Title of Program: GRADEing the Quality and Strength of the Evidence

Speakers/Moderators: Roger F. Soll, Myra Wyckoff

Planning Committee: Jeffery D. Horbar, Madge E. Buus-Frank, Roger F. Soll

Date: March 28, 2018

Learning Objectives:

The goal of this session is for participants to be able to define the domains of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Classification system. Participants will also be able to determine which clinical outcomes to consider, which evidence to include for each outcome, how to assess the quality of that evidence, and how to determine if the intervention does more good than harm, and to formulate the strength of a recommendation using examples from systematic reviews of neonatal interventions.

DISCLOSURE:

Is there anything to disclose? No financial interests to disclose

COMMERCIAL SUPPORT ORGANIZATIONS (if applicable): No Commercial Support

In support of improving patient care, this activity has been planned and implemented by The Robert Larner College of Medicine at The University of Vermont and Cochrane Neonatal. The University of Vermont is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The University of Vermont designates this live activity for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This program has been reviewed and is acceptable for up to 1 Nursing Contact Hours.
“GRADEing” the Quality and Strength of the Evidence

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

Coordinating Editor, Cochrane Neonatal
President, Vermont Oxford Network

Cochrane Web Seminar March 28th 2018

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
Cochrane
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
Sponsorship
Editorial Team

Michael Bracken
Yale University

Jeffrey Horbar
University of Vermont

Bill McGuire
Hull York Medical School

Gautham Suresh
Baylor University
Disclosure

Roger F. Soll is the Coordinating Editor of Cochrane Neonatal and President of Vermont Oxford Network
Evidence Based Medicine

Individual Clinical Expertise

Improved Patient Outcomes

Patient’s Values & Expectations

Best Available Clinical Evidence
Vermont Oxford Network  
Infants Gestational Age 24 to 26 Weeks  
Interquartile Ranges 2014

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lowest Quartile</th>
<th>Highest Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal steroids</td>
<td>71%</td>
<td>95%</td>
</tr>
<tr>
<td>Nasal CPAP</td>
<td>55%</td>
<td>90%</td>
</tr>
<tr>
<td>NCPAP before ETT</td>
<td>0%</td>
<td>45%</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td>HIFI ventilation</td>
<td>24%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Over 13,000 Infants at NICUs in the Vermont Oxford Network
If we are all reading the same information...

Why aren’t we operating from the same playbook?
Are the results clinically important?

Are the results 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”)
What is bias?

Difference in risk bias can help explain variation in the results of studies.

How is bias different from precision?

Bias: Systematic error
- Repeating the study multiple times would reach the wrong answer on average

Imprecision: Random error
- Different effect estimates because of sampling variation
- Smaller studies...greater sampling variation...less precision
- Reflected in confidence interval

Modified from Cochrane Training
Sources of bias in randomized controlled trials

<table>
<thead>
<tr>
<th>Type of bias</th>
<th>Description</th>
<th>Relevant domains in the Collaboration’s ‘Risk of bias’ tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias.</td>
<td>Systematic differences between baseline characteristics of the groups that are compared.</td>
<td>● Sequence generation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Allocation concealment.</td>
</tr>
<tr>
<td>Performance bias.</td>
<td>Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.</td>
<td>● Blinding of participants, personnel and outcome assessors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Other potential threats to validity.</td>
</tr>
<tr>
<td>Attrition bias.</td>
<td>Systematic differences between groups in withdrawals from a study.</td>
<td>● Incomplete outcome data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Blinding of participants, personnel and outcome assessors.</td>
</tr>
<tr>
<td>Detection bias.</td>
<td>Systematic differences between groups in how outcomes are determined.</td>
<td>● Blinding of participants, personnel and outcome assessors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Other potential threats to validity.</td>
</tr>
<tr>
<td>Reporting bias.</td>
<td>Systematic differences between reported and unreported findings.</td>
<td>● Selective outcome reporting.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● (see also Chapter 10).</td>
</tr>
</tbody>
</table>
Sequence generation

Mechanism for allocating intervention to participants

- **Adequate methods (randomization):**
  - Random number table, computer random number table, coin toss, throwing dice

- **Inadequate methods (non-random):**
  - Date of birth, alternation, allocation by judgement of the investigator

- **Unclear:**
  - “We randomly allocated” “using a randomized design”
Selection bias

Systematic differences in participants characteristics at the start of the trial

Intervention group
Apples

/ and

Control group:
Oranges
Preventing foreknowledge of the next allocations

- What is used to implement the sequence?
- Don’t confuse with blinding of participants, personnel, etc.
Adequate methods
- Central allocation - sequentially numbered opaque sealed envelopes

Inadequate methods
- Posted list of random tables, alternation, date of birth, envelopes

Unclear
- Insufficient information to make a judgement e.g. Use of envelopes to describe but no indication of other components
Randomized Controlled Trials: Allocation Concealment
## Conclusions Regarding Treatment Effect Based on Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cheating Difficult</th>
<th>Cheating Easy</th>
<th>Not Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Imbalance</td>
<td>14%</td>
<td>27%</td>
<td>58%</td>
</tr>
<tr>
<td>Significant Difference</td>
<td>9%</td>
<td>24%</td>
<td>58%</td>
</tr>
<tr>
<td>Favors Experimental Rx</td>
<td>30%</td>
<td>31%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Emphasis should be placed on blinding of participants, providers and outcome assessors.

Could lack of blinding bias the actual outcomes e.g. “Differential crossover” or the assessment of outcomes.

All outcome assessment can be influenced but especially for subjective outcomes.

Situations where blinding is impossible (oral vs intravenous medication; CPAP vs CMV).

Modified from Cochrane Training.
What to consider when assessing:

- who was and who was not blinded?
- risk of bias in actual outcomes to a lack of blinding in the study (co-intervention or differential behavior)
- risk of bias and outcome assessments (subjective vs objective)

Assessments of risk may need to be made for different (groups of) outcomes
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>
Allocation concealment vs. blinding

Modified from Cochrane Training
Systematic differences, other than the intervention being investigated, in the two treatment groups

- Occurs at the time of performing intervention

- Avoid performance bias by:
  - blinding the care provider and
  - blinding the participant

Modified from [Cochrane Training]
Incomplete outcome data

- Missing outcome data
- Incomplete outcome data: dropouts for exclusions
- “Missing”: participant’s outcome is not available
- Some exclusions may be justifiable and should not be considered as leading to missing outcome data
- When possible and appropriate, can re-include participants into an analysis (exclusions were inappropriate and data was available)
Attrition bias

Systematic differences in the loss of data to follow-up between groups

- Occurs over the duration of follow-up.

- Avoid attrition bias by:
  - describe a portion of participants lost to follow-up
  - use intention to treat analysis

Participants lost to follow-up are not included in the outcome assessment and could be different from those that remained in the trial!

Modified from Cochrane Training
Selective outcome reporting

Selection of a subset of the original variables recorded on the basis of the results from inclusion in the publication of trial.

- Concern: Statistically non-significant results may be selectively excluded from publication.

- Bias resulting from selected reporting of different measures and outcomes seems likely

- Need to consider whether or not an outcome was collected but not reported or simply not collected

Modified from Cochrane Training
Other items to consider:

- Comparing the trial report as published protocol if available.
- Checking abstracts of subsequently published trials for outcomes not in the published version.
- Occurrences of missing data that seem sure to have been collected.
- If suspicion of or direct evidence of selective outcome reporting, ask the study authors for more information.
Other sources of bias

Potential sources of bias should not be included here if more appropriately covered in the previous domains.

Other sources of bias that are important to consider in your review include:

- inappropriate influence of funders
- inappropriate co-intervention
- contamination
- selective reporting of subgroups
- baseline imbalance in important factors

Modified from Cochrane Training
What is GRADE?

GRADE is a systematic and explicit approach to making judgements about quality of evidence and strength of recommendations.

It was developed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group, and it is now widely seen as the most effective method of linking evidence-quality evaluations to clinical recommendations.
How does it work?

GRADE addresses many of the perceived shortcomings of existing models of evidence evaluation.

The GRADE approach specifically assesses:

- Methodological flaws within the component studies
- Consistency of results across different studies
- Generalizability of research results to the wider patient base
- How effective the treatments have been shown to be.

Treatment comparisons are given one of four GRADE scores reflecting the quality of the evidence — high-, moderate-, low-, or very low-quality evidence.
The focus of GRADE is on clinical outcomes that matter to patients — meaning those outcomes that patients themselves are aware of in relation to their condition — for example, symptom severity, quality of life, disability, and survival.

- Less interested in proxy outcomes such as decrease in FiO2 or mean airway pressure.

- Each review has a dedicated outcomes section and only report and evaluate evidence on our prespecified outcomes.
- Type of evidence
- Inconsistency
- Indirectness
- Effect size
- Strength of recommendation
## Types of Evidence

<table>
<thead>
<tr>
<th>Limitation in observational studies</th>
<th>Explanations</th>
</tr>
</thead>
</table>
| Failure to develop and apply appropriate eligibility criteria  (inclusion of control population) | • under or over-matching in case-control studies  
• selection of exposed and unexposed in cohort studies from different populations |
| Flawed measurement of both exposure and outcome | • differences in measurement of exposure (e.g. recall bias in case-control studies)  
• differential surveillance for outcome in exposed and unexposed in cohort studies |
| Failure to adequately control confounding | • failure of accurate measurement of all known prognostic factors  
• failure to match for prognostic factors and/or adjustment in statistical analysis |
| Incomplete or inadequately short follow-up | |
Types of Evidence

<table>
<thead>
<tr>
<th>Limitation in randomized controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ lack of concealment</td>
</tr>
<tr>
<td>❖ intention to treat principle violated</td>
</tr>
<tr>
<td>❖ inadequate blinding</td>
</tr>
<tr>
<td>❖ loss to follow-up</td>
</tr>
<tr>
<td>❖ early stopping for benefit</td>
</tr>
<tr>
<td>❖ selective outcome reporting</td>
</tr>
</tbody>
</table>
Inconsistency of results (Heterogeneity)

- Clinical heterogeneity vs statistical heterogeneity
- $I_2$? Overlapping confidence intervals?
- If inconsistency noted, look for explanation
  - patients, intervention, comparator, outcome
- If unexplained inconsistency, lower quality
Sources of heterogeneity

- Study population
- Intervention
  - Formulation
  - Dosage
  - Timing
Inconsistency

Forest plot A versus Forest plot B

Favours treatment  Favours control  Favours treatment  Favours control
Directness of Evidence

Generalizability, transferability, applicability, differences in
- populations/patients
- interventions
- comparator appropriate
- outcomes (clinically important – surrogate)

Indirect comparisons
- interested in A versus B
- have A versus C and B versus C
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.
Hierarchy of outcomes according to importance to patients to assess effect of prophylactic indomethacin

- Mortality: Important but not critical for decision making
- Neurodevelopmental outcome: Important but not critical for decision making
- Severe IVH: Not important for decision making – of lower importance to patients
- PDA ligation: Critical for decision making
- PDA murmur: Not important for decision making – of lower importance to patients
Publication Bias

Publication bias should always be suspected
• Only small “positive” studies
• For profit interest

Various methods to evaluate – none perfect, but clearly a problem
Language Bias

PROPORTION OF CONTROLLED TRIALS PUBLISHED IN GERMAN AND ENGLISH

EGGER 1997
Imprecision

- Small sample size
  - small number of events

- Wide confidence intervals
  - uncertainty about magnitude of effect
<table>
<thead>
<tr>
<th>STUDY (N)</th>
<th>Odds Ratio (95% CI)</th>
<th>Decreased Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVERKAMP 1979 (462)</td>
<td>0.20 (0.01, 4.19)</td>
<td>0.2</td>
<td>4.0</td>
</tr>
<tr>
<td>MACDONALD 1985 (13,084)</td>
<td>0.45 (0.23, 0.88)</td>
<td>0.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Imprecision

**Interpretation**

- Insufficient evidence to confirm or exclude on important difference
- Statistically significant difference, unclear if it's important to patients
- Statistically significant difference, not important to patients
- No evidence of an important difference
- Important difference

**Predefined limits of equivalence**

- Line of no effect
  - (relative risk, odds ratio = 1, risk difference = 0)

**Characteristics of confidence interval**

- Crossing line of no effect and one or both limits of equivalence
- Doesn't cross line of no effect, but does cross equivalence limit
- Entirely within limits of equivalence, but doesn't cross line of no effect
- Entirely within limits of equivalence and crosses line of no effect
- Entirely outside limits of equivalence
Randomized Controlled Trials

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>
Quality of the Evidence

Study design
- Randomized controlled trial
- Observational study

Quality of the evidence
- HIGH
- MODERATE
- LOW
- VERY LOW

Decreased by
- Limitations in the design
- Inconsistent results
- Lack of direct evidence
- Imprecision
- Publication bias

Increased by
- Strong or very strong association
- Dose-response gradient
- Consideration of the potential confounding factors
<table>
<thead>
<tr>
<th>Factors that can strengthen a recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the evidence</td>
<td>The higher the quality of evidence, the more likely is a strong recommendation.</td>
</tr>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely weak recommendation warranted.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak recommendation warranted.</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention – that is, the more resources consumed – the less likely is a strong recommendation warranted.</td>
</tr>
</tbody>
</table>
The **strength of a recommendation** reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects across the range of patients for whom the recommendation is intended.
• **Strong Recommendation**: benefits outweigh risks of the intervention

• **Weak Recommendation**: most informed people would chose this recommendation, but a substantial number would not
So how does this work in the real world?
Guest Discussant

Myra Wyckoff, M.D.
Professor of Pediatrics
UT Southwestern Medical Center
Use of GRADE to Establish ILCOR Guidelines for Neonatal Resuscitation

Myra H. Wyckoff, MD
Professor of Pediatrics
UT Southwestern Medical School

Chair, International Liaison Committee on Resuscitation (ILCOR) Neonatal Task Force 2016-2020
ILCOR: Achieving Consensus on Resuscitation Science

- Since 2000, a Neonatal Life Support (NLS) Task Force (composed of members from participating resuscitation councils from across the world), joins with the International Liaison Committee on Resuscitation (ILCOR) for a complete review of neonatal resuscitation science every 5 years.
- 23 new questions reviewed by the NLS Task Force for the 2015 Guidelines
ILCOR 2015
Neonatal Life Support Working Group
ILCOR Consensus on Science and Treatment Recommendations for Neonatal Resuscitation

- New ILCOR Consensus on Science with Treatment Recommendations (CoSTR) document available since October 15, 2015

- CoSTR co-published in open access format in Circulation, Resuscitation and Pediatrics

- Download at: www.heart.org/cpr
CoSTR Used to Develop Regional Guidelines

- The various resuscitation councils use the ILCOR CoSTR document to adapt/develop their own guidelines appropriate for their own region or country using the science and treatment recommendations summarized in the CoSTR.
  - ERC
  - AHA/AAP for USA/Canada
  - Brazil
2015 New USA/Canadian Algorithm

Part 13: Neonatal Resuscitation
2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Myra H. Wyckoff, Chair; Khalid Aziz; Marilyn B. Escobedo; Vishal S. Kapadia; John Kattwinkel; Jeffrey M. Perlman; Wendy M. Simon; Gary M. Weiner; Jeanette G. Zaichkin

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 ILCOR Evaluation Process

- Task Force identifies and develop the PICO questions that need scientific review (with public input)
  - May have to be refined after initial evidence search
  - Rank Outcomes for importance

- Prioritize the questions and assign reviewers
  - At least 2
  - Try to use reviewers from different parts of the globe

- Minimum requirements for every search strategy are specified and done by professional librarians
  - Medline, Embase, and Cochrane Systematic Reviews
  - Hand searches
ILCOR Uses the GRADE Process

- Every reviewer rates the level and quality of evidence using the standardized evidence evaluation of the GRADE system

- The systematic reviews are presented to the ILCOR Neonatal Life Support Task Force
  - Debate regarding the science and GRADE Tables
  - Consensus reached regarding
    - Methodological flaws of the available studies
    - Consistency of results
    - Generalizability of findings
    - How effective is the treatment
    - Quality of Evidence
    - Strength of the recommendation
    - Exact wording of treatment recommendation
    - Values and Preferences (of medical providers as well as patients)
ILCOR Uses the GRADE Process

- Unless the recommendation is based on moderate or strong evidence....
  - We advocate for more research
  - Important that the recommendations do not “squelch” research
Umbilical Cord Milking
(NLS PICO #849)
Conflict of Interest (COI) Disclosure

- Evidence Reviewer #1: Marya Strand, MD, MS from AAP/AHA, COI#222
  - Commercial/industry
    - None
  - Potential intellectual conflicts
    - None
- Evidence Reviewer #2: Takahiro Sugiura, MD from RCA, COI#224
  - Commercial/industry
    - None
  - Potential intellectual conflicts
    - None
NLS PICO #849
Umbilical Cord Milking

**Population:** Very preterm infants (≤28 wks EGA)

**Intervention:** Umbilical cord milking

**Comparison:** Immediate umbilical cord clamping

**Outcomes:**
- 9—Infant death
- 8—Neurodevelopmental outcome at 2-3 years
- 8—Severe intracranial hemorrhage
- 7—All grade intracranial hemorrhage
- 7—Cardiovascular stability (initial MBP)
- 7—Temperature on admission
- 6—Hematologic indices
  - Initial hemoglobin, Need for PRBC transfusion
- 6—Hyperbilirubinemia
  - Phototherapy, Need for exchange transfusion
Inclusion/Exclusion & Articles Found

- **Inclusions/Exclusions**
  - Randomized or observational studies
  - Infants born at ≤ 28 weeks’ gestation

- Search terms initially identified 690 potential articles

- Number Included in GRADE Evidence Profile tables
  - RCTs: 4
  - non-RCTs: 1
## Risk of Bias in Studies

### <RCT>

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Total Patients</th>
<th>Population</th>
<th>Industry Funding</th>
<th>Allocation: Generation</th>
<th>Allocation: Concealment</th>
<th>Blinding: Participants</th>
<th>Blinding: Assessors</th>
<th>Outcome: Complete</th>
<th>Outcome: Selective</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alan</td>
<td>2014</td>
<td>RCT</td>
<td>48</td>
<td>≤32 wks &amp; &lt;1500g</td>
<td>No</td>
<td>Unclear</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Hosono</td>
<td>2007</td>
<td>RCT</td>
<td>40</td>
<td>24-28 wks</td>
<td>No</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Katheria</td>
<td>2014</td>
<td>RCT</td>
<td>60</td>
<td>23-32 wks</td>
<td>No</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>March</td>
<td>2013</td>
<td>RCT</td>
<td>75</td>
<td>24-28 wks</td>
<td>No</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

### <Non-RCT>

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Total Patients</th>
<th>Population</th>
<th>Industry Funding</th>
<th>Eligibility Criteria</th>
<th>Exposure/Outcome</th>
<th>Confounding</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takami</td>
<td>2012</td>
<td>non RCT</td>
<td>50</td>
<td>&lt;29 wks &amp; &lt;1250g</td>
<td>No</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
### Outcome - Infant death

**<RCT>**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Events</th>
<th>Milked Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosono 2008</td>
<td>2</td>
<td>20</td>
<td>3</td>
<td>20</td>
<td>37.2%</td>
<td>0.63 [0.09, 4.24]</td>
</tr>
<tr>
<td>Katheria 2014</td>
<td>2</td>
<td>30</td>
<td>1</td>
<td>30</td>
<td>12.9%</td>
<td>2.07 [0.18, 24.15]</td>
</tr>
<tr>
<td>March 2013</td>
<td>2</td>
<td>36</td>
<td>4</td>
<td>39</td>
<td>50.0%</td>
<td>0.51 [0.09, 3.00]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>86</strong></td>
<td><strong>89</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.76 [0.25, 2.29]</td>
</tr>
</tbody>
</table>

Total events: 6

Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%

Test for overall effect: Z = 0.49 (P = 0.62)

**<Non-RCT>**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Events</th>
<th>Milked Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takami 2012</td>
<td>0</td>
<td>26</td>
<td>2</td>
<td>24</td>
<td>100.0%</td>
<td>0.17 [0.01, 3.72]</td>
</tr>
</tbody>
</table>

Total events: 0

Heterogeneity: Not applicable

Test for overall effect: Z = 1.13 (P = 0.26)
# Evidence profile table - Infant Death

## <RCT>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>not serious 2</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Author(s):** Takahiro Sigiura, Marya Strand

**Date:** 2015-01-30

**Question:** Should Death be used for Death?

**Settings:**

**Bibliography:** Sigiura T, Strand M. Cord milking for very preterm infants. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

## <Non-RCT>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>1</td>
<td>observational studies¹</td>
<td>serious ¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ case-control

² Only one study
### Outcome-Intracranial Hemorrhage (ICH)

#### <Any ICH-RCT>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosono 2008</td>
<td>3</td>
<td>20</td>
<td>5</td>
<td>20</td>
<td>22.8%</td>
<td>0.53 [0.11, 2.60]</td>
<td>0.53 [0.11, 2.60]</td>
</tr>
<tr>
<td>March 2013</td>
<td>9</td>
<td>36</td>
<td>20</td>
<td>39</td>
<td>77.2%</td>
<td>0.32 [0.12, 0.85]</td>
<td>0.32 [0.12, 0.85]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>12</td>
<td>56</td>
<td>59</td>
<td></td>
<td>100.0%</td>
<td>0.37 [0.16, 0.84]</td>
<td>0.37 [0.16, 0.84]</td>
</tr>
</tbody>
</table>

Total events: 12, 25

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%

Test for overall effect: Z = 2.37 (P = 0.02)

#### <Any ICH non-RCT>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takami 2012</td>
<td>3</td>
<td>26</td>
<td>6</td>
<td>24</td>
<td>100.0%</td>
<td>0.39 [0.09, 1.78]</td>
<td>0.39 [0.09, 1.78]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3</td>
<td>26</td>
<td>24</td>
<td></td>
<td>100.0%</td>
<td>0.39 [0.09, 1.78]</td>
<td>0.39 [0.09, 1.78]</td>
</tr>
</tbody>
</table>

Total events: 3, 6

Heterogeneity: Not applicable

Test for overall effect: Z = 1.21 (P = 0.23)
# Evidence profile table-ICH

### <RCT>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intraventricular hemorrhage</td>
<td>very preterm infants</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>Any IVH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12/56 (21.4%)</td>
<td>25/59 (42.4%)</td>
<td>OR 0.37 (0.16 to 0.64)</td>
<td>210 fewer per 1000 (from 42 fewer to 318 fewer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe IVH (grade III or greater)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2/20 (10.0%)</td>
<td>4/20 (20.0%)</td>
<td>OR 0.44 (0.07 to 2.76)</td>
<td>101 fewer per 1000 (from 183 fewer to 208 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### <Non-RCT>

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cord milking</td>
<td>Control</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
</tr>
<tr>
<td>Any IVH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 cases 6 controls</td>
<td>6/24 (25%)</td>
<td>OR 0.39 (0.09 to 1.78)</td>
<td>135 fewer per 1000 (from 221 fewer to 122 more)</td>
</tr>
</tbody>
</table>

---

1 case-control
2 Only one study, with small number
Outcome - hematologic indices

<Initial hemoglobin: RCT>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Mean</th>
<th>Milked SD</th>
<th>Milked Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosono 2008</td>
<td>34</td>
<td>9</td>
<td>20</td>
<td>28</td>
<td>8</td>
<td>20</td>
<td>42.7% 6.00 [0.72, 11.28]</td>
</tr>
<tr>
<td>Katheria 2014</td>
<td>41</td>
<td>9</td>
<td>30</td>
<td>36</td>
<td>9</td>
<td>30</td>
<td>57.3% 5.00 [0.45, 9.55]</td>
</tr>
</tbody>
</table>

Total (95% CI) 50

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)

<Initial hemoglobin: non-RCT>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Mean</th>
<th>Milked SD</th>
<th>Milked Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takami 2012</td>
<td>16.8</td>
<td>1.6</td>
<td>26</td>
<td>14.1</td>
<td>1.6</td>
<td>24</td>
<td>2.70 [1.81, 3.59]</td>
</tr>
</tbody>
</table>

Total (95% CI) 26

Heterogeneity: Not applicable
Test for overall effect: Z = 5.96 (P < 0.00001)

<Received transfusion: RCT>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Milked Events</th>
<th>Milked Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosono 2008</td>
<td>7</td>
<td>20</td>
<td>14</td>
<td>20</td>
<td>31.3%</td>
<td>0.23 [0.06, 0.87]</td>
</tr>
<tr>
<td>Katheria 2014</td>
<td>11</td>
<td>30</td>
<td>22</td>
<td>30</td>
<td>47.9%</td>
<td>0.21 [0.07, 0.63]</td>
</tr>
<tr>
<td>March 2013</td>
<td>30</td>
<td>36</td>
<td>38</td>
<td>39</td>
<td>20.9%</td>
<td>0.13 [0.02, 1.15]</td>
</tr>
</tbody>
</table>

Total (95% CI) 86

Total events 48 74

Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)
Evidence profile table - hematologic indices

### Initial hemoglobin

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MD 2.27 higher (1.57 higher to 2.98 higher)</td>
<td>-</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

#### Need for transfusion

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR 0.2 (0.09 to 0.44)</td>
<td>-</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 335 fewer per 1000 (from 147 fewer to 524 fewer)</td>
<td>-</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 381 fewer per 1000 (from 190 fewer to 531 fewer)</td>
<td>-</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

### Initial hemoglobin (Better indicated by lower values)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MD 2.7 higher (1.81 to 3.59 higher)</td>
<td>-</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

1 case-control
2 Only one study, with small number
For the critical outcome of **death** we found low quality evidence (downgraded for imprecision) from 3 RCTs [Hosono 2008, F14; Katheria 2014, 1045; March 2013, 1] that there is no difference in death (OR 0.76, 95% CI 0.25-2.29).

We did not identify any evidence to address the critical outcome of “**neurologic outcome** at 2-3 years”.

For the critical outcome of **cardiovascular stability** we found low quality evidence (downgraded for imprecision) from 2 studies [Hosono 2008, F14; Katheria 2014, 1045] that the initial mean blood pressure was 5.43 mm Hg higher (1.98-8.87 mm Hg) in the intervention group.
Proposed Consensus on Science Statements

- For the important outcome of **IVH**, we found low quality evidence (downgraded for imprecision) from 2 RCT studies [Hosono 2008, F14; March 2013, 1] of a reduction of any IVH (OR 0.37, 95% CI 0.18-0.77) but no difference (from 1 study [Hosono 2008, F14]) in severe IVH (OR 0.44, 95% CI 0.07-2.76).

- For the important outcome of **hematologic indices**, we found low quality evidence (downgraded for imprecision) from 2 studies [Hosono 2008, F14; Katheria 2014, 1045] that cord milking increased the initial hemoglobin measurement (2.27 g/dl, 95% CI 1.57-2.98 g/dl) and low quality evidence (downgraded for imprecision) from 3 studies [Hosono 2008, F14; Katheria 2014, 1045; March 2013, 1] that cord milking decreased transfusion (OR 0.2, 95% CI 0.09-0.44).
Proposed Consensus on Science Statements

- **Cost:**
  
  There is *little or no cost* associated with the intervention of umbilical cord milking.
Treatment Recommendations

- We suggest against the routine use of cord milking for infants born at less than 29 weeks of gestation but cord milking may considered a reasonable alternative to immediate cord clamping to improve initial mean blood pressure, hematological indices and ICH. However, there is no evidence for improvement or safety in long term outcomes. (Weak recommendation, low level of evidence)

- All studies included in this evidence review milked 20 cm of umbilical cord toward the umbilicus 3 times while the infant was held at the level of the introitus or below the level of the placenta prior to cord clamping.
Values and Preferences
Statement

In making this recommendation we place a high value on the simplicity/economy of this intervention with no demonstrated negative outcome, acknowledging the lack of evidence regarding critical long-term outcomes.
Knowledge Gaps

- Specific research required
  - There are insufficient subjects in the reviewed studies to make strong recommendations for or against this intervention. We need the results of several on-going international trials that are not yet completed.
  
  - We need information on important long-term neuro-developmental outcomes

- Cord milking vs Delayed cord clamping
  - One RCT [Rabe 2011] demonstrated similar hematologic indices between cord milking and delayed cord clamping.
Continuous Evidence Evaluation
- 56 PICOs identified regarding clinical questions that are the back bone of the neonatal resuscitation algorithm
- Electronic queries designed to identify new science on a monthly basis
- When sufficient new evidence available to warrant a new systematic review...
  - PICO activated and systematic review using GRADE initiated by the ILCOR NLS Task Force
  - Current PICOx under systematic review regarding oxygen use in the delivery room for both term and preterm infants
Questions/Discussion?
Next Cochrane Neonatal Web Seminar

Antenatal strategies: steroids, magnesium, and best obstetric practices

June 2018
CME Credit Survey:
https://www.surveymonkey.com/r/WPL2Z77

Nursing Contact Hours Survey:
https://www.surveymonkey.com/r/SKMNX36

- The surveys will be opened within an hour of the end of the webinar. We will send an email with the links after the webinar is over.

- You must take a survey within 2 weeks of the webinar in order to receive credit.

- Once you take the survey you will be redirected to our website where you can download and save a certificate for your records.

- Credit can only be given to those who participate in the live webinar. You cannot receive credit for watching the recording of the webinar, which will be posted on our website within approximately 2 weeks.

Please contact Jennifer Spano at Jennifer.Spano@med.uvm.edu with questions.