand what other factors, such as personal and contextual factors may influence the act of prognostication and physician attitudes towards its certainty.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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