Ethical Considerations in the Management of Infants Born at Extremely Low Gestational Age

Naveed Hussain* and Ted S. Rosenkrantz*

With ongoing improvements in technology and the understanding of neonatal physiology, there has been increasing debate regarding the gestational age and birth weight limits of an infant's capability of sustaining life outside the womb and how this is to be determined. The objective of this review was to address this issue with an analysis of current data (following the introduction of surfactant therapy in 1990) from published studies of survival in extremely low gestational age infants. We found that survival was possible at 22 completed weeks of gestation but only in < 4% of live births reported. Survival increased from 21% at 23 weeks gestational age to 46% at 24 weeks gestational age. Historically, despite continual advances in neonatology, the mortality at 22 weeks has not improved over the past three decades. Combining the data from studies on survival with evidence from developmental biology, we believe that it is not worthwhile to pursue aggressive support of infants born at < 23 weeks gestational age. Given the complicated issues related to morbidity and mortality in infants born at 22 to 25 weeks gestational age and the ethical implications of the available evidence, we propose the need for a consensus derived framework to help in decision-making.

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With the introduction of new therapies, improved technologies and greater experience in the management of extremely premature infants, survival for infants with birth weights of 500 to 1,000 g (1 lb. 2 oz-2 lbs. 3 oz) has shown improvement. This enhanced survival has encouraged some health care providers and families to contemplate lowering the threshold for offering intensive care, now 23 to 24 weeks gestation and ~500 g birth weight, to a lesser gestational age or weight at birth. The medical and ethical considerations in this matter are not well defined at present. The evolving literature on the outcomes of extremely premature infants includes new information on the range of morbidities in survivors, especially neurodevelopmental issues that have life-long implications for these infants and their families. This review 1) presents evidence from the latest survival and neurodevelopmental outcome data and 2) incorporates this new information into an evidence-based discussion of ethical dilemmas and decision-making for extremely premature infants.

Survival of Extremely-Low-Gestational-Age Infants

The survival of low birth weight babies predates modern neonatal intensive care units (NICUs). However, subsequent to the development of surfactant therapy, the survival of large numbers of extremely premature infants has become routine. Until recently, reports of short- and long-term outcomes have been largely retrospective, single center studies with small populations. Moreover, direct comparisons of survival reports are hampered by lack of uniformity in reporting data including analyses by birth weight versus gestational age, inclusion/exclusions of stillbirths and delivery room deaths and use of prenatal steroids, surfactant therapy and other recent technologies since the early 1990s. Recently, published reports from large multicenter and regional NICU-based studies have added substantially to the data to facilitate making better informed, evidence-based, ethical decisions.

From the Division of Neonatology, Departments of Pediatrics, University of Connecticut School of Medicine, Farmington, CT. Address reprint requests to Naveed Hussain, MBBS, DCH, University of Connecticut School of Medicine, 263 Farmington Ave, Farmington, CT 06030-2948; e-mail: hussain@nso1.uchc.edu. © 2003 Elsevier Inc. All rights reserved. 0146-0005/03/2706-0005/$30.00/0 doi:10.1053/j.semperi.2003.10.005

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The present dilemma is the inherent uncertainty in defining: at what milestone in an infant's fetal development does the infant achieve the capability of sustaining life outside the womb and how is this to be determined? It has been clearly shown that gestational age is a better predictor of survival than birth weight.\textsuperscript{7} Gestational age is designated in completed weeks after the last menstrual period. Therefore an infant with gestational age of 23 weeks and 6 days is still considered 23 weeks. The period of conception is about 2 weeks after the last menstrual period and therefore a gestational age (GA) of 23 weeks corresponds to a conceptional age of 21 weeks. By convention all analyses in clinical perinatal medicine and neonatology are made using the GA in completed weeks based on the last menstrual period. Is there a gestational age where it is biologically improbable that an infant can sustain life outside the womb? The question is complex and needs to be addressed from multiple perspectives including review of evidence, ethical principles and socio-economical underpinnings.

**Data From Developmental Biology**

The major factor limiting survival in infants of extremely-low-gestational-age is the maturity of the lung and its ability to perform effectively as the organ for gas exchange. A large part of the technology involved in sustaining life in the extremely-low-gestational-age infants relates to effective support for lung function (eg, surfactant replacement, ventilators).

The vascular elements responsible for gas exchange in the fetal lung are not functional until 21 weeks GA (19 weeks conceptional age).\textsuperscript{8} The development of an effective air exchange interface for gas diffusion is also not developed until about 23 weeks GA (21 weeks conceptional age).\textsuperscript{9,10} Therefore, structurally and physiologically the lung of a human fetus at 22 weeks gestational age is largely incapable of effective gas exchange and any life supporting technology that is designated to support lung function will not usually be effective at this gestation. Unless there is an alternative treatment option that is developed to facilitate gas exchange that does not involve the lung (artificial placenta, extracorporeal membrane oxigenator [ECMO]), the support of life at 22 weeks' gestation will in all likelihood be ineffective. Biological variations or inconsistency of pregnancy dates may account for the occasional survivors that are reported.

**Data From Studies on Survival**

Survival in premature infants has been significantly improved by the use of surfactant therapy and newer ventilator technology in the 1990s.\textsuperscript{11} The age at which there is most controversy regarding survival is in infants born at $\leq 25$ weeks GA.\textsuperscript{12}

Therefore, we have focused on reports from studies of $\leq 25$ weeks GA infants or birth weight $< 750$ g born after 1990 (Tables 1 and 2, respectively). Only studies conducted in developed countries with health care sophistication comparable to the United States were compiled in the tables.

Large population-based reports such as the publications from the National Center for Health Statistics linked birth-infant death cohort files are not very useful in making determinations of survival at extremely low GAs due to possible inaccuracies in gestational ages.\textsuperscript{13} Therefore, more specific data from centers focused on the care of extremely low gestation infants needs to be the basis for evaluation. In this review, we have compiled published studies from developed countries of extremely low gestational age infants born between the years 1990 and 2000 (Table 1). Significant among these studies have been some large multicenter NICU based reports from the National Institute of Child Health and Human Development (NICHD) and the Vermont-Oxford Network. They have reported survival and short-term neurodevelopmental outcomes from participating institutions.\textsuperscript{1,14-17} The NICHD network reported that the post-surfactant era survival for infants is $\sim 20\%$ for infants born at 23 weeks' gestation; $47\%$ for infants born at 24 weeks and $68\%$ for infants born at 25 weeks' gestation. The Vermont-Oxford Network reported similar trends in survival.\textsuperscript{18} A summary of the compiled data from table 1 shows that survival was $< 3.5\%$ at 22 weeks, $21\%$ at 23 weeks, $46\%$ at 24 weeks, and $66\%$ at 25 weeks' gestation.

A similar compilation of studies published before 1997 was conducted by Hack and Fanaroff, who analyzed world and local (United States) outcomes and found that survival varies
Table 1. Survival in Extremely Low Gestational Age Infants (1990-2000)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country-center</th>
<th>From</th>
<th>To</th>
<th>Total n</th>
<th>Surv-n</th>
<th>Surv-%</th>
<th>Total n</th>
<th>Surv-n</th>
<th>Surv-%</th>
<th>Total n</th>
<th>Surv-n</th>
<th>Surv-%</th>
<th>Include</th>
<th>Survival to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishida</td>
<td>Japan-multiple</td>
<td>1990</td>
<td>1990</td>
<td>36</td>
<td>3 (8.3)</td>
<td></td>
<td>118</td>
<td>42</td>
<td>(36)</td>
<td></td>
<td></td>
<td></td>
<td>LB 1-mo end</td>
<td></td>
</tr>
<tr>
<td>Hagan</td>
<td>Aust-region</td>
<td>1990</td>
<td>1991</td>
<td>128</td>
<td>0 (0)</td>
<td></td>
<td>40</td>
<td>33</td>
<td>(83)</td>
<td>118</td>
<td>42</td>
<td>(36)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Philip</td>
<td>US-single</td>
<td>1990</td>
<td>1991</td>
<td>27</td>
<td>1 (3.7)</td>
<td></td>
<td>27</td>
<td>2 (7.4)</td>
<td></td>
<td>40</td>
<td>16</td>
<td>(40)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Hack</td>
<td>US-single</td>
<td>1990</td>
<td>1992</td>
<td>6</td>
<td>0 (0)</td>
<td></td>
<td>22</td>
<td>9 (41)</td>
<td></td>
<td>31</td>
<td>21</td>
<td>(68)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>B.-Singh</td>
<td>US-single</td>
<td>1990</td>
<td>1993</td>
<td>16</td>
<td>3 (19)</td>
<td></td>
<td>43</td>
<td>17</td>
<td>(40)</td>
<td>37</td>
<td>20</td>
<td>(54)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Kilpatrick</td>
<td>US-single</td>
<td>1990</td>
<td>1994</td>
<td>37</td>
<td>18</td>
<td>(49)</td>
<td>103</td>
<td>36</td>
<td>(35)</td>
<td></td>
<td></td>
<td></td>
<td>LB 1 year</td>
<td></td>
</tr>
<tr>
<td>Emsley</td>
<td>UK-single</td>
<td>1990</td>
<td>1994</td>
<td>32</td>
<td>13</td>
<td>(41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Batton</td>
<td>US-single</td>
<td>1990</td>
<td>1995</td>
<td>6</td>
<td>0 (0)</td>
<td></td>
<td>40</td>
<td>19</td>
<td>(48)</td>
<td>66</td>
<td>59</td>
<td>(89)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Battin</td>
<td>Canada-single</td>
<td>1991</td>
<td>1993</td>
<td>49</td>
<td>1 (2)</td>
<td></td>
<td>78</td>
<td>13</td>
<td>(17)</td>
<td>103</td>
<td>36</td>
<td>(35)</td>
<td>LB 1 year</td>
<td></td>
</tr>
<tr>
<td>Tin</td>
<td>UK-region</td>
<td>1991</td>
<td>1994</td>
<td>32</td>
<td>5 (16)</td>
<td></td>
<td>42</td>
<td>25</td>
<td>(60)</td>
<td>59</td>
<td>39</td>
<td>(66)</td>
<td>NICU Disch</td>
<td></td>
</tr>
<tr>
<td>Effer</td>
<td>Canada-multiple</td>
<td>1991</td>
<td>1996</td>
<td>7</td>
<td>0 (0)</td>
<td></td>
<td>13</td>
<td>0</td>
<td>(0)</td>
<td>49</td>
<td>37</td>
<td>(76)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Joseph</td>
<td>Canada-multiple</td>
<td>1991</td>
<td>1996</td>
<td>92</td>
<td>11 (12)</td>
<td></td>
<td>80</td>
<td>24</td>
<td>(30)</td>
<td>116</td>
<td>57</td>
<td>(49)</td>
<td>LB 120d</td>
<td></td>
</tr>
<tr>
<td>Doyle</td>
<td>Aust-region</td>
<td>1992</td>
<td>1996</td>
<td>22</td>
<td>1 (4.5)</td>
<td></td>
<td>31</td>
<td>6</td>
<td>(19)</td>
<td>41</td>
<td>19</td>
<td>(46)</td>
<td>LB* 1 year</td>
<td></td>
</tr>
<tr>
<td>Cartlidge</td>
<td>UK-region</td>
<td>1993</td>
<td>1994</td>
<td>9</td>
<td>4 (44)</td>
<td></td>
<td>18</td>
<td>9</td>
<td>(50)</td>
<td>19</td>
<td>14</td>
<td>(74)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Stevenson</td>
<td>US-multiple</td>
<td>1993</td>
<td>1994</td>
<td>9</td>
<td>2 (22)</td>
<td></td>
<td>9</td>
<td>5</td>
<td>(56)</td>
<td>10</td>
<td>8</td>
<td>(80)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Ahner</td>
<td>US-single</td>
<td>1993</td>
<td>1997</td>
<td>18</td>
<td>9 (50)</td>
<td></td>
<td>19</td>
<td>14</td>
<td>(74)</td>
<td>19</td>
<td>14</td>
<td>(74)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Teberg</td>
<td>US-single</td>
<td>1994</td>
<td>1995</td>
<td>9</td>
<td>2 (22)</td>
<td></td>
<td>9</td>
<td>5</td>
<td>(56)</td>
<td>10</td>
<td>8</td>
<td>(80)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Costeloe</td>
<td>UK + Ireland</td>
<td>1995</td>
<td>1995</td>
<td>22</td>
<td>2 (9.1)</td>
<td></td>
<td>131</td>
<td>26</td>
<td>(20)</td>
<td>298</td>
<td>100</td>
<td>(34)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td>UK-region</td>
<td>1995</td>
<td>1995</td>
<td>241</td>
<td>26 (11)</td>
<td></td>
<td>882</td>
<td>100</td>
<td>(26)</td>
<td>424</td>
<td>186</td>
<td>(44)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Lemons</td>
<td>US-multiple</td>
<td>1995</td>
<td>1996</td>
<td>216</td>
<td>65</td>
<td>(30)</td>
<td>301</td>
<td>151</td>
<td>(50)</td>
<td>379</td>
<td>280</td>
<td>(74)</td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Macfarlane</td>
<td>UK-region</td>
<td>1995</td>
<td>2000</td>
<td>84</td>
<td>0 (0)</td>
<td></td>
<td>162</td>
<td>13</td>
<td>(8)</td>
<td></td>
<td></td>
<td></td>
<td>LB Disch</td>
<td></td>
</tr>
<tr>
<td>Horbar</td>
<td>International</td>
<td>1996</td>
<td>1996</td>
<td>479</td>
<td>112 (23)</td>
<td></td>
<td>767</td>
<td>425</td>
<td>(55)</td>
<td>825</td>
<td>612</td>
<td>(74)</td>
<td>LB Disch</td>
<td></td>
</tr>
</tbody>
</table>

Summary: 1208 41 (3.4) 1946 406 (21) 3671 1623 (46) 4355 2823 (66)

NOTE. Data shown as number (percent) for survivors (Surv).
Abbreviations: LB, All live born infants except otherwise stated; Disch, survived to discharge from institution; NICU, Only NICU admissions.
* Malformations excluded.
† Excluded from present calculations.
### Table 2. Survival in Infants With Birth Weight ≤750 g (1990-2000)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country-center</th>
<th>Birth Date</th>
<th>&lt; 500 g</th>
<th>Survival n (%)</th>
<th>500-600 g</th>
<th>Survival n (%)</th>
<th>500-750 g</th>
<th>Survival n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishida^54</td>
<td>Japan-multiple</td>
<td>1990</td>
<td>66</td>
<td>6 (9.1)</td>
<td>63</td>
<td>17 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philip^56</td>
<td>US-single</td>
<td>1990-91</td>
<td>9</td>
<td>3 (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hack^57</td>
<td>US-single</td>
<td>1990-92</td>
<td>67</td>
<td>1 (1.5)</td>
<td>38</td>
<td>6 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harper^62</td>
<td>US-single</td>
<td>1990-98</td>
<td>39</td>
<td>19 (49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanaroff^1</td>
<td>US-multiple</td>
<td>1991-92</td>
<td>321</td>
<td>74 (23)</td>
<td>869</td>
<td>382 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Battin^64</td>
<td>Canada-single</td>
<td>1991-93</td>
<td>16</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joseph^68</td>
<td>Canada-multiple</td>
<td>1991-96</td>
<td>41</td>
<td>27 (66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottoms^12</td>
<td>US-multiple</td>
<td>1992-93</td>
<td>86</td>
<td>5 (5.8)</td>
<td>49</td>
<td>9 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartlidge^70</td>
<td>UK-region</td>
<td>1993-94</td>
<td>26</td>
<td>1 (3.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevenson^71</td>
<td>US-multiple</td>
<td>1993-94</td>
<td>363</td>
<td>116 (32)</td>
<td>999</td>
<td>490 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teberg^74</td>
<td>US-single</td>
<td>1994-95</td>
<td>22</td>
<td>10 (45)</td>
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<tr>
<td>Tyson^81</td>
<td>US-multiple</td>
<td>1994-95</td>
<td>322</td>
<td>103 (32)</td>
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<tr>
<td>Hernandez^75</td>
<td>US-multiple</td>
<td>1991-96</td>
<td>360</td>
<td>19 (5.3)</td>
<td>247</td>
<td>103 (42)</td>
<td>497</td>
<td>157 (32)</td>
</tr>
<tr>
<td>Costoloe^5</td>
<td>UK-multiple</td>
<td>1995</td>
<td>33</td>
<td>2 (6.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemons^6</td>
<td>US-multiple</td>
<td>1995-96</td>
<td>195</td>
<td>21 (10.8)</td>
<td>317</td>
<td>92 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horbar^78</td>
<td>International</td>
<td>1996</td>
<td>481</td>
<td>80 (16.6)</td>
<td>776</td>
<td>287 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anonymous^82</td>
<td>Aust-region</td>
<td>1997</td>
<td>5</td>
<td>0 (0)</td>
<td>17</td>
<td>5 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darlow^83</td>
<td>NZ-center</td>
<td>1998-99</td>
<td>13</td>
<td>5 (38.5)</td>
<td></td>
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<tr>
<td>Summary</td>
<td></td>
<td></td>
<td>1337</td>
<td>140 (10.5)</td>
<td>2609</td>
<td>845 (32)</td>
<td>2631</td>
<td>1147 (44)</td>
</tr>
</tbody>
</table>

**NOTE.** All infants were live born infants. All survival was evaluated at discharge unless otherwise noted. Data shown as number (percent) for survivors.

^*Survival at 1 month after close of study.

†Survival at 2yr.

‡Malformations excluded.
The reported survival ranges for infants born at 23 weeks gestation were 2%-35%; at 24 weeks were 17%-58%, and at 25 weeks were 35%-85%.11 These wide variations were reported both within and between developed nations. Evidence from Japan provides a unique perspective. Here, the Eugenics Protection Act mandated resuscitation and support of infants born at 22 weeks and they reported that survival at 22 weeks is not impossible. However, the likelihood for survival to discharge from the hospital was still <10% in this population. Even if this is not due to difference in prenatal care, racial difference or regional variation, the very low percent survival in this age group is not encouraging.

The contrary perspective is from a study of practices in developing countries where a majority of neonatal centers consider the gestational age of viability as 28 weeks.19 It could be inferred that “viability” is as much a biologic threshold as it is a socio-economic reality; and in a world where resources are not limitless, this fact needs to be given sufficient consideration.

Most of the evidence for the improbability of technology helping in survival of an infant born at 22 weeks comes from a compilation of available published data from developed nations like United States, Canada, United Kingdom, Japan and Australia; as shown in Table 1. Considering that there is an inherent bias in published data for evaluating results of only those infants that survived long enough to be admitted to the intensive care units, the survival rate of < 3.5% gives us an overly optimistic outcome. Therefore, for all practical purposes, survival of an infant born at 22 weeks is extremely improbable. The fact that this corresponds so closely to the patho-physiologic limit of effective gas exchange in the fetus reinforces its scientific basis.

Evidence From Temporal Trends in Survival of Extremely-Low-Gestational-Age Infants

As shown in Figure 1, the gestational age at which premature infants survived has become lower over the past 30 years. In the early 1900s, survival was highly unlikely in infants < 32-34 weeks. The beginning of neonatology as a discipline in the 1960s saw survivals at much younger GA (28-30 weeks). In the 1970s, 24-26 weeks infant survival became possible with more effective use of neonatal ventilators.20 Surfactant therapy in the late 80s started to show improvements in survival and became standard in early 1990s. The NICHD reported the outcomes of 3 cohorts of very low birth weight infants (<1500 g or 3 lbs. 5 oz) born prior to and after
the licensure of surfactant. Survival steadily improved from presurfactant reports (1987-88) to the mid-1990s. As of 1995-1996, about half (54%) of 501-750 g birth weight infants and over 80% of 751-1000 g infants survived to discharge home. However, a major report from the Vermont-Oxford Network from a total of 118,448 infants (501-1500 g birth weight) born between 1991-1999 from 363 institutions showed no significant improvement in survival rates for infants 501-750 g, especially after 1994. One of the explanations offered to this leveling off of mortality was that, “we may have reached the limits of current technology to support preterm infants at gestational ages near the limits of viability.”

With respect to the earliest gestational age at which survival was seen as a reasonable possibility, there does not appear to have been a significant change since the routine use of prenatal steroid and postnatal surfactant therapy as shown in Figure 1. The NY State Task Force on Life and Law: Report on Fetal Extrauterine Survivability of extremely premature infants in the mid 1980s concluded that 23 weeks was the lower limit of viability. The advent of surfactant replacement therapy for the lungs (1991), increased use of prenatal steroids (mid 1990s) and the use of new and sophisticated ventilatory strategies in the 1990s have not lowered the threshold of viability (Fig 1). This may be considered historical evidence of the gestational age-limit at which viability is considered a reasonable possibility.

Polled Opinions of Health Care Providers and Academics

There have been a number of surveys with questionnaires designed to determine the opinion of doctors, nurses, parents of premature infants and lay people regarding setting limits for active treatment of extremely premature infants. None suggested initiation of aggressive therapy at 22 weeks unless it was an exceptional situation. Guidelines from various professional groups including the NY State Task Force on Life and Law: Report on Fetal Extrauterine Survivability, Canadian Pediatric Society, British Association of Perinatal Medicine, and the American Academy of Pediatrics also reiterate that active treatment of 22 weeks infants is not indicated except in some special situations. The International Guidelines for Neonatal Resuscitation states that “the non-initiation of resuscitation in the delivery room is appropriate for infants with confirmed gestation < 23 weeks or birth weight < 400 g. In cases of uncertain prognosis including uncertain gestational age, resuscitation options include a trial of therapy and noninitiation or discontinuation of resuscitation after assessment of the infant.”

Influence of Site of Delivery On Survival

Does the site of delivery have an impact on the survival or quality of life in survivors? Hack noted that there are wide variations in survival among developed and developing countries. Even among the developed countries like the United States, there are variations in outcome related to the site of the infant’s birth. Yeast recently revisited this issue in a comparison of live births and neonatal mortality (death < 28 days) in the state of Missouri for the periods 1982-1986 vs. 1990-1994. There was significantly decreased mortality with increased levels of care of the birth hospital. Extremely premature infants (500-1000 g) had 66% mortality if born at a center providing only basic newborn care (level 1); 51% mortality at a center with short-term care facilities for sick newborns (level 2), and only 32% mortality at a center equipped to provide comprehensive multispecialty neonatal intensive care (level 3).

A regional study from Vienna, Austria showed a lower morbidity in infants who were transported prenatally in utero to tertiary care centers. In another large study of infants born between 1968-1994 in North Carolina, Bode found decreases in mortality for infants with birth weights 500-1000 g with increasing levels of available care. A regional evaluation from the Victorian Infant Collaborative Study Group in Australia also concluded that the prognosis for infants born at ≤ 27 weeks gestation is better when delivered at tertiary care centers. These studies and others continue to support the survival advantages of birth in hospitals providing comprehensive and subspecialty care for extremely premature infants.
A number of studies have reported on neurodevelopmental outcomes in survivors of extremely low gestational age infants. A summary of the reports of infants born after 1990 classified by gestational age at birth is shown in Table 3. One of the largest and best designed studies on developmental and functional outcomes in infants was recently reported from the NICHD.40 Fourteen hundred and eighty (1,480) surviving infants born between 1993-1994 with birth weights 500-1000 g, were evaluated for neurodevelopmental, neurosensory and functional assessment at 18-22 months of age corrected for their prematurity. Results were reported by 100 g birth weight increments. On the Bayley Scales of Infant Development-II Mental Development Index (MDI), two thirds (66%) of the surviving infants scored <85 and a third (37%) scored <70 (in the mental retardation range). The Psychomotor Development Index (PDI) scores were similar. The incidence of cerebral palsy (abnormal neurological examination) was 17%. The incidence of one or more major neurodevelopmental handicaps (cerebral palsy, mental retardation, blindness or deafness) was seen in 49% of infant survivors born with birth weights 500-1000 g.

### Table 3. Neuro-developmental Disabilities in Survivors of Extremely Low Gestational Age Infants (1990-2000)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country-center</th>
<th>Birth date</th>
<th>Total n</th>
<th>Disabled n (%)</th>
<th>Assess</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hack47</td>
<td>US-single</td>
<td>1990-1992</td>
<td>All GA combined</td>
<td>49</td>
<td>7 (14%)</td>
<td>VHM</td>
</tr>
<tr>
<td>B-Singh58</td>
<td>US-single</td>
<td>1990-1993</td>
<td>Total N = 49</td>
<td>26</td>
<td>5 (20%)</td>
<td>Predict</td>
</tr>
<tr>
<td>Pieuch61</td>
<td>US-single</td>
<td>1990-1994</td>
<td>3</td>
<td>2 (66%)</td>
<td>VHCM</td>
<td>1 yr</td>
</tr>
<tr>
<td>Emsley62</td>
<td>UK-single</td>
<td>1990-1994</td>
<td>5</td>
<td>2 (40%)</td>
<td>VHCM</td>
<td>19 mo-10 yr</td>
</tr>
<tr>
<td>Doyle63</td>
<td>Aust-region</td>
<td>1991-1992</td>
<td>1</td>
<td>0 (0%)</td>
<td>VHCM</td>
<td>18 mo</td>
</tr>
<tr>
<td>Battin64</td>
<td>Canada-single</td>
<td>1991-1993</td>
<td>1</td>
<td>0 (0%)</td>
<td>VHCM</td>
<td>18 mo</td>
</tr>
<tr>
<td>Tin65</td>
<td>UK-region</td>
<td>1991-1994</td>
<td>1</td>
<td>0 (100)</td>
<td>VHCM</td>
<td>1 year</td>
</tr>
<tr>
<td>Jacob66</td>
<td>Austria-single</td>
<td>1991-1994</td>
<td>5</td>
<td>1 (20%)</td>
<td>VHCM</td>
<td>18-24 mo</td>
</tr>
<tr>
<td>Bottoms12</td>
<td>US-multiple</td>
<td>1992-1993</td>
<td>5</td>
<td>4 (80%)</td>
<td>Predict</td>
<td>Disch-120d</td>
</tr>
<tr>
<td>Ahner73</td>
<td>US-single</td>
<td>1993-1997</td>
<td>3</td>
<td>1 (33%)</td>
<td>VHCM</td>
<td>1 yr</td>
</tr>
<tr>
<td>Wood76</td>
<td>UK-region</td>
<td>1995-1997</td>
<td>2</td>
<td>1 (50%)</td>
<td>VHCM</td>
<td>30 mo</td>
</tr>
<tr>
<td>Rijken85</td>
<td>Dutch-region</td>
<td>1996-1997</td>
<td>25</td>
<td>14 (56%)</td>
<td>VHCM</td>
<td>2 yr</td>
</tr>
</tbody>
</table>

Abbreviations: V, visual deficit; H, hearing deficit; C, cerebral palsy; M, mental retardation; Disch, assessment done at discharge; Predict, predicted assessment based on neonatal findings; Assess, parameters assessed at follow-up; Time, age at which follow-up evaluation done.
consecutive extremely low birth weight (<1000 g) survivors born between 1991-1992 in Victoria region of Australia showed significant cognitive, educational and behavioral deficits at 8 years of age compared to normal birth weight controls.42 Furthermore, school function may deteriorate over time as academic tasks become more complex. Botting followed a cohort of 138 very low birth weight infants throughout school and found that the performance in all areas of academic achievement was worse at 12 years old than it was at 6 years.43

Newer evidence has begun to correlate decreased neurological function with decreased brain volume in specific areas of the cerebral cortex even in infants where there were no lesions identified on ultrasound evaluations in the neonatal period.44,45 It is quite possible that the development of the brain in these extremely immature infants does not proceed normally and the reasons may be related to their illness, nutritional deprivation or other unknown factor(s).

Evidence-based Ethics

What are the ethical implications of the evolving data on survival and morbidities for families and health care providers caring for these extremely premature infants? Earlier generations of health care providers had only single center studies, their own hospital’s results and their “hopes” for improved outcomes for these tiniest of patients to guide their decision-making. However, practicing neonatologists and families are now empowered by an evolving literature of short- and intermediate-term survival and neurodevelopmental outcomes.

The ethical implications of this “new” literature encompass a number of areas of potential controversy and conflict including:

1. Where does the current lower limit of viability lie?
2. What is the role of parental input in resuscitation and ongoing care decisions for extremely premature infants in light of current outcomes data?
3. What should happen when health care providers and parents disagree?

The Current Limit Of Viability

Since the advent of modern newborn intensive care the “lower limit of viability” has been re-assessed due to changes in therapies and outcomes. In 1988, the NY State Task Force on Life and Law: Report on Fetal Extrateruterine Survivability, reported that epidemiological and biologic evidence suggested that the lower limit of viability was 23-24 weeks gestational age.21 The studies cited earlier in this review on survival and neurodevelopmental outcomes for extremely premature infants continue to reinforce that we have reached a current lower biologic limit at 23 weeks’ gestation and approximately 400-500 g birth weight. While there have been isolated reports of surviving infants who are born at < 23 weeks’ gestation or with birth weights < 400 g, these unusual survivals probably represent the outliers in any normative population and fail to make a compelling argument for routinely offering resuscitation to less mature and/or smaller infants. Even though the determination of “limit of viability” is a clinically and ethically simplistic goal,46 the vast majority of health care providers in the United States express the need for non-binding guidelines that will establish standards of care while leaving room for individual decisions in exceptional circumstances.47

In addition to the high mortality, especially for infants born at 23-24 weeks’ gestation, evolving information also indicates that extremely premature infants are at very high risk for neurological and cognitive impairment. In the NICHD neurodevelopmental outcomes study of infants born in the mid-1990s, even infants with birth weights close to 1000 g had mean developmental quotients in the low average/borderline range.

The American Academy of Pediatrics (AAP) has published policy recommendations for management of extremely premature infants.34 However, the AAP statement is vague and does not give substantive recommendations. The joint group of the Canadian Pediatric Society and the Maternal-Fetal Medicine Committee and Society of Obstetricians and Gynecologists of Canada have developed practical recommendations based upon available data and provide a good example of evidence-based medicine in this field.32,33 Consistent with the data, the Canadian guidelines recommend 1) withholding resuscita-
tion for infants born at < 23 weeks’ gestation; 2) joint decision-making with families for infants born at 23-24 weeks’ gestation; and 3) routine initiation of resuscitation for most infants born at 25 weeks’ gestation or older.

Important pieces of evidence can be derived from reports from institutions that have tried a policy of resuscitating infants at extremely low gestational ages; and after reviewing the dismal outcomes have reverted their policy.48,49 One is based on a study from Leiden, Netherlands where a policy of resuscitating infants born at <25 weeks resulted in an unacceptably high mortality and morbidity.49 The other is a study based on a 4-year experience (1994-1998) in a single center in California, of instituting aggressive resuscitation for all infants ≥ 450 g or ≥ 22 weeks GA.48 Their review of death and morbidity led them to revise their policy to offer resuscitation only to those infants’ ≥ 500 g or ≥ 24 weeks. Resuscitation below 500 g birth weight or at < 23 weeks was considered only in exceptional circumstances. The available evidence from these quality assessment cycles of “new policy→implementation→ assessment→policy revision”, needs to be considered in designing future policy.

The Role of Parental Input in Resuscitation Decisions for Extremely Premature Infants

The philosophical framework for shared medical decision-making for infants between parents and health care providers recognizes the primary responsibility and right of parents to make medical decisions in the best interests of their children. Within this framework, parents are given considerable latitude to make decisions, even if unpopular with the health care team. However, this responsibility is not absolute and inevitably, there will be occasional conflicts between parents making decisions and health care providers who have a different view of a child’s best interests.

Several reports suggest that the vast majority of neonatologists consider parental wishes when making resuscitation decisions for infants born at 23 weeks gestational age.24,50 However, as gestational age increases by weekly increments from 24 to 26 weeks’ gestation, neonatologists become increasingly uncomfortable with a priori decisions “not to resuscitate.”29 Among other considerations, the knowledge that continued re-evaluation of the benefits of ongoing intensive care after resuscitation can reopen discussions with parents may comfort some neonatologists who are ambivalent about initiating intensive care in tiny babies.

Societal support for the role of parental decision-making in these complex cases is illustrated by the State vs. Messenger case. While legal action was taken against a father who discontinued life support in a NICU from his critically ill 25 weeks gestational age infant, the jury acquitted the father of charges of manslaughter.51 Such tragic cases continue to remind health care providers of the importance of dialogue with families, of consistency with other health care providers in agreements with families, and of the importance of re-evaluating care if the response to initial resuscitation is poor or other complications intervene.52,53

Disagreements Between Parents and Health Care Providers

For those few situations in which health care providers and families find themselves in irreconcilable conflict, several avenues for conflict resolution are present. Often consultation with a peer colleague and continued discussion with the parents will lead to reasoned resolution of the previous disagreement. If that fails, neonatologists should take advantage of ethical consultation or formal review by an infant care review team after informing the parents. The opportunity to openly discuss difficult issues with the full range of health care providers with the family present, if desired, often clarifies medical issues and gives comfort to both the parents and the health care team that the infant’s best interests are being considered and protected. The recommendations of the infant care review team are considered opinions only and are nonbinding.

In extremely unusual cases, either the parents or the health care team will find it necessary to seek legal action to resolve a health care crisis. If a medical decision-making conflict appears to be heading in the direction of outside intervention, formal legal advice must be promptly sought. The physician and health care team must also
realize that legal action is easier initiated than
carried on to its final resolution. The last place
one really wants to be with any medical/ethical
conflict is in a court of law where decisions are
often made based upon narrowly defined legal
precepts. Both the health care provider(s) and
the family may find the outcome unacceptable.

Who decides if the burdens of life saving tech-
nology for a particular infant are worth the ben-
etit? The following is a list of the possible final
decision makers and their challenges:

1. Parent or family unit alone – Historically,
legal opinions have favored the family’s right
to make decisions. Unfortunately the family
in the vast majority of situations lacks com-
plete understanding of the infants’ problems
or potential outcomes and therefore is not in
the best situation to make informed deci-
sions.

2. Parent-Physician team dialogue: This is the
best way to get informed opinion and consent
for potentially burdensome and untested
therapy and gives credence to surrogate (par-
tent) autonomy, gives weight to benefit-risk
analysis and has the potential to avoid non-
malfeasance. However, each circumstance
needs a complete reappraisal of available
data and in practice, there may not be
enough time or opportunity to do this.

3. Institutional policy or protocol: This provides
an equitable approach to the problem but
suffers from lack of autonomy of both the
parent and physician group. Moreover, if dif-
ferent institutions have varying policies, there
will be confusion and the potential for legal
contentions may increase.

4. Societal policy-guidelines: This provides a just
and equitable approach and also takes into
account larger socio-economic and policy
issues. It takes the agony of constant re-inter-
pretation of ethical principles away from the
delivery room or the intensive care unit and
provides a framework in which individual dis-
cussions can best be made. These are models
for effective use of this approach in the guide-
lines in use in Canada and in some states in
the United States. The limitation of parental
autonomy may have to be the price that is
paid with this approach.

Future Directions
What Should We Do With This Evolving
Information?

Given the currently available information on the
survival and intermediate-term neurodevelop-
mental outcomes of extremely premature in-
fants, our efforts should focus upon improving
short- and long-term outcomes for infants for
whom we currently care, not on altering the
lower limit of viability. As part of these efforts, we
should ensure that families are given useful in-
formation both prior to and after delivery to
enhance their decisional capabilities and to em-
power them to advocate for their infants both in
the short and long-term. This information
should include current survival information and
morbidities both for the birth hospital and for
some regionally or nationally recognized com-
parison group. Given the available information
on outcomes of infants based upon the level of
neonatal services in the birth hospital, families
who will potentially deliver an extremely prema-
ture infant should routinely be offered transfer
to a center offering comprehensive neonatal in-
tensive care services, if time and circumstances
allow.

Meeting the needs of developing, former pre-
mature infants will require cooperation and col-
laboration among families, neonatologists, pri-
mary health care providers after discharge, early
interventionists and educators. Neonatologists
need to extend their influence outside the nurs-
ery and into the community to ensure that the
anticipated needs of their smallest patients are
optimally addressed. They should provide data
to local schools and state Departments of Edu-
cation to assist in their planning for the ongoing
educational needs of these tiny survivors. Cur-
rent data suggests that nearly all surviving ex-
tremely premature boys and about two thirds of
girls will require special help in school.

Finally, we need to encourage and support
multicenter, collaborative follow-up efforts to
obtain feedback on the outcomes of these criti-
cally ill infants. Large datasets on extremely pre-
mature infants from birth through adolescence
are essential to assist us in informing parents and
planning for the future of these infants.

The advent of modern newborn intensive
care and critical technologies such as prenatal steroids and surfactant have dramatically enhanced the likelihood of survival for extremely premature infants, especially for those born at greater than 24 weeks' gestation. However, both short- and long-term morbidity remains high. Barring dramatic technological breakthroughs such as an artificial placenta, we have probably reached a biologic limit at 23 weeks' gestation and/or 400–500 g birth weight. The challenge now lies in addressing the issues compromising the quality of survival of the tiniest and most vulnerable of our patients.

Acknowledgment

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