

# **KEY ISSUES IN NEONATOLOGY 2018**



**AVROY A. FANAROFF, M.D.  
PROFESSOR EMERITUS  
DEPARTMENT OF PEDIATRICS  
CWRU SCHOOL OF MEDICINE  
EMERITUS ELIZA HENRY BARNES PROFESSOR OF NEONATOLOGY  
RAINBOW BABIES & CHILDREN'S HOSPITAL  
CLEVELAND, OHIO**





**JOHN CLEMENTS  
AND MARY ELLEN  
AVERY  
SURFACTANT  
1980'S-90**

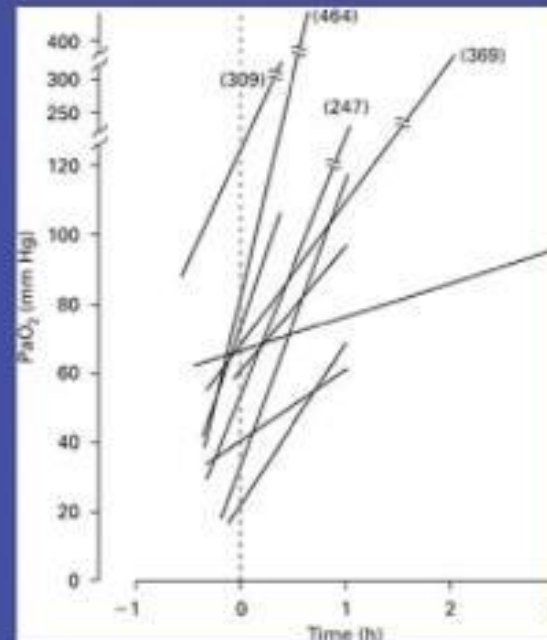
***Research into the effectiveness of exogenous surfactant for the prevention and treatment of HMD has been distinguished by a particularly high standard of design and execution. Is it too much to hope that the continuing record of accomplishment in the surfactant world will encourage the advocates of ECMO to adopt equally valid research strategies in the future J.SINCLAIR***



**Tetsuro Fujiwara**  
1931 –

- Surfactant TA
- 10 infants
- 30 wk; >1500 g
- 9 had PDA
- 2 died

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)



**Fujiwara et al: Lancet 1980; i:55-59**



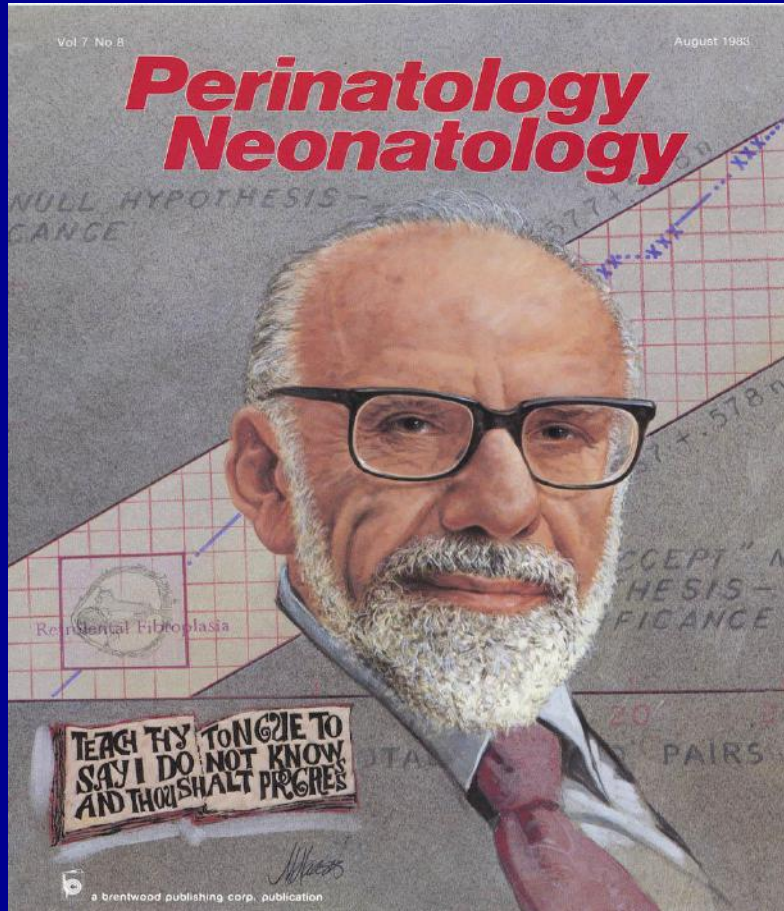
*Treatment of idiopathic  
respiratory distress  
syndrome with continuous  
positive airway pressure*

<b>Weight</b>	<b>N</b>	<b>PaO<sub>2</sub> (pre)</b>	<b>PaO<sub>2</sub> (post)</b>
<b>930-1500</b>	<b>10</b>	<b>37.1</b>	<b>116.4</b>
<b>1501-2000</b>	<b>5</b>	<b>38.1</b>	<b>114.8</b>
<b>2001-3830</b>	<b>5</b>	<b>48.6</b>	<b>96.0</b>

**Gregory et al. N Engl  
J Med 284: 1333, 1971**



# Bill Silverman



**“ We cannot always make our patients better but we can always make them worse!”**

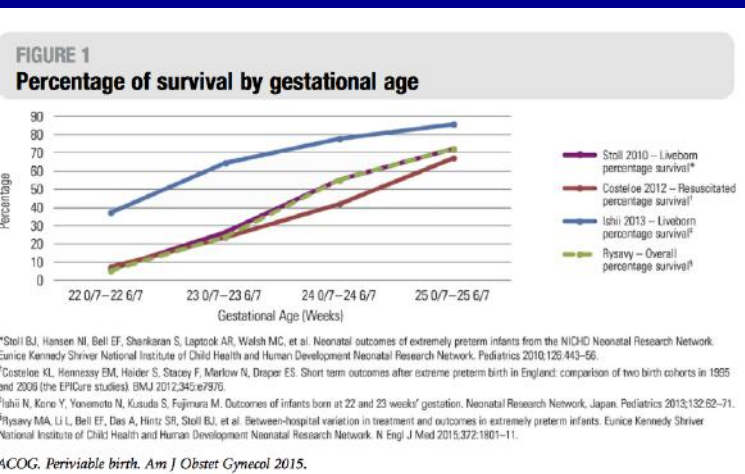
# ***KEY ISSUES IN NEONATOLOGY***

- ***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

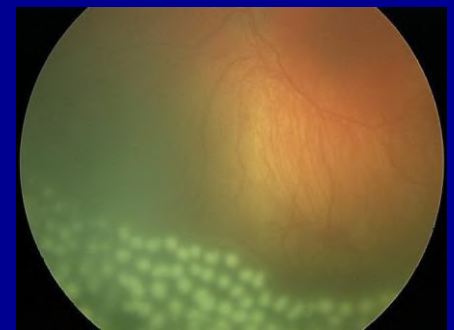
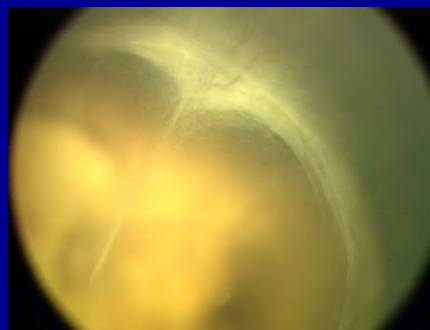


- **SURVIVAL CAN BE IMPROVED**
- **MANY TRIALS HAVE CONFLICTING OUTCOMES – CLEAR BENEFITS **BUT HARM** MAY INCLUDE INCREASED MORTALITY**
- **AGGRESSIVE NUTRITIONAL SUPPORT IMPROVES OUTCOMES- **HUMAN MILK IS VITAL****



# ***FIRST DO NO HARM- high versus low oxygen***

<u><b>Year</b></u>	<u><b>Problem</b></u>	<u><b>Treatment</b></u>	<u><b>Iatroepidemic</b></u>
<b>1940 - 1960</b>	<b>Respiratory distress Blindness from ROP</b>	<b>Liberal use of O<sub>2</sub> Restriction in use of O<sub>2</sub></b>	<b>Retinopathy of prematurity Increased mortality and cerebral palsy</b>



# ***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**

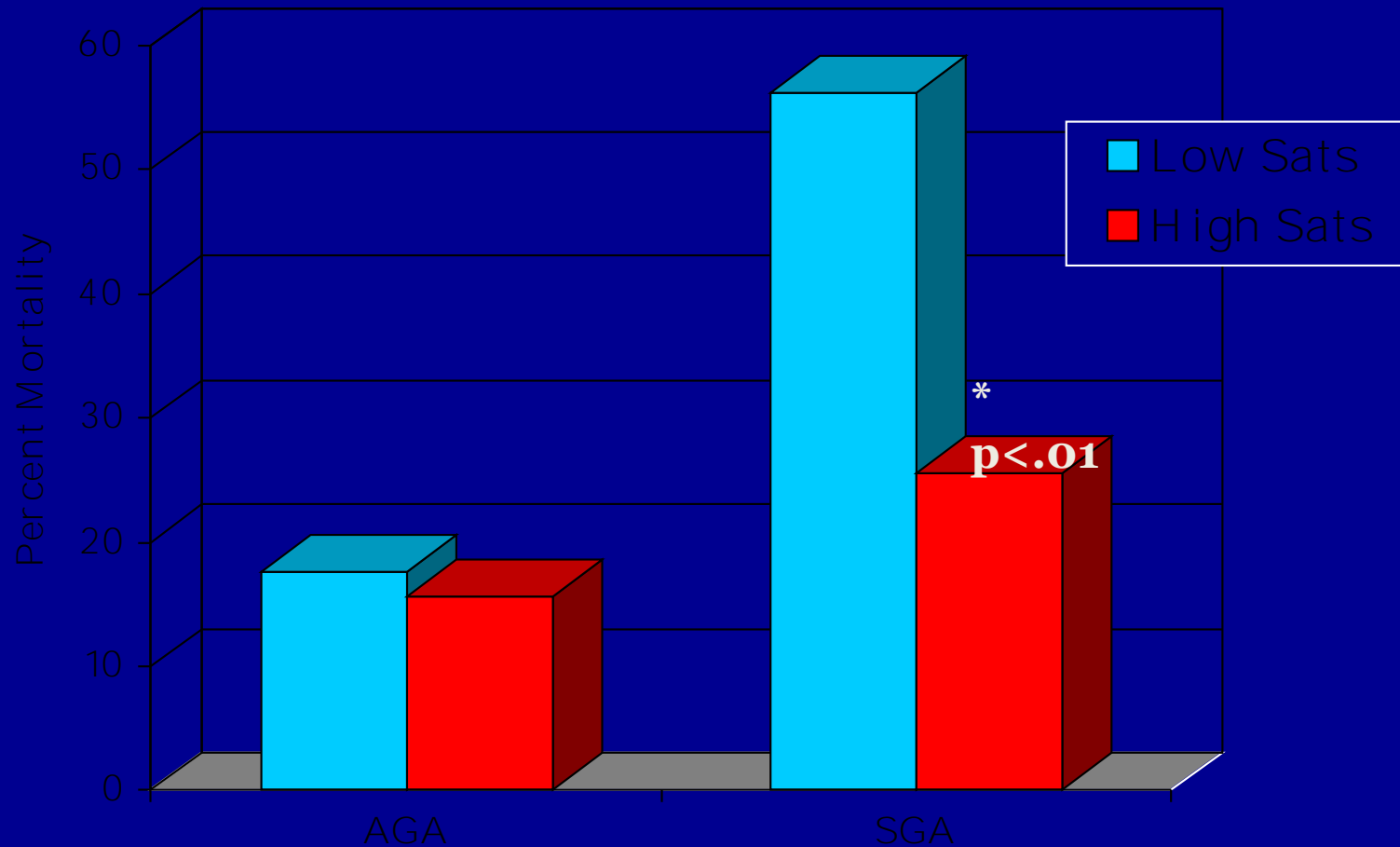
**ANTENATAL CORTICOSTEROIDS- DECREASE MORBIDITY AND Mortality except in developing world .**

**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<sub>2</sub> Target Groups



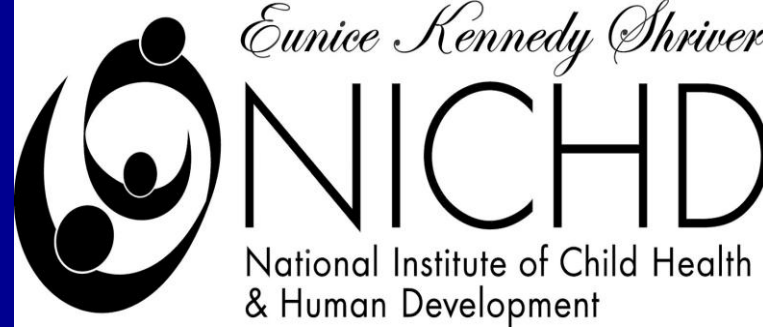
Walsh MC, Di Fiore JM, Martin RJ & SUPPORT Investigators: *JAMA Pediatr* 2016



# 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 H<sub>2</sub>O x 15 seconds and if needed 25 cm H<sub>2</sub>O 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.***

## ***PREMATURITY AND SURVIVAL***

***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.***

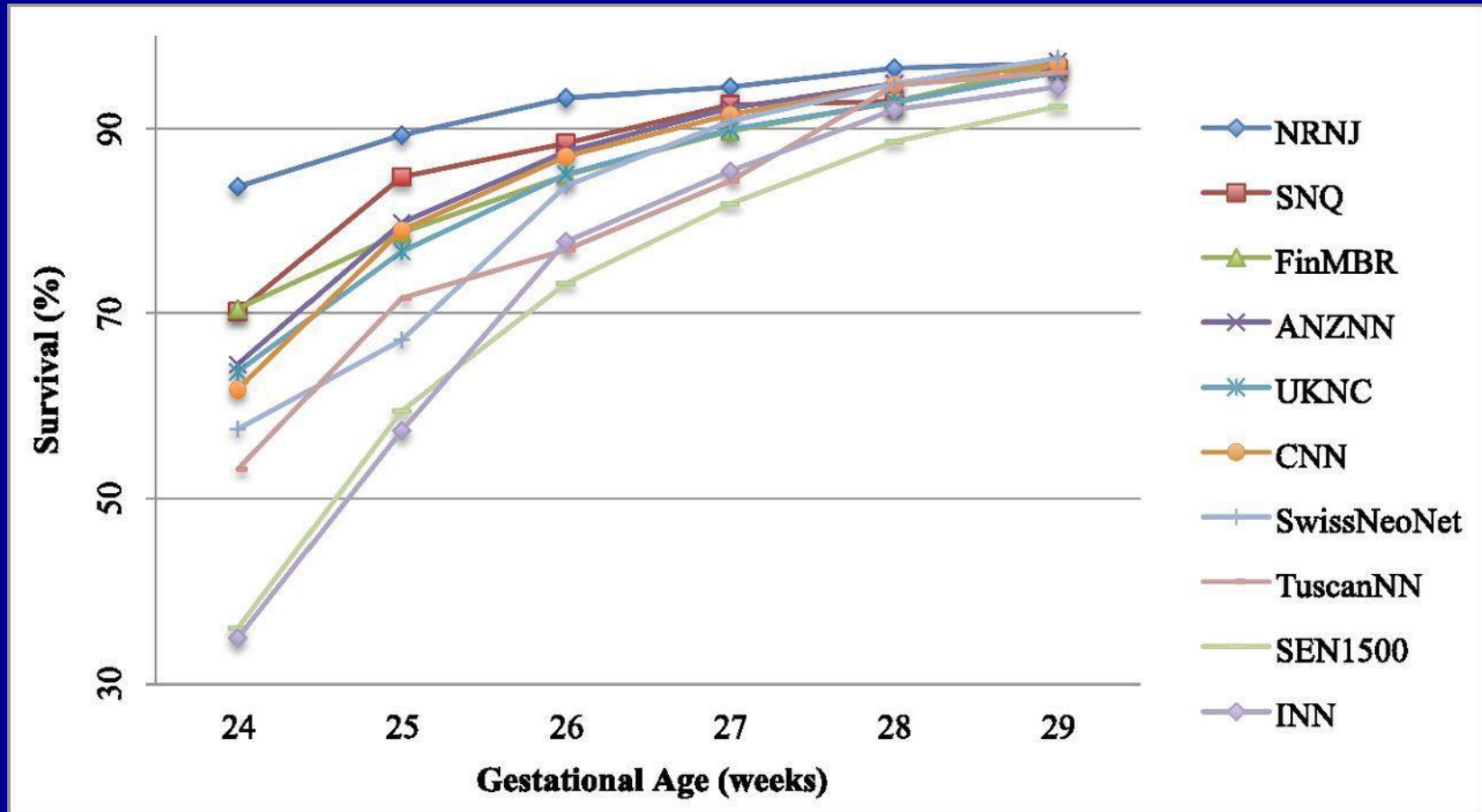
# Survival in Preterm Infants; an International Comparison of 10 national Neonatal Networks Helenius K Pediatrics

## ***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.



Kjell Helenius et al. *Pediatrics*  
2017;140:e20171264

# ***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.***

# ***Survival in Preterm Infants; an International Comparison of 10 national Neonatal Networks***

## ***HeleniusK Pediatrics***

### **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.***

# Survival in Preterm Infants; an International Comparison of 10 national Neonatal Networks

## 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.*



# ***CENTER VARIABILITY***

- ***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’?***

# ***CENTER VARIABILITY***

- ***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.***

**BETWEEN HOSPITAL VARIATION IN TREATMENT AND  
OUTCOMES IN EXTREMELY PRETERM INFANTS  
RYSAVY N.ENG.J.MED 2015;372;331**

- 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

# **OVERVIEW-QUALITY IMPROVEMENT**

**WORLDWIDE** Zaka N *Implement Sci.* 2018 Jan 25;13(1):20

- *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.*

# **OVERVIEW-QUALITY IMPROVEMENT**

**WORLDWIDE** Zaka N *Implement Sci.* 2018 Jan 25;13(1):20

- *Quality improvement (QI) initiatives can reduce the burden of mortality and morbidity for hospitalized newborns in these settings.*

# QUALITY IMPROVEMENT

**Pharande** *J Paediatr Child Health. 2018*

- **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.”***

***Travers CP et al Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids.(ANC) Am J Obstet Gynecol. 2018;218:130.e1-130.e13.***

- ***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%).***



*Travers CP et al Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. Am J Obstet Gynecol. 2018;218:130.e1-130.e13.*

- **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.*

*Travers CP et al Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. Am J Obstet Gynecol. 2018;218:130.e1-130.e13.*

- **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.***

**Bassler D.et al. Long-Term Effects of Inhaled Budesonide for Bronchopulmonary Dysplasia N Engl J Med 2018;378:148-157.**

- **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**).*

# ***FOGARTY –CORD CLAMPING-meta-analysis and systematic review- AJOG2017***

- ***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)***

***FOGARTY –meta-analysis and  
systematic review-AJOG2017***

***In 3 trials in 996 infants  $\leq 28$   
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**

***Plana MN, Zamora J, Suresh G, et al. Pulse oximetry screening for critical congenital heart defects. Cochrane Database Syst Rev. 2018 Mar 1;3:CD011912.***

- ***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).***



*Plana MN, Zamora J, Suresh G, et al. Pulse oximetry screening for critical congenital heart defects. Cochrane Database Syst Rev. 2018 Mar 1;3:CD011912.*

- *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.*

***Plana MN, Zamora J, Suresh G, et al. Pulse oximetry screening for critical congenital heart defects. Cochrane Database Syst Rev. 2018 Mar 1;3:CD011912.***

- 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 pneumothorax and TTNB or sepsis***

*Plana MN, Zamora J, Suresh G, et al. Pulse oximetry screening for critical congenital heart defects. Cochrane Database Syst Rev. 2018 Mar 1;3:CD011912.*

- **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 than 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***

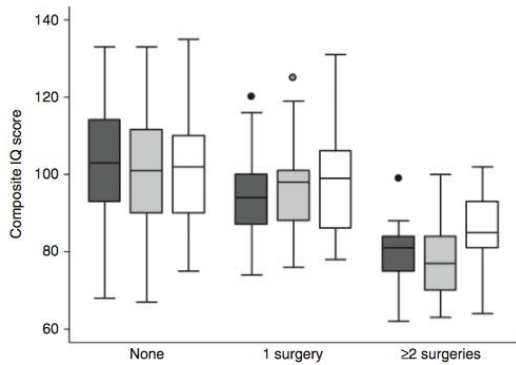
- Gopel studying genetic polymorphisms in over 11,000 infants with a B.W.<1500 G g found that babies with **a high serum iron levels due to rs855791 genotype** were less likely to develop surgical NEC (Odds ratio 0.265, C.I. 0.11-0.65), whereas carriers of the same gene with the A Allele had a higher incidence of NEC. This could be reduced with probiotics.
- ***Pediatric research 2018;83;57-62***

# ***GENETICS; IRON AND NECROTIZING ENTEROCOLITIS***

- ***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***



**Figure 1.** Composite IQ scores by number of surgeries prior to term-equivalent age. Box plot demonstrating composite full-scale (dark gray), performance (light gray), and verbal (white) IQ scores in children by the number of surgeries prior to term-equivalent age (TEA). Circles represent outliers.

- ***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***

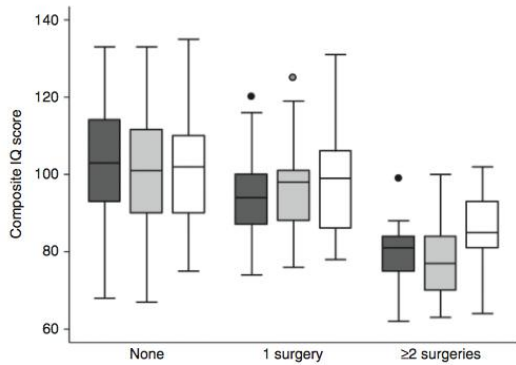
# ***HOW TO IMPROVE NEURO-DEVELOPMENTAL OUTCOME***

- ***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***



**Figure 1.** Composite IQ scores by number of surgeries prior to term-equivalent age. Box plot demonstrating composite full-scale (dark gray), performance (light gray), and verbal (white) IQ scores in children by the number of surgeries prior to term-equivalent age (TEA). Circles represent outliers.

- ***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***

