**What has Cochrane Done for Babies?**

Roger F. Soll, MD

H. Wallace Professor of Neonatology
University of Vermont College of Medicine

Coordinating Editor, Cochrane Neonatal
President, Vermont Oxford Network

Cochrane Neonatal Web Seminar
September 29th 2017


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**The Basics**

- Follow slides on the Internet
- Listen on your phone or speakerphone
- Chat feature - questions anytime
- Your phone will be muted during talks
- Questioner unmuted during Q&A

Use the raised hand icon to queue up for questions

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**Editorial Team**

**Cochrane Neonatal**

Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

**Cochrane Neonatal**

Prepares and disseminates evidence-based reviews of the effects of therapies in the field of neonatal medicine

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**Editorial Team**

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Disclosure  
Roger F. Soll is the Coordinating Editor of Cochrane Neonatal previously supported by a contract from the NICHD and President of Vermont Oxford Network

Why These Webinars?  
To develop an understanding of the evidence supplied by systematic reviews in neonatal perinatal medicine (as well as other large well conducted trials) and discuss how this evidence might influence your practice.

COCHRANE COLLABORATION  
Cochrane Collaborative Groups
- Over 50 Collaborative Review Groups
- Most address specific disease entities/health problems
- The Cochrane Neonatal Review Group; one of the rare groups that address the needs of a population

COCHRANE NEONATAL  
What do we do?
- prepare and disseminate evidence-based reviews of the effects of therapies in the field of neonatal medicine.
- reviews follow a standard method:
  - a well formulated question
  - a comprehensive search for eligible trials
  - critical appraisal of trial quality
  - quantitative synthesis of the results using meta-analysis
- reviews are regularly updated as new trials are published.
SYSTEMATIC OVERVIEW

- Applies specific research strategies to identify, appraise, and synthesize data from all relevant clinical studies

Quantitative systematic reviews include meta-analyses:
- statistical methods to combine the results of similar randomized controlled trials to produce a typical estimate of the effect size

META-ANALYSIS

What’s the use of meta-analysis?

- increase statistical power
- increase precision of estimate
- explore differences between study results
- create structure for incorporating new evidence

COCHRANE NEONATAL

These Cochrane systematic reviews are published in the Cochrane Database of Systematic Reviews which is contained in the Cochrane Library.

COCHRANE NEONATAL

What has Cochrane Neonatal done for me lately?
Or more importantly...

What has it done for babies?

SOMETIMES COCHRANE REVIEWS CHANGE THE WAY WE PRACTICE AND SAVE BABIES’ LIVES!
CORTICOSTEROIDS FOR PRETERM BIRTH

Since 1972,
- there are multiple randomized controlled trials (N=18)
- involving a large number of infants (3735 infants)

but...
Antenatal corticosteroids
were not utilized in the vast majority of patients until...

PROPHYLACTIC CORTICOSTEROIDS PRIOR TO PRETERM BIRTH

OVERVIEW OF 18 RANDOMIZED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>Outcome (# of trials)</th>
<th>Typical Relative Risk (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS (14)</td>
<td>0.64 (0.56, 0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular hemorrhage (4)</td>
<td>0.57 (0.41, 0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis (4)</td>
<td>0.60 (0.33, 1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (3)</td>
<td>1.38 (0.90, 2.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal death (13)</td>
<td>0.63 (0.51, 0.77)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crowley (1992)

PROPHYLACTIC CORTICOSTEROIDS PRIOR TO PRETERM BIRTH

OVERVIEW OF 15 RANDOMIZED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>Outcome (# of trials)</th>
<th>Typical Relative Risk (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth (12)</td>
<td>0.84 (0.59, 1.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal/neonatal infection (15)</td>
<td>0.84 (0.60, 1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal infection (11)</td>
<td>1.26 (0.99, 1.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological abnormality (3)</td>
<td>0.65 (0.39, 1.08)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crowley (1992)

CORTICOSTEROIDS FOR PRETERM BIRTH

"Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs”
We're so proud of this, we made it part of our logo…

SOMETIMES COCHRANE REVIEWS TELL US WHAT WE ALREADY KNOW!

SURFACTANT THERAPY

EFFECT ON PNEUMOTHORAX

<table>
<thead>
<tr>
<th>TYPES OF STUDIES (%)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPHYLACTIC SURFACTANT</td>
<td>SYNTHETIC SURFACTANT (6)</td>
<td>-0.05 (-0.09, -0.03)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>NATURAL SURFACTANT (8)</td>
<td>-0.15 (-0.20, -0.11)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>RESCUE SURFACTANT</td>
<td>SYNTHETIC SURFACTANT (5)</td>
<td>-0.09 (-0.12, -0.06)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>NATURAL SURFACTANT (12)</td>
<td>-0.17 (-0.21, -0.13)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Soll 1997

Typical Relative Risk (95% CI)

SURFACTANT THERAPY

EFFECT ON NEONATAL MORTALITY

<table>
<thead>
<tr>
<th>TYPES OF STUDIES (%)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPHYLACTIC SURFACTANT</td>
<td>SYNTHETIC SURFACTANT (7)</td>
<td>-0.07 (-0.11, -0.03)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>NATURAL SURFACTANT (8)</td>
<td>-0.07 (-0.12, -0.03)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>RESCUE SURFACTANT</td>
<td>SYNTHETIC SURFACTANT (5)</td>
<td>-0.05 (-0.07, -0.02)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>NATURAL SURFACTANT (12)</td>
<td>-0.09 (-0.13, -0.05)</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Soll 1997

Typical Relative Risk (95% CI)

EXOGENOUS SURFACTANT TREATMENT

VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2010

% VLBW INFANTS

1991 1993 1995 1997 1999 2001 2003 2005 2007 2009

EXOGENOUS SURFACTANT TREATMENT

FDA APPROVAL

% ELBW INFANTS


INTRODUCTION OF ANTENATAL STEROIDS AND POSTNATAL SURFACTANT TREATMENT

EFFECT ON MORTALITY IN ELBW INFANTS

% ELBW INFANTS


- ANTENATAL STEROIDS
- SURFACTANT THERAPY
- MORTALITY
SOMETIMES COCHRANE REVIEWS REFINE HOW WE PRACTICE!

PROPHYLACTIC SURFACTANT AND STEROIDS

EFFECT ON MORTALITY DUE TO RDS

DELIVERY ROOM vs. TREATMENT SURFACTANT

EFFECT ON NEONATAL MORTALITY

STUDY

<table>
<thead>
<tr>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Kendig 1991
Dunn 1991
Egberts 1993
Kattwinkel 1993
Walti 1995
Bevilacqua 1996
Bevilacqua 1997
TYPICAL ESTIMATE
Soll and Morley 2001

Relative Risk and 95% CI

PROPHYLACTIC SURFACANT vs. SELECTIVE TREATMENT OF RDS

NEONATAL MORTALITY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hospital</th>
<th>Control</th>
<th>Selective</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRF</td>
<td>114</td>
<td>125</td>
<td>114</td>
<td>957</td>
<td>1.07</td>
</tr>
<tr>
<td>SRF/ST</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
</tr>
<tr>
<td>NS/ST</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
</tr>
<tr>
<td>NS</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Test for overall effect F = 1.65 (P = 0.49)
Test for heterogeneity Q = 1.28 (P = 0.53)

PROPHYLACTIC SURFACANT vs. SELECTIVE TREATMENT OF RDS

DEATH OR BPD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hospital</th>
<th>Control</th>
<th>Selective</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRF</td>
<td>219</td>
<td>225</td>
<td>219</td>
<td>1550</td>
<td>1.07</td>
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<tr>
<td>SRF/ST</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
</tr>
<tr>
<td>NS/ST</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
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<tr>
<td>NS</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>155</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Test for overall effect F = 1.65 (P = 0.49)
Test for heterogeneity Q = 1.28 (P = 0.53)
**Role of Inflammation**

Chorioamnionitis and Bronchopulmonary Dysplasia


**Postnatal Steroid Therapy: Mechanism of Action**

- Stabilize cellular or lysosomal membranes
- Decrease inflammatory response
- Decrease pulmonary edema

**Postnatal Steroid Therapy: Potential Risks**

- Hypertension
- Hyperglycemia
- Infection
- Cardiomyopathy
- GI bleeding/perforation
- Decreased somatic growth
- Decreased brain growth
- Neurodevelopmental problems

**Postnatal Steroid Therapy: Systematic Overview**

- Early Steroid Treatment:
  - Before or at 7 Days
  - Studies 32
  - Enrolled infants 4395
- Late Steroid Treatment:
  - After 7 Days
  - Studies 21
  - Enrolled infants 1424

**Sometimes Cochrane Reviews Stop Us From Doing Things That Might Injure Our Babies!**
**EARLY (≤ 7 DAYS) POSTNATAL STEROID THERAPY**

**META-ANALYSIS OF 32 RANDOMIZED CONTROLLED TRIALS**

<table>
<thead>
<tr>
<th>Outcome (N Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased • Risk • Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD @ 28 DAYS (17)</td>
<td>-0.07 (-0.10, -0.03)</td>
<td></td>
</tr>
<tr>
<td>CLD @ 36 WEEKS (24)</td>
<td>-0.07 (-0.09, -0.04)</td>
<td></td>
</tr>
<tr>
<td>DEATH/CLD @ 36 WKS (25)</td>
<td>-0.06 (-0.09, -0.03)</td>
<td></td>
</tr>
<tr>
<td>MORTALITY (30)</td>
<td>-0.01 (-0.03, 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

Doyle 2017

**EARLY (≤ 7 DAYS) POSTNATAL STEROID THERAPY**

**EFFECT ON COMPLICATIONS OF PREMATURITY**

<table>
<thead>
<tr>
<th>Outcome (N Studies)</th>
<th>Decreased • Risk • Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY AIR LEAK (16)</td>
<td></td>
</tr>
<tr>
<td>PATENT DUCTUS ARTERIOSUS (24)</td>
<td></td>
</tr>
<tr>
<td>INFECTION (25)</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSION (11)</td>
<td></td>
</tr>
<tr>
<td>GI HEMORRHAGE (12)</td>
<td></td>
</tr>
<tr>
<td>SEVERE IVH (26)</td>
<td></td>
</tr>
<tr>
<td>SEVERE ROP (14)</td>
<td></td>
</tr>
</tbody>
</table>

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**LATE (> 7 DAYS) POSTNATAL STEROID THERAPY**

**META-ANALYSIS OF 21 RANDOMIZED CONTROLLED TRIALS**

<table>
<thead>
<tr>
<th>Outcome (N Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased • Risk • Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD @ 28 DAYS (6)</td>
<td>-0.11 (-0.17, -0.05)</td>
<td></td>
</tr>
<tr>
<td>CLD @ 36 WEEKS (11)</td>
<td>-0.15 (-0.22, -0.07)</td>
<td></td>
</tr>
<tr>
<td>DEATH/CLD @ 36 WKS (11)</td>
<td>-0.18 (-0.25, -0.11)</td>
<td></td>
</tr>
<tr>
<td>MORTALITY (19)</td>
<td>-0.03 (-0.07, 0.02)</td>
<td></td>
</tr>
</tbody>
</table>

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**LATE (> 7 DAYS) POSTNATAL STEROID THERAPY**

**NEURODEVELOPMENTAL OUTCOME IN SURVIVORS**

<table>
<thead>
<tr>
<th>Outcome (N)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased • Risk • Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAYLEY MDI &lt; 2SD (7)</td>
<td>-0.03 (-0.10, 0.05)</td>
<td></td>
</tr>
<tr>
<td>BAYLEY PDI &lt; 2SD (1)</td>
<td>-0.04 (-0.17, 0.09)</td>
<td></td>
</tr>
<tr>
<td>ABNORMAL NEURO EXAM (4)</td>
<td>0.15 (-0.00, 0.30)</td>
<td></td>
</tr>
<tr>
<td>CEREBRAL PALSY (15)</td>
<td>-0.02 (-0.08, 0.03)</td>
<td></td>
</tr>
<tr>
<td>MOD/SEVERE IMPAIRMENT (9)</td>
<td>0.03 (-0.03, 0.08)</td>
<td></td>
</tr>
</tbody>
</table>

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**POSTNATAL CORTICOSTEROIDS TO TREAT OR PREVENT CHRONIC LUNG DISEASE IN PRETERM INFANTS**

RECOMMENDATIONS FROM THE COMMITTEE ON THE FETUS AND NEWBORN 2002

On the basis of limited short-term benefits, the absence of long-term benefits, and the number of serious short-term and long-term complications, the routine use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended.
Outside the context of a randomized controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (e.g., 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 treat.
SOMETIMES COCHRANE REVIEWS PROVIDE RESULTS THAT MAY BE CONFUSING!

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**Prophylactic Indomethacin**

Meta-analysis of 19 trials

**EFFECT ON PATENT DUCTUS ARTERIOSUS (PDA)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT DUCTUS ARTERIOSUS (7)</td>
<td>-0.27 (-0.32, -0.21)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>SYMPTOMATIC PDA (14)</td>
<td>-0.24 (-0.28, -0.21)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>PDA LIGATION (8)</td>
<td>-0.05 (-0.08, -0.03)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
</tbody>
</table>

**Prophylactic Indomethacin**

Meta-analysis of 19 trials

**EFFECT ON CENTRAL NERVOUS SYSTEM INJURY**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRAVENTRICULAR HEMORRHAGE (14)</td>
<td>-0.04 (-0.08, -0.01)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>SEVERE IVH (14)</td>
<td>-0.05 (-0.07, -0.02)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>PROGRESSIVE IVH (2)</td>
<td>-0.08 (-0.26, 0.13)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>PERIVENTRICULAR LEUKOMALACIA (5)</td>
<td>-0.05 (-0.08, -0.01)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
<tr>
<td>WHITE MATTER INJURY (1)</td>
<td>-0.04 (-0.07, 0.00)</td>
<td><img src="Image" alt="Decreased Risk" /></td>
<td><img src="Image" alt="Increased Risk" /></td>
</tr>
</tbody>
</table>

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**Long-Term Effects of Indomethacin Prophylaxis in ELBW Infants**


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**The New England Journal of Medicine**

**Long-Term Effects of Indomethacin Prophylaxis in Extremely-Low-Birth-Weight Infants**

Barbara Schmidt, M.D., Peter Davis, M.D., Diane Moddemann, M.D., Arne Ohlsson, M.D., Robin S. Roberts, M.Sc., Saroj Saigal, M.D., Alforno Soliman, M.D., Michael Vincer, M.D., and Linda L. Wright, M.D., for the Trial of Indomethacin Prophylaxis in Preterm Investigators*  

Schmidt and colleagues randomly assigned 1202 extremely low birth weight infants to receive either indomethacin (0.1 mg/kg) or placebo intravenously once daily for three days.

The primary outcome was a composite of death, cerebral palsy, cognitive delay, deafness, and blindness at a corrected age of 18 months.

Secondary short-term outcomes were patent ductus arteriosus, pulmonary hemorrhage, chronic lung disease, ultrasonographic evidence of intracranial abnormalities, necrotizing enterocolitis, and retinopathy.

Secondary long-term outcomes were hydrocephalus necessitating the placement of a shunt, seizure disorder, and microcephaly within the same time frame.

### Prophylactic Indomethacin

**Meta-analysis of 19 trials**

**STATUS AT LATEST FOLLOW UP**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at follow up (18)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy (4)</td>
<td>0.00 (-0.03, 0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe ND impairment (3)</td>
<td>-0.01 (-0.05, 0.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Relative Risk and 95% CI**

FOWLIE 2010: THE COCHRANE LIBRARY

### Indomethacin

**VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2015**

- **Prevents**: Symptomatic PDA, severe IVH
- **Does not alter**: Neurodevelopmental outcome
SOMETIMES WE IGNORE THE FINDINGS FROM RANDOMIZED CONTROLLED TRIALS AND THE REVIEWS OF THESE TRIALS!

ELECTIVE HIGH FREQUENCY OSCILLATORY VENTILATION
META-ANALYSIS OF 19 RANDOMIZED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>OUTCOME (STUDIES)</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY AIRLEAK (13)</td>
<td>0.04 (0.01, 0.07)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>IVH (12)</td>
<td>0.02 (-0.01, 0.05)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SEVERE IVH (18)</td>
<td>0.01 (-0.01, 0.04)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>PVL (17)</td>
<td>0.00 (-0.01, 0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SEVERE RETINOPATHY (12)</td>
<td>-0.04 (-0.07, -0.01)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>CHRONIC LUNG DISEASE (17)</td>
<td>-0.05 (-0.08, -0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>DEATH (17)</td>
<td>-0.01 (-0.03, 0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>CLO/DEATH @ 36 WKS PMA (17)</td>
<td>-0.05 (-0.08, -0.01)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

COOLS 2013

High Frequency Ventilation
VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2014

CHRONIC LUNG DISEASE IN VLBW INFANTS
VERMONT OXFORD NETWORK ANNUAL REPORTS 1994-2010

MORTALITY IN VLBW INFANTS
VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2010
NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants

Taken as a whole, the available evidence does not support use of iNO in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks’ gestation who require respiratory support.

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. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.

Inhaled Nitric Oxide in VLBW Infants

Vermont Oxford Network Annual Reports 2000-2012

SOMETIMES THE COCHRANE REVIEW TELLS US THAT WE SHOULD BE READY TO CONSIDER CHANGE (AND NEW PRACTICES)
HYPOTHERMIA FOR THE TREATMENT OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

ILCOR recommendations

“Intensive care nurseries should now consider adopting one of the validated protocols for the selection of term infants with HIE, be appropriately equipped and train staff to offer hypothermia according to the protocol of the currently published large hypothermia trials.”

“Because HIE is a relatively uncommon condition, it would be highly desirable where possible to centralize this treatment to larger intensive care units.”

“With the data presently available, there is no longer any reasonable justification to deny this apparently efficacious treatment for those who most urgently need it.”

Hoehn and coworkers. Resuscitation 2008

DIFFICULTY OF TRANSLATING EVIDENCE TO PRACTICE

Efficacy:

Mild hypothermia is a promising therapy in a highly selected population of infants with moderate to severe hypoxic ischemic encephalopathy when treated before 6 hours of age

DIFFICULTY OF TRANSLATING EVIDENCE TO PRACTICE

Effectiveness and Efficiency:

• Does it work in the most affected infants? Does it provide a benefit to less severely affected infants?
• Does it work outside the restricted time window predicted by animal models and tested in clinical trials?
• Does selective or whole body hypothermia work better?
• What is the relationship of hypothermia to other therapeutic interventions?

ENCEPHALOPATHY REGISTRY:

Hypothermic Therapy 2006 to 2011

• 99 participating centers
• 2457 infants treated with hypothermia
• 726 (30%) did not meet criteria from RCTs
  – 40% with mild encephalopathy
  – 60% treated after 6 hours
  – 17% of all infants < 36 weeks gestation

Pfister. PAS, 2013

PROBLEMS WITH META-ANALYSIS

Only fair agreement between large clinical trials and meta-analyses

LeLorier 1997
META-ANALYSIS

Methodological flaws in meta-analyses

- Publication bias
  The tendency for investigators to preferentially submit studies with positive results, and the tendency for editors to choose positive studies for publication

- Heterogeneity
  Concerning variation in the direction or the degrees of results between individual studies

META-ANALYSIS OF MULTIPLE SMALL STUDIES COMPARED TO SINGLE LARGE STUDY

ASPIRIN FOR PREVENTION OF PRE-ECLAMPSIA

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>Odds Ratio (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>META-ANALYSIS</td>
<td>0.30 (0.20, 0.42)</td>
<td>0.2</td>
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<tr>
<td>SINGLE LARGE RCT</td>
<td>0.82 (0.72, 1.05)</td>
<td>0.2</td>
<td>2.0</td>
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</tbody>
</table>

 META-ANALYSIS

PROBLEMS WITH COCHRANE REVIEWS AND META-ANALYSIS

Too many reviews that end with the conclusion that “more trials are needed.”

TRIALS BASED (at least in part) on RESULTS OF META-ANALYSIS

- Prophylactic Indomethacin
- Vitamin A
- Emollient Ointments
- DART Trial
- Inositol
- Caffeine

SEARCH: "Neonate"
Limit: all infants; randomized controlled trial
7059 RCT identified

Cochrane Neonatal
1355 RCTs included
COCHRANE NEONATAL

SYSTEMATIC REVIEWS ARE USEFUL

• In guiding evidence-based practice
• To formulate research questions
• To create a context in which to view new evidence

So what is the fate of Cochrane Neonatal?

Bridging funds: University of Vermont Cochrane Central

Possible future sponsorship: Vermont Oxford Network

Questions

For CME Credits use the following link:
https://www.surveymonkey.com/r/V59O22

For Nursing Contact Hours use the following link:
https://www.surveymonkey.com/r/FJPJRZ

Future webinars!

Prevention and Treatment of Retinopathy of Prematurity