Resuscitation in the delivery room: what’s new for what’s blue

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Topic outline:
from consensus to controversies

- Consensus
  - NRP resuscitation guidelines
- Advances
  - Meconium management
- Controversies
  - Room air resuscitation
  - Non-initiation/discontinuation of resuscitation
    (at the limit of viability)

Resuscitation in infants

- Long-standing practice of mouth-to-mouth resuscitation
  - “And the Lord God formed man from the dust of the ground and breathed into his nostrils the breath of life, and the man became a living being (Genesis 2:7).”
- Estimated 10% of newborns require intervention
  - 4-7 million newborns worldwide
  - 23,000 in US (AHA, JAMA, 1992)
- More likely to need resuscitation at birth than any other time save the last day of life.
- High likelihood of requiring resuscitation
  - Prematurity
  - Fetal distress
  - Birth trauma
  - Congenital anomalies
  - Often require more intensive resuscitation
  - Special adjustments to routine neonatal resuscitation

Resuscitation in infants

Changes in NRP guidelines: consensus

- Assessment: “Is the baby pink?” deleted
- Selective intubation for meconium
- Medications: IV epinephrine preferred to ET
- Temperature control
- New technologies
  - Endotracheal CO₂ detection for ET placement
  - Laryngeal mask airway (LMA) if intubation attempts fail
  - T-piece resuscitator
- Out-of-hospital resuscitation
- Resuscitation of preterm infants
  - Compressed air and oxygen
  - Blender
  - Pulse oximetry
- Current investigation: room air resuscitation; high-dose epinephrine; hypothermia
- Controversy: discontinuation/non-initiation of resuscitation

Airway management: how to prevent meconium aspiration?

Background on suctioning

- Combined suctioning effective, safe, and reduces incidence of MAS
  - Efficacy in preventing MAS
  - Endotracheal [Gregory et al, 1974]; perineal suction effective [Carson et al, 1976]
  - Aggressive suction reduced MAS incidence and death (>21,000 stained infants) (Wiswell and Tuggle)
  - Un-suctioned infants have increased risk PPHN, pneumothorax (>2X), long-term mechanical ventilation
  - Safety: ET suction safe (by Apgars) and prevents MAS & death [Ting and Brady, 1977]
  - Reports of dangers of routine endotracheal suctioning
    - Retrospective data showing increased use of ET suction with potential risks [Sepkowitz, 1987]
    - Persistent hoarseness/stridor in 2 of 306 infants [Linder et al, 1988]
    - Other complications transient, some rare complications severe:
      - Brachycephaly, laryngospasm, atelectasis trauma, perforation of pharynx or larynx
  - 1992 Guidelines (AAP/AHA)
    - No endotracheal suction if delivery suctioning at perineum, the MSAF, and vigorous infants
    - Immediate intubation suctioning indicated for:
      - Meconium staining with fetal distress, or thick/moderately thick/mucoid meconium
      - Depressed infants (requiring positive pressure)
    - Reports of danger for meconium below cords based on judgment
    - More recent preliminary study showed no difference in MAS with suctioning, but no randomized controlled clinical trials until 2000

- Prospective, randomized multi-center controlled trial
- No informed consent by parents
- n= 2094 vigorous meconium-stained term infants (≥ 37 wks GA, assessed immediately after birth):
  - HR> 100,
  - spontaneous respiratory activity,
  - some muscle tone (spontaneous movement/extremity flexion)

1051 INTUBATION; 1043 EXPECTANT MANAGEMENT

Results:
- Groups had similar clinical characteristics
- Apgar scores at 1 minute lower in intubated infants (p< 0.002)
- Overall incidence of MAS (n=62) did not differ:
  - INTUB 3.2% vs EXPECT 2.7%, NS

Intrapartum perineal suctioning

- Evidence supporting standard of care
  - Carson et al (1976): study of ET intubation + intrapartum suctioning
  - Wiswell et al: study of selective endotracheal suction for vigorous infants
    - higher rate of MAS in those who did not receive intrapartum suctioning before delivery of shoulders vs those suctioned 8.5% vs 2.7%, OR 3.35 (1.55, 7.27)

- Current controversy
  - Timing of perineal suctioning
    - No difference in MAS between early OB suctioning (before delivery of chest) and late OB suctioning (after delivery of chest) (Falciglia et al.; Falciglia et al.)
  - Recent –and the only– RCT of perineal suctioning in 2514 patients with any MSAF in 12 hospitals (Vain et al.) found no significant differences in:
    - incidence of MAS -- 52 (4%) vs 47 (4%); RR = 0.9 (0.6, 1.3)
    - need for mechanical ventilation -- 24 (2%) vs 18 (1%); RR = 0.8 (0.4, 1.4)
    - mortality -- 9 (1%) vs 4 (0.3%); RR= 0.4 (0.1, 1.5)
    - duration of oxygen treatment, mechanical ventilation, or hospital care.

Recent studies: Surfactant Rx for MAS

Rationale: Meconium inhibits surfactant function:
- Inhibition of surface tension lowering properties of surfactant
- Displacement of surfactant from alveolar surfaces
- Cytotoxic effect of type II pneumocytes
- Decreased levels of SP-A and SP-B

- Halliday et al 1996 (54 infants Rx’d w/ Curosurf, 1988-95):
  - 18% had marked response, 44% had minimal/no response
  - improved oxygen index from 25 (at 1-2 h) to 10 (at 12-24 h)
  - 81% survived; 20% PTx, 4% pulmonary hemorrhage, 7% ICH
- Findlay et al 1996 RCT of 40 infants Rx’d w/ Surfactant:
  - improved oxygenation cumulatively after 2nd and 3rd doses
  - no air leaks + 1 ECMO in rx’d vs 6 air leaks and 6 ECMO in controls (p<0.05).
  - No mortality either group.
  - reduced risk for ECMO RR = 0.64 (95%CI: 0.46 – 0.91)
  - no difference in mortality RR = 1.86 (95%CI: 0.35 – 9.89)

Is room-air resuscitation a good idea?

Controversy

Brief history: benefits and risks of supplemental oxygen

- 1604: Sendivogius discovered oxygen (aerial nitre) – "elixir of life"
- 1772-80: Re-discovery (Scheele, Priestly, Lavoisier) leads to increased use in adult respiratory diseases
- 1780: After first administration to newborns (mouth-to-mouth), increasing use of oxygen for infants from 1800s-1950s
- 1942-1954: Oxygen improved survival of preterm infants with RDS
- 1954: Unmonitored oxygen use linked as causal factor in ROP

Physiologic benefits of oxygen

- Rationale
  - Requirement for aerobic metabolism
  - Reverses normal intrapartum fetal hypoxia and hypoxic depression of ventilation and myocardial function
  - Constriction → closure of ductus arteriosus
  - Overcomes diffusion barriers
  - Pulmonary vasodilatation
  - Better survival and outcome in normoxic infants
- Oxygen has become one of the most frequently used drugs
  - first-line resuscitative measure without rigorous examination of safety and efficacy
  - conflicting guidelines for use of oxygen in resuscitation at birth

- Studies comparing room air versus oxygen for resuscitation
Resair 2 study (Saugstad 1998)
Quasi-randomized unmasked study room air versus oxygen resuscitation in 609 infants (147 preterm)
- No difference in heart rates
- Apgar scores same or better
  - 1 min Apgar higher in RA group
  - 5 and 10-minute Apgars similar
- Delay in time to first cry in oxygen group
  - 1.1 min in RA group
  - 1.5 min in O2 group
- Larger proportion with first breath @ >3 minutes
  - 9.9% in RA group
  - 19.2% in O2 group

BUT,
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Adverse outcomes:
Room air at least equivalent to oxygen resuscitation

<table>
<thead>
<tr>
<th>Event</th>
<th>RA</th>
<th>O2</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 7 d</td>
<td>12.2</td>
<td>15.0</td>
<td>0.78 (0.49-1.26)</td>
</tr>
<tr>
<td>Death within 24 d</td>
<td>13.9</td>
<td>19.0</td>
<td>0.69 (0.44-1.09)</td>
</tr>
<tr>
<td>Death within 7 d or HIE</td>
<td>15.0</td>
<td>20.7</td>
<td>0.76 (0.43-1.35)</td>
</tr>
<tr>
<td>HIE grade II or III</td>
<td>18.3</td>
<td>17.1</td>
<td>0.94 (0.62-1.45)</td>
</tr>
</tbody>
</table>

Long-term outcome similar between two groups
Weight, length, head circumference
Development
Sit, pull up, stand, walk
Qualitatively no “abnormal development”

- Shorter time to regular respiration w/ RA
- Shorter time to first cry (by 0.5 min)

- Hyperoxemia and length of PPV associated with oxidative stress
- Hyperoxia → prolonged end-organ oxidative stress

Meta-analysis:
332 term and some preterm infants with BW>1000g
- Only 11% randomized and masked some infants double counted

Failure of Resuscitation
- Hyperoxic-ischemic encephalopathy
  - Death, 100<sup>th</sup> percentile
  - Seizure, 50<sup>th</sup> percentile
  - Fluid in brain, 50<sup>th</sup> percentile

Humans 2001, Lancet
- Longer time to regular respiration w/ RA
- Shorter time to first cry (by 0.5 min)

- Hyperoxia and leukemia
  - Naumburg 2002: Case-control study from Sweden, retrospective data from 578 medical charts
  - Overall OR 2.57 (1.21-6.82)
  - With PPV>3 minutes: OR 3.54 (1.16-10.8)

- Oxygen and cancer
  - 48 cancers in 60,000 pregnancies
  - 1 min Apgar<7: HR 2.27 (1.39-3.72)
  - Oxygen>3 min: HR 2.87 (1.46-5.66)
  - Adjusted for Apgar: HR 1.39 (ns)

- Decrease in respiratory rate, increase in work of breathing (Morton 1992)
- 5 minutes of 100% O2

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Guidelines

- WHO 1997
  - “Additional oxygen is not necessary for basic resuscitation…when the newborn’s colour does not improve despite effective ventilation, oxygen should be given if available”

- ILCOR 2005
  - “Insufficient evidence to specify the concentration of oxygen to be used at initiation of resuscitation”
  - “Lung inflation/ventilation should be the priority”
  - “Excessive tissue oxygen may cause oxidant injury and should be avoided, especially in the premature infant”

Sensible recommendations

- Most newborns needing resuscitation respond to PPV
- Set routine FiO2 for resuscitation
  - Consider starting at 40% O2 or lower
- Special caution in resuscitation of preterm infants
- Have 100% O2 available if necessary, especially for severe asphyxia
- Ensure equipment to allow titration of FiO2
- Early titration of FiO2 based on repeated clinical assessment that infant’s response is unacceptable

Non-initiation and discontinuation of resuscitation

- AAP/NRP (2000)
  - At the time of delivery, and regardless of the circumstances of the delivery, the medical condition and prognosis of the newly born infant should be assessed. At that point, decisions about withholding or discontinuing medical treatment that is considered futile may be considered by the medical care providers in conjunction with the parents acting in the best interest of their child.

Non-initiation:
- Confirmed gestation < 23 weeks
- Birthweight < 400 grams
- Trisomy 13 or 18

Discontinuation:
- After 15 minutes of absent heart rate despite resuscitation

ACOG: No published cut-off criteria

Population-based survival data:
EPICare study (UK)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>22 wks (n=138)</th>
<th>23 wks (n=241)</th>
<th>24 wks (n=382)</th>
<th>25 wks (n=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died in DR</td>
<td>116 (84%)</td>
<td>110 (46)</td>
<td>84 (22)</td>
<td>67 (16)</td>
</tr>
<tr>
<td>Admitted to ICN</td>
<td>22 (16)</td>
<td>131 (54)</td>
<td>298 (78)</td>
<td>357 (84)</td>
</tr>
<tr>
<td>Died in ICN</td>
<td>20 (14)</td>
<td>105 (44)</td>
<td>198 (52)</td>
<td>171 (40)</td>
</tr>
<tr>
<td>Survived to d/c</td>
<td>2 (1)</td>
<td>26 (11)</td>
<td>100 (26)</td>
<td>186 (44)</td>
</tr>
</tbody>
</table>

Futility vs beneficial treatment

<table>
<thead>
<tr>
<th>% respondents</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 wks (1-6)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22 wks (6-10)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22 wks (10-15)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22 wks (15-20)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22 wks (20-25)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>22 wks (25+</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td></td>
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(Furtado et al. J Pediatr 2004)
Thresholds for resuscitation: California

Resuscitation preferences differ: parents opt for more aggressive intervention than physicians for extremely premature infants (< 26 wks GA)

Survival without severe IVH or severe ROP:
by EGA and BW

<table>
<thead>
<tr>
<th>BW</th>
<th>23 wks</th>
<th>24 wks</th>
<th>25 wks</th>
<th>26 wks</th>
<th>27 wks</th>
<th>28 wks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>250-500</td>
<td>5%</td>
<td>20%</td>
<td>30%</td>
<td>20%</td>
<td></td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>501-750</td>
<td>17%</td>
<td>34%</td>
<td>51%</td>
<td>63%</td>
<td>78%</td>
<td>65%</td>
<td>46%</td>
</tr>
<tr>
<td>751-1000</td>
<td>39%</td>
<td>53%</td>
<td>72%</td>
<td>83%</td>
<td>85%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>1001-1250</td>
<td>71%</td>
<td>85%</td>
<td>93%</td>
<td></td>
<td></td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>1251-1500</td>
<td>82%</td>
<td>89%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>Total</td>
<td>14%</td>
<td>33%</td>
<td>50%</td>
<td>68%</td>
<td>82%</td>
<td>88%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Pediatrics, 1998-2000 (11,252 neonates from 98 hosps in 26 states)

Quality of life of NICU graduates

- NICU graduates’ perspective
  - While 10% of ELBW infants at age 20 had neurosensory impairments (Hack et al. 2002), nearly 1/4 of ELBW adolescents (and parents) rated their health as excellent or nearly so (just < ratings by normal BW controls) (Saper et al. JAMA 1998, Pediatrics 2000).
  - “[O]ne who has never known the pleasures of mental operation, ambulation, and social interaction surely does not suffer from their loss as much as one who has….Life and life alone, whatever its limitations, might be of sufficient worth to him.” (John Robertson)
- Fiscal “value of life”
  - Value of one year of life = $70,000 - $100,000
  - From willingness to pay studies (air bag, fire alarm)
  - Cost/QALY of neonatal care in context (Chapman, 2000):
    - Hip replacement $2,000
    - Care for <1,000g $6,101
    - Kidney transplant $7,500
    - Hospital hemodialysis $35,000

Current milieu for decision-making:
parents, guidelines, and the media

- “...guidelines continue to be controversial, and the families of infants born at 21 or 22 weeks may pressure clinicians to resuscitate these infants. The situation is becoming more common as a result of increasing rate of premature births, advanced maternal age, the increased use of assisted reproductive technology, and the publicity about ‘miracle babies’ in the media.”

Setting limits at the border of viability: Should we?

- Lorenz and Paneth, J Pediatrics 137:593, 2000
  - Those that (most) everyone agrees should receive intensive care: ≥ 25 wks.
  - Those that everyone agrees should not be intubated and ventilated: ≤ 22 wks.
  - Those in optional intensive care zone: 23-24 wks (500-650 g AGA) “where disagreement about appropriateness of intensive care is both ethical and legitimate.”
- UCSF protocol: fetal distress and neonatal resuscitation
  - Guidelines apply only if good data on fetal GA
  - Based on Perinatology & Neonatology discussions with family
  - GA ≥ 23/67 wks
    - No C/S for distress
    - Neonatology
      - Present if > 500g
        - Delivery, trial of resuscitation
        - Discharged: 2/18/2007
        - “Trial of therapy” (Meadow et al.)
US federal legislation

- Child Abuse Prevention and Treatment Act (CAPTA), 1984
  - Mandates that quality-of-life considerations are not permissible in decision-making involving infants < 1 year of age
  - Ties federal funding for state child protective services to local implementation of federal standard

- Emergency Treatment and Labor Act (EMTALA)
  - An enforcement statute obligating providers to medically stabilize or transfer any “person” or “individual” presenting to a hospital with emergency medical condition

US federal legislation

- Born Alive Infant Protection Act of 2002
  - Legal definition (2002): any infant “born alive” defined as a person regardless of gestational age or the means by which the delivery occurs, and accordingly has a right to appropriate medical care
  - Guidelines for enforcement (April 2008):
    - Requirements:
      - “. . . a prudent layperson observer” assessment
      - Conclusion: based on the born-alive infant’s appearance or behavior, that the born-alive infant were suffering from an emergency medical condition
      - “. . . hospital and its medical staff . . . required to perform a medical screening examination. . . ”
      - “. . . the born-alive infant were suffering from an emergency medical condition, there would then arise an obligation to admit the infant, or to comply with either the stabilization requirement or the transfer requirement . . . ”
  - Violations could be investigated under EMTALA or CAPTA
  - “. . . we will investigate all circumstances where individuals and entities are reported to be withholding medical care from an infant born alive in potential violation of federal statutes for which we are responsible.”
  - DHHS “would take proactive steps to educate state officials, health care providers, hospitals, and child protection agencies about their obligations to born-alive infants.”

Effects of BAIPA legislation: neonatologists’ perspectives

- Majority of neonatologists unaware of both legislation and enforcement guidelines
- Enforcement of BAIPA unfavorably regarded:
  - Affect options to withhold or withdraw life-sustaining medical therapies: 61%
  - Unethical palliative care only options for infants who are unlikely to survive: 67%
  - Increase the number of premature infants being resuscitated: 91%
  - Could lead to overly aggressive treatment of infants who will not survive: 91%

Cost/utility analysis (Sendowski et al., 2005)
- Mandated resuscitation of live born immature infants (20-24 wks) would save more (n=49) damaged than unaffected (n=30) children, at a cost of $2,425,781 / life saved

Legal precedent: Miller v. HCA (Texas 2003) (above, with Drs. MC Allen and S Korones)
- Grants physicians the unilateral right to resuscitate marginally viable newborns regardless of parental preference given “emergent circumstances”
- “… impossible for the courts to calculate the relative benefits of an impaired life versus no life at all.”
- “Below a certain age of gestation no baby should be kept going without a very thorough scrutiny of what the prognosis for that baby is.” - Baroness Warnock of the UK Nuffield Council on Bioethics
- “It is expensive to keep adults alive who may not pull through in intensive care but, in their case, we do not say ‘let’s use the money for something else.” - Bonnie Green on Bliss, UK charity focused on prematurity
- “One bioethical issue, however, is as intractable today as it was 30 years ago: . . . the extent of parental authority to refuse [or insist on] life-sustaining medical treatment for an extremely premature infant. Who decides for the newborn, and on what basis, when there is conflict between the parents and the physician?” - George Annas
- If I do not speak for myself, who will? If not now, when? (Torah)

Diverging opinions