Introduction

- Over past two decades, survival of extremely preterm infants (ELBW) <1000gm or <=27wk GA has gradually improved.

- Advances in:
  - OB care
  - Antenatal referral to major centers
  - Antenatal corticosteroid use
  - Advances in respiratory support (eg, surf, vents)
  - Improved nutrition/TPN
  - Improved nursing care
  - Quality Improvement Initiatives (eg, iatrogenic infections)

Outcomes at 24 to 26 Weeks Gestation

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William H. Tooley Intensive Care Nursery
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Survival vs. intact survival

- What is the current GA at which at least half of the infants survive?
  - 1960s: 30-31 weeks GA
  - Currently: 23-24 weeks GA

- But the pace of improvement in long-term neurodevelopmental outcomes has lagged.

- Concerns remain over long-term outcomes which may influence policy and guidelines for resuscitation.

How to proceed?

- Practice patterns at the threshold of viability are influenced by many factors.

- What should be considered?
  - National/Worldwide data on mortality of ELBW?
  - National/Worldwide data on long-term outcomes?
  - Population/Institution-specific data on mortality and long-term outcomes?
  - Parental wishes (Patient Autonomy)?
  - Physician judgment (Futility)?
**Describing “survival limits”**

- **<23 weeks GA (below ~<400-500gm):**
  - Outcomes remain poor
  - Mortality > 90%
  - Morbidity among survivors even worse.

- **>26 weeks GA (above ~750gm):**
  - Outcomes are pretty good
  - Mortality ≤ 30%

- What happens in between 23-26 weeks?
  - “The Gray Zone”

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**Grey zone by birth weight or gestational age?**

500gm (~23wk GA) to 1000gm (~27wk GA)

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**What is the data on outcomes of extremely low birth weight infants?**

**National/Worldwide MORTALITY**

- **346 Vermont Oxford Network NICU’s worldwide**
- **n = 4172 infants born with BWt=400-500gm**
- **mean BWt: 457.8gm**
- **mean GA: 23.3 ±2.1 weeks**
- **52% died in DR**
- **63% of initial survivors died in NICU**
- **Overall survival to discharge: 17%**

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Cotéelie K, et. al., EPICure2, 2009
Robertson C, et. al., Ped Neurol, 2009
Singh J, et. al., Pediatrics, 2007
Vohr B, et. al., Pediatrics, 2000

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Lucey, JF, et. al., Vermont Oxford Network, Pediatrics, Jun 2004
Characteristics of Survivors vs. Deaths among 400-500gm (VON: 1996-2000)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NICU Survivors (N = 690)</th>
<th>NICU Deaths (N = 1253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age</td>
<td>25.3 ± 2.0 wk</td>
<td>23.8 ± 2.0 wk</td>
</tr>
<tr>
<td>Mean birth weight</td>
<td>467.4 ± 27.1 g</td>
<td>460.5 ± 28.4 g</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>14/690 (2%)</td>
<td>50/1253 (4%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>228/690 (33%)</td>
<td>593/1253 (47%)</td>
</tr>
<tr>
<td>Singleton</td>
<td>538/690 (78%)</td>
<td>878/1253 (68%)</td>
</tr>
<tr>
<td>SGA</td>
<td>559/690 (79%)</td>
<td>550/1252 (44%)</td>
</tr>
<tr>
<td>1-min Apgar &lt; 4</td>
<td>322/656 (48%)</td>
<td>806/1226 (66%)</td>
</tr>
<tr>
<td>Delivered by cesarean</td>
<td>523/690 (76%)</td>
<td>553/1252 (44%)</td>
</tr>
<tr>
<td>Prenatal care</td>
<td>668/690 (97%)</td>
<td>1169/1245 (94%)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>530/688 (79%)</td>
<td>668/1247 (53%)</td>
</tr>
</tbody>
</table>

ELBW 28d survival in the 1990’s
EPICure Study (Mar ‘95 – Dec ‘95)

- All ELBW births in UK (276 Maternity Hosp)
- 4004 births recorded ≤ 25 (20-25) wk GA
  - <23 wk GA: 92% died in DR (median BWt=490gm)
  - 23 wk GA: 50% died in DR (median BWt=600gm)
  - 24 wk GA: 18% died in DR (median BWt=680gm)
  - 25 wk GA: 8% died in DR (median BWt=760gm)
- 811 admitted to NICU
- 495/811 (61%) died before discharge
- 55% deaths d/t withdrawal of care

ELBW 28d survival after 2000
EPICure 2 (study period: 2006)

- After improvements in NICU care, repeated Epicure study in 2006.
- 4008 eligible births at <27 wks (22-26 6/7th wk)
- 17% terminations and 22% antepartum stillbirths
- Outcomes reported for n=2180 (alive at onset of labor, or delivered by c/s prior to onset of labor)

Costeloe K, et. al., EPICure Study Group, Pediatrics, 2000

Costeloe K, et. al., 2009 Pediatric Academic Society Meeting, Baltimore, MD
ELBW survival to 28 days 
EPICure2 (2006)

<table>
<thead>
<tr>
<th></th>
<th>22wk</th>
<th>23 wk</th>
<th>24 wk</th>
<th>25 wk</th>
<th>26 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at labor onset or c/s</td>
<td>258</td>
<td>393</td>
<td>462</td>
<td>515</td>
<td>552</td>
</tr>
<tr>
<td>Intra-partum stillbirth</td>
<td>110</td>
<td>75</td>
<td>51</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Live birth</td>
<td>148</td>
<td>318</td>
<td>411</td>
<td>490</td>
<td>539</td>
</tr>
<tr>
<td>Neonatal death in DR</td>
<td>128</td>
<td>118 (30%)</td>
<td>55 (13%)</td>
<td>21 (4%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>20 (7.7%)</td>
<td>200 (51%)</td>
<td>336 (77%)</td>
<td>469 (91%)</td>
<td>532 (90%)</td>
</tr>
<tr>
<td>Early neonatal death in NICU</td>
<td>9</td>
<td>86</td>
<td>87</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td>Late neonatal death</td>
<td>5</td>
<td>33</td>
<td>60</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>Alive at 28 d</td>
<td>6 (2%)</td>
<td>81 (21%)</td>
<td>209 (45%)</td>
<td>358 (70%)</td>
<td>439 (80%)</td>
</tr>
</tbody>
</table>

Costeloe K, et. al., 2009 Pediatric Academic Society Meeting, Baltimore, MD

What is the data on outcomes of extremely low birth weight infants?

Population/Single-Institution MORTALITY

What is the 28 day survival rate for infants born at 24 weeks gestational age?

A. <5%
B. 25%
C. 45%
D. 75%
Overall survival by GA between 1986 and 2000 (*among survivors to admission)

<table>
<thead>
<tr>
<th>Period</th>
<th>n</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-1989</td>
<td>496</td>
<td>49%</td>
</tr>
<tr>
<td>1990-1999</td>
<td>749</td>
<td>68%</td>
</tr>
<tr>
<td>2000-2002</td>
<td>233</td>
<td>71%</td>
</tr>
</tbody>
</table>

Survival between 500gm-999gm

- n = 1478 live born infants with BWt 500-999gm
- Single Perinatal Center (Case Western Reserve)
- Three epochs examined:
  - Period I (1982-1989): n = 496
  - Period II (1990-1999): n = 749
- Improved 20 month CA survival only through 1990’s:
  - Period I (1982-1989): 242/496 = 49%
  - Period II (1990-1999): 508/749 = 68%
  - Period III (2000-2002): 165/233 = 71%

Survival between 24-28 wk GA

Piecuch, et al., Pediatrics, 2000
What is the data on outcomes of extremely low birth weight infants?

MORBIDITY

EPI Cure (1995) long term follow-up

Do our assessment tools underestimate impairment?

- 6 year outcomes of UK infants born ≤ 25 wk GA.
- 21% of survivors showed cognitive and neurologic impairment by standardized testing
- 41% showed cognitive and neurologic impairment compared to classmates.
- Disability was:
  - Mild: 34%
  - Moderate 24%
  - Severe 22%
  - Disabling cerebral palsy 12%

Marlow, N, et. al., EPI Cure Study Group, New Eng J Med, Jan 2005

Comparing outcomes by periods

1995 (EPI Cure) vs. 2006 (EPI Cure2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1995</th>
<th>2006</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival of admissions to d/c</td>
<td>40%</td>
<td>52%</td>
<td>P&lt;0.0001, sig incr b/t 24-&gt;25 wks (not &lt;24wks), Increased survival in first week.</td>
</tr>
<tr>
<td>% survivors with HC or cysts</td>
<td>15%</td>
<td>13%</td>
<td>NS</td>
</tr>
<tr>
<td>% survivors on O2 at 36 wks</td>
<td>75%</td>
<td>74%</td>
<td>NS</td>
</tr>
<tr>
<td>% survivors treated for ROP</td>
<td>13%</td>
<td>21%</td>
<td>P= 0.008 – Not believed to be increase in ROP disease, but changes in screening and treatment thresholds.</td>
</tr>
</tbody>
</table>

Costeloe K, et. al., 2009 Pediatric Academic Society Meeting, Baltimore, MD

Morbidity among 400-500gm


TABLE 5. Outcomes of NICU Survivors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NICU Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>651/660 (94%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>77/660 (11%)</td>
</tr>
<tr>
<td>PDA</td>
<td>335/660 (52%)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>447/660 (65%)</td>
</tr>
<tr>
<td>Surgical PDA ligation</td>
<td>96/660 (14%)</td>
</tr>
<tr>
<td>Coagulase-negative staph sepsis</td>
<td>253/667 (37%)</td>
</tr>
<tr>
<td>Late bacterial sepsis</td>
<td>351/667 (27%)</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>366/667 (55%)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>76/667  (11%)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>60/660 (9%)</td>
</tr>
<tr>
<td>Cranial ultrasound obtained</td>
<td>677/660 (98%)</td>
</tr>
<tr>
<td>IVH (grades 1-4)</td>
<td>579/667 (26%)</td>
</tr>
<tr>
<td>Severe IVH (grades 3-4)</td>
<td>55/667 (8%)</td>
</tr>
<tr>
<td>ROP examination performed</td>
<td>670/660 (97%)</td>
</tr>
<tr>
<td>ROP</td>
<td>596/660 (88%)</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>268/660 (40%)</td>
</tr>
<tr>
<td>Chronic lung disease at 36 wks</td>
<td>498/667 (74%)</td>
</tr>
</tbody>
</table>

Lucey, JF, et. al., Vermont Oxford Network, Pediatrics, Jun 2004
Comparing outcomes by periods
Intact survival in the 1990’s (Case Western Reserve)

Comparing outcomes by periods
Intact survival after 2000 (Case Western Reserve)

Comparing outcomes by periods
Intact survival after 2000 (Case Western Reserve)

Outcomes at 18-24 months of ELBW
400-1000gm (VON:2000-2005)

**TABLE 6** Neurodevelopmental Outcomes at 20 Months’ CA

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>12(3)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>.009</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>13(5)</td>
<td>5(2)</td>
<td>2(2)</td>
<td>.003</td>
</tr>
<tr>
<td>Hyptertrophy</td>
<td>16(5)</td>
<td>2(1)</td>
<td>18(2)</td>
<td>.017</td>
</tr>
<tr>
<td>Severe dependent hydrocephalus</td>
<td>4(2)</td>
<td>1(1)</td>
<td>3(2)</td>
<td>.321</td>
</tr>
<tr>
<td>Blindness</td>
<td>10(3)</td>
<td>4(2)</td>
<td>2(1)</td>
<td>.003</td>
</tr>
<tr>
<td>Death</td>
<td>6(2)</td>
<td>3(1)</td>
<td>1(1)</td>
<td>.003</td>
</tr>
</tbody>
</table>

* Severe disability: bilat. blindness, hearing impairment req amplification, inability to walk without support, CP, or Bayley MDI<70.

2001-2005 combined cohort for 400-1000gm BWt
- eligible infants = 6,636
- evaluated at 10-24mos = 3745
- severe disability (among survivors) = 31.5%
University of California, San Francisco
William H. Tooley Intensive Care Nursery
High-Risk Follow-up Clinic Outcomes

- 24 weeks
  - 60% survival
  - 21% “intact survival” with normal/borderline cognition
- 25 weeks
  - 70% survival
  - 38% intact
- 26 weeks
  - 75% survival
  - 40% intact
- 28 weeks
  - >85% survival.
  - follows bell-shaped curve

What is the “intact survival” (at >18 month follow-up) for ELBW infants born at 25wks GA?

A. 10-20%
B. 35-45%
C. 60-70%
D. 75-85%

AAP and ACOG Statements

- ACOG Practice Bulletin: No 163, Pediatrics, 1995

“Perinatal Care and the Threshold of Viability”

- Emphasizes need to inform parents of survival rates and outcomes to clarify risks and benefits of different approaches to treatment.
- Stresses importance of keeping parents aware throughout the infant's course of the potential complications of prolonged ICU care.

Predicting outcomes?

- Neonatal Research Network of the NICHD
- 4446 infants born at 22 to 25 weeks’ gestation
- Related risk factors to likelihood of:
  - survival
  - survival w/o profound ND impairment
  - survival w/o ND impairment at 18-22 months
- Multivariate analysis found improved outcomes associated with four factors (independent of GA): antenatal steroids, female sex, singleton birth and higher birth weight.


Emphasizes need to inform parents of survival rates and outcomes to clarify risks and benefits of different approaches to treatment.

Stresses importance of keeping parents aware throughout the infant’s course of the potential complications of prolonged ICU care.
Conclusions

- Survival of ELBW infants (<1000gm) has gradually improved in last 20 years.
- Similar improvements in neurodevelopmental outcomes lagged in the 1990’s but maybe improving since 2000.
- However, cognitive and neurologic impairment is still common among ex-ELBW children at school age and current assessment tools may underestimate impairments in ex-ELBW children.
- Discussions with parents must include the most up to date information on survival and outcomes to properly weigh risks and benefits in the current era.

Thank You