KEY ISSUES IN NEONATOLOGY
2018

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Research into the effectiveness of exogenous surfactant for the prevention and treatment of HMD has been distinguished by a particularly high standard of design and execution. Is it too much to hope that the continuing record of accomplishment in the surfactant world will encourage the advocates of ECMO to adopt equally valid research strategies in the future? J. SINCLAIR
1. Worked in Adams’ laboratory in Los Angeles, California in the 1960s and the 1970s

2. Returned to Japan and treated ten preterm babies with a modified natural surfactant (Surfactant-TA)

Tetsuro Fujiwara
1931 –
• Surfactant TA
• 10 infants
• 30 wk; >1500 g
• 9 had PDA
• 2 died

Treatment of idiopathic respiratory distress syndrome with continuous positive airway pressure

<table>
<thead>
<tr>
<th>Weight</th>
<th>N</th>
<th>(\text{PaO}_2) (pre)</th>
<th>(\text{PaO}_2) (post)</th>
</tr>
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<tbody>
<tr>
<td>930-1500</td>
<td>10</td>
<td>37.1</td>
<td>116.4</td>
</tr>
<tr>
<td>1501-2000</td>
<td>5</td>
<td>38.1</td>
<td>114.8</td>
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<tr>
<td>2001-3830</td>
<td>5</td>
<td>48.6</td>
<td>96.0</td>
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</tbody>
</table>

Bill Silverman

“We cannot always make our patients better but we can always make them worse!”
KEY ISSUES IN NEONATOLOGY

• HISTORY/FIRST DO NO HARM/Q.I
• CHANGES IN SURVIVAL/CENTER VARIABILITY
• ANTENATAL STEROIDS
• CORD CLAMPING
• SURFACTANT/INHALED CORTICOSTEROIDS
• SCREENING FOR CCCHD
• OXYGEN
• NEC
KEY ISSUES IN NEONATOLOGY

• BPD AND MESENCHYMAL STEM CELLS
• BILIRUBIN
• PDA
• IMPROVING LONG TERM OUTCOME
  – HUMAN MILK/NUTRITIONAL SUPPORT
  – SINGLE FAMILY ROOMS
  – STEM CELLS FOR CEREBRAL PALSY
KEY LESSONS LEARNED

• **SURVIVAL CAN BE IMPROVED**

• **MANY TRIALS HAVE CONFLICTING OUTCOMES – CLEAR BENEFITS BUT HARM MAY INCLUDE INCREASED MORTALITY**

• **AGGRESSIVE NUTRITIONAL SUPPORT IMPROVES OUTCOMES - HUMAN MILK IS VITAL**
<table>
<thead>
<tr>
<th>Year</th>
<th>Problem</th>
<th>Treatment</th>
<th>Iatroepidemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940-1960</td>
<td>Respiratory distress</td>
<td>Liberal use of $O_2$</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>Blindness from ROP</td>
<td>Restriction in use of $O_2$</td>
<td>Increased mortality and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cerebral palsy</td>
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FIRST DO NO HARM-ALL THESE INTERVENTIONS INCREASED MORTALITY

- DELIVERY ROOM – starting with room air in very immature babies INCREASED MORTALITY –

- 85-89% SATURATION VERSUS 90-94% SUPPORT AND BOOST TRIALS

ANTENATAL CORTICOSTEROIDS- DECREASE MORBIDITY AND Mortality except in developing world .

Increased use in Late Preterms
FIRST DO NO HARM-ALL THESE INTERVENTIONS INCREASED MORTALITY

- Sustained inflation – mortality first 48 hours
- JAUNDICE EXTREMELY PRETERM- Brenda Morris NICHD Trial - INCREASED MORTALITY IN AGGRESSIVE PHOTOTHERAPY GROUP BUT FEWER HEARING AND NEURO DEVELOPMENTAL PROBLEMS
- Bassler – Budesonide Mortality  BPD
- Prolonged antibiotics - Longer than 5 days increased mortality - Pediatrix
Differential Mortality in Low vs High $O_2$ Target Groups

Walsh MC, Di Fiore JM, Martin RJ & SUPPORT Investigators: JAMA Pediatr 2016
Sustained inflation to Aerate Infants’ Lungs (SAIL) Trial

- PIs: H. Kirpalani, M. Keszler, P. Davis, S. Ratcliffe
- Population: (infants 23-26 weeks gestation requiring resuscitation
- SI: 20 cm H₂O x 15 seconds and if needed 25 cm H₂O x 15 seconds
Sustained inflation to Aerate Infants’ Lungs (SAIL) Trial

- Study stopped by the DSMB after 460/592 infants were enrolled*
- There was no statistically significant reduction in the primary outcome of Death/BPD in either of the gestational age strata
- Early death (< 48 hours) was increased in the SI group. (5.29 (CI 1.6-18.2)
PREMATURITY AND SURVIVAL

• Very early deliveries result in the majority of neonatal deaths and more than 40% of infant morbidity.

• An increasing number of extremely low birth weight infants now survive with proactive care.
According to CDC, the mortality rate for US preterm infants was 3.46% in 2013, a survival rate of more than 96%. (In 2016 CDC reported 9.8% prematurity rate up from 9.6% in 2015)
Survival in Preterm Infants; an International Comparison of 10 national Neonatal Networks
HeleniusK Pediatrics 2017

**METHODS:**

- A cohort study of very preterm infants, born between 24 and 29 weeks' gestation and weighing <1500 g, admitted to participating neonatal units between 2007 and 2013 in the International Network for Evaluating Outcomes of Neonates.
RESULTS:

• Network populations differed with respect to rates of cesarean birth, exposure to antenatal steroids and birth in non tertiary hospitals.

• Network Survival Ratios were highest in Japan (SR: 1.10; 99% C.I: 1.08-1.13) and lowest in Spain (SR: 0.88; 99% CI: 0.85-0.90).
GA-specific survival for infants (24–29 weeks’ gestation, birth weight <1500 g) born between 2007 and 2013 and admitted to neonatal care in the iNeo networks.
Survival in Preterm Infants: an International Comparison of 10 national Neonatal Networks

HeleniusK Pediatrics

RESULTS:

- The overall survival differed from 78% to 93% among networks, the difference being highest at 24 weeks’ gestation (range 35%-84%).
- The median age at death varied from 4 days to 13 days across networks.
RESULTS:

- **Survival rates increased and differences between networks diminished with increasing gestational age (GA) (range 92%-98% at 29 weeks' gestation); yet, relative differences in survival followed a similar pattern at all GAs.**
CONCLUSIONS:

• These findings warrant further assessment of the representativeness of the study populations, organization of perinatal services, national guidelines, philosophy of care at extreme G.A.s,

• HELENIUS K., PEDIATRICS 2017 Dec;140(6).
CENTER VARIABILITY

- Neonatal intensive care units (NICUs) aim to provide safe, high-quality medical and surgical care for all newborns.

- The creation of, and widespread participation in, NICU quality collaboratives has no doubt accelerated progress in the field of neonatal quality improvement and safety.

- However, there still remains limited evidence of overall efficacy of these collaboratives.
This unexplained variability in outcomes between NICUs begs the question: What is the secret sauce? Why do some NICUs consistently outshine others in spite of the application of the same ‘potentially best practices’?
To answer these questions, it becomes necessary to determine those factors that contribute to success or failure of improvement programmes, including less tangible aspects such as NICU culture/environment, leadership, team work and organizational structure.
• Overall rates of active treatment ranged from
• 22.1% ([IQR], 7.7 to 100) among infants born at 22 weeks G.A
• 99.8% (IQR, 100 to 100) among those born at 26 weeks of gestation
• An estimated 2.6 million newborns died in 2016; over 98.5% of deaths occurred in low- and middle-income countries.
• Neonates born preterm and SGA are particularly at risk given the high incidence of infectious complications, cardiopulmonary, and neurodevelopmental disorders in this group.
Quality improvement (QI) initiatives can reduce the burden of mortality and morbidity for hospitalized newborns in these settings.
• **Late Onset Sepsis** decreased from 4.3 to 1.6 per 1000 patient days ($P < 0.001$), and the central line-associated bloodstream infection rate dropped from 25 in 2003 to 5 in 2016 per 1000 central line; $P = 0.001$).

• **Hand hygiene compliance rates remained consistent**, over 80%. 
QUALITY IMPROVEMENT

Pharande J Paediatr Child Health. 2018

• They concluded
• “Multifaceted infection control bundle practices with a concerted team effort in the implementation, with continuing education, feedback and reinforcement of best infection control practices, can sustain the gains achieved by infection control for a long period of time.”

- **RESULTS:**
  - Infants exposed to any ANC had a lower rate of death (23%) compared to non-exposed (42%).
  - Infants exposed to a partial course of ANC also had a lower rate of death (26.0%) compared to infants without exposure (41.5%).

• **RESULTS**

• The rate of death due to respiratory distress syndrome, surfactant use, and the rate of mechanical ventilation were lower in infants exposed to any antenatal corticosteroids compared to infants without exposure.

• Between 23 and 27 weeks, infants exposed to a complete course of ANC had lower mortality before discharge compared to infants without exposure.
• **CONCLUSION:**

• Among infants 22-28 weeks' gestational age, any or partial antenatal exposure to corticosteroids compared to no exposure is associated with a lower rate of death while the rate of bronchopulmonary dysplasia in survivors did not differ.
• **RESULTS**

  • *There was NO significant difference in any of the individual components of the prespecified outcome.*

  • *There were more deaths in the budesonide group than in the placebo group (82 [19.9%] of 413 infants vs. 58 [14.5%] of 400 infants for whom vital status was available; RR, 1.37; 95% CI, 1.01 to 1.86; P=0.04).*
Eighteen RCTs compared delayed vs early clamping in 2834 infants.

Most infants allocated to have delayed clamping were assigned a delay of 60 seconds or more.

Delayed clamping reduced hospital mortality (RR 0.69, 95% CI 0.52 to 0.91, P=0.009)
In 3 trials in 996 infants ≤28 weeks G.A, delayed clamping reduced hospital mortality (RR 0.70, 95% CI 0.51 to 0.95, P=0.02, number needed to benefit 20,
ACOG RECOMMENDATIONS RE CORD CLAMPING

• In term delayed clamping increases Hb levels at birth, improves iron stores in first months which has favorable effect on developmental outcomes

• In preterm infants delayed clamping improves transitional circulation, decreases need for transfusions, reduces NEC and IVH
CORD MESENCHYMAL STEM CELLS

• Cord Mesenchymal Stem Cells (MSC) improve survival and enhance bacterial clearance in model of sepsis.
• In experimental HIE and IVH mesenchymal stem cells are neuroprotective.
• Meta-analysis of experimental BPD, MSC’s improved primary end point alveolarization, ameliorated pulmonary hypertension, lung inflammation, fibrosis, angiogenesis and apoptosis.
• PROSPECTIVE RANDOMIZED UNBIASED TRIALS URGENTLY NEEDED

- Nineteen studies provided data for the primary analysis (oxygen saturation threshold < 95% or ≤ 95%; N = 436,758 participants).
- The overall sensitivity of pulse oximetry for detection of CCHD was 76.3% (95% CI 69.5 to 82.0).
- Specificity was 99.9% (95% CI 99.7 to 99.9), with a false-positive rate of 0.14% (95% CI 0.07 to 0.22) (high certainty of the evidence).

• These results showed that out of 10,000 apparently healthy late preterm or full-term newborn infants, six will have CCHD.

• Screening by pulse oximetry will detect five of these infants as having CCHD and will miss one case.

• In addition, screening by pulse oximetry will falsely identify another 14 infants out of the 10,000 as having suspected CCHD when they do not have it.

• The false-positive rate for detection of CCHD was lower when newborn pulse oximetry was performed >24 hours after birth than when it was performed within 24 hours.

• However, many of the false positives have respiratory disorders including pneumonia and TTNB or sepsis
CONCLUSIONS: Pulse oximetry is a highly specific and moderately sensitive test for detection of CCHD with very low false-positive rates.

Current evidence supports the introduction of routine screening for CCHD in asymptomatic newborns before discharge from the well-baby nursery.
THOUGHTS ON NECROTIZING ENTEROCOLITIS

• The focus of attention has tended to shift from feeding volumes to the composition of the intestinal microbiota and how to modify it. Promising NEC prevention strategies that alter the intestinal microbiota include probiotics, prebiotics, synbiotics, lactoferrin, and human milk. Antibiotics increase NEC.
HUMAN MILK AND NECROTIZING ENTEROCOLITIS

• The movement to exclusive use of human milk and human milk products appears to have reduced the incidence of NEC, with one meta-analysis finding that infants fed formula had 2.8 greater incidence of NEC that those fed donor milk.
Q.I.- FEEDING PROTOCOL NECROTIZING ENTEROCOLITIS

• A standardized feeding protocol for very VLBW infants employed strategies to increase the use of human milk, maximize intestinal perfusion, and promote a healthy microbiome.

• NEC decreased from 0.17 cases/100 VLBW patient days to 0.029, an 83% reduction, while the compliance with a standardized feeding protocol improved.
GENETICS; IRON AND NECROTIZING ENTEROCOLITIS

• Gopel studying genetic polymorphisms in over 11,000 infants with a B.W.<1500 G g found that babies with a high serum iron levels due to rs855791 genotype were less likely to develop surgical NEC (Odds ratio 0.265, C.I. 0.11-0.65), whereas carriers of the same gene with the A Allele had a higher incidence of NEC. This could be reduced with probiotics.

• *Pediatric research* 2018;83;57-62
They postulated that polymorphisms inducing lower intestinal iron uptake, which modifies intestinal bacteria, like the rs855791 A allele might be a risk factor for NEC.
LOW RESOURCE - KEY LESSONS LEARNED

- DELAYED CORD CLAMPING IS BENEFICIAL
- HUMAN MILK FEEDING ESSENTIAL
- AVOID SURGERY WHEN POSSIBLE
- QUALITY IMPROVEMENT IS IMPROVING OUTCOMES – INFECTION, AVOIDING HYPOTHERMIA
- LONG TERM FOLLOW UP IS VITAL
HOW TO IMPROVE NEURO-DEVELOPMENTAL OUTCOME

• ANTENATAL CORTICOSTEROIDS-REDUCE IVH

• OPTIMAL CORD CLAMPING/MILKING

• HUMAN MILK

• SINGLE PATIENT ROOMS

• KANGAROO CARE

• TALKING TO BABIES
HOW TO IMPROVE NEURO-DEVELOPMENTAL OUTCOME

• AVOID FENTANYL

• AVOID GENERAL ANESTHESIA

• Magnesium sulphate for women at risk of preterm birth for fetal neuroprotection can prevent cerebral palsy.

• Prophylactic antibiotics for women in preterm labor with intact membranes, and immediate rather than deferred birth of preterm babies with suspected fetal
LOW RESOURCE-KEY LESSONS LEARNED

- DELAYED CORD CLAMPING IS BENEFICIAL
- HUMAN MILK FEEDING
- AVOID SURGERY WHEN POSSIBLE
- QUALITY IMPROVEMENT IS IMPROVING OUTCOMES – INFECTION, AVOIDING HYPOTHERMIA
- LONG TERM FOLLOW UP IS VITAL