Rescue Therapies in Neonatology

February 2014
Bill Walsh
Monroe Carell Jr Children’s Vanderbilt
Off Label Use-Disclaimer

• All discussion in this talk concerns off-label use of nitric oxide, steroids, and surfactant, and includes opinion and speculation.

• Conflict-Chair DSMB iKaria iNO trial
Rescue ??

- Bill Walsh: Hey Alan I have some questions:

- ???
Rescue

• “Who? From what? Which therapies?”

• **Dr Spitzer:**

  • “When you think about bailing on what you are currently doing “

  • “I know you will do it well and I very much look forward to your presentation.”
Does “Rescue”=“Shotgun”?

• It’s a trap!!:

• Evidence-Based Neonatal Pharmacotherapy
  Edited by Alan R. Spitzer and Dan L. Ellsbury
  • Clinics- Volume 39, Issue 1, Pages 1-268 (March 2012)

• “Shotgun” therapy, where anything that can be tried will be tried, has now become part of the history of medicine.
Rescue versus Standard of Care

- Evidence not clear. But does exist
Rescue

• Has some risks or costs.

• Some folks use and some do not.

• =NOT STANDARD of Care
Three “Respiratory Rescue” therapies

- Premie iNO
- Post-natal Steroids
- Late Surfactant
Rescue Therapy #1 Premie iNO
The case: 920 gram 28 weeker

- PPPROM @ 21 weeks delivery at 28 weeks.
• Mother treated with steroids x 2, antibiotics

• Surfactant given.

• FiO2 80% Pip 24/5- TV only 3 ml/kg,
  – rate 40

• Blood Gas PaO2- 32, PaCO2 98, pH 6.99
Not rescue
iNO for this 28 week Premie?
PPHN N.O. trails

• iNO rescue may work in preterm infants at 34 weeks and above gestation.

• They are included in the successful trial of iNO but numbers of premies were small and supposedly all ECMO candidates.
Relative Risk of ECMO

Study

- NINOS (n = 235)
- CINRGI (n = 248)
- INOSG (n = 58)
- Boston (n = 90)
- Ohmeda (n = 155)
- Total (n = 538)

Relative Risk of ECMO
1997-1999

• We did a double-blind, randomized controlled trial in 12 perinatal centers that provide tertiary care.
• 80 premature neonates (gestational age ≤34 weeks) with severe hypoxemic respiratory failure.
• Randomly assigned inhaled nitric oxide (n=48) or no nitric oxide (n=32, controls).
• Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial

• John P Kinsella et al.

• The Lancet, September 1999
PaO₂FiO₂ results at baseline and 60 min after treatment * p>0.05 vs control.

John P Kinsella, William F Walsh, Carl L Bose, Dale R Gerstmann, JJ Labella, Smeeta Sardesai, Michele C Walsh...

Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial

The Lancet Volume 354, Issue 9184 1999 1061 - 1065
Our study- Conclusion

- Death 52% versus 47% no difference.

- Conclusion; Really, really, really sick premies die and improving PaO2 a little, is not enough.
Inhaled Nitric Oxide in Preterm Infants Undergoing Mechanical Ventilation

Roberta A. Ballard, M.D., William E. Truog, M.D., Avital Cnaan, Ph.D., Richard J. Martin, M.D., Philip L. Ballard, M.D., Ph.D., Jeffrey D. Merrill, M.D., Michele C. Walsh, M.D., David J. Durand, M.D., Dennis E. Mayock, M.D., Eric C. Eichenwald, M.D., Donald R. Null, M.D., Mark L. Hudak, M.D., Asha R. Puri, M.D., Sergio G. Golombek, M.D., Sherry E. Courtney, M.D., Dan L. Stewart, M.D., Stephen E. Welty, M.D., Roderic H. Phibbs, M.D., Anna Maria Hibbs, M.D., Xianqun Luan, M.S., Sandra R. Wadlinger, M.S., R.R.T., Jeanette M. Asselin, M.S., R.R.T., and Christine E. Coburn, M.S.N., for the NO CLD Study Group*
The rate of survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age was 43.9 percent in the group receiving nitric oxide and 36.8 percent in the placebo group (P = 0.042).

Less than 28 weeks 7-14 days of age
Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure

John P. Kinsella, M.D., Gary R. Cutter, Ph.D., William F. Walsh, M.D., Dale R. Gerstmann, M.D., Carl L. Bose, M.D., Claudia Hart, M.D., Kris C. Sekar, M.D., Richard L. Auten, M.D., Vinod K. Bhutani, M.D., Jeffrey S. Gerdes, M.D., Thomas N. George, M.D., W. Michael Southgate, M.D., Heather Carriedo, M.D., Robert J. Couser, M.D., Mark C. Mammel, M.D., David C. Hall, M.D., Mariann Pappagallo, M.D., Smeeta Sardesai, M.D., John D. Strain, M.D., Monika Baier, Ph.D., and Steven H. Abman, M.D.*
• **Results our trial**

• Overall, there was no significant difference in the incidence of death or broncho-pulmonary dysplasia between patients receiving inhaled nitric oxide and those receiving placebo (71.6 percent vs. 75.3 percent, P = 0.24).
The Changing use:

- The changing pattern of inhaled nitric oxide use in the neonatal intensive care unit.
- Reese, Alan Spitzer et al
- Pediatrix data only 494,255 .
- 43% of iNO use in infants< 34 weeks
iNO use in Premies over time

- *Age at which iNO was started, n (%)*,
  - < 3 days old 2000 - 85 (66.9)
  - 2003 278 (57.9)
  - 2006 600 (57.2)

- Died (30.7%), (37.7%), (37%)

- Still being used still no change as of 2006
Data from 3298 infants in 12 trials

• Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of Randomized Trials

• Askie et al Sept 2011 Pediatrics
• Seven trials studied ventilated < 35 weeks, preterm infants with evidence of respiratory failure within the first 3 days

• The oxygenation indices ranged from 12 to 32.

• No statistically significant reduction in death or CLD was noted (typical RR 1.05, 95% CI 0.91, 1.22).
• NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide
• F. Sessions Cole et al, Pediatrics Jan 2011
What iNO does not do for Premies:

• There was no statistically significant effect of iNO on death or CLD (59% vs 61%: relative risk .96).

• Does NOT prevent Death nor CLD when used routinely
Changes in Use of iNO in the NICU

Data from Pediatrix Medical Group Clinical Data Warehouse Courtesy Reese Clark
Nitric Oxide in Preterm infants?

- Can you use a rescue therapy that has been “Proven” to not work? Or at least not been shown to work?

- Bias - Very Superstitious by Bud Light - Daily Videos on FunnyPlace.org

- Very superstitious, writing's on the wall
  When you believe in things that you don't understand
  Then you suffer
  Superstition ain't the way
¡NO works in premies?
Back to my Case

- My unit in July 2013, 920 gms, PPPROM at 21 weeks then anhydramnios,
- Delivery @ 28 weeks with 1,2,6 Apgars, “responded” to ventilation with improved HR, CO2 in 80s.
- Saturation 76 after surfactant, RX of pneumothorax and fluid resuscitation.
- 20 PPM iNO added, Saturation 76 to 96 no change CO2.
- Anecdotal-and only Saturation improvement
Survived so far…

• Extubated but….Multiple problems (SIP) (CLD), discharged in January “survived”.
the Consensus Panel concluded that taken as a whole, the available evidence does not support use of iNO in the early-routine, early rescue, or later-rescue regimens in the care of premature infants.
iNO in Premies

• Is an acute and anecdotally compelling change in Oxygen Saturation in the short term an indication to use for RESCUE??

• Other Data ? No data in ANY study showing significant HARM.
• Inhaled Nitric Oxide for Preterm Premature Rupture of Membranes, Oligohydramnios, and Pulmonary Hypoplasia.
  • Valerie Y. Chock et al .. the NICHD Neonatal Research Network
  • Am J Perinatology Apr 2009
Search for evidence to support my “belief” and practice

- 12 infants out of the 449 in the premie iNO trial met criteria of suspected pulmonary hypoplasia from Oligohydramnios.

- Fortunately 6 received placebo, 6 iNO
ONLY- 12 Babies

• The 6 iNO babies had a mean increase in PaO2 of 39 +/- 50 mm Hg versus a mean decrease of 11 +/- 15 mm Hg in the control group.
• Mortality was 33% versus 67%,
• BPD (2/5) 40% versus (2/2) 100%,
• Severe IVH or PVL (1/5) 20% versus (1/2) 50% in the iNO and control groups.
• None of these changes were statistically significant!
Use premie iNO “Rescue”?  

- WALSH- Personal opinion and OFF LABEL: IF ever only for rare and selected cases:
  - 1) Documented Pulmonary Hypoplasia and Pulmonary hypertension.
  - 2) Trial of iNO, if no response stop. Response = Saturation 5% increase.

- Warning- off label and unreimbursed !!
NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants

• “There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants of < 34 weeks gestation. “

• Loophole?
Last month - Loophole gone
• An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
Increased usage continues

- 6 fold increase in usage- greatest increase occurred among infants who were born at 23 to 26 weeks’ gestation (0.8% to 6.6%)

- Awaiting results of the large iKaria trial and TOLSURF trials, just completed, excellent studies.

- I am sure premie iNO does not work on insurance companies
Rescue Therapy #1 Premie iNO
#2 More rescue?

Steroids??

NICU
ARTICLES

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS


From the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, New Zealand
Historic article October 1972

Watergate
Roe v Wade
Vietnam

• Liggins and Howe - *antenatal steroid*
mortality 3.2 % versus 15% in controls-

• *Pediatrics* 1972; 50; 515

• Same Journal very next article:
Postnatal Steroids?

A CONTROLLED TRIAL OF HYDROCORTISONE THERAPY IN INFANTS WITH RESPIRATORY DISTRESS SYNDROME

Melvin Baden, LTC, MC, Charles R. Bauer, M.D., Eleanor Colle, M.D., George Klein, Ph.D., H. William Taeusche, Jr., M.D., and Leo Stern, M.D.

From the McGill University-Montreal Children's Hospital Research Institute, Montreal, Canada

• LTC Mel Baden, in San Antonio
• 2nd Lt Walsh- Medical Student UTHSC
Trial of Postnatal Steroids

• 44 babies-22 per group, placebo controlled

• Two doses Hydrocortisone 15 mg/kg 12 hours apart on day one.

• No effect on -A-a, oxygen, ABGs, survival, days on vent.

• The end of post-natal steroids?
1985

The Internet's Domain Name System is created
Madonna's "Like a Virgin," album goes #1 for 3 weeks

• **Controlled Trial of Dexamethasone in Respirator-Dependent Infants with Bronchopulmonary Dysplasia**

• Gordon B. Avery, Anne B. Fletcher, Michael Kaplan and D. Spencer Brudno

• *Pediatrics* 1985;75;106
Eleven premature infants with hyaline membrane disease, whose gestational ages were 27-36 weeks, required ventilatory support and supplemental oxygen. Their clinical course indicated irreversible lung damage. Due to advancing stage II BPD on Xray and continued oxygen and ventilator dependence, they were started on a course of Dexamethasone (Decadron, MSD). Within forty eight hours, each patient showed a clinical response with increasing pulmonary compliance, a diminishing oxygen and ventilator requirement and a halt in the progression of the disease on Xray. A double blind study is now being set up to evaluate the usefulness of steroids in BPD. Our present evidence indicates prompt clinical improvement in lung disease, but with associated risk and side effects including hypertension, susceptibility to sepsis, gastric ulcers, cushinoid syndrome and difficulties in weaning which complicate management. It appears that in the inflammatory phase of developing BPD, Decadron is a useful, but not benign, new approach to this life threatening lung disease.
Kramer 1978

• 11 patients treated due to progressive worsening of Lung Disease

• All 11 responded
1985

• Controlled Trial of Dexamethasone in Respirator-Dependent Infants with Bronchopulmonary Dysplasia
• Gordon B. Avery, Anne B. Fletcher, Michael Kaplan and D. Spencer Brudno
• *Pediatrics* 1985;75;106
• Seven consecutive pairs favored dexamethasone in weaning from the respirator (ie, the treated baby weaned and the paired control baby did not wean within 72 hours).
• “In the long run, risk and benefit must be carefully balanced lest the cure be worse than the disease.”

• Wise words- Probably from Dr Avery but not sure
Postnatal steroid use in very low birthweight infants in the Vermont Oxford Network, 1990–2005. (Adapted from Walsh *et al.*-) Michelle Not me

- **Cerebral palsy** (39/80 (49%) v 12/79 (15%) odds ratio
- (OR) 4.62 -95% CI up to 10
- **Developmental delay** (55%) vs. (29%);
- OR 2.87
- More periventricular leukomalacia and less intraventricular hemorrhage
American Academy of Pediatrics (AAP), in a policy statement regarding the use of postnatal corticosteroids for prevention or treatment of CLD in preterm infants, concluded that routine dexamethasone therapy for the prevention or treatment of CLD could not be recommended.
Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants.

Soll R F Neoreviews 2011;12:e8-e12
Early (<8 days) postnatal corticosteroids for causing CP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Steroid n/N</th>
<th>Control n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td>2/25</td>
<td>3/25</td>
<td></td>
<td>3.4%</td>
<td>0.67 [0.12, 3.65]</td>
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<tr>
<td>Romagnoli 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sanders 1994</td>
<td>3/19</td>
<td>1/21</td>
<td></td>
<td>2.1%</td>
<td>3.32 [0.38, 29.23]</td>
</tr>
<tr>
<td>Shinwell 1996</td>
<td>36/132</td>
<td>12/116</td>
<td></td>
<td>27.2%</td>
<td>2.78 [1.53, 5.07]</td>
</tr>
<tr>
<td>Sarkin 2000</td>
<td>4/32</td>
<td>1/27</td>
<td></td>
<td>2.2%</td>
<td>3.38 [0.40, 28.42]</td>
</tr>
<tr>
<td>Stark 2001a</td>
<td>11/111</td>
<td>12/109</td>
<td></td>
<td>16.3%</td>
<td>0.90 [0.42, 1.85]</td>
</tr>
<tr>
<td>Subhedar 1997</td>
<td>0/21</td>
<td>2/21</td>
<td></td>
<td>1.1%</td>
<td>0.20 [0.01, 3.93]</td>
</tr>
<tr>
<td>Yeh 1997</td>
<td>17/132</td>
<td>9/130</td>
<td></td>
<td>16.4%</td>
<td>1.86 [0.86, 4.02]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**
- Total events: 75 (Steroid), 40 (Control)
- Heterogeneity: Chi² = 9.13, df = 6 (P = 0.17); I² = 34%
- Test for overall effect: Z = 2.90 (P = 0.0038)

<table>
<thead>
<tr>
<th>Hydrocortisone</th>
<th>Steroid n/N</th>
<th>Control n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baden 1972</td>
<td>2/22</td>
<td>1/22</td>
<td></td>
<td>1.8%</td>
<td>2.00 [0.20, 20.49]</td>
</tr>
<tr>
<td>Bonsante 2007</td>
<td>2/25</td>
<td>2/25</td>
<td></td>
<td>2.8%</td>
<td>1.00 [0.15, 6.55]</td>
</tr>
<tr>
<td>Peltoniem 2005</td>
<td>2/25</td>
<td>0/26</td>
<td></td>
<td>1.1%</td>
<td>5.19 [0.26, 103.07]</td>
</tr>
<tr>
<td>Watterberg 1999</td>
<td>1/13</td>
<td>2/13</td>
<td></td>
<td>1.9%</td>
<td>0.50 [0.05, 4.86]</td>
</tr>
<tr>
<td>Watterberg 2004</td>
<td>16/180</td>
<td>18/180</td>
<td></td>
<td>23.8%</td>
<td>0.89 [0.47, 1.69]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**
- Total events: 23 (Steroid), 23 (Control)
- Heterogeneity: Chi² = 1.98, df = 4 (P = 0.74); I² = 0.0%
- Test for overall effect: Z = 0.12 (P = 0.91)

**Total (95% CI)**
- Total events: 98 (Steroid), 63 (Control)
- Heterogeneity: Chi² = 14.07, df = 11 (P = 0.23); I² = 22%
- Test for overall effect: Z = 2.34 (P = 0.020)
- Test for subgroup differences: Chi² = 2.96, df = 1 (P = 0.09), I² = 66%

Soll R F Neoreviews 2011;12:e8-e12

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Chemical Adrenalectomy

• This effect, and high potency and long half-life, may help explain the observed adverse effects of dexamethasone on the neurodevelopmental outcomes of preterm infants.

• Kristi Watterberg
CNS effect

- Dexamethasone is associated with neuronal apoptosis in the hippocampus both in vitro and in animal models.
• High dosages of dexamethasone (eg, ≥0.5 mg/kg/d) may decrease the incidence of BPD, but have been associated with numerous short- and long-term adverse effects. Based on existing evidence, this therapy cannot be recommended.

• Watterberg 2012
Lower doses of dexamethasone (≤0.2 mg/kg/d) may be equally efficacious, facilitate extubation, and result in fewer adverse effects; however, data from RCTs are currently insufficient to allow an evidence-based recommendation for this therapy.
• Limited to exceptional clinical circumstances (eg, an infant on maximal ventilatory and oxygen support). In those circumstances, parents should be fully informed about the known short- and long-term risks and agree to treatment.”
Are postnatal steroids ever justified to treat severe bronchopulmonary dysplasia?

Eric C Eichenwald and Ann R Stark 2007

• In infants with life-threatening respiratory disease who require substantial ventilatory support and supplemental oxygen (fractional inspired oxygen >0.8), it is reasonable to consider a therapeutic trial of corticosteroid treatment.
Policy Statement

• Postnatal Corticosteroids to Prevent or Treat Bronchopulmonary Dysplasia
• Kristi L. Watterberg for the COFN AAP
• Oct 2010
  – For infants at the highest risk of BPD, the beneficial effect of dexamethasone in reducing lung disease seemed to outweigh its adverse effect of increasing the risk of CP.
New data ?-No

• Two RCTs that using low doses of dexamethasone revealed no significant increase in CP or other neurodevelopmental impairments when compared with placebo.

• Because only a total of 96 dexamethasone-treated infants were evaluated in these studies, the results must be interpreted with caution.
Finding the Optimal Postnatal Dexamethasone Regimen for Preterm Infants at Risk of Bronchopulmonary Dysplasia: A Systematic Review of Placebo-Controlled Trials -

*Pediatrics* 2009;123;367

Wes Onland, et al. Netherlands

- 1136 patients in 12 trials were analyzed by using meta-analysis and metaregression. Additional data were provided.
- Moderately-early-treatment studies the risk of mortality or cerebral palsy decreased by 6.2%, and the risk of a Mental Developmental Index below 2 SDs.
- **Decreased by 6.6%** for each incremental mg/kg cumulative dexamethasone dose.
Criteria for “Rescue”? Walsh Opinion

• We reviewed all deaths at Vanderbilt from “Lung Disease”:  
• No respiratory deaths in babies that did not meet these criteria:  
  • Birth-weight < 1300g (average weight less than 750)  
  • Gestational age at birth < 31 weeks (Males less than 27 but the females were less than 25)  
  • Postnatal age ≥ 10 days  
  • Characteristic chest X-ray  
  • Fraction of inspired oxygen (FiO2) > 0.8  
  • Mean airway pressure (MAP) > 8 cm H2O
What to do???

• “RCT urgently needed”- Watterberg

• We use them “judiciously”.
• 8 day course low dose Dex or HC in babies that meet those criteria after discussion with family.

• vuneo.org (Titans/Millie)

• [http://www.vuneo.org/npsystemicsteroids.htm](http://www.vuneo.org/npsystemicsteroids.htm)
RESCUE #3
“Late” Surfactant?

• In ___term___ babies with significant respiratory disease surfactant not too controversial?
Exogenous Surfactant

• Lotze et al, 1998
  – 328 newborns randomized to treatment with Survanta® vs placebo in multicenter RCT
  – Mean OI at entry = 25
  – Reduced need for ECMO only in surfactant-treated group with OI <23
  – Increased incidence of hypoxia and endotracheal tube occlusion in surfactant group
July 2013- Impact of Surfactant and inhaled iNO therapies. Term/Late preterm neonates with moderate HRF JO Perinatology. Konduri GG et al

• 299 infants, OI <25 - Progression to Death or ECMO.
• 13% in Surfactant treated vs 30.8% with no surfactant.
• Almost identical to Lotze trail.
• Conclusion - early surfactant is beneficial.
• But Mean gestational age 38.6 (2.0)
How about “rescue”, late surfactant in the premie

- The two week dwindles ??
• Patterns of Respiratory Disease During the First 2 Postnatal Weeks in Extremely Premature Infants
  • Matthew Laughon, et al for the ELGAN Study Investigators
  • Pediatrics 2009;123;1124
2 week dwindles

- One fifth (20%) of the infants had consistently low fraction of inspired oxygen.
- Two fifths (38%) had pulmonary deterioration, “dwindles”
- Two fifths (43%) had consistently high fraction of inspired oxygen (early and persistent lung dysfunction).
Our Case

• 800 gram 25 week infant with respiratory distress. No antenatal steroids precipitous delivery. Initial response to surfactant weaned near to extubation.

• But on day 8 has gradual increase in oxygen requirement from 30 to 75% escalation of CPAP, evaluation for infection, PDA, fluid overload negative.
Variable course

- “Typical course” improves then deteriorates and in this case deteriorates to the point of Respiratory failure cannot be extubated.
• Rule out infection –Ureaplasma ?, Ductus likely causative?, Fluid overload.

• Surfactant inactivation??
Late Surfactant?

- Biologic plausible: patients recovering from RDS who required higher continuous positive airway pressure after extubation or reintubation have a lower level of intrapulmonary surfactant than those who did well after extubation.

- Pulmonary surfactant kinetics of the newborn infant: novel insights from studies with stable isotopes

- V P Carnielli, et al

Surfactant Dysfunction?

- Dysfunction of Pulmonary Surfactant in Chronically Ventilated Premature Infants - *Pediatrics Research* 2004 56:918
- Jeffrey D Merrill, et al
• 247 tracheal aspirate samples from 68 infants
• Seventy-five percent of the infants had one or more surfactant samples with abnormal function.
• Most premature infants requiring continued respiratory support after 7 d of age experience transient episodes of dysfunctional surfactant.
Secondary surfactant administration in neonates

- R Bissinger, et al
- Described **three** premature infants (<27 weeks gestation) who developed acute respiratory decompensation after 1 week of life.
- All three were treated with a secondary course of surfactant administration with improvement in both their blood gases and their need for ventilator support.
Case 3

![Chart showing changes in PCO₂ (mm Hg) / FiO₂ % over time after surfactant dose. The chart includes graphs for PCO₂ (black diamonds), FiO₂ (yellow triangles), and pH (red squares). There is a 'Dose' label indicating the point of surfactant administration.]
• Secondary surfactant administration in neonates with respiratory decompensation.

• R Bissinger, C Carlson, Y Michel, C Dooley, T Hulsey and D Jenkins

Late Surfactant- 2008 Bissinger JOP

- Not randomized;
- SHORT outcome:
- change in oxygenation and ventilation at 12 and 24 h

- 19 treated - At the time of respiratory decompensation all the infants were diagnosed with either pneumonia or confirmed sepsis.
• A Pilot Randomized, Controlled Trial of Later Treatment With a Peptide-Containing, Synthetic Surfactant for the Prevention of Bronchopulmonary Dysplasia

• Laughon M et al. Pediatrics 2009;123:89-96
Not exactly “Rescue”

• > .30 FiO2, 3-10 days of age.

• Infants with severe lung disease, defined as treatment with FiO2 ≥0.80 and mean airway pressure ≥12 cmH2O were excluded
Late Surfactant (Lucinactant)

- Of 136 infants enrolled at 34 sites,
- 44 received placebo,
- 47 received 90 mg/kg total phospholipid,
- 45 received 175 mg/kg total phospholipid
Mean Fio2 according to treatment group at 15 minutes before the first dose, every 3 hours for 24 hours after the first dose, and 48 hours after the first dose.


©2009 by American Academy of Pediatrics
Repeat surfactant therapy for postsurfactant slump


- [Diagram showing patient distribution](#)
Repeat surfactant therapy for postsurfactant slump

- L A Katz and J M Klein – University of Iowa

- Patients who developed postsurfactant slump after 6 days of life were first placed on HFV.
- If their oxygenation did not improve, repeat surfactant therapy was given to patients requiring a $\text{FiO}_2 > 0.70$ for more than 6 to 8 h despite optimizing HFV.
- All patients who received repeat surfactant therapy were on HFV at that time and had the surfactant manually bagged in.
- Additional repeat doses were given if the FiO2 increased above 0.70 more than 24 h after the first repeat dose.
• Retrospective report of actions done.

• Definition a little circular

• “Postsurfactant slump defined by getting surfactant”
RSS equals MAP times FiO2

• Pilot trial of late booster doses of surfactant for ventilated premature infants, J D Merrill et al

Entry criteria:

• 500 to 1250 g birth weight were enrolled if they were intubated and required ventilatory support between 7 and 10 days of age.

• 87 babies treated no controls
Transient improvement no adverse events - Merrill JOP 2011
Late administration of surfactant replacement therapy increases surfactant protein-B content: a randomized pilot study
Pediatric research 2012 vol 72 613-619, Keller et al

RANDOMIZED, BLINDED, PILOT STUDY
LATE ADMINISTRATION OF DOSES (CALFACTANT) IN COMBINATION WITH PROLONGED INHALED NITRIC OXIDE (INO) IN INFANTS ≤1,000 G BIRTH WEIGHT (BW).

Results: 85 infants randomized 7-14 days of age

Entry criteria <1000 grams and ventilated at 7-14 days

Improved for one day
• SURFACTANT TREATMENT RESULTED IN MODEST SIGNIFICANT DECREASES IN RSS AT 1 H AND 2 H AFTER THE STUDY DRUG DOSE;
• \(-0.25, P = 0.03\), \(-0.33, P = 0.01\)
• DIFFERENCES AT 24 AND 48 H WERE NO LONGER STATISTICALLY SIGNIFICANT
TOLSURF TRIAL

- Patients receive inhaled nitric oxide and scheduled doses of Infasurf on study days 0, 3, 7, 10, and 14.

- Control infants receiving inhaled nitric oxide will not receive additional doses of Infasurf.

- Important study, done and results being analyzed. January 2014.
Inclusion Criteria
- < 28 0/7 wk gestational age
- Day of life 7-14
- Intubated and mechanically ventilated
- Plan to treat with iNO
Hot off press Jan 2014

- Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress
  - Richard A. Polin, Waldemar A. Carlo and COMMITTEE ON FETUS AND NEWBORN
  - *Pediatrics* 2014;133;156;
  - Does not really address “Late Surfactant” for premies
• Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg, pulmonary hemorrhage, meconium aspiration syndrome, or sepsis/pneumonia) (Recommendation).
Late Surfactant

• Lots of enticing data no great outcomes so far.

• Cannot recommend routine use. Rescue?

• TOLSURF - Trial results should answer!
Rescue vs Shotgun? Difference?

• Carefully considered (if I use it is Rescue therapy, if you use it and I do not agree it is Shotgun?)
Late rescue surfactant

- Bill Walsh- Conclusion: Safe probably not effective longterm.

- Future studies will define better population or product or delivery …..
• “Perhaps nowhere are evidence-based approaches and clinical outcomes more important than in the use of medications in the neonatal intensive care unit (NICU). “

• Alan Spitzer
Avoid Iatrogenic Disease

• Simplest rescue may be to not get in trouble to begin with.
Rescue Therapies-had enough?
Mindfully fight the urge to just do “something” but Keep informed- things change continuously. Thank you!