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## Short and Long-Term Outcomes for Extremely Preterm Infants

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### Abstract

Prematurity is the leading cause of infant mortality worldwide. In developed countries, extremely preterm infants contribute disproportionately to both neonatal and infant mortality. Survival of this high-risk population has incrementally improved in recent years. Despite these improvements, approximately 1 in 4 extremely preterm infants dies during the birth hospitalization. Among those who survive, respiratory and other morbidities are common, although their effect on quality of life is variable. In addition, long-term neurodevelopmental impairment is a large concern for patients, clinicians and families. However, the interplay of multiple factors contribute to neurodevelopmental impairment, with measures that change over time and outcomes that can be difficult to define and predict. Understanding outcomes of extremely preterm infants can help better counsel families regarding antenatal and postnatal care and guide strategies to improve survival without morbidity. This review summarizes recent evidence to provide an overview into the short- and long-term outcomes for extremely preterm infants.

### Keywords

prematurity; low birth weight; neurodevelopment; survival; morbidity; periviable

### Introduction

Extremely preterm (EPT) birth is a leading cause of infant death and morbidity. The World Health Organization defines EPT infants as those born before 28 weeks (wk) gestational age (GA) and studies from the NICHD Neonatal Research Network (NRN) define EPT infants as those born before 29wk GA. Despite the subtle variability in definitions of EPT, these infants contribute disproportionately to preterm-related morbidity and mortality. Globally, EPT births account for 5.2% of all preterm births < 37wk GA<sup>1</sup>. In the United States in 2013, 11.4% of infants were born preterm, with 0.7% of infants born before 28wk GA, a proportion that has been relatively constant since 2000<sup>2</sup>. Despite the relatively small number of EPT births, these infants and slightly more mature infants born between 28 and < 32wk GA account for over half of all infant deaths in the US<sup>3</sup>. This review focuses on providing

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an overview of outcomes for EPT infants, using data from the US and other developed countries. Given the wide ranging literature on the multitude of neonatal outcomes covered, this review is intended to be an overview, rather than a systematic review, of short- and long-term outcomes for EPT infants. The goal is to provide the reader with an understanding of EPT outcomes in the context of other important review articles in this special theme issue on preterm birth.

## Survival

Following decades long trends, survival continues to improve for EPT infants. Recent data from several sources indicate improvements in survival for EPT infants in the US<sup>4-6</sup> and other international developed nations<sup>7-11</sup>. Based on estimates from the NRN, 74% of EPT infants survive the initial birth hospitalization<sup>4,5</sup>, although each decreasing GA week has substantial effects on mortality, particularly for infants born at 22-25wk GA (Figure 1).

### Gestational age-specific survival

A number of recent cohort studies in the US<sup>4,5</sup>, France<sup>7</sup>, Japan<sup>10</sup>, Taiwan<sup>11</sup>, UK<sup>12</sup>, Sweden<sup>13</sup>, and Singapore<sup>14</sup> have provided estimates of GA-specific survival that can be utilized as a starting point for understanding outcomes and international variations in survival for EPT infants (Table 1). However, international comparisons of EPT survival among countries are limited by differences in the data sources, ascertainment of death, selection of denominators, and definitions of live-births<sup>15</sup>. International collaborative groups, such as the International Network for Evaluating Outcomes (iNEO) have undertaken efforts to provide a better framework for comparisons of health outcomes for preterm infants amongst developed countries<sup>16</sup>. Such efforts should ensure consistent reporting of outcomes, including systematic measurement of numerators and denominators for comparisons.

### Effect of variation in active treatment on survival

Variation in active treatment with resuscitation after birth, particularly for those infants less than 25wk GA, is likely to account for a significant portion of the variation in GA-specific survival between countries (Figure 1). In the US, between-hospital variation in active treatment for infants less than 24wk GA has a large effect on center differences in survival of the most immature infants<sup>17</sup>. In a study by Rysavy et al., the investigators found that 78% of variation in survival for infants born before 26wk GA among 24 academically-affiliated hospitals was accounted for by variation in the use of active treatment with potentially lifesaving interventions after birth (e.g. intubation, ventilation). For infants at 22wk and 23wk GA, the variation in mean rates of active treatment by hospital ranged from 0% to 100% and 25% to 100%, respectively. Understanding the frequency and spectrum of adverse outcomes for EPT infants is important, as the decision to forgo active lifesaving treatment is often reached after antenatal counselling regarding EPT outcomes. As the authors note, data from infants that did not receive active treatment are often included in population estimates of survival, which may lead to a “self-fulfilling prophecy” and provide potentially misleading estimates when considering the possible outcomes if active treatment (i.e. resuscitation) is pursued for an EPT infant. For example, overall survival to hospital discharge for inborn live births at 22wk and 23wk GA is 5% and 24%, respectively<sup>17</sup>.

However, when only infants receiving active treatment with life-saving interventions are evaluated (i.e. excluding infants receiving only comfort care), survival estimates change to 23% at 22wk GA (n=79) and 33% at 23wk GA (n=542). Understanding these data are important in counselling families and caring for fetuses and neonates at a periviable GA, which is broadly defined as 20 0/7 to 25 6/7 weeks by a recent NICHD workshop<sup>18</sup>. Even at a periviable GA, long-term neurodevelopmental disability is not universal and prediction can be uncertain as discussed later in this review.

### Causes of death

Death among EPT infants is often broadly attributable to preterm birth or short-gestation, particularly in national vital statistics datasets<sup>3</sup>. Identifying the specific causes of death from underlying complications of preterm birth is important in understanding contributors to mortality in EPT infants, although attribution of singular causes of death can be challenging as EPT infants often have multiple co-morbid complications of prematurity. Among very preterm infants less than 32wk GA in the United Kingdom, complications of preterm birth predominated as the cause of neonatal and infant death, while malformations largely accounted for deaths among more mature preterm infants 32-36wk GA<sup>19</sup>. Recent data from the NRN reports “immaturity” as the leading cause of death among EPT infants, with most of these infants receiving comfort care in the delivery room without active treatment and dying within 12 hours of birth<sup>5</sup>. The second most common cause of death is pulmonary, comprised of respiratory distress syndrome and bronchopulmonary dysplasia (BPD). Over half of recent improvements in survival for EPT infants from 2000 to 2011 in the NRN was accounted for by decreases in pulmonary-related deaths. By contrast, data from the NRN<sup>5</sup>, Sweden<sup>20</sup> and the UK<sup>21</sup> suggest a greater proportion of EPT infants are dying from necrotizing enterocolitis (NEC) in recent years. NEC becomes a larger proportionate cause of mortality as GA increases, particularly at 26-27wk GA. In addition, data from a prospective study in 46 US neonatal intensive care units (NICU) found NEC to be the second most common cause of death among all infants (term and preterm) born at 22wk GA, accounting for 10% of NICU deaths<sup>22</sup>. Only deaths due to extreme prematurity were more common, accounting for 14% of all NICU deaths.

### Short-term morbidities

EPT birth leads to loss of months of fetal development, leaving the infant vulnerable to morbidities, many of which are unique to the preterm population. Among infants who survive, the percent who leave the hospital without severe morbidities range from 0% at 22wk GA to 54% at 28wk GA based on data from the NRN<sup>4</sup>. Overall, 39% of EPT infants <29wk GA who survive to discharge leave the hospital without severe morbidity. A large component of morbidity among surviving infants is driven by the high frequency of BPD, ranging from 88% of infants at 22wk to 24% of infants at 28wk GA based on NRN data from 2008-2012<sup>4</sup>. Data from EPIPAGE-2 in France, by contrast, shows a higher proportion of surviving infants leaving the hospital without serious morbidity (70% for infants 23-28wk GA)<sup>7</sup>. This may be due to the lower incidence of BPD, likely due to differences in definitions of BPD as well as fewer infants surviving at 22-24wk GA. Survival with 3 severe morbidities at hospital discharge (BPD, serious brain injury and severe ROP) is an important

predictor of interval death or disability at 5 years of age<sup>23</sup>. A summary of common and serious comorbidities among EPT infants is reviewed below.

### **Respiratory distress syndrome (RDS)**

RDS is a leading cause of death among EPT infants, as previously discussed, and many infants with RDS will go on to develop BPD. The understanding of the ubiquitous respiratory disease, also known as hyaline membrane disease, that currently affects almost all EPT infants changed in 1959, when Avery and Mead reported on the relationship between surface tension and RDS<sup>24</sup>. Follow-up studies identified surfactant as the missing lipid in preterm lungs, and in 1980 Fujiwara et al. first described the successful treatment of RDS with surfactant<sup>25</sup>. RDS presents soon after birth in the delivery room and affects 86% to 95% of EPT infants, depending on the GA<sup>26</sup>. The mainstay of treatment is to provide continuous positive airway pressure (CPAP) therapy and surfactant, when necessary<sup>27</sup>. The use of surfactant to treat RDS increased from 65% in 1993-1997 to 76% in 2008-2012 among EPT infants<sup>4</sup>. In addition, data supports the early use of surfactant among infants requiring mechanical ventilation, compared to delaying treatment until the severity of RDS worsens<sup>28</sup>. In the delivery room, studies suggest that initial CPAP, rather than intubation and surfactant, is a potentially more favorable approach to reduce long-term respiratory morbidity in EPT infants with RDS<sup>29</sup> and is a recommended approach in EPT infants who are spontaneously breathing in the delivery room<sup>30</sup>.

### **Bronchopulmonary dysplasia**

First characterized by Northway et al. in 1967 in a description of the sequela of RDS in a cohort of 32 infants<sup>31</sup>, BPD is the most common serious morbidity affecting EPT infants. Neonates with BPD are at high-risk of long-term pulmonary disease, adverse neurodevelopmental outcomes, and readmission to the hospital in the first year of life<sup>32</sup>. Older data suggest that the effects of BPD persist into adolescence and early adulthood, with problems such as airway hyperreactivity, decreased lung function and airway obstruction<sup>33</sup>. However, for many infants with BPD, symptoms improve over time.

Recent epidemiological data indicate an increasing incidence of BPD among EPT infants<sup>4</sup>, which may be a result of improved survival. Pharmacologic therapies to prevent BPD include caffeine<sup>34,35</sup>, intramuscular administration of vitamin A<sup>36</sup> and corticosteroids<sup>37</sup>. While both caffeine and vitamin A have been shown to be safe, concerns regarding the adverse central nervous system effects of corticosteroids, particularly dexamethasone, have limited its use<sup>38</sup>. Inhaled corticosteroids may be a potential alternative to systemic administration, and the effects of early prophylactic use on preventing BPD are promising, although further studies are needed to ensure its safety<sup>39</sup>. In addition, earlier initiation of caffeine within the first 2 days after birth may have more favorable treatment effects than later initiation on the risk of BPD<sup>40-42</sup>.

### **Patent ductus arteriosus (PDA)**

A PDA is a common finding in EPT infants, occurring in 32-60% of infants 22-28wk GA<sup>26</sup>. Observational studies have reported associations with a PDA and adverse neonatal outcomes, including intraventricular hemorrhage (IVH)<sup>43,44</sup>, BPD<sup>45</sup> and death<sup>46,47</sup>. A recent

observational study found that more frequent early screening for a PDA, which leads to more treatment, is associated with a decreased risk of hospital death (OR 0.73; 95% CI 0.54-0.98)<sup>48</sup>. However, a contrasting study found that surgical ligation of a PDA, after accounting for the propensity to receive such a treatment, is associated with worse outcomes including a higher risk of a composite of death or BPD, severe IVH, NEC, and severe ROP (adjusted OR 2.0; 95% CI 1.57-2.54)<sup>49</sup>. In the Trial of Indomethacin Prophylaxis in Preterms (TIPP), treatment with indomethacin, compared to placebo, substantially reduced the risk of a PDA (adjusted OR 0.3; 95% CI 0.2-0.4) and severe IVH (aOR 0.6; 95% CI 0.4-0.9) but had no effect on BPD (aOR 1.2; 95% CI 0.9-1.6), NEC (aOR 1.1; 95% CI 0.8-1.7), or death or neurosensory impairment (aOR 1.1; 0.8-1.4)<sup>50</sup>. These data add more uncertainty as to the benefit of treating a PDA, and highlight the need for randomized trials in which confounding factors associated with a decision to evaluate and treat a PDA can be appropriately accounted for to better understand the risks and benefits of pharmacologic and surgical treatment<sup>51</sup>.

### Infection

Infection is a serious and potentially lethal complication in EPT infants. Common pathogens include coagulase-negative Staphylococcus, Staphylococcus aureus, Escherichia coli and Candida albicans, which in one study comprised 48%, 8%, 5% and 6%, respectively, of late-onset sepsis episodes among very low birth weight (VLBW) infants<sup>52</sup>. By contrast, early-onset sepsis within the first 72 hours after birth is mostly caused by Escherichia coli and Group B streptococcal infections. However, culture-proven early-onset sepsis is relatively uncommon, affecting 1.1% of VLBW infants<sup>53</sup>. Although gram-positive infections are more frequent in EPT infants, case-fatality rates are higher among fungal and gram-negative organisms, with rates as high as 44% for Candida albicans and 75% for Pseudomonas sepsis<sup>52</sup>.

For those infants that survive an episode of sepsis, infection is associated with poor growth and adverse long-term neurodevelopmental outcomes. In a study by Stoll et al. of extremely low birth weight (ELBW) infants from 1993-2001<sup>54</sup>, 65% developed at least 1 infection. ELBW infants with infection had a higher risk neurodevelopmental impairment (ORs 1.3-1.8 depending on the definition of infection) and cerebral palsy (ORs 1.3-1.6). An additional study reported on the association between candida infection and worse adverse neurodevelopmental outcomes in ELBW infants<sup>55</sup>. Although fluconazole prophylaxis has been shown to substantially reduce the risk of invasive candida infection, its use has not had an effect on either mortality or neurodevelopmental impairment<sup>56</sup>, raising questions of whether invasive candida infection is a comorbid complication or causal factor in neonates with death or neurodevelopmental impairment. Fortunately, the incidence of late-onset sepsis has decreased over the last 20 years from 1993 to 2012<sup>4</sup>, following similar trends in the incidence of invasive fungal infections<sup>57</sup>.

### Necrotizing enterocolitis

NEC is the most common serious gastrointestinal complication in EPT infants, affecting approximately 1 in 10<sup>58</sup>. Cause-specific mortality from NEC is high, estimated at 30-40% for ELBW infants<sup>59</sup>. Infants who survive the disease, particular those who undergo surgical

intervention, commonly have long-term complications, including poor growth, short bowel syndrome, and neurodevelopmental impairment<sup>60</sup>. Often, the interval between initial clinical symptoms and extensive intestinal necrosis is short, limiting the effectiveness of therapeutic interventions and underscoring the importance of prevention<sup>61</sup>. Although the etiology of NEC is not fully understood, several key factors in addition to prematurity are postulated to be important determinants: abnormal intestinal bacterial colonization, immature gut barrier, impaired intestinal blood flow, and type of enteral feeding<sup>62</sup>. One of the most important strategies to prevent NEC is breastfeeding<sup>63</sup>, and the use of an exclusive human milk diet with human milk-based fortifiers has shown promise in decreasing the risk of NEC<sup>64</sup>. However, the effect of an exclusive human milk diet on growth and long-term neurodevelopment needs further study. Additional strategies to prevent NEC include probiotic therapy, which has been widely studied and has a strong treatment effect in reducing NEC<sup>65</sup>. However, questions regarding the optimal dose and preparation of probiotic therapy, lack of a Food and Drug Administration (FDA) approved preparation, and risk of probiotic-associated sepsis have limited widespread use. Reducing the use of acid-suppression medications<sup>66</sup> and decreasing prolonged empiric antibiotic therapy<sup>67,68</sup> may also have benefit in decreasing the risk of NEC.

### Retinopathy of prematurity (ROP)

ROP is a leading cause of blindness in EPT infants and is thought to be caused by excessive supplemental oxygen administration that leads to suppression of vascular endothelial growth factor (VEGF) and delayed retinal vascular growth<sup>69</sup>. Prevention of ROP has focused on limiting supplemental oxygen administration, which has been shown to decrease the risk of ROP. However, based on trials finding an increased risk of mortality with lower oxygen saturation targets (85-89% vs 91-95%)<sup>70,71</sup>, many centers have abandoned lower oxygen targeting. The effect of these changes in practice may be leading to increases in ROP<sup>72</sup>. Once an infant develops severe ROP, treatment has historically been limited to cryotherapy or laser photocoagulation. Because these treatments can impact residual vision, particularly peripheral vision, newer treatments such as intravitreal bevacizumab that inhibit VEGF are promising alternatives<sup>73</sup>. However, further studies are needed to assess the safety of these therapies, given their potential for antiangiogenic effects in the developing EPT infant. A second later phase of ROP is characterized by hypoxia-induced pathological vessel growth. This mechanistic insight was the rationale for a trial of supplemental oxygen to target oxygen saturations of 96-99% to prevent progression of ROP<sup>74</sup>. Although a negative overall trial, the findings suggested some potential benefit of higher oxygen targeting in infants with pre-threshold ROP without plus disease in a *post-hoc* subgroup analysis. However, these potential benefits were offset by an increased risk of adverse pulmonary outcomes, including longer duration of need for supplemental oxygen and pneumonia.

### Neurodevelopmental outcomes, including effects of short-term neurologic injury

Neurodevelopmental impairment among EPT infants who survive the initial birth hospitalization follows a wide spectrum of outcomes, with some measures demonstrating dynamic improvements over time and others remaining severe and fixed. As both clinicians

and families share in the concern for adverse long-term neurologic outcomes among EPT infants, understanding the spectrum of impairment is important to guide conversations with families and provide estimates of outcomes that are as unbiased as possible. Estimates of neurodevelopmental impairment should be considered alongside the competing outcome of death in EPT infants, particularly at early GAs where overall survival is low.

### **Cognitive impairment and dynamic changes over time**

Cognitive impairment, commonly measured using the cognitive scale or mental developmental index (MDI) of the Bayley Scales of Infant and Toddler Development (Bayley), is typically the most common measure of neurodevelopmental impairment among EPT infants. The challenges of assigning a diagnosis of cognitive impairment includes the selection of an appropriate cut-point for a Bayley score as well as the variability of the reference population on which the Bayley is standardized<sup>75</sup>. While several studies suggest neurodevelopmental outcomes are improving in EPT infants<sup>76-78</sup>, the changes in the measurement tool from the 2<sup>nd</sup> to 3<sup>rd</sup> Bayley edition have made it difficult to determine how much of the changes in neurodevelopmental outcomes are related to changes in measurement. In a study by Vohr et al., the incidence of neurodevelopmental impairment among ELBW infants decreased from 43% in 2006-2007 to 13% in 2008-2011, but the measurement tool also changed from the 2<sup>nd</sup> edition to 3<sup>rd</sup> edition of the Bayley between the periods<sup>76</sup>.

Studies have shown that the MDI component of the Bayley-2<sup>nd</sup> edition improves over time, with a mean score increase of 20 points between measures of cognition using the Bayley-2<sup>nd</sup> edition at 18 months and the Wechsler Preschool and Primary Scale of Intelligence III IQ at 5 years<sup>35</sup>. This may lead to misclassification of infants as impaired at 18 months who fall well within the normal population distribution of IQ scores at 5 years. These findings suggest that the Bayley-2<sup>nd</sup> edition may measure developmental delay, rather than fixed impairment, and may potentially overestimate adverse neurodevelopmental outcomes. By contrast, the Bayley-3<sup>rd</sup> edition, using the scale mean of 100 as a reference, may underestimate delay at 2yr of age<sup>79</sup>. Concerns have also been raised regarding how well the Bayley-3<sup>rd</sup> edition performed at 2yr predicts 4yr cognitive outcomes<sup>80</sup>. In addition, a recent study demonstrates that parental socioeconomic status has an important effect in cognitive gains over time<sup>81</sup>. In this study, infants born to parents with higher education and whose caregivers were employed had greater cognitive gains in neurodevelopmental assessments between 18 months and 5 years of age.

As the cognitive scales of the Bayley accounts for a large portion of commonly used composite measures of neurodevelopmental impairment defined by researchers<sup>82</sup>, it is important to evaluate the specific measures of neurodevelopmental impairment (e.g. mild or none, moderate, severe) to better understand the spectrum of impairment among survivors (Table 2). Marlow et al., on behalf of the EPICure Study Group, compared the assignment of the severity of disability at 30mo with that at 6yr of age<sup>82</sup>. At 6yr, approximately 2 out of 5 of infants who were diagnosed with severe disability at 30mo no longer had severe disability. By contrast, 1 in 4 infants without any disability at 30mo were found to have moderate or severe disability at 6yr. These findings highlight the importance of evaluation

of school-age outcomes in ascertaining neurodevelopment impairment in EPT infants. Data from 3 cohort studies, two population-based cohorts from Sweden (EXPRESS Group)<sup>83</sup> and the United Kingdom (EPICure)<sup>78</sup> and a multicenter cohort of US academic centers (NRN)<sup>17</sup>, provides recent estimates of neurodevelopmental impairment among EPT infants, including the spectrum of gestational age-specific disability (Figure 2).

### **Cerebral palsy and motor impairment**

Cerebral palsy (CP), a permanent neurologic disorder that impairs movement and muscle coordination, is estimated to occur in approximately 8-9% of infants 22-32 wk GA<sup>78,84</sup> and 14% of infants 22-25 wk GA<sup>78</sup>. The most common type of CP in EPT infants is bilateral spastic cerebral palsy, accounting for over two-thirds of cases. The assessment of motor impairment in EPT infants is performed by physical examination, as well as formal assessments including the Bayley-3<sup>rd</sup> edition and Gross Motor Function Classification System (GMFCS). Similar to the problems with the Bayley cognitive scales, use of a higher cut-point of a motor composite score of < 85 for a Bayley-3<sup>rd</sup> edition may overestimate impairment<sup>85</sup>. However, many ELBW infants have motor coordination difficulties that persist into adulthood<sup>86</sup>.

### **Intraventricular hemorrhage and periventricular leukomalacia (PVL)**

Intraventricular and periventricular hemorrhage is a common finding in EPT infants, with worse outcomes associated with higher grades of IVH. A study from 2006-2008 by Payne et al. reported IVH in 31% of infants <27wk GA who underwent ultrasound screening<sup>87</sup>. The study reported severe IVH (Grade 3 or 4) was associated with an increased risk of all adverse neurodevelopmental outcomes, including CP (OR 3.4; 95% CI 2.2-4.3), GMFCS > 2 (OR 2.5; 95% CI 1.4-4.4) and a Bayley 3<sup>rd</sup> edition MDI <85 (OR 1.8; 95% CI 1.3-2.6), when compared to infants without IVH. Infants with low grade IVH had a similar risk of adverse outcomes as those without IVH. By contrast, a study of infants 23-28 wk GA from 1998-2004, found that even low grade IVH, compared to no IVH, was associated with a higher risk of neurosensory impairment (OR 1.7; 95% CI 1.2-2.5), with an overall IVH incidence of 22%<sup>88</sup>. Other studies have found that late imaging (cranial ultrasound or magnetic resonance imaging (MRI)) is a better predictor of long-term outcomes at 18-22 months when compared to early cranial ultrasound<sup>89</sup>. Additional studies have demonstrated a potential benefit to late MRI imaging among high-risk EPT infants<sup>90</sup>, as MRI is better at identifying diffuse white matter and cerebellar injury than ultrasound. However, the presence of PVL on ultrasound strongly correlates with a high risk of CP<sup>91</sup>.

Among those infants with severe IVH, the development of post-hemorrhagic hydrocephalus requiring shunt placement confers a worse outcome<sup>92</sup>. Neurodevelopmental impairment was seen in 92% of ELBW infants with a Grade 4 IVH requiring shunt placement, compared to 55% of ELBW infants with a Grade 3 IVH without need for a shunt and 35% of infants without IVH. Among infants with severe IVH, the rates of hearing impairment ranged from 2-6% and vision impairment from 17-33%, both higher than the respective rates of 1% and 9% for infants without IVH. Despite the challenges that disabilities may pose, many former EPT infants report quality of life that is equivalent to term counterparts and that is less impacted by EPT birth over time<sup>93,94</sup>.

## Counseling at periviable gestation

A recent consensus statement from the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommends clinicians provide accurate, balanced, and unbiased guidance when counseling families regarding care for fetuses and infants at periviable gestational ages<sup>18</sup>. Information presented in several ways, including providing estimates of both survival and mortality to prevent framing bias<sup>95</sup>, using visual aids<sup>96</sup> and providing estimates for only infants receiving active treatment<sup>17</sup> are some strategies to accomplish this goal. The consensus statement also suggests institutions develop consensus guidelines, because individual providers may have variable approaches based on personal beliefs or professional experiences.

## Conclusion

Survival continues to incrementally improve for EPT infants. Understanding short- and long-term outcomes may help in caring for EPT infants and informing discussions with families. Ultimately, reducing preterm birth is necessary to substantially reduce the burden of mortality and morbidity for EPT infants.

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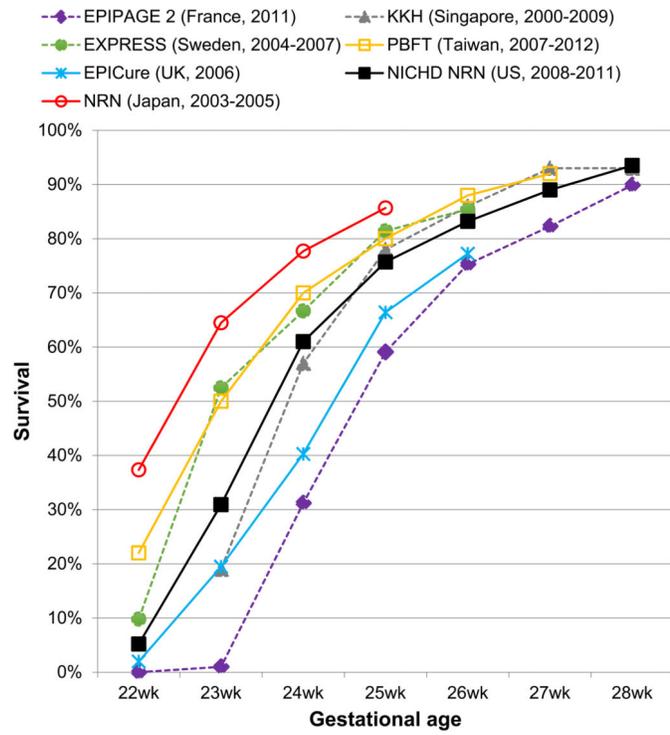
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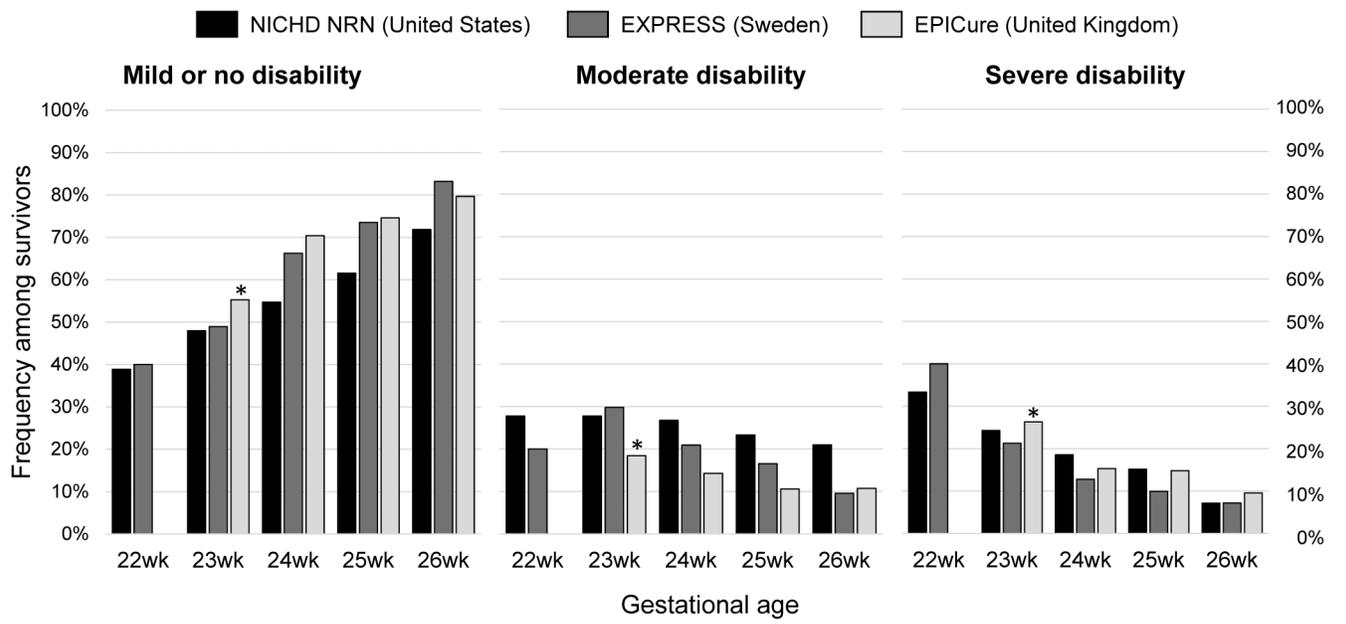
**Figure 1. Gestational Age Specific Survival for Extremely Preterm Infants**  
Characteristics of the data sources are shown in Table 1.

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**Figure 2. The Spectrum of Disability Among Surviving Extremely Preterm Infants**  
 Characteristics of the data sources are shown in Table 2. \*Estimates reported for infants 23wk gestational age.

**Table 1**  
**Characteristics of Select Cohort Studies Reporting Gestational Age Specific Survival for Extremely Preterm Infants**

Study	NICHD NRN	EPiPAGE-2	NRN	PBFT	EPiCure	EXPRESS	KKH
<b>Country</b>	United States	France	Japan	Taiwan	United Kingdom	Sweden	Singapore
<b>Year(s)</b>	2008-2011	2011	2003-2005	2007-2012	2006	2004-2007	2000-2009
<b>Sample size</b>	7124	1911	1057	1718	2034	707	887
<b>Gestational ages</b>	22 <sup>0/7</sup> -28 <sup>6/7</sup> wk	22 <sup>0/7</sup> -28 <sup>6/7</sup> wk	22-25 wk	<29 wk	<27 wk	<27 wk	<29 wk
<b>Numerator</b>	Survival to discharge	Survival to discharge	Survival to discharge	Survival to discharge	Survival to discharge	Survival to 1 year	Survival to discharge
<b>Denominator</b>	Live births (inborn)	Live births	Live births	Live births admitted to centers	Live births	Live births	Live births admitted to center
<b>Study cohort</b>	25 academic medical centers	Population-based cohort	48 tertiary centers	5 centers part of PBFT	Population-based cohort	Population-based cohort	Single large tertiary referral center
<b>Reference</b>	5	7	10	11	12	13	14

Abbreviations: NICHD, National Institute of Child Health and Human Development; NRN, Neonatal Research Network; EPiPAGE-2, Etude Epidémiologique sur les Petits Ages Gestationnels 2; PBFT, Premature Baby Foundation of Taiwan; EXPRESS, Extremely Preterm Infants in Sweden Study; KKH, KK Women's and Children's Hospital.

**Table 2**  
**Characteristics of Select Cohort Studies Evaluating Long-term Outcomes for Extremely Preterm Infants**

Study (Country)	Follow-up	Details	Definition of moderate disability	Definition of severe disability
NICHD NRN <sup>17</sup> (United States)	18-22 mo corrected age	Multicenter cohort evaluating 2630 (65%) of 4329 inborn live births receiving active treatment with survival to 18-22 corrected age.	Bayley-III cognitive or motor score 1-2 SD below mean, moderate CP, or a GMFCS level of 2 or 3.	Bayley-III cognitive or motor score >2 SD below mean, severe CP, GMFCS level of 4 or 5, bilateral blindness, or severe hearing impairment not corrected with bilateral amplification.
EXPRESS <sup>83</sup> (Sweden)	2.5 yr	Population-based cohort evaluating 491 (69%) of 707 live births surviving to 30mo corrected age.	Bayley-III score 2-3 SD below mean (any scales), moderate CP, moderate visual or hearing impairment.	Bayley-III composite cognitive, language or motor score <3 SD below mean, severe CP, or bilateral blindness or deafness.
EPICure <sup>78</sup> (United Kingdom)	3 yr (range of 27-48 mo)	Population based cohort evaluating 584 (57%) of 1031 live births surviving to 3 yr. Age at assessment was variable, with use of multiple scales.	Ambulant CP (GMFCS 2), functionally impaired vision, hearing loss improved by aids, or a developmental score within 2-3 SD below mean.	Non-ambulant CP (GMFCS 3-5), blindness, profound sensorineural hearing loss not improved by aids, or a developmental quotient <3 SD below mean.

Abbreviations: Bayley-III, Bayley Scales of Infant and Toddler Development-3rd edition; SD, standard deviation; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System.