Review Article

Withdrawal and withholding of life sustaining treatment (WWLST): an under recognised factor in the morbidity or mortality of periviable infants?—a narrative review

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Background and Objective: The morbidity and mortality of infants born extremely preterm varies substantially across networks, within countries and throughout the globe. Most of the literature tends to focus on the management at birth and choices around active resuscitation of extremely preterm infants. Withdrawal and withholding of life sustaining treatment (WWLST) is an important and central process in the neonatal intensive care unit (NICU) and practices vary substantially. As such, our objective in this review was to explore whether end of life decisions also contribute to variations in the morbidity and mortality of periviable infants.

Methods: This narrative literature review is based on studies from the last 15 years found using several searches of medical databases (OVID Medline, Scopus and Cochrane Systematic Reviews) performed between March 2021 and December 2023.

Key Content and Findings: Just as outcomes in periviable infants vary, the rates of and processes behind WWLST differ in the periviable population. Variation increases as gestational age decreases. Parental involvement is crucial to share decision making but the circumstances and rates of parental involvement differ. Strict guidelines in end-of-life care may not be appropriate, however there is a need for more targeted guidance for periviable infants as a specific population. The current literature available relating to periviable infants or WWLST is minimal, with many datasets rapidly becoming outdated.

Conclusions: Further research is needed to establish the role of WWLST in variation of periviable infants' outcomes. The unification of data, acquisition of more recent datasets and inclusion of variables relating to end-of-life decisions in data collection will aid in this process.

Keywords: Withdrawal and withholding of life sustaining treatment (WWLST); periviable infants; extremely preterm infants; variation in outcomes; neonatal intensive care unit (NICU)

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Introduction

Background and rationale

Rates of preterm birth have increased in recent decades (1). Infants born extremely preterm are at a disadvantage compared to their term peers in mortality, in-hospital morbidities and long term health (2). These effects are particularly noted at the limits of viability, however outcomes are improving (3,4). Despite only 5% of preterm births being <28 weeks (extremely preterm) (5), these infants have been reported to contribute to up to half of the total infant mortality rate (6). This review focuses on periviable infants, a high-risk subset of extremely premature infants. Periviable birth is defined as those births occurring from gestational ages 20+0 to 25+6 weeks (7-9). However, over the last decade with improving technology and management of periviable infants there has been a shift to increased resuscitation in younger gestations, creating the "grey zone" at 22 to 24 weeks' gestational age (9-11). There has been increased focus on periviable infants in recent years with improving capability to resuscitate infants and keep them alive at lower gestational ages.

Substantial variations in rates of active resuscitation and management in extremely preterm (and thus periviable) infants exist worldwide and within countries, networks and regions and this has significant implications on survival (7,12,13). *Table 1* highlights key studies over the last fifteen years which reported survival statistics in periviable infants in high income countries. The International Network for Evaluating Outcomes (iNeo) of very low birthweight, very premature neonates have shown substantial variations in morbidity and mortality across a large multinational cohort (36). Consistently, the variation in survival is more pronounced with decreasing gestational age (14,37). In addition to differences in survival across units, similar patterns have been found in the rates of neurodevelopmental impairment (38).

The source of this variation has been extensively investigated in the literature. Surveys of neonatal clinicians have found individual neonatologists' thresholds for resuscitation at periviability vary between and even within countries (12,13). Rysavy *et al.* (14) examined survival and neurodevelopmental outcomes infants <27 weeks and found that when controlling for confounding factors they could attribute 75% of the variation in survival without neurodevelopmental impairment to active resuscitation rates in different units. Santhakumaran *et al.* noted that regional variation in survival rates in England could not be explained by patient characteristics alone (37). Reinforcing outcome variation in those infants at the edge of viability, Alleman *et al.* found that variable centre intervention rates predicted mortality for infants <25 weeks' gestation but not those ≥25 weeks (39). Finally, Steurer *et al.* found that the difference in rates of active management could result infants being as much as 4.5 times as likely to survive in the best performing neonatal intensive care unit (NICU) compared to the worst (40). In a targeted cohort of periviable infants (22 to 25 weeks), the same patten persists—regions with higher rates active management are positively correlated with survival (41). This difference in survival between units has been likened to the magnitude of improvement in survival attributed to antenatal corticosteroids, use of surfactant (39,42) or an extra week of gestational age (43). Neurodevelopmental impairment is an outcome of significant interest in previable infants. It has been noted that survival without neurodevelopmental impairment has improved over time, however the proportion of those infants who survive with ongoing neurodevelopmental deficits has remained the same (3,42).

An increase in the presence and adoption of policies at the threshold of viability has been accompanied by improving survival (44). Active management, however, results in prolonged time to death in those infants that do not survive (15,42). While at face-value this may seem unethical, this prolongation allows a trial of life, which may facilitate survival in infants who would otherwise have been deemed too ill at birth. Subsequent decisions can then take place with the consideration of withdrawal and withholding of life sustaining treatment (WWLST) if expected prognosis remains poor.

WWLST relates to the decision to limit the escalation of (withholding) or cease (withdrawal) life sustaining practices in the NICU. In most cases, "life sustaining treatment" refers to mechanical ventilation. It may also include, but is not limited to, ionotropic support, cardiopulmonary resuscitation, nutrition, and hydration. WWLST is most often considered in infants with severe complications where death is not imminent, but neonatologists predict mortality or poor outcomes will arise (45-47).

Previous studies have attributed variability in outcomes in periviable infants to a combination of population risk, attitudes to management and resuscitation thresholds at birth (14,39) however these may not entirely explain differences in survival (48). The focus in the current literature is on the initial management phase at birth while the decisions and practices surrounding end of life in the

Table 1 Summary of published studies reporting survival of periviable infants by gestational age (3,4,9,14-35)

Study	Study type	Years of data	Survival from	Survival to	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks
Backes *et al.* 2021	Systematic review and meta-analysis	2000 to 2020	Live birth	Discharge	29%	–	–	–	–
Anderson *et al.* 2016	Retrospective cohort	2007 to 2011	Live birth	One year	6%	–	–	–	–
Rysavy *et al.* 2015	Retrospective cohort	2006 to 2011	Live birth	18 to 22 months	5.1%	–	–	–	81.4%
Sharp *et al.* 2018	Retrospective cohort	2004 to 2010	Live birth	12 months	5%	46%	77%	–	–
Myrhaug *et al.* 2019	Meta-analysis	2000 to 2017	Live birth	Variable (discharge to 6 years)	7.3%	25.7%	53.9%	74%	–
Bourke *et al.* 2019	Retrospective cohort	1983 to 2010	Live birth	25 years (NB: disability free survival)	4.1%	19.7%	42.4%	53.0%	–
Boland *et al.* 2021	Population-based cohort	2009 to 2017	Live birth actively managed	One year	0%	50%	66%	–	–
Backes *et al.* 2015	Retrospective cohort	2004 to 2013	Live birth	Discharge	–	59%	–	–	–
Bolisetty *et al.* 2015	Population-based retrospective cohort	2007 to 2011	NICU admission	Discharge	–	27%	59%	76%	–
Uccella *et al.* 2015	Retrospective cohort	2003 to 2010	All births	Discharge	–	16%	38%	74%	–
Stoll *et al.* 2015	Prospective registry cohort	2012	Live birth	Discharge	–	33%	65%	–	–
Kiechl-Kohlendorfer *et al.* 2019	Population based cohort	2011 to 2016	Live birth	Study period	–	47.1%	73.4%	84.9%	88.2%
Ancel *et al.* 2015	Prospective population based	2011	All births	Discharge	0.7%		31.2%	59.1%	75.3%
Watkins *et al.* 2020	Retrospective cohort	2006 to 2015	NICU admission	Discharge	78%		89%		–
Norman *et al.* 2019	Prospective population based	2011 to 2012	Live birth	One year			77%		
Sinclair *et al.* 2019	Retrospective population based	2000 to 2011	All births	Discharge			46%		
Younge *et al.* 2017	Prospective cohort	2000 to 2011	All births	18 to 22 months		36%		–	–
Marrs *et al.* 2016	Retrospective secondary analysis	1997 to 2004	NICU admission	18 to 22 months	–		74%		–
Shah *et al.* 2015	Retrospective cohort	2010 to 2012	NICU admission	Survived without major morbidity	71%		–	–	–
Hasselager *et al.* 2016	Retrospective cohort	2011	Live birth	Unknown		57%			–
Dawes *et al.* 2020	Retrospective cohort	2017 to 2018	Live birth	Discharge	–	–	–	–	–
Shukla *et al.* 2022	Retrospective cohort	2009 to 2016	NICU admission	Discharge	56%	–	–	–	–

Table 1 (*cotinued*)

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Study	Study type	Years of data	Survival from	Survival to	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks
Morgan *et al.* 2022	Retrospective cohort (combining EPIPAGE-2, Epicure-2, EXPRESS)	2004 to 2011	Alive at maternal admission to hospital	Discharge	–	0.2% to 11.7%	10.5% to 19.1%	32.8% to 33.2%	36.2% to 56.4%
Kulali *et al.* 2020	Retrospective cross-sectional study	2011 to 2015	Admission to the NICU	Discharge	–	7.5%	29.1%	43.5%	–
Cohen *et al.* 2021	Retrospective cohort study	2018 (data reported from 2000-2018)	Admission to NICU	Discharge	–	30.2%		–	–

This table shows variable survival statistics reported by studies over the last 15 years. Importantly, there are variable definitions of survival based on the denominator (number of infants included based on total births, live births, actively managed births, or admissions to the NICU). Most of the data spans the last two decades but not more recent years. Further, the length of assessment time also varies from discharge through to young adulthood. Survival was also not always assessed at each gestational week in these studies. Generally, survival increased with increasing gestational age. NB: the author recognises a more comprehensive list might include the recent annual reports of each neonatal research network however this was not included as these are both difficult to access and not the primary focus of the review. NICU, neonatal intensive care unit.

ensuing days to weeks remain largely unexplored. Thus, we must investigate whether WWLST might be a crucial source of outcome variation in periviable infants.

Objective

Our objective was to analyse the literature surrounding WWLST in the NICU and explore its contribution to variations in morbidity and mortality in periviable infants. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-468/rc).

Methods

OVID Medline, Scopus, and Cochrane Systematic Reviews databases were searched for articles relating to the topic. Multiple searches were conducted over a period from March 2021 to June 2023 delving into different aspects of the topic, allowing for a wide base of literature from which to draw. Other articles were sourced from scoping searches and from the references of included papers. This review includes studies in English describing end of life practices in developed countries only, as the characteristics of a periviable population in a low-resource setting might not be comparable. Studies up to fifteen years old were consulted to balance the need for data reflecting recency of practice and finding an adequate range of studies in what has previously been a sparsely published topic. Titles and abstracts were used to decide which studies might be relevant to the review. Studies relating to the use and processes behind WWLST, morbidity and mortality, ethical dilemmas, and background literature on extremely preterm infants were included. The few studies related to periviable infants alone (<26 weeks' gestation) therefore this paper includes studies with an expanded population of extremely preterm infants (up to 28 weeks) but with a focus on the periviable period. One author, I.G. independently selected the literature to include but would consult the other authors if the study's importance or relevance was unclear.

Tables 2,3 outline the search strategy in detail.

Literature review

WWLST in the NICU

Despite the best care healthcare teams in the NICU provide, some infants may not survive. WWLST is the

Table 2 Summary of search strategy

Items	Specification
Date of search	3rd March 2021 to 9th December 2023
Databases and other sources searched	OVID Medline, Scopus, and Cochrane Systematic Reviews
Search terms used	MeSH: extremely premature infant, infant mortality, perinatal mortality, mortality, morbidity, survival, survival rate, withholding treatment, palliative care
	Non-MeSH search terms included: extremely preterm infant(s), periviable, micropremie, outcome(s), variation(s), difference(s), withholding and withdrawal or life sustaining treatment, withholding, withdrawing, end of life decision making, decision(s), survival, mortality, morbidity
	See *Table 3* for example search strategy
Timeframe	March 2021 to December 2023, intermittent searches culminating in final search in June 2023, with small additions added in that latter part of 2023
Inclusion criteria	Study type: journal articles—commentaries and reviews, observational studies, interventional studies, systematic reviews, and meta-analyses. Some other reports and guidelines included
	Language: English
	Cohort: periviable or extremely preterm infants, high income countries
	Years: last 15 years
Selection process	As this was not a formal systematic review, the selection of articles was predominantly performed by I.G., with guidance provided by K.T. and C.C.R. In addition: select articles from previous scoping searchers that were relevant to the topic

Table 3 Example search—OVID Medline

Line	Search terms	Number of studies returned
Line 1	Extremely preterm infants.mp. or Infant, Extremely Premature	4,518
Line 2	periviable.mp.	210
Line 3	(Withdrawal and withholding of life sustaining treatment).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	24
Line 4	withdrawal.mp.	100,412
Line 5	Withholding Treatment/or withholding.mp.	17,381
Line 6	Mortality/or mortality.mp.	1,258,700
Line 7	Survival Rate/or Survival/or survival.mp.	1,340,123
Line 8	1 or 2	4,642
Line 9	3 or 4 or 5	115,708
Line 10	6 or 7	2,183,881
Line 11	8 and 9 and 10	32

Please note, these were not the only combination of search terms used over the course of the search period.

most common mode of death in the NICU (49-51), preceding anywhere between 38% to 82.4% of deaths (46,47,49,50,52-55). Very few studies look at the periviable period specifically but studies on general NICU populations found higher rates of WWLST in lower gestations, especially those infants 22–23 weeks (47,56). Some studies suggest that neonatologists are increasingly deciding to institute WWLST (49,57). This may be a better recognition of medical futility (49), or potentially because neonatologists are increasingly routinely resuscitating infants of lower gestational ages at birth who are at greater risk of subsequent deterioration. In most cases, withdrawal is by cessation of respiratory support (47,53). WWLST is commonly used to provide a peaceful and controlled death to avoid suffering, pain or expected poor long-term outcomes (50). The most common reasons documented by physicians for WWLST are futility of treatment in the face of limited life expectancy, poor expected neurodevelopmental outcome and to relieve suffering (50,52,54). When WWLST is the mode of death, causes of death have included extreme prematurity, neurological damage, infection, respiratory failure and congenital anomaly (49,50,52-55).

End of life decision making

Discussions about WWLST may occur throughout the NICU admission. The proportion of infants in a given cohort who have WWLST discussions ranges from 15.4% to 84% (40,50,55). Factors that have been associated with discussions about WWLST include being male, white ethnicity, <24 weeks gestation, small for gestational age, congenital malformations/syndromes, early-onset sepsis, severe brain injury and necrotising enterocolitis (46,47), which would reflect commonly recognised neonatal clinical indicators. Life sustaining treatment (LST) is also more likely to be withheld in white infants than in Black or Hispanic infants (46,48,53) and families of white infants are more likely to be approached for discussions about WWLST (46). It has been suggested that this may be due to differences in values, religious or cultural beliefs or the perceived or actual mistrust of healthcare professionals (46,47). This disparity could also be due to Black infants possibly having improved chances of survival in extremely preterm infants when compared to white infants (58,59).

Shared decision making about WWLST requires the involvement of the infant's parents. Clinicians usually raise the discussion about WWLST (83% of the time in 19 tertiary units in Canada) (50), but parents are very involved in the subsequent decisions between 86.5% and 98% of the time (49,52,55,60). This involvement has increased over the last 20 years (57). However, when an infant died on full intensive care measures and received cardiopulmonary resuscitaiton, as few as 47% of parents were involved in end of life decision making (49). This is likely the result of insufficient time to engage in end-of-life planning when imminent death presented itself.

While parents and neonatologist usually agree on when WWLST might be indicated (50), this is not always the case. A UK study found that almost half of parents who had discussed WWLST obtained a second opinion. Reasons for continuing LST after discussions about its limitation (namely non escalation of treatment, usually cardiopulmonary resuscitation, if there is deterioration on intensive care) or withdrawal were multifactorial, including non-acceptance of prognosis/diagnosis, religion, culture, personal and in some cases the reason was unknown (54). Furthermore, it has been demonstrated that parents have differing levels of acceptance towards the risk of disability after active resuscitation (61) thus it is likely similar variations exist when making the decision to undergo WWLST. However, up to three-quarters of parents eventually withdraw or limit LST after discussions about WWLST (46,54).

Outcomes after WWLST

About one-quarter (22–24%) of parents decide to continue life sustaining care following WWLST discussions (46,54). These infants are more likely to have major morbidities, neurodevelopmental impairment, re-hospitalisation and a higher mortality rate post-discharge compared to infants without WWLST discussions (46). This is possibly an indication that WWLST discussions are largely occurring in sicker infants with projected poorer outcomes.

While most infants die after WWLST, some survive. This is an eventuality that should be addressed when counselling parents about WWLST. The proportion varies; 1.2% to 21% (46,54,62). Total numbers of infants in this unique subgroup are low, making statistical comparisons difficult but outcomes seem to vary from mild long term motor, neurodevelopmental and health consequences to profound impairment in one or multiple domains. Two studies found that a majority if not all of the infants who survived after WWLST had neurodevelopmental impairment (46,63). Brecht *et al.* (64) analysed the outcomes of treatment limitation discussions in a specific cohort of

infants with clinically diagnosed brain injury. They found that of the 22 infants who survived following treatment limitation discussions, eight survivors (32%) had been infants where the decision had been made to WWLST. Three died in infancy, four of the remaining five had a degree of cerebral palsy as well as comorbidities such as epilepsy, needing a gastrostomy and hearing loss. One infant survived without apparent disability into childhood (64). In Boutillier *et al.*'s cohort, of 34 infants who survived to discharge after a WWLST decision, 24 survived to two years of age, all received ongoing subspecialty care and 14 of the infants (58%) had moderate to severe functional limitations (62). James *et al.* found that all of the five infants who survived after WWLST had three or more major in-hospital morbidities. Infants who had discussions about WWLST occur were more likely to have severe neurodevelopmental impairment than those infants who never had WWLST suggested (46). It is important to note that assessing the accuracy of the clinical judgement that led to WWLST using the outcomes of those who survive is complicated as it is difficult to separate the preceding from the proceeding factors in the outcomes of these infants. Did they have poorer outcomes because they were already very unwell, or did the act of withdrawing support worsen their prognosis if they survived? Nonetheless, it would be interesting in future research to understand whether decreased rates of WWLST are associated with poorer neurodevelopmental outcomes in survivors.

Variation in practice

Countries vary widely in thresholds and reasons for WWLST (50,65). This practice variation is unsurprisingly more prominent in lower gestational ages (46). Pignotti *et al.* was one of the earlier studies to suggest that the difference in WWLST rates between a British and French cohort of infants 22 to 25 weeks might have implications on overall survival statistics (66). Not only does variation in WWLST exist between countries, but many have noted differences even between units in the same country (46,47,50). This was particularly well documented by Dworetz *et al.* who found significant inter-unit variation in rates of WWLST between American NICUs. Notably, the infants born at the centre with the highest rate of WWLST was 4.89 times more likely than average to undergo WWLST process (47). This variation has been documented in other studies (46,54). While some of this difference may be attributable to population characteristics and acuity of the patient cohort, this is a substantial difference between units, which should be considered as a contributor to overall variation in periviable infants' outcomes.

Reasoning behind WWLST differs between countries (65). For instance, four units of similar size and acuity in the US, Canada and the Netherlands differed in reasons for WWLST, with Chicago notably not withdrawing LST for quality-of-life reasons compared to other units (53). A recent single-centre study in France on outcomes in infants post WWLST decisions found that the most common reason for withdrawal in preterm infants was high grade intraventricular haemorrhage or periventricular leukomalacia (62). Neurological injury as a result of intracranial haemorrhage is a significant differing factor in WWLST decision making. Grade IV intraventricular haemorrhage is commonly a reason for palliation in Australia, New Zealand, and Switzerland, but not so much in other countries. This has been associated with lower rates of survivors with neurodevelopmental impairment (65). In Canada, there was large variation in WWLST for severe neurological injury in preterm infants but 85% of physicians were confident about their decision (50). It would seem it is not lack of decisiveness that causes differences in decisions, but rather differences in what is believed acceptable and the ethical culture of the unit. However, as Chevallier *et al.* points out, the outcomes due to intracranial haemorrhage are often uncertain and different depending on site, laterality, and subsequent neurological symptoms. Papile grading [a radiological grading system denoting the severity of intracranial haemorrhage from I (mild) to IV (severe)] (67) alone may not be an effective prognostication tool for making decisions about withdrawal of active treatment (68).

Dworetz *et al.* suggested that several factors might be involved in the variation between units with regards to WWLST including institutional policy, geographic region, personal differences in race/ethnicity, culture, religion or spirituality and medical differences related to the population characteristics of that specific cohort of infants (47). So far, there has been limited research into the effect of each of these on the rate of WWLST or WWLST discussions. In the Netherlands, there is emphasis on quality of life in their goals of care and this may contribute to increased WWLST (13). Differences in attitudes towards decision making at the end of life have also been noted between linguistic regions of Switzerland, with German-speaking parents preferring for the family to have the final call, while French- and Italian-speakers prefer physicians to have more decision making power (69). Religion, culture, racial

bias and acceptance of diagnosis have also been cited in the literature as reasons for variation in decision making by neonatal teams (54,70,71). Personal biases might also play a role—clinicians who have children are more likely to be conservative in managing periviable infants (72). Equally, legal factors may be involved, as the Dutch adopted a more interventionalist approach after legislation supporting neonatal euthanasia came about in the Netherlands 15 years ago (73). Separate to cultural practices in different regions of the world is the specific "ethical culture" of the unit, that is, the implicit ethical consciousness and sensitivity which guides decision making and moral judgement (50). This likely relates to the combination of individuals in a unit and their own experiences, values and spirituality and would likely vary substantially as a result.

While the literature is largely biased towards European and American units, a few studies have examined the potential differences in end-of-life care in Asian NICUs and shed light on some of the potential cultural, religious, and values-based factors which might lead to practice variation. Kim *et al.* (74) noted that there has been an overall trend in Asian countries away from aggressive "do everything" approaches in recent times. The rate of parental involvement in decisions about WWLST was lower than in many Western countries at 60%. The cultural taboo of discussing death and dying in many Asian countries could have been a barrier to having these discussions, as well as the practicalities around the preference for the extended family being more involved in decision making (74). Yotani *et al.* looked specifically at neonatal physicians and their NICUs in Japan, finding that rates of WWLST were lower than in Europe or America. They suggested barriers to WWLST discussions and decisions may be due to greater emphasis on family and familial harmony in decision making, differences in the understanding of the prognosis between family and physicians and not having the laws and guidelines in place for legal protection (75). Both of the above studies mentioned lack of education or training as a barrier to engaging in discussions about WWLST (74,75). This hasn't been formally addressed in other studies so it is unclear if this is specific to Asian NICUs, however it is an important consideration and may be improved with consensus guidelines published about WWLST in previable neonates.

The extent of parental involvement in decision making also differs and could further change rates of WWLST between units. Some countries limit parental responsibility in decision making to relieve the burden this creates (76). Whereas, a Belgian study showed parents had almost equal influence in WWLST decisions as neonatologists, especially in infants <26 weeks (77). This is important as perceived parental involvement has been found to be associated with lower long term grief scores (78). Interestingly, the estimated chance of survival as a threshold for when neonatologists will intervene over parental wishes ranges widely (79). Acceptance of risk is also different between parents and clinicians. Findings suggest neonatologists are inherently pessimistic about survival rates and risk of major neurodevelopmental injury (80). Another study suggests that parents of preterm infants see death as the worst outcome and would save the infant at all costs as compared to healthcare workers and parents of term infants who rated severe disability as the worst outcome (81). Furthermore, Australasian parents seem to tolerate a higher level of risk over neonatologists (90% *vs.* 70% mortality risk) when deciding whether to continue active treatment (82). This is important as framing statistics positively or negatively in perinatal counselling can affect parental decision making (83,84). Parental perspectives surrounding end of life care in the NICU have only recently stared to be explored (68). It seems only natural, then, that the extent of parental involvement in shared decision making about WWLST might also be a significant contributor to variation in outcomes.

It has been suggested that more consideration should be paid to the difference between withholding and withdrawal of LST and the implications this has on outcomes. Boutillier *et al.* noted that of the unstable infants, 18 of 29 infants survived to discharge where LST was withheld (i.e., no further escalation of cares) compared with 4 of 41 infants where LST was withdrawn (62). Thus, some variation in the WWLST processes may surround the proportion of infants where LST is withheld rather than withdrawn since this distinction is rarely made.

More detailed comparisons between units managing periviable neonates in future would aid in better understanding these WWLST differences and their implications on survival. Important points of investigation might include who is involved in decision making and to what extent, the proportion of infants offered and then followed through WWLST, the timing of WWLST discussions, parental perspectives, the conditions, and reasons for WWLST and how unit culture might affect WWLST and end of life practices as a whole.

Table 4 Summary of guidelines/guidance articles relating to WWLST in periviable infants—high income countries over the last 15 years

Publisher/author	Year	Purpose	Population	Country
British Association of Perinatal Medicine	2010	Guideline for palliative care in infants	Any infant qualifying for palliative care	Great Britain
Warrick *et al.*	2011	Review of consensus statements and guidelines	Neonates—focus on critical care setting	Great Britain
Together for Short Lives	2015	Palliative care standards framework	All children	England/Wales/Scotland
Larcher *et al.*	2015	Framework for practice in decision making for life-limiting and life-threatening conditions	All children	Great Britain
Weise *et al.–American Academy of Paediatrics*	2017	Policy statement on forgoing life sustaining treatment	All children	America
Queensland Health	2017	Guideline for end-of-life care in children	All children	Australia
Safer Care Victoria, Published 2014, updated 2022	2022	Guideline for end-of-life care in neonates	Neonates	Australia
Rholl *et al.*	2023	Outlining the logistics of WWLST	NICU patients	Across high income countries

WWLST, withdrawal and withholding of life sustaining treatment; NICU, neonatal intensive care unit.

Implications for future practice—is there a need for clinical practice guidelines in standardising rates and practices of WWLST?

A handful of guidelines exist for end-of-life care in neonates and children, however few are specific to extremely preterm or periviable infants. While this review focuses on literature and guidelines from the last 15 years pertaining to WWLST in high-income countries (summarised in *Table 4*), it is important to note that publications regarding WWLST in paediatrics from pre-2008 have formed the basis of subsequent recommendations. One such document is the Nuffield Council of Bioethics report on critical care decisions in fetal and neonatal medicine, which focussed on infants <26 weeks gestational age (85). It details several ethical and legal implications of infant care at the edge of viability and includes a small section on WWLST. Since, the British Association of Perinatal Medicine have released a palliative care specific guideline published in 2010 (86). Other more recent palliative care guidelines relating to the broader paediatric population include 'Together for Short Lives' (87) and Queensland Health guidelines (88). The Queensland Health Care Plan for the Dying Child Guideline is an extensive and practical document which outlines step-by-step the process by which a team might recognise, plan and execute end of life care. Similarly, guideline from Safer Care Victoria outlines the process of end-of-life care in neonates from recognising the diagnosis through to post-mortem (89). Further articles detail the practicalities, ethical issues and importance of communication (90-92). None of the above guidelines are specific to WWLST processes in the periviable population. Arguably, the factor that separates this group from other children possibly eligible for end-of-life discussions is the variability and uncertainty in outcomes previously discussed which makes it difficult to make fully informed decisions as to whether WWLST is in the best interests of the infant.

Due to difficulty in prognostication, each of the above guidelines emphasises the need for shared decision making with parents and for open communication. The practical advice for this is consistent and is summarised below (86,87,89-94).

- Open and timely communication should occur with clear documentation of all discussions and their nature during the end of life process.
- Parents should be provided with clear, unbiased information as to the prognosis of their child, the reasons, benefits, and consequences of both continuing LST and WWLST. Uncertainty in prognosis should be recognised.
- Decision making should take part with the multidisciplinary team and those involved should identify themselves and their roles clearly.
- A care plan should be agreed to and revisited with

changing information or prognosis.
- ❖ Shared decision making can reduce the parental burden and stress of making complex medical decisions about their child alone.
- ❖ It is appropriate to encourage the sourcing of a second opinion where either party is unsure.

Several studies have been performed on shared decision making in end-of-life care within paediatrics and the NICU specifically. No systematic review currently exists in this area and would be interesting to further verify the above advice in future research.

The question of whether guidelines are necessary or appropriate in periviability is an important one however much of the research on this topic relates to active resuscitation rather than decisions to WWLST. While neonatologists have a desire for guidelines regarding the thresholds of resuscitation, they may not agree on levels of standardisation (95). However, other authors suggest introduction of standardising documents might allow for better collaboration in the multidisciplinary team in relation to end of life decisions (45). Furthermore, some authors have commented on the ethical dilemmas surrounding the development of guidelines, suggesting rigid recommendations may not be in periviable infants' interests (96-98). Despite this, there may be other advantages to guidelines such as education and legal or moral protection of decision makers. Ultimately, the intention of guidelines for WWLST of periviable infants should focus on the process and execution of WWLST in periviable infants, rather than creating a set of rigid clinical criteria on which to determine a periviable infant's likely course of treatment.

Evaluating the literature

Significant gaps remain in the literature for the periviable population and very few studies address these infants specifically, especially when the age group for periviability has gradually evolved to younger gestations. Variation in the preparedness to resuscitate infants at the threshold of viability increases with decreasing gestational age (12). In addition, WWLST is more prevalent in lower gestational ages (47,56). Given inter-unit differences in WWLST practices are most prevalent in the periviable age group (46) we may learn the most by focusing on them. One could also consider whether a "periviable" population should be expanded to include extremely low birthweight infants regardless of gestation as this is another significant indicator of survival (10).

It is difficult to compare survival statistics for premature neonates, with especially wide ranges in lower gestations (4,37). The existing international datasets relating to premature birth are relatively heterogenous, without clear definitions or protocols for standardisation between them (99). Moreover, varying denominators and timeframes are used when quantifying survival (see *Table 1*)—taken as a proportion of all births, live births or NICU admissions. This was well illustrated by Myrhaug *et al.* where all the estimates of survival were much lower when expressed as a percentage of all live births as compared with NICU admissions (4). Up to date outcome statistics from recent years are lacking across the board. While this data may exist in annual reports from neonatal networks, it is yet to make it to published studies. This delay means that most published research studies on extremely preterm/periviable infants relate to cohorts five to ten years old at best. Additionally, many studies from the last 15 years re-analyse a limited data pool from existing large population based studies such as EPICURE (100) and EPIPAGE-2 (16) which supports the need for more comparative and up to date survival data (101).

Another challenge in studying periviability is that sample sizes are small, due to few of these infants being born per hospital per year. Many studies mitigate this by including all infants within a network, region or country such as in the iNeo collaboration, the Neonatal Research Network or Australian and New Zealand Neonatal Network. Large network-based studies increase sample size which is beneficial for improving statistical power and capturing trends and variation across time and across units. However, given that this data is likely collected by hundreds of different unit data collectors, reliability might be compromised. Unification of definitions and commonly collected data points would aid in determining more accurate statistics and comparisons. Large multi-unit network studies also may not be suitable for obtaining qualitative data such as parental perspectives on end-of-life decision making and processes for WWLST. Smaller single unit studies in periviable infants would be useful for this, however given that variation exists between units, it might be better to compare clusters of units to understand differences. Unit level morbidity and mortality rates are also important to be able to give parents and neonatologists as much specific and up to date information as possible when engaging in end-of-life decisions. This author proposes

more unified collection of WWLST processes, discussions, and outcomes to better characterise its role in overall outcomes for periviable infants.

Strengths and limitations of this review

This review is based on a broad search of the literature over multiple years. The search strategy has been advantageous in allowing a greater capture of information in a narrow topic of interest with few published studies. Despite this, it is important to recognise that a wide and evolving search strategy does not conform to a strict protocol therefore is poorly reproducible by others. The author has attempted to make the methods as clear and detailed as possible to retain transparency. A further advantage of the review is that it takes a novel approach to the well documented variation in preterm outcomes, an issue most significant in the tiniest of infants. While research on WWLST is growing, it has rarely been explored as a contributory factor in periviable outcome variability.

The review also excluded studies published longer than 15 years ago, deliberately, as these often have datasets from over 20 years ago which may not represent current prevailing clinical practice. Having said this, many of the studies included in this report also use datasets from the early to mid 2000/2010s, which may not reflect more recent advances in the management of periviable infants.

It is important to be aware of potential biases in this review. The study only included those published in English which may skew the available studies to have a Western predominance and fail to reflect those results from other countries in Asia and the Middle East. It was noted that the published studies found were largely from Europe and America but where possible this review has attempted to include studies from other regions of the world. Given this narrative review did not follow the strict search protocols of a systematic review, it is possible that publication bias may exist wherein studies were missed or excluded where they were not clinically or statistically significant.

Conclusions

Management of infants at edge of viability is an necessary consideration for the overall variation in outcomes of extremely preterm infants. While factors relating to management and survival at birth and resuscitation have been extensively explored, end of life decisions and their effect on mortality warrant further investigation. Given the large variation in WWLST practices and subsequent direct impacts on mortality, it is likely that this contributes to overall variation in periviable infant outcomes. Better understanding of these practices, as well as updated and unified outcome data in the periviable population is important for future management of these infants. While strict practice guidelines based on gestational age thresholds may not be necessary, nor appropriate in end-of-life decision making, guidelines for working though the decision making process behind WWLST could hopefully see a decrease in inter-centre variability, or at the very least, minimise lack of education as a barrier to engaging in WWLST discussions. This review aimed to understand the role WWLST might play in periviable infants' variable morbidity and mortality. We found that that while we have some understanding of WWLST a lot more could be learned with research on both a population and unit level. Ultimately, the goal is to understand the processes and implications of WWLST to improve outcomes and experiences in such a complex clinical situation for parents and healthcare workers alike.

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Footnote

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