How to Evaluate the Quality of the Evidence

Roger F. Soll MD
President, Vermont Oxford Network
H. Wallace Professor of Neonatology
University of Vermont
Burlington, VT

Dr. Soll is the H. Wallace Professor of Neonatology at University of Vermont College of Medicine, the President of Vermont Oxford Network, and Director of Network Clinical Trials. Dr. Soll is an authority in evidence-based medicine and randomized clinical trials. He is the coordinating editor of the Cochrane Neonatal Review Group of the Cochrane Collaboration and author or co-author of the Cochrane Reviews of surfactant therapy. He is the author of numerous peer reviewed articles and book chapters on the subject of surfactant replacement therapy and evidence-based medicine. A native of New York City, Dr. Soll graduated from Cornell University with a degree in Genetics and History of Science in 1975. He received his MD degree from the University of Health Sciences/Chicago Medical School in 1978. He returned to New York City to complete his residency training in Pediatrics at Bellevue Hospital/New York University Medical Center in 1981. After 2 years with the Public Health Service, Dr. Soll returned to academic training. He completed the post graduate fellowship in Neonatal Perinatal Medicine at the University of Vermont in 1983 and has remained in Vermont ever since.

Annual Quality Congress Breakout Session, Sunday, October 4, 2015
How to Evaluate the Quality of the Evidence
Objectives:
Apply 3 key strategies that can be used to evaluate the clinical evidence.
How to Evaluate the Quality of the Evidence

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How to Evaluate the Quality of the Evidence

To develop an understanding of the evidence supplied by randomized controlled trials and systematic reviews in neonatal-perinatal medicine and discuss how this evidence might influence my practice.

Evidence Based Medicine

“The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”


Vermont Oxford Network

INFANTS 501 TO 750 GRAMS
INTERQUARTILE RANGES 2013

<table>
<thead>
<tr>
<th></th>
<th>Lowest Quartile</th>
<th>Highest Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal steroids</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>Nasal CPAP</td>
<td>50%</td>
<td>84%</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>0%</td>
<td>38%</td>
</tr>
<tr>
<td>HIFI ventilation</td>
<td>23%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Over 9,000 Infants at NICUs in the Vermont Oxford Network
How to Evaluate the Quality of the Evidence
Roger F. Soll MD

Vermont Oxford Network
INFANTS 501 TO 750 GRAMS
INTERQUARTILE RANGES 2013

<table>
<thead>
<tr>
<th></th>
<th>Lowest Quartile</th>
<th>Highest Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td>CLD @ 36 wks</td>
<td>40%</td>
<td>84%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>0%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Over 9,000 Infants at NICUs in the Vermont Oxford Network

Evidence Based Medicine

If we are all reading the same information...
Why aren’t we operating from the same playbook?

The Spectrum of Evidence

Strength of the evidence: Perry Mason

- Multiple eyewitnesses
- One sober eyewitness who got a good look
- Physical evidence at the crime scene
- Pattern of previous criminal activity
- Round up the usual suspects

Is the evidence I found valid?

Classifying the Quality of the Evidence

1. Systematic review of multiple well designed randomized controlled trials.
2. Properly designed randomized controlled trial of appropriate size.
3. Well-designed trials without randomization
4. Well-designed non-experimental studies
5. Opinions of respected authorities (based on clinical evidence, descriptive studies or reports of expert committees) (no longer seen as “evidence”)

Evidence Based Medicine

The strengths and weaknesses of the evidence

- experience/opinion
- case series
- studies with formal controls
- randomized controlled trials
- meta-analyses
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Clinical Impressions

Fundamentally the source of all discovery
Also, the source of all erroneous conclusions

Clinical Impressions

One case: “in my experience...”
Two cases: “in case after case...”
“time and again...”
Three cases: “in my series...”

Clinical Impressions

During the 1960’s, obstetricians interested in parturition noted that lambs whose mothers were given corticosteroids in an attempt to initiate labor, had less respiratory distress and increased survival Followed by detailed randomized controlled trials both in the animal model and in humans

Clinical Impressions

During the 1950’s, obstetricians reported the successful use of diethylstilbesterol (DES) in maintaining the pregnancy of a woman who previously had a series of miscarriages Followed by widespread use despite limited data from randomized controlled trials

Cases and Case Series Without Formal Controls

sometimes the outcome of current forms of therapy can be predicted with such certainty that past experience provides a valid basis for interpreting current observation

Evidence Based Medicine

Did we need randomized controlled trials to know the value of:
• Penicillin for meningitis
• NCPAP for RDS
• ECMO for respiratory failure in term infants
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Cases and Case Series Without Formal Controls
if a particular form of care is associated with an abnormal outcome that has not been seen before, observations without formal controls may be an adequate basis for abandoning the form of care in question

Cases and Case Series Without Formal Controls
• Thalidomide embryopathy
• E ferol in premature infants

Cases and Case Series Without Formal Controls
• although past experience suggests that caution is appropriate in interpreting the results of uncontrolled case series, it is often not exercised
• prone to selective reporting
• enthusiasm for treatment has been shown to be inversely related to number of patients studied

Evidence Based Medicine
“Therapeutic reports with controls tend to have no enthusiasm, and reports with enthusiasm tend to have no controls”
- Sackett 1986

Studies With Formal Controls
• Historical controls
• Case control studies
• Non randomized concurrent controls
• Randomized controls

Historical Controls
comparison between people who have received a relatively recently introduced form of care with other individuals cared for in a different way during an earlier era
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Differences in Live Birth Rates
Diethylstilbestrol (DES) Treated and Control Groups Using Either Historical or Randomized Controls

<table>
<thead>
<tr>
<th>Type of Controls (number of studies)</th>
<th>% Liveborn</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DES Treated</td>
<td>Control</td>
</tr>
<tr>
<td>HISTORICAL</td>
<td>85%</td>
<td>56%</td>
</tr>
<tr>
<td>- Unadjusted (4)</td>
<td>45%</td>
<td>8%</td>
</tr>
<tr>
<td>- Adjusted (1)</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>RANDOMIZED (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomized (RCT) vs Historical (HCT) Controlled Trials
Six Therapies: 50 RCT’s, 56 HCT’s

• 79% Historical Controlled Trials supported intervention
• 20% Randomized Controlled Trials supported intervention

Historical Controls

Sacks 1982

Historical Controls

• When substantial differences in outcome are noted between two different time frames, this may only reflect changes in other undocumented factors that have modified outcome
• Inferences based solely on studies that use historical controls tend to lead to conclusions that new forms of care are effective, when less biased comparisons suggest that they are not, or that the estimate is exaggerated

Non Randomized Concurrent Controls

Comparison of two or more cohorts of individuals who happen to have received alternative forms of care concurrently

Reducing Nosocomial Infection

Ignaz Philipp Semmelweis

- Hungarian physician
- Puerperal fever
- Hand washing
- Maternal Mortality

Non Randomized Concurrent Controls

Semmelweis 1861

Two wards in hospital were on intake for admissions on different days of the week
• one staffed by medical students and physicians
• the other by midwives and midwifery students

October 4, 2015
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Non Randomized Concurrent Controls
Maternal Mortality at Vienna Maternity Hospital 1841-1846

<table>
<thead>
<tr>
<th>Ward</th>
<th>Survived</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Ward</td>
<td>90.1%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Midwifery Ward</td>
<td>96.6%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Semmelweis 1861

Non Randomized Concurrent Controls

Bias from unrecorded and often unrecognized risk factors will undermine confidence in causal inferences based on comparisons of different forms of care using non randomized concurrent controls.

Non Randomized Concurrent Controls

Delivery of the extremely low birth weight infant: cesarean section or vaginal delivery?

- Many reports of improved outcome with cesarean section
- Does not account for vastly different risk of death or morbidity in the two groups

Randomized Controlled Trials

Scurvy

"On the 20th of May 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all..."
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Randomized Controlled Trials

- cider
- elixir vitriol
- vinegar
- sea water
- oranges/lemons
- nutmeg

Randomized Controlled Trials

“The consequence was that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days, fit for duty.”

James Lind 1753

Randomized Controlled Trials

Need for randomization:

- likely to provide equivalent groups at study entry
- provides theoretical basis for statistical comparisons
- minimizes selection bias in treatment assignment

The Real World Results

Lind’s therapeutic findings made little impact on medical opinion in Britain.

The year after publication of the treatise, the Navy’s ‘Sick and Hurt Board’ rejected a proposal to provide sailors with supplies of fruit juice

It was not used for 30 years...

Randomized Controlled Trials

Minimize systematic error (bias)

- Study entry (selection bias)
- Exposure to intervention (performance bias)
- Completeness of follow up (exclusion bias)
- Measurement of outcomes (assessment bias)

Randomized Controlled Trials

Limitations of Randomized Controlled Trials

- Evaluation of preventive therapy
- Multiple therapeutic candidates
- Minor changes in therapeutic agents
- “Instability” of available therapy
- Long-term adverse effects of therapy
- Evaluation of etiologic agents
- Evaluation of diagnostic technology
- Evaluation of process or structure
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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
meta-analysis demands the same methodological quality expected in a randomized controlled trial:
- prospectively designed protocol
- comprehensive and explicit search strategy
- strict criteria for inclusion of studies
- standard definitions of outcomes
- standard statistical techniques

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

Determinants of Quality
Five factors that can lower quality

Limitations of design and execution (risk of bias)
- Selection bias
- Use of placebo treatment/intervention
- Need for appropriate sample size to demonstrate meaningful clinical outcome
- Intention to treat analysis
- Use of post hoc sub-group analysis

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

www.cochrane.org
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Randomized Controlled Trials: Selection Bias

Conclusions Regarding Treatment Effect Based on Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cheating Difficult</th>
<th>Cheating Easy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Imbalance</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>Significant Difference</td>
<td>9%</td>
<td>24%</td>
</tr>
<tr>
<td>Favors Experimental Rx</td>
<td>30%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Conclusions Regarding Treatment Effect Based on Use of a Placebo

Relief from leg cramps

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium</th>
<th>No Treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammar 1981</td>
<td>91%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Hammar 1987</td>
<td>63%</td>
<td></td>
<td>73%</td>
</tr>
</tbody>
</table>

SMALL vs. LARGE RANDOMIZED CONTROLLED TRIALS

EFFECT OF INTENSIVE FETAL MONITORING ON NEONATAL SEIZURES

<table>
<thead>
<tr>
<th>STUDY (N)</th>
<th>Odds Ratio (95% CI)</th>
<th>Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVERKAMP 1979 (462)</td>
<td>0.20 (0.01, 4.19)</td>
<td></td>
</tr>
<tr>
<td>MACDONALD 1985 (13,084)</td>
<td>0.45 (0.23, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

The need for collaborative research: sample size requirements

<table>
<thead>
<tr>
<th>effect size</th>
<th>change in rate</th>
<th>sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>25% to 22.5%</td>
<td>9254</td>
</tr>
<tr>
<td>15%</td>
<td>25% to 21.25%</td>
<td>3574</td>
</tr>
<tr>
<td>20%</td>
<td>25% to 20%</td>
<td>2268</td>
</tr>
<tr>
<td>30%</td>
<td>25% to 17.5%</td>
<td>986</td>
</tr>
</tbody>
</table>

Effect of Beta Blockers in the Treatment of Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Astrological Sign</th>
<th>Reduction in Odds of Death</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scorpio</td>
<td>-48%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>All other Astrological Signs</td>
<td>-12%</td>
<td>NS</td>
</tr>
<tr>
<td>Overall</td>
<td>-15%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Collins 1987
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### 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

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### Deficiencies in Trials

REVIEW OF RCTs 1993-1998 (N=119)

- No identifiable primary outcome 24% (28/119)
- Minority had discreet outcome 38% (45/119)
- Only 4% (5/119) had a long-term outcome and the trials were designed to detect implausibly large differences in effect (RR greater than 40%)

  Zhang 2001

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### Determinants of Quality

**Five factors that can lower quality**

- Limitations of design and execution (risk of bias)
- **Inconsistency (heterogeneity)**
- Indirectness (patient population and applicability)
- Imprecision (limitations in sample size, confidence intervals
- Publication bias

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### Inconsistency

Differences in direction but minimal heterogeneity

- Substantial heterogeneity, but of questionable importance

- Substantial heterogeneity, of unequivocal importance

  *Journal of Clinical Epidemiology 2011*

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### Determinants of Quality

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- **Inconsistency (heterogeneity)**
- **Indirectness (patient population and applicability)**
- Imprecision (limitations in sample size, confidence intervals
- Publication bias
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Indirectness

We are more confident in the results when we have direct evidence.

By direct evidence, we mean research that

1. directly compares the interventions in which we are interested
2. delivered to the populations in which we are interested and
3. measures the outcomes important to patients.

PROPHYLACTIC INDOMETHACIN
EFFECT ON PATENT DUCTUS ARTERIOSUS (PDA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT DUCTUS ARTERIOSUS (7)</td>
<td>-0.27 (-0.32, -0.22)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SYMPTOMATIC PDA (14)</td>
<td>-0.24 (-0.28, -0.21)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>PDA LIGATION (8)</td>
<td>-0.05 (-0.08, -0.03)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

FOWLIE: THE COCHRANE LIBRARY

PROPHYLACTIC INDOMETHACIN
EFFECT ON CENTRAL NERVOUS SYSTEM INJURY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRAVENTRICULAR HEMORRHAGE (14)</td>
<td>-0.04 (-0.08, -0.01)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SEVERE IVH (14)</td>
<td>-0.05 (-0.07, -0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>PROGRESSIVE IVH (2)</td>
<td>-0.08 (-0.29, 0.13)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>PERIVENTRICULAR LEUKOMALACIA (5)</td>
<td>-0.05 (-0.08, 0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>WHITE MATTER INJURY (1)</td>
<td>-0.03 (-0.08, 0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

FOWLIE: THE COCHRANE LIBRARY

PROPHYLACTIC INDOMETHACIN
STATUS AT LATEST FOLLOW UP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORTALITY AT FOLLOW UP (18)</td>
<td>-0.01 (-0.04, 0.02)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>CEREBRAL PALSY</td>
<td>0.00 (-0.03, 0.04)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>SEVERE NEUROSENSORY IMPAIRMENT</td>
<td>0.00 (-0.05, 0.04)</td>
<td>0.2</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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PROPHYLACTIC INDOMETHACIN:
GLASS HALF FULL OR HALF EMPTY?

PREVENTS:
SYMPTOMATIC PDA
SEVERE IVH

DOES NOT ALTER NEURODEVELOPMENTAL OUTCOME
Determinants of Quality

Five factors that can lower quality

Limitations of design and execution (risk of bias)
Inconsistency (heterogeneity)
Indirectness (patient population and applicability)
Imprecision (limitations in sample size, confidence intervals)
Publication bias
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Assessing the Quality of the Evidence

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Quality of Evidence</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>High</td>
<td>Large effect</td>
<td>+1 Large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very large</td>
<td>+2 Very large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose response</td>
<td>+1 Evidence of a gradient</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
<td>All plausible confounding</td>
<td>+1 Would suggest a spurious effect or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 More acausal effect when independent of no effect</td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>Publication bias</td>
<td>-1 Inadequate data</td>
<td></td>
</tr>
</tbody>
</table>

(Clinic Epidemiology 2011 64, 383-394DOI: (10.1016/j.jclinepi.2010.04.026)

So how does this work in real life?

Cooling for infants with hypoxic ischaemic encephalopathy

Modified from Jacobs 2007

Hypothermia for hypoxic ischaemic encephalopathy

Whole body cooling and selective head cooling

<table>
<thead>
<tr>
<th>Study</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased 0.2</th>
<th>Decreased 0.5</th>
<th>Decreased 1.0</th>
<th>Increased 2.0</th>
<th>Increased 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective head cooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>-0.05 (-0.14, 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major disability</td>
<td>-0.09 (-0.24, 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or major disability</td>
<td>-0.09 (-0.21, 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole body cooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>-0.10 (-0.16, -0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major disability</td>
<td>-0.18 (-0.29, -0.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or major disability</td>
<td>-0.16 (-0.23, -0.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Hypothermia for the treatment of hypoxic ischaemic encephalopathy

Summary of findings tables

09-Apr-2014

Therapeutic hypothermia versus standard care compared to for newborns with hypoxic ischaemic encephalopathy

Settings:
Intervention: Therapeutic hypothermia
Comparison: Standard care

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Therapeutic hypothermia versus standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Follow-up: mean = 10 months</td>
</tr>
<tr>
<td>Mortality</td>
<td>142 per 1000</td>
</tr>
<tr>
<td>NR-KTE</td>
<td>0.04 (0.03)</td>
</tr>
<tr>
<td>HIL</td>
<td>0.57 (0.04)</td>
</tr>
<tr>
<td>OSI</td>
<td>114 (4.08)</td>
</tr>
<tr>
<td>NTO</td>
<td>8.81 (6.09)</td>
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Resuscitation 2008

October 4, 2015
How to Evaluate the Quality of the Evidence
Roger F. Soll MD

COOLING IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

What are we supposed to do?

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 best?
- What is the relationship of hypothermia to other therapeutic interventions?

Factors that influence the strength of recommendation

Balance between desirable and undesirable effects: The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted.

Quality of evidence: The higher the quality of evidence, the more likely a strong recommendation is warranted.

Values and preferences: The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted.

Costs (resource allocation): The higher the costs of an intervention the less likely a strong recommendation is warranted.

Questions?

"I figure there's a 40% chance of showers and a 30% chance we know what we're talking about."