WHAT WE HAVE LEARNED AND APPLIED FROM LITERATURE

AVROY A FANAROFF
PROFESSOR DEPARTMENT OF PEDIATRICS
CWRU SCHOOL OF MEDICINE
ELIZA HENRY BARNES PROFESSOR OF NEONATOLOGY
RAINBOW BABIES AND CHILDRENS HOSPITAL,
CLEVELAND, OHIO
GREETINGS FROM CLEVELAND

• **RESULTS:** Seventy neonatal trials were identified in four general medical journals: Lancet, NEJM, BMJ, and JAMA

• 43 (61.4%) of studies reported the presence of a DMC,

• 36 (51.4%) explicitly mentioned interim analysis,

• Stopping rules were reported in 15 (21.4%) RCTs and seven (10%) trials were terminated early.

• The NEJM most frequently reported these parameters compared to the other three journals reviewed.

• **CONCLUSION:**
• While the majority of neonatal RCTs report on DMC involvement and interim analysis, there is still scope for improvement.
• Clear documentation of safety-related issues should be a central component of reporting in neonatal trials involving newborn infants.
NICHD/NIH TRIALS STOPPED EARLY

DMC’s stopped these trials early either because of harm or inability to show benefit

Glutamine= no decrease in sepsis

Early Corticosteroids- spontaneous GI perforation, hypertension, hyperglycemia

Inhaled NO and late surfactant- no benefit

Inositol to prevent BPD- particles in inositol solutions

Tin mesoporphyrin to inhibit Heme oxygenase- FDA needed more data on the fate of the tin

- **OBJECTIVE:**

- To evaluate the effect of cord milking on short term morbidity and hematologic parameters at 6 weeks in preterm neonates requiring resuscitation.
• **METHODS:**
• This trial randomized preterm infants requiring resuscitation to milking group and no milking group.
• Multiple pregnancy, Rh negative mothers, hydrops, cord abnormalities were excluded.
• The primary outcome was hemoglobin and serum ferritin at 6 weeks of life.
• Secondary outcomes were common preterm morbidities and mortality.
• RESULTS:
• 60 neonates were included in the study.
• Infants in the milking group had higher hemoglobin (10.07 g/dl vs 8.9 g/dl; p 0.003) and higher serum ferritin level (244.8 ng/ml vs 148.5 ng/ml; p 0.04) compared to no milking group
CONCLUSIONS:

In preterm neonates requiring resuscitation, umbilical cord milking results in higher hemoglobin and ferritin at 6 weeks of life.

It can be used as a placental transfusion strategy in preterm neonates requiring resuscitation with no significant adverse effects.
THE SAFETY CULTURE

CAPT. CHESLEY “SULLY” SULLENBERGER
WITH JEFFREY ZASLOW

HIGHEST DUTY
My Search for What Really Matters

ATUL GAWANDE
BESTSELLING AUTHOR OF
BETTER AND COMPLICATIONS
SIR ISAAC NEWTON

Thought to be “as good as dead” at birth. He was such a “tiny mite” that he could be placed in a quart mug.

ANNA PAVLOVA

A premature, so puny and weak, she was wrapped in cotton wool for three months.
• Barriers to heat loss Plastic wrap or bag versus routine care!

• Plastic wraps improved core body temperature on admission to the neonatal intensive care unit (NICU) or up to two hours after birth), and fewer infants had hypothermia on admission to the NICU or up to two hours after birth NNTB 4, 95% CI 4 to 5; 10 studies; 1417 infants).
• **Barriers to heat loss Plastic wrap or bag versus routine care!**

• **Risk of hyperthermia on admission to the NICU or up to two hours after birth was increased in infants in the wrapped group (NNTH) 25, 95% CI 17 to 50; 12 studies; 1523 infants), but overall, fewer infants receiving plastic wrap were outside the normothermic range**
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• **Barriers to heat loss** Plastic wrap or bag versus routine care!

• **Evidence was insufficient** to suggest that plastic wraps or bags significantly reduce risk of death during hospital stay or other major morbidities, with the exception of reducing risk of pulmonary haemorrhage.

- **External heat sources**
- **Skin to skin care (SSC)** was shown to be effective in reducing risk of hypothermia when compared with conventional incubator care for infants with birth weight ≥ 1200 and ≤ 2199 grams NNTB 2, 95% CI 1 to 4).
• Cerebral palsy (CP) is a common disability which results in permanent chronic motor disability appearing in early childhood.

• Recently human umbilical cord blood mesenchymal stem cell (hUCB-MSC) infusion has emerged as a promising therapeutic strategy for CP, and the treatment efficacy remains to be confirmed by clinical trials.

• The changes in the total proportion of gross motor function movement (GMFM-88) and total scores of comprehensive function assessment CFA in the hUCB-MSC infusion group were significantly higher than that in control group at 3, 6, 12, 24 months post treatment.

- Less diffuse slow waves were noticed after hUCB-MSC infusion in patients with slowing of EEG background rhythms at baseline.
- Improvements in cerebral structures based on routine MRI exams were rare after treatment.
- Serious adverse events were not observed during the whole study period.
- The results of the study indicated that hUCB-MSC infusion with basic rehabilitation was safe and effective in improving gross motor and comprehensive functions in children with CP.
CORD MESENCHYMAL STEM CELLS (MSC).

• MSC’s improve survival and enhance bacterial clearance in models 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

• APPROACHING CLINICAL TRIALS
Frontal lobe porencephaly
Notable questions include the following:

1. What is the worldwide prevalence of the disease?
2. What is the mechanism of bilirubin neurotoxicity?
3. What role do genetics play in resistance to bilirubin neurotoxicity?
WHERE DO WE STAND IN THE FIELD OF NEONATAL JAUNDICE  Riordan & Gazzin Pes Res 2018

4. Can patient screening be improved?

5. Are there any unintended side effects of Phototherapy?

6. Do current treatment guidelines for exchange transfusion need to be re-examined?
WHERE DO WE STAND IN THE FIELD OF NEONATAL JAUNDICE  Riordan & Gazzin Pes Res 2018

- 60–80% of newborns are classified as jaundiced.
- Considerable effort goes into screening and treatment (phototherapy (PT) or exchange transfusion) to prevent this condition from escalating into the development of brain damage and its resulting sequelae, known as kernicterus.
To date there has been an **Underestimation** of the real incidence of neurological sequelae in severe hyperbilirubinemia, and the need for improved risk assessment.

Multiple terms, including chronic bilirubin encephalopathy, bilirubin-induced neurological disorder (BIND), and the narrow definition of severe kernicterus, has led to confusion.
Classic Kernicterus has varying degrees of auditory and motor dysfunction (opisthotonus) occasionally associated with oculo-motor dysfunction and dental staining.

Although it is not disputed that the source of brain damage in kernicterus is elevated unbound “free” bilirubin depositing into the brain during extreme jaundice, numerous questions still remain about the condition.
Clinical unbound or free bilirubin (Bf) measurement remains a need, not only to reduce the number of children, especially those born premature, who may develop kernicterus, but also to reduce the unnecessary treatment of children with exchange transfusion (ET) or PT.

Also novel treatment strategies are needed e.g. cooling
CONCLUSIONS:

Prophylactic rhEPO improved the cognitive development of very preterm infants, as assessed by the MDI at a corrected age of 18 to 24 months, without affecting other ND outcomes. Current and future RCTs should investigate optimal dosing and timing of prophylactic rhEPO and plan for long-term neurodevelopmental follow-up.
Meta-analysis of data from 25 RCTs (rEPO compared with placebo) showed that rEPO significantly decreased the risk of any stage NEC [cases/total sample: 120/2058 (5.83%) compared with 146/1967 (7.42%); RR: 0.77; 95% CI: 0.61, 0.97; P = 0.03].

Meta-analysis of data from 15 RCTs showed a significant reduction in late-onset sepsis after rEPO administration (RR: 0.81; 95% CI: 0.71, 0.94; P = 0.004).

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- Meta-analysis of data from 15 RCTs showed a significant reduction in late-onset sepsis after rEPO administration (RR: 0.81; 95% CI: 0.71, 0.94; P = 0.004).

- Meta-analysis of 13 RCTs showed no significant effect of rEPO on mortality, ROP, and BPD.
- Prophylactic rEPO had no effect on stage II or higher NEC, but reduced any stage NEC, probably by reducing feeding intolerance, which is often labeled as stage I NEC.
- Adequately powered RCTs are required to confirm these findings.
B. MACULAR HEMORRHAGE SPARING FOVEA
C. EXTENSIVE HEMORRHAGE
Callaway presents the 1-year results of the first universal retinal image screening performed in healthy term infants in the USA.

Overall 20-30% of newborns exhibit retinal hemorrhages which are present in both eyes in almost 75% of the subjects.

The hemorrhages are of various shapes and distribution.
• More babies delivered with vacuum assist and per vaginum have hemorrhages than those delivered by Cesarean section.

• Those delivered by emergency section have a higher incidence of hemorrhage than elective section.

• If an infant has a cephalohematoma it is almost certain that there will be accompanying retinal hemorrhage.
RETINAL HEMORRHAGE

- Two thirds of hemorrhages have cleared by one week after birth in term infants but some resolve at a slower pace.
- All should resolve within a month.
- Long standing hemorrhage affecting the macula may interfere with the visual pathways and lead to visual deprivation and amblyopia.
- These lesions must be identified at birth rather than at the school examination.
RETINAL HEMORRHAGE

• Whereas there is no therapy for the hemorrhage, early identification of those at risk for visual impairment could receive early intervention including patching, cycloplegics, and correcting refractive errors which would optimize the child’s vision potential.
Fig. 3.—Lowest surface tension measured on compression of the surface. Open circles=infants dying from causes other than hyaline membrane disease. Closed circles=infants dying with hyaline membrane disease. Triangle=stillborn infant of a diabetic mother.


• In a large cohort study of the German Neonatal Network (GNN) we aimed to evaluate whether less invasive surfactant administration (LISA) strategy is associated with complications of preterm birth.
• Within the observational period n = 7533 VLBWI with G.A.22 0/7 to 28 6/7 weeks were enrolled in GNN;
• n = 1214 VLBWI never received surfactant,
• n = 2624 VLBWI were treated according to LISA procedure,
• n = 3695 VLBWI had surfactant via endotracheal tube (ETT).
• **LISA was associated with a reduced risk for adverse outcome measures including**
  
  • **Mortality** [odds ratio (OR) 0.66 (95% CI: 0.51-0.84), \( p < 0.001 \)]
  
  • **BPD** (OR 0.55 (95% CI: 0.49-0.62), \( p < 0.001 \)]
  
  • **Intracerebral hemorrhage (ICH) grade II-IV** [OR 0.55 (95% CI: 0.48-0.64), \( p < 0.001 \)]
  
  • **ROP**; OR 0.62 (95% CI: 0.45-0.85), \( p < 0.001 \).
• Notably, LISA was associated with an increased risk for focal intestinal perforation [FIP; OR 1.49 (95% CI: 1.14-1.95), p = 0.002].

• The differences in FIP rates were primarily observed in VLBWI born<26 weeks (LISA: 10.0 vs. ETT: 7.4%, p = 0.029).

• Our observational data confirm that LISA is associated with improved outcome.
• In infants <26 weeks we noted an increased risk for FIP.
• Future randomized controlled trials including LISA need to integrate safety analyses for this particular subgroup.
• (LARGE COHORT BUT RETROSPECTIVE AND NOT RANDOMIZED)
To check for robustness, we performed repeated matching. LISA-treated infants required significantly less mechanical ventilation during hospital stay ($p < 0.001$) and days with supplemental oxygen ($p = 0.03$).

Analgesics and sedatives were used less often during the stay ($p < 0.001$).

Infants treated with LISA had significantly lower rates of BPD ($p = 0.003$).

LISA failure infants were identified as more likely to be SGA and more immature.

• CONCLUSION:

• Our study complements former results with advantages for LISA-treated infants in reduced need for mechanical ventilation and less bronchopulmonary dysplasia.

• (NOT RANDOMIZED

• SMALL POPULATION

• NOT SUCCCESSFUL IN SGA AND VERY IMMATURE INFANTS)
Despite increasing emphasis on conservative management of patent ductus arteriosus (PDA) in preterm infants, different pharmacotherapeutic interventions are used to treat those developing a hemodynamically significant PDA.

• Objectives:

To estimate the relative likelihood of hemodynamically significant PDA closure with common pharmacotherapeutic interventions and to compare adverse event rates.
• Main Outcomes and Measures: Primary outcome: hemodynamically significant PDA closure; secondary: included surgical closure, mortality, necrotizing enterocolitis, and intraventricular hemorrhage.

• RESULTS

• In 68 randomized clinical trials of 4802 infants, 14 different variations of indomethacin, ibuprofen, or acetaminophen were used as treatment modalities.

• The overall PDA closure rate was 67.4% (2867 of 4256 infants).

• **RESULTS**

• A high dose of oral ibuprofen was associated with a significantly higher odds of PDA closure vs a standard dose of intravenous ibuprofen ([OR], 3.59; 1.64-8.17; absolute risk difference, 199 more per 1000 infants) and a standard dose of intravenous indomethacin ([OR], absolute risk difference, 124 more per 1000 infants).
• RESULTS

• Based on the ranking statistics, a high dose of oral ibuprofen ranked as the best pharmacotherapeutic option for PDA closure (mean surface under the cumulative ranking [SUCRA] curve, 0.89 [SD, 0.12]) and to prevent surgical PDA ligation (mean SUCRA, 0.98 [SD, 0.08]).
**RESULTS**

- There was no significant difference in the odds of mortality, necrotizing enterocolitis, or intraventricular hemorrhage with use of placebo or no treatment compared with any of the other treatment modalities.
Conclusions and Relevance:

A high dose of oral ibuprofen was associated with a higher likelihood of hemodynamically significant PDA closure vs standard doses of intravenous ibuprofen or intravenous indomethacin;

Placebo or no treatment did not significantly change the likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage.
• **OBJECTIVES:**

• To determine the effectiveness and safety of intravenous or oral paracetamol compared with placebo or no intervention, intravenous indomethacin, intravenous or oral ibuprofen, or with other cyclo-oxygenase inhibitors for treatment of an echocardiographically diagnosed PDA in preterm or low birth weight infants.
Main Results: We included eight studies that reported on 916 infants.

One of these studies compared paracetamol to both ibuprofen and indomethacin.

Five studies compared treatment of PDA with paracetamol versus ibuprofen and enrolled 559 infants.
MAIN RESULTS

There was no significant difference between paracetamol and ibuprofen for failure of ductal closure after the first course of drug administration (typical risk ratio (RR) 0.95, 95% confidence interval (CI) 0.75 to 1.21; typical risk difference (RD) -0.02, 95% CI -0.09 to 0.09); $I^2 = 0\%$ for RR and RD; moderate quality of evidence.
MAIN RESULTS Four studies (n = 537) reported on gastrointestinal bleed which was lower in the paracetamol group versus the ibuprofen group (typical RR 0.28, 95% CI 0.12 to 0.69; typical RD -0.06, 95% CI -0.09 to -0.02); I² = 0% for RR and RD; number needed to treat for an additional beneficial outcome (NNTB) 17 (95% CI 11 to 50); moderate quality of evidence.

• **MAIN RESULTS**

• The serum levels of creatinine were lower in the paracetamol group compared with the ibuprofen group in four studies (moderate quality of evidence), as were serum bilirubin levels following treatment in two studies (n = 290).

**MAIN RESULTS**

- Platelet counts and daily urine output were higher in the paracetamol group compared with the ibuprofen group. One study reported on long-term follow-up to 18 to 24 months of age following treatment with paracetamol versus ibuprofen.
• MAIN RESULTS

• There were no significant differences in the neurological outcomes at 18 to 24 months (n = 61); (low quality of evidence). Two studies compared prophylactic administration of paracetamol for a PDA with placebo or no intervention in 80 infants.
MAIN RESULTS

Paracetamol resulted in a lower rate of failure of ductal closure after 4 to 5 days of treatment compared to placebo or no intervention which was of borderline significance for typical RR 0.49 (95% CI 0.24 to 1.00; P = 0.05); but significant for typical RD -0.21 (95% CI -0.41 to -0.02); I² = 0 % for RR and RD; NNTB 5 (95% CI 2 to 50); (low quality of evidence)
• Neonatal hypoxic ischemic encephalopathy (HIE) presents a significant clinical burden with its high mortality and morbidity rates globally.

• Therapeutic hypothermia (TH) is now standard of care for infants with moderate to severe HIE, but has not definitively changed outcomes in severe HIE.
Therapies that are beneficial and agents that hold promise for neuroprotection include endogenous pathway modifiers such as erythropoietin and analogues, melatonin.

Stem cells have therapeutic potential in this condition, as in many other neonatal conditions.
Of the agents listed, only erythropoietin and analogues are currently being evaluated in large RCTs.

Exogenous therapies such as argon and xenon, allopurinol, monosialogangliosides, and magnesium sulfate continue to be investigated.

• The recognition of tertiary mechanisms of brain damage has opened up new research into therapies not only to attenuate brain damage but also to promote cell repair and regeneration in a developmentally disorganized brain long after the perinatal insult.

• These alternative modalities may be especially important in mild HIE and in areas of the world where there is limited access to expensive hypothermia equipment and services.
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• The recognition of tertiary mechanisms of brain damage has opened up new research into therapies not only to attenuate brain damage but also to promote cell repair and regeneration in a developmentally disorganized brain long after the perinatal insult.

• These alternative modalities may be especially important in mild HIE and in areas of the world where there is limited access to expensive hypothermia equipment and services.

• Erythropoietin (EPO) plays an important role in the development and maturation of the gastrointestinal tract.

• Recombinant EPO (rEPO) has been used to prevent anemia of prematurity.

• The gastrointestinal trophic effects of EPO may reduce feeding intolerance and necrotizing enterocolitis (NEC) in preterm neonates.
The aim of this systematic review of randomized controlled trials (RCTs) was to evaluate the effects of rEPO on clinical outcomes such as feeding intolerance, stage II or higher NEC, any stage NEC, sepsis, ROP, and BPD in preterm neonates.

- Twenty-five RCTs (intravenous: 13; subcutaneous: 10; enteral: 2; n = 4025) were eligible for inclusion.

- Meta-analysis of data from 17 RCTs (rEPO compared with placebo) with the use of a fixed-effects model showed no significant effect of rEPO on stage II or higher NEC (RR: 0.87; 95% CI: 0.64, 1.19; P = 0.39).
• Meta-analysis of data from 25 RCTs (rEPO compared with placebo) showed that rEPO significantly decreased the risk of any stage NEC [cases/total sample: 120/2058 (5.83%) compared with 146/1967 (7.42%); RR: 0.77; 95% CI: 0.61, 0.97; P = 0.03].

• Only one RCT reported on time to full feedings.

- **Meta-analysis of data from 15 RCTs showed a significant reduction in late-onset sepsis after rEPO administration (RR: 0.81; 95% CI: 0.71, 0.94; P = 0.004).**

- **Meta-analysis of 13 RCTs showed no significant effect of rEPO on mortality, ROP, and BPD.**

- Prophylactic rEPO had no effect on stage II or higher NEC, but it reduced any stage NEC, probably by reducing feeding intolerance, which is often labeled as stage I NEC.

- Adequately powered RCTs are required to confirm these findings.

• Since the 1990s, the most relevant pillars in the treatment of neonatal respiratory distress syndrome (RDS) have been improvements in ventilation strategies, the introduction of exogenous surfactant replacement therapy, better control and monitoring of oxygenation by means of pulse oximetry and the use of antenatal steroids.
• Lately, in addition to the standard INSURE (INtubation-SURfactant administration-Extubation) method to administer surfactant, a new technique has been gaining increasing popularity.

• It is the so-called less invasive surfactant administration (LISA) method, which has shown promising results in preventing bronchopulmonary dysplasia and in reducing mortality in preterm neonates.

- The rationale behind this technique is to avoid ET intubation and PPV so that surfactant is delivered through a thin catheter while the neonate is maintained on CPAP.
There have been few small randomized trials on LISA to determine the short and long-term outcomes, so many questions still remain unanswered.

We aim at hypothesizing the main mechanisms behind the efficacy of LISA, considering it as a single maneuver in a comprehensive approach for RDS management in the delivery room.