ADVANCES IN NEONATOLOGY – TRIUMPHS AND TRAGEDIES

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RAINBOW BABIES AND CHILDRENS HOSPITAL, CLEVELAND, OHIO
SELECTED TRAGEDIES

• SULFONAMIDES-KERNICTERUS
• OXYGEN-RETINOPATHY
• DES- CANCER/BIRTH DEFECTS
• THALIDOMIDE- BIRTH DEFECTS
• VITAMIN E – LIVER FAILURE/DEATH
SELECTED TRAGEDIES

- PHISOHEX - CYSTIC BRAIN LESIONS
- CHLORAMPHENICOL – GREY BABY SYNDROME
- FORMULA- NEONATAL SEIZURES
- BENZYL ALCOHOL – IVH,GASPing,DEATH
NEONATAL TRAGEDIES
IATROGENESIS ASSOCIATED WITH PREVENTION OF INFECTION

- Sulfisoxazole
- Chloramphenicol
- Novobiocin
- Hexachlorophene
- Kanamycin
- Diaper laundering, and
- Equipment cleaning.

HAMLET
REPORT CARD NEONATAL PERINATAL MEDICINE

- Prevent prematurity
- Reduce asphyxia
- Eliminate GBS & nosocomial infections
- Reduce IVH
- Prevent BPD
- Avoid iatro genesis
- Avoid medical errors
- Slow progress
- Minimal reduction
- Remarkable progress
- Accomplished
- Some progress
- High priority
- High priority
TRIUMPHS- PREVENTION

- Blindness - Ophthalmia neonatorum
- Hemorrhagic disease – Vitamin K
- Retardation – neonatal screening
- Rh disease – Rhogam
- Liver cancer – Hepatitis B Immunization
- Infections– Intrapartum antibiotics/cord care
- Birth defects – folic acid and periconceptual glucose control in diabetics
MAJOR THERAPEUTIC TRIUMPHS

- Rhogam
- Total parenteral nutrition
- Antenatal corticosteroids
- Intrapartum antibiotics
- CPAP/ mechanical ventilation
- Surfactant
- Cryotherapy/Laser therapy
- ECMO
EFFECTIVE INTERVENTIONS

• Prostaglandins to keep ductus open
• Nitric oxide for pulmonary hypertension
• Back to sleep
• Metabolic screening
• Hearing screening
CURRENT GOALS

✓ Practice evidence based medicine
✓ Apply best practices and reduce center variability
✓ Avoid medical errors
✓ Prevent prematurity
✓ Prevent birth defects
✓ Prevent infection and major morbidities
✓ Optimize nutritional support – enhance and promote use of human milk
✓ Minimize invasive procedures and provide humane pain relief
CURRENT GOALS

- Provide stimulating and nurturing environment for patients and staff
- Support and educate nursing and ancillary staff
- Communicate with, inform, educate and support the parents/family and encourage them to visit and participate in care. Be truthful, attempt to be optimistic but always realistic.
- ATTEMPT cost-effective care
ADVANCES AND CHALLENGES FACING NEONATOLOGY 2012/2013

• Prematurity with its attendant morbidity/mortality-Antenatal corticosteroids- ? Start at 23weeks GA
• Fetal diagnosis and therapy -Fetal versus postnatal surgery for Meningomyelocele
• Early versus delayed cord clamping
• Understanding encephalopathy in preterm infants and treatment in term infants
• Value of lung ultrasound in distinguishing TTNB from RDS
• The ongoing saga of caffeine therapy
ADVANCES AND CHALLENGES FACING NEONATOLOGY 2011/2012

• Prevention, recognition and treatment of infection - the role of AIPI
• PDA- to treat or observe?
• Recognition/management of acute kidney injury
• Prevention and treatment of retinopathy of prematurity. Are newer therapies better?
• Environmental toxins as Teratogens
• Screening for cyanotic congenital heart disease
CONSENSUS ELGAN

- Every day IN UTERO increases survival by 3%.
- Benefits of a full course of antenatal steroids (but when to initiate?)
- Girls have approximately 1 week advantage over boys.
- Confounding problem of multiple birth.
- Influence of malformations and the baby’s condition at delivery.
• Extreme prematurity is both uncommon and complex and should be managed in high volume tertiary centers that are familiar with the necessary facets for decision making.
PERCENTAGE SURVIVAL 23-28 WEEKS BY ANTENATAL CORTICOSTEROIDS

<table>
<thead>
<tr>
<th>G.A. wks</th>
<th>Total</th>
<th>ANS %</th>
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<td>Total</td>
<td>3562</td>
<td>82</td>
<td>62</td>
<td>82</td>
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</table>
ANTENATAL CORTICOSTEROIDS

• **Results**  Reduced death or neurodevelopmental impairment at 18 to 22 months for infants who had been exposed to antenatal corticosteroids.
  
  • 23 wks 83% vs 91% AOR, 0.58 [95% CI, 0.42-0.80]),
  
  • 24 wks (68% vs 80% AOR, 0.62 [95% CI, 0.49-0.78]),
  
  • 25 wks (53% vs 67.9%AOR, 0.61 [95% CI, 0.50-0.74]) but not in those infants born at 22 weeks' gestation (90.2% with exposure to antenatal corticosteroids vs 93.1% without exposure; AOR, 0.80 [95% CI, 0.29-2.21]).

• Carlo JAMA 2012
Antenatal Corticosteroids and RDS Incidence in 10,541 Infants - 1993-2009 in NICHD-Neonatal Research Network – 74% Exposure to ANS

No Data on Incidence of RDS

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>% Treated with Surfactant</th>
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<tr>
<td></td>
<td>+ ANS</td>
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<tr>
<td>22 wks</td>
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<td>23 wks</td>
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<tr>
<td>24 wks</td>
<td>90%</td>
</tr>
<tr>
<td>25 wks</td>
<td>87%</td>
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<tr>
<td>Total 22-25 wks</td>
<td>87%</td>
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Carlo, et al., JAMA, 2011
Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

• **OBJECTIVE:** To identify changes in mortality and neonatal morbidities for infants with birth weight 501 to 1500 g born from 2000 to 2009.

• Horbar Pediatrics 2012
Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

• METHODS: There were 355,806 infants weighing 501 to 1500 g who were born in 2000–2009.

• Mortality during initial hospitalization and major neonatal morbidity in survivors (early and late infection, chronic lung disease, necrotizing enterocolitis, severe retinopathy of prematurity, severe IVH, and PVL) were assessed by using data from 669 North American hospitals in the Vermont Oxford Network.

• Horbar Pediatrics 2012
Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

**RESULTS:** From 2000 to 2009, mortality for infants weighing 501 to 1500 g decreased from 14.3% to 12.4% (difference, −1.9%; 95% C.I, −2.3% to −1.5%).

- Major morbidity in survivors decreased from 46.4% to 41.4% (difference, −4.9%; 95% C.I, −5.6% to −4.2%).
Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

• RESULTS:
  • In 2009, mortality ranged from 36.6% for infants 501 to 750 g to 3.5% for infants 1251 to 1500 g, whereas major morbidity in survivors ranged from 82.7% to 18.7%.
  • In 2009, 49.2% of all very low birth weight infants and 89.2% of infants 501 to 750 g either died or survived with a major neonatal morbidity.
• Horbar Pediatrics 2012
Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

• **CONCLUSIONS**: Mortality and major neonatal morbidity in survivors decreased for infants with birth weight 501 to 1500 g between 2000 and 2009.

• However, at the end of the decade, a high proportion of these infants still either died or survived after experiencing ≥1 major neonatal morbidity known to be associated with both short- and long-term adverse consequences.

• **Horbar Pediatrics 2012**
Mortality and major neonatal morbidity in survivors in 2009 compared with 2000 by birth weight category for infants 501 to 1500 g.


©2012 by American Academy of Pediatrics
<table>
<thead>
<tr>
<th>GA</th>
<th>NICHD</th>
<th>JAPAN</th>
<th>DANI</th>
<th>SWEDEN</th>
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<tr>
<td>22 wk</td>
<td>5 %</td>
<td>40 %</td>
<td>2%</td>
<td>10%(4-23)</td>
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<tr>
<td>23 wk</td>
<td>26 %</td>
<td>60 %</td>
<td>13%</td>
<td>53%(44-63)</td>
</tr>
<tr>
<td>24 wk</td>
<td>56 %</td>
<td>80 %</td>
<td>35%</td>
<td>67%(59-75)</td>
</tr>
<tr>
<td>25 wk</td>
<td>76 %</td>
<td>85 %</td>
<td>56%</td>
<td>82% (76-87)</td>
</tr>
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</table>
KEY ISSUES TO REDUCE MORBIDITY AND MORTALITY IN ELGAN’S

• Deliver at tertiary center
• Antenatal corticosteroids and tocolysis
• Liberal use of Caesarean section
• Promote cord transfusion
• Avoid oxidant injury and hypothermia commencing in the delivery room-
surfactant as indicated
• Outcomes for survivors improving-
Sweden (22-26wks GA) 45% intact
## Comparison of Recent NICHD Network Bayley Scores and NDI Rates

<table>
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<tbody>
<tr>
<td>Infants &lt; 27 wk</td>
<td>N = 577</td>
<td>N=468</td>
<td>Cognitive median</td>
<td>N=346</td>
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<tr>
<td>MDI median</td>
<td>79</td>
<td>77</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>PDI median</td>
<td>86</td>
<td>86</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>% MDI &lt; 70</td>
<td>36%</td>
<td>40%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>% PDI &lt; 70</td>
<td>27%</td>
<td>28%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>% Neurodevel Impairment*</td>
<td>43%</td>
<td>46%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

* Cerebral palsy, bilateral blindness, deafness, MDI < 70 for Bayley II, Cognitive or Language score < 70 for Bayley III  
  Vohr 2010 PAS Abstract
Multiple Impairments

Neurological:
- Cerebral Palsy
- Blindness
- Deafness

Developmental

Non-neurological:
- Home oxygen
- NGT feeds
- Growth <-3 SD

Global cognitive dysfunction

Epicure 1999
KEY ISSUES TO REDUCE MORBIDITY AND MORTALITY IN ELGAN’S

- **Respiratory support - prevent BPD**
  - CPAP versus intubation and surfactant (? Role of surfactant admin without intubation)
  - Ideal oxygen saturation level?
  - Caffeine
  - *Early nutritional support* – TPN; minimal enteral nutrition and HUMAN MILK
KEY ISSUES TO REDUCE MORBIDITY AND MORTALITY IN ELGAN’S

• Aggressive phototherapy
• Prevention of infection
  – Hand hygiene
  – Intrapartum antibiotics
  – CLABSI bundles**
  – Fluconazole prophylaxis/specific monoclonal antibodies eg CNS
  – Prebiotics/Probiotics/Lactoferrin

• Prevention of Necrotizing enterocolitis
  – Prebiotics, Probiotics, Lactoferrin.
  – Human milk with fortifiers
  – Minimize blood transfusions

**Central line associated blood stream infections
KEY ISSUES TO REDUCE MORBIDITY AND MORTALITY IN ELGAN’S

- Practice evidence based medicine
- Involve parents
- Provide stimulating environment
- Avoid medical errors
- Provide careful and continuing follow up with early recognition and remedy of disabilities including vision and hearing
Delayed clamping or milking of the cord is associated with

• Increased blood volume

• Strauss et al, 2003: Red cell volume higher after delayed clamping (42.1 ± 7.8 ml/kg) vs immediate clamping (36.8 ± 6.3 ml/kg), or approximately 10 ml/kg difference in blood volume

• Alaganady et al, 2006: Blood volume higher after delayed clamping (74.4 ml/kg vs 62.7 ml/kg)
Delayed clamping or milking of the cord is associated with

- Improved circulatory and respiratory function
- Reduced need for transfusion
- Improved cerebral oxygenation
- In preterm infants, reduced IVH, NEC, and late-onset sepsis
Delayed clamping or milking of the cord is associated with

- More stable blood pressure
- Increased transfer of stem cells
- Decreased risk of intraventricular hemorrhage
- Increased urine output
- Decreased risk of sepsis
- Less anemia and better iron status at 4-6 months
DELAYED CORD CLAMPING

- The benefits of delayed cord clamping clearly outweigh the convenience factor which drives immediate clamping and cutting and the marginal increase in jaundice.

- For every 20 cases of delayed cord clamping 1 case of iron deficiency anemia is prevented. The global impact is enormous.

- Andersson 2011
CORD MILKING

• Milking of the umbilical cord at birth provides a practical alternative to delayed cord clamping (Hosono *et al.*, 2008).

• The volume of blood contained in a doubly-clamped 30-cm length of umbilical cord is 6 to 25 ml (15.4 ± 6.3 ml/kg) for 20 infants with birth weight 500-1200 grams (Hosono, 2011 personal communication to Dr. E Bell).
CORD MILKING

• Erickson–Owens (2012) showed higher hematocrits after cord milking compared with early cord clamping in term infants delivered by Caesarean section.

• Takeshi (2012) showed higher hematocrits as well as left ventricular output, cerebral tissue and lower cerebral fractional oxygen extraction after cord milking compared with immediate clamping.

DEVELOYED CORD CLAMPING

• "The balance of maternal risks and infant benefits of delayed cord clamping now clearly favors the child."

• How much more evidence is needed to convince obstetricians and midwives that it is worthwhile to wait for three minutes to allow for placental transfusion, even in developed countries?"

• Van Rheenen  BMJ. 2011;343:d7127.
FETAL TREATMENT FUTURE

- Stem cell transplantation
- Gene therapy
- Correction of birth defects
- Wound healing without scars
SCREENING FOR CONGENITAL CARDIOVASCULAR MALFORMATIONS (CCVMs)

• There is a strong consensus regarding the need for screening for congenital cardiovascular malformations (CCVMs).

• They are relatively common with a prevalence of 5-10 per 1000 live births, and are the major cause of death due to a birth defect, which is the leading cause of neonatal mortality in the USA.

• Delayed or missed diagnoses can result in significant morbidity and mortality
SCREENING FOR CONGENITAL CARDIOVASCULAR MALFORMATIONS (CCVMs)

- In an analysis of pooled studies of oximetry assessment performed after 24 hours of life, whereas the estimated sensitivity for detecting CCHD was 69.6%, and the positive predictive value 47.0%; false-positive screens that required further evaluation occurred in only 0.035% of infants.
SCREENING FOR CONGENITAL CARDIOVASCULAR MALFORMATION (CCVMs)

• “A screen is considered positive if
• (1) any oxygen saturation measure is <90% (in the initial screen or in repeat screens);
• (2) oxygen saturation is <95% in the right hand and foot on three measures, each separated by one hour;
• (3) a >3% absolute difference exists in oxygen saturation between the right hand and foot on three measures, each separated by one hour.
• Any screening that is ≥95% in the right hand or foot with a ≤3% absolute difference in oxygen saturation between the right hand or foot is considered a negative screen and screening would end.
WHAT CAN WE LEARN FROM LUNG ULTRASOUND? SLIDES COURTESY OF LUIGI CATTAROSSI FROM UDINE

NORMAL LUNG - LONGITUDINAL SCAN
NORMAL LUNG-TRANSVERSE SCAN

REGULAR PLEURAL LINE

A LINES

A LINES

REGULAR PLEURAL LINE – A LINES – ”LUNG SLIDING”
ALVEOLAR-INTERSTITIAL SYNDROME

“COMET-TAIL” ARTIFACTS / B LINES OR “ULTRASOUND LUNG COMETS” (ULCs)
DEGREE OF THE ALVEOLAR-INTERSTITIAL SYNDROME

FEW ULCs

ECHOGRAFIC "WHITE LUNG"
TRANSIENT TACHYPNEA OF THE NEWBORN
Ultrasound findings

APEX

REGULAR PLEURAL LINE

BASE

NUMEROUS ULCs

COMPACT ULCs AT LUNG BASE
TRANSIENT TACHYPNEA OF THE NEWBORN
Ultrasound findings

“DOUBLE LUNG POINT” NOT OBSERVED IN HEALTHY INFANTS, INFANTS WITH RDS, PNEUMONIA, PULMONARY HEMORRHAGE OR PNEUMOTHORAX
RDS
Ultrasound findings

APEX
WIDE COMPACT ULCs (ECHOGRAPHIC “WHITE LUNG”)

BASE
RDS
Ultrasound findings

ATTENUATION, IRREGULARITY, THICKENING AND COARSE ASPECT OF PLEURAL LINE
Why lung US appearance does not change after surfactant?

NO CHANGE -Because US looks at pulmonary interstitium while X-ray at lung aeration.
<table>
<thead>
<tr>
<th>Caffeine (mg)</th>
<th>Short (8 oz)</th>
<th>Tall (12 oz)</th>
<th>Grande (16 oz)</th>
<th>Venti (20-24 oz)</th>
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</thead>
<tbody>
<tr>
<td>Brewed Coffee*</td>
<td>180</td>
<td>260</td>
<td>330</td>
<td>415</td>
</tr>
<tr>
<td>Brewed Decaf Coffee</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Caffè Americano</td>
<td>75</td>
<td>150</td>
<td>225</td>
<td>300</td>
</tr>
<tr>
<td>Tazo Black Tea Latte</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td>125</td>
</tr>
<tr>
<td>Tea: 3 min = 44mg/cup</td>
<td>1 teaspoon nescafe= 80 mg</td>
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CAP TRIAL

EQUIVALENT OF 6 CUPS OF COFFEE PER DAY

Schmidt B.
Results

- Of 963 infants who were assigned to caffeine and who remained alive at a postmenstrual age of 36 weeks, 350 (36%) received supplemental oxygen, as did 447 of the 954 infants (47%) assigned to placebo (adjusted OR, 0.63; 95 percent CI, 0.52 to 0.76; P<0.001).

THAT IS REDUCED BPD.

Caffeine reduced weight gain temporarily

## Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caffeine</th>
<th>Placebo</th>
<th>OR</th>
<th>p value</th>
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<tbody>
<tr>
<td>Death or disability</td>
<td>40%</td>
<td>46%</td>
<td>0.77</td>
<td>0.006</td>
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<tr>
<td>Cerebral palsy</td>
<td>4.4%</td>
<td>7.3%</td>
<td>0.58</td>
<td>0.009</td>
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<td>MDI&lt;85</td>
<td>34%</td>
<td>38%</td>
<td>0.80</td>
<td>0.035</td>
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Schmidt, NEJM 2008
Caffeine - The silver bullet in Neonatology

Standard of Care:
- Apnea of Prematurity
- Extubation of ventilated babies
- Post-operative apnea prevention

Non-intended Benefits:
- BPD-
- PDA
- ROP
- Prevention of Cerebral Palsy,
- Cognitive impairment
- RDS (?)

COURTESY J.ARANDA
Caffeine, VEGF, IGF-1, ROP

- Caffeine increases retinal VEGF during Hyperoxia/hypoxia but decreases VEGF during recovery in room air.
- Effects of caffeine on VEGF and IGF-1 are dose dependent and influenced by normoxia or hyperoxia.
- Low serum IGF-1 during caffeine therapy suggest that caffeine does not exert its protective effect via increasing IGF-1 levels.
- Effect of Caffeine on VEGF signaling is one of the mechanisms underlying the protective drug effect on ROP.
- Aranda J.
The combined outcome of death or disability was not significantly different for the 833 children assigned to caffeine from that for the 807 children assigned to placebo (21.1% vs 24.8%; odds ratio adjusted for center, 0.82; 95% CI, 0.65-1.03; \( P = .09 \)).
The rates of death, motor impairment, behavior problems, poor general health, deafness, and blindness did not differ significantly between the 2 groups.

The incidence of cognitive impairment was lower at 5 years than at 18 months and similar in the 2 groups (4.9% vs 5.1%; odds ratio adjusted for center, 0.97; 95% CI, 0.61-1.55; P = .89).
• Conclusion

• Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights who were assessed at 5 years.
Schmidt JAMA 2012

• A secondary analysis of the full range of motor outcomes suggests that the improved motor function observed at 18 to 21 months in the caffeine group was sustained at 5 years.
• Compared with the placebo group, fewer infants treated with caffeine had any cerebral palsy and affected children had significantly better scores on the GMFCS.
These results may have longer-term implications, because GMFCS levels at 6 to 7 years of age are predictive of function in adult life.
A DISASTER AVERTED

Gastrostomy Sequential-Analysis

“United” Pairs Favoring Gastrostomy

Gastrostomy Survival > Control

Gastrostomy Survival < Control

Total “Untied” Pairs

Cornblath, M.
### Controlled Study of Feeding Gastrostomy in LBW Infants - Outcomes

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<th>Matched Pairs 54</th>
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<td>Tied (34)</td>
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<td>Untied (20)</td>
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<tr>
<td>Lived</td>
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<table>
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<td>Lived</td>
<td>31</td>
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<tr>
<td>Died</td>
<td>3</td>
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<tr>
<td>Died</td>
<td>7</td>
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<td>Died</td>
<td>13</td>
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<tr>
<td>Lived</td>
<td>13</td>
</tr>
<tr>
<td>Died</td>
<td>7</td>
</tr>
</tbody>
</table>

M. Cornblath
“During the 14-month period of this study, the over-all mortality among infants with birth weights between 750 and 1250 grams in the premature nursery of the Cook County Hospital dropped by 13 percent from that of the previous two years. Had this study lacked concurrent controls, the improvement in survival would have been ascribed to the feeding gastrostomy.”

Cornblath, M.
The burden of neonatal SEPSIS: Antibiotic use in VLBW in USA (data from the U.S. NICU national registry)

<table>
<thead>
<tr>
<th></th>
<th>Episodes</th>
<th>Incidence rate</th>
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<tbody>
<tr>
<td>Late-onset Sepsis</td>
<td>1313 of 6215</td>
<td>21%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3459 of 6215</td>
<td>56%</td>
</tr>
<tr>
<td>Early-onset Sepsis</td>
<td>147 of 7606</td>
<td>1.9%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3652 of 7606</td>
<td>48%</td>
</tr>
</tbody>
</table>

CONS
S. Aureus
C. albicans
E. coli

Kaufman, 2004


> 3 days
**Results**: *LactoFerrin+LactobacillusGG vs.PLACEBO*

<table>
<thead>
<tr>
<th></th>
<th>LF + LGG (n=137)</th>
<th>PLACEBO (n=153)</th>
<th>R.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-Onset sepsis (all agents)</td>
<td>11/137 (8.0%)</td>
<td>37/153 (24.2%)</td>
<td>0.23</td>
<td>0.13-0.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Total IFI (%)</td>
<td>3/137 (2.2%)</td>
<td>12/153 (7.8%)</td>
<td>0.33</td>
<td>0.08-0.78</td>
<td>0.02</td>
</tr>
<tr>
<td>NEC</td>
<td>0/137 (0%)</td>
<td>10/153 (6.5%)</td>
<td>0.11</td>
<td>0.18-0.54</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>6/137 (4.4%)</td>
<td>13/153 (8.5%)</td>
<td>0.41</td>
<td>0.08-1.09</td>
<td>0.09</td>
</tr>
</tbody>
</table>
### RESULTS:

**LF combined (alone or with LGG) vs. PLACEBO**

<table>
<thead>
<tr>
<th></th>
<th>LF combined n = (139+137) = 276</th>
<th>PLACEBO n = 153</th>
<th>R.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-Onset sepsis (all agents)</td>
<td>23/276 (8.3%)</td>
<td>37/153 (24.2%)</td>
<td>0.28</td>
<td>0.16-0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS by Gram-Positive</td>
<td>1.8%</td>
<td>7.8%</td>
<td>0.21</td>
<td>0.07-0.62</td>
<td>0.002</td>
</tr>
<tr>
<td>LOS by Gram-Negative</td>
<td>5.4%</td>
<td>10.5%</td>
<td>0.48</td>
<td>0.35-0.98</td>
<td>0.05</td>
</tr>
<tr>
<td>LOS by Candida spp</td>
<td>1.8%</td>
<td>7.8%</td>
<td>0.21</td>
<td>0.07-0.62</td>
<td>0.002</td>
</tr>
<tr>
<td>NEC</td>
<td>2/276 (0.7%)</td>
<td>10/153 (6.5%)</td>
<td>0.10</td>
<td>0.02-0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality (all causes prior to discharge)</td>
<td>3.3%</td>
<td>8.5%</td>
<td>0.36</td>
<td>0.15-0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>Death OR NEC</td>
<td>4.7%</td>
<td>12.4%</td>
<td>0.34</td>
<td>0.16-0.72</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Power calculations: 0.95 for LOS, 0.74 for NEC, 0.65 for IFI, 0.45 for mortality
Bovine Lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial.

• CONCLUSION:

• Compared with placebo, Bovine Lactoferrin supplementation alone or in combination with Lactobacillus rhamnosus GG (LGG) reduced the incidence of a first episode of late-onset sepsis in VLBW neonates.

Conclusions

Therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis.
PREVENTION OF INFECTION

- Hand hygiene.
- Prompt removal of central lines!
- Group B streptococci- IPA
- Prevention of tetanus neonatorum
- Fluconazole for fungal prevention
- Prebiotics, Probiotics, Lactoferrin
Can we detect protein **biomarkers** that define NEC & Sepsis and predict progression of disease?
Inter-alpha inhibitor proteins

- Inter-alpha inhibitor proteins (IaIp) are serine proteases inhibitors that modulate endogenous protease activity and have been shown to improve survival in adult models of sepsis.

- Beneficial effects of IaIp are via suppression of proinflammatory cytokines such as TNF-[alpha] rather than augmentation of IL-10.

Inter-alpha inhibitor proteins

- Polymorphisms of FUT2 are common resulting in variable expression of H antigen and 20% of population, with increased risk of inflammatory bowel disease do not secrete any H antigen.
Inter-alpha inhibitor proteins

- Secretor H antigen normally increases in the saliva of premature infants in first postnatal weeks.
- Non secretor genotype and low expression of H antigen in infants saliva were predictive of an increased incidence of death and NEC.
- Targeting novel biomarkers may be useful surveillance tools for VLBW infants.
The Role of Inter-Alpha Inhibitor Proteins (IaIP) in the Diagnosis of Neonatal Sepsis
CHAABAN,H et al J Pediatr154;620-2

• PILOT STUDY; Chabaan evaluated Inter-alpha inhibitor proteins (IaIp) as a diagnostic marker in neonatal sepsis.
• Samples were collected from 573 neonates WITH suspected sepsis.
• IaIp level was significantly lower in the septic group (121 ±71 mg/L) than in the non-septic group (322± 91 mg/L).
The Role of Inter-Alpha Inhibitor Proteins (IaIP) in the Diagnosis of Neonatal Sepsis
CHAABAN, H et al J Pediatr 154; 620-2

- **PILOT STUDY:** The optimal cutoff value with the receiver operating characteristic curve was <177 mg/L (Sensitivity 89%; Specificity 99%; PPV 88%, NPV 99%) with area under the curve of 0.94.

- **Conclusion:** IaIP is a more reliable diagnostic marker for neonatal sepsis than other available tests.
Figure 1. Ialp level in culture proven sepsis and culture negative newborns. Ialp levels was significantly lower in the blood culture proven sepsis (121.71 mg/L; 95% CI 100–143, \( n = 45 \)) compared to the blood culture negative group (322.91 mg/L, 95% CI; 314–330, \( n = 528 \)) \( P = .0001 \).
Inter-alpha inhibitor proteins--biomarker for NEC? J Peds 2010;157 ;757

- Objectives To compare inter-alpha inhibitor protein (IaIp) levels in neonates with proven necrotizing enterocolitis (NEC) and neonates with other, nonspecific abdominal disorders.
Inter-alpha inhibitor proteins--biomarker for NEC? J Peds 2010;157 ;757

- Plasma IaIp levels were quantitated by enzyme-linked immunosorbent assay.
- Results Seventeen neonates had confirmed NEC, and 34 neonates had nonspecific abdominal disorders that improved rapidly.
- GA, postnatal age, weight, sex, maternal obstetric variables, ROM, and mode of delivery did not differ between the two groups.
Inter-alpha inhibitor proteins--biomarker for NEC? J Peds 2010;157 ;757

• Mean IaIp level was significantly lower in the NEC group compared with the control group (137± 38 mg/L; 95% confidence interval [CI], 118-157 mg/L versus 258 ± 53 mg/L; 95% CI, 238-277 mg/L; P < .0001).
Inter-alpha inhibitor proteins--biomarker for NEC? J Peds 2010;157;757

• Conclusions The finding of significantly lower IaIp levels in neonates with NEC suggests that IaIp might be a useful, sensitive biomarker, allowing initiation of appropriate therapy and reducing antibiotic overuse in neonates with suspected but unproven NEC.

• Administration of IaIp may significantly reduce the severity of systemic inflammation and associated tissue injury.
In summary, IaIp levels are significantly decreased in patients with NEC stage II/III compared with a control group with nonspecific abdominal disorders.

We hypothesize that IaIp is involved in the pathogenesis of NEC. As one of the critical acute phase reactants during the host response to inflammation and tissue injury.
Inter-alpha inhibitor proteins--biomarker for NEC? J Peds 2010;157 ;757

• SUMMARY

• *lalp* proteins decrease at time of evaluation for NEC - approximately 50%- this decrease separated population with NEC from those without NEC