Title of Program: Oxygen in the Delivery Room: Evidence from Systematic Reviews

Speakers/Moderators: Roger F. Soll, MD, Neil Finer, MD, William Tarnow-Mordi, FRCPCH

Planning Committee: Jeffery D. Horbar, MD, Madge E. Buus-Frank, RN, MS, APRN-BC, FAAN, Roger F. Soll, MD

Date: March 10, 2017

Learning Objectives:

Participants will be presented with evidence from clinical trials and systematic reviews and will be able to evaluate and translate the evidence in the field of neonatology to better serve their practices. Specifically, evidence for strategies regarding the use of supplemental oxygen during the resuscitation of term and preterm infants will be presented and critiqued.

DISCLOSURE:

Is there anything to disclose? No financial interests to disclose

COMMERCIAL SUPPORT ORGANIZATIONS (if applicable): No Commercial Support

The University of Vermont College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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PowerPoint Slide presented at start of program
Oxygen in the Delivery Room: Evidence from Systematic Reviews

Conference begins at 12 Noon EST
March 10, 2017

Supported by:
The National Institute of Child Health and Human Development and Vermont Oxford Network

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
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Yale University

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University of Vermont

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Guest Discussant

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Emeritus Professor
University of California, San Diego
Guest Discussant

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Director, Neonatal and Perinatal Trials, NHMRC Clinical Trials Centre
Support

Eunice Kennedy Shriver
National Institute of Child Health & Human Development

Vermont Oxford Network
Disclosure

Roger F. Soll is the Coordinating Editor of Cochrane Neonatal 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.
Oxygen in the Delivery Room: Evidence from Systematic Reviews

We will review the evidence from randomized trials and meta-analyses and discuss the different approaches that teams around the world are using regarding the use of oxygen in the delivery room.
Oxygen in the Delivery Room: The Basics
Oxygen was introduced in newborn care more than 200 years ago.

In 1777, Dr. Chaussier developed a device for the use of oxygen in neonatal resuscitation and made oxygen the first drug to be used specifically in neonates.

Within a few years, oxygen was widely used in neonatal resuscitation throughout Europe....
Saugstad demonstrated that hypoxanthine, a purine metabolite, accumulates during hypoxia.

Introducing oxygen in the aftermath of hypoxia could lead to an explosive generation of oxygen-free radicals.

These studies represent the basis for understanding the hypoxia–reoxygenation or ischemia-reperfusion injury that has puzzled medicine far beyond neonatology

Saugstad 2010
Oxygen in the Delivery Room: Evidence in Term Infants
Resuscitation of Newborn Infants with 21% or 100% Oxygen: An Updated Systematic Review and Meta-Analysis

Saugstad O.D., Ramji S., Soll R.F., Vento M.

Methods: Randomized or quasi-randomized studies of depressed newborn infants resuscitated with 21 or 100% O2 with or without masking of treatment were considered for inclusion.

Results: Ten studies fulfilled the inclusion criteria. Of these, 6 studies were identified as being strictly randomized. In total, 1,082 infants were allocated to resuscitation with 21% O2 and 1,051 infants with 100% O2. The risk of neonatal mortality was reduced in the 21% O2 group compared to the 100% O2 group both in the analysis of all studies (typical RR 0.69, 95% CI 0.54, 0.88) and in the analysis of strictly randomized studies (typical RR 0.32, 95% CI 0.12, 0.84). A trend toward a decrease in the risk of hypoxic ischemic encephalopathy stage 2 and 3 was noted with resuscitation in 21% O2 in the analysis of all studies (typical RR 0.88, 95% CI 0.72, 1.08).

Neonatology 2008;94:176–182 (DOI:10.1159/000143397)
# Room Air vs. 100% Oxygen for Delivery Room Stabilization of Term Neonates

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>N</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramji (1993)</td>
<td>quasi-random</td>
<td>84</td>
<td>Birth weight &gt; 999 grams with apnea, HR &lt; 80 bpm, or both</td>
</tr>
<tr>
<td>Saugstad (1998)</td>
<td>quasi-random</td>
<td>609</td>
<td>Birth weight 999 grams, apnea or gasping, HR &lt; 80 bpm, or both</td>
</tr>
<tr>
<td>Vento (2001)</td>
<td>random</td>
<td>40</td>
<td>Term infants with hypotonia, unresponsive to stimuli and HR &lt; 80 bpm, or both</td>
</tr>
<tr>
<td>Vento (2003)</td>
<td>random</td>
<td>151</td>
<td>Term infants with apnea, hypotonia, unresponsive to stimuli, HR &lt; 80 bpm, and pH &lt; 7.05. Birth weight &gt; 999 grams</td>
</tr>
<tr>
<td>Ramji (2003)</td>
<td>quasi-random</td>
<td>431</td>
<td>Birth weight &gt; 1000 grams, HR &lt; 100 bpm, apneic, or both, and unresponsive to stimulation.</td>
</tr>
<tr>
<td>Bajaj (2005)</td>
<td>quasi-random</td>
<td>204</td>
<td>Birth weight 1000 grams or more with apnea or gasping respiration and/or heart rate less than 100 beats/min requiring positive pressure ventilation after initial steps of resuscitation</td>
</tr>
<tr>
<td>Vento (2005)</td>
<td>random</td>
<td>39</td>
<td>Severely asphyxiated term neonates. Severe asphyxia was defined as pale color, presence of bradycardia (&lt; 80 beats/min), nonresponsive to stimuli, a cord pH of 7.0 or less at birth, and an Apgar score of 5 or less for more than 5 min.</td>
</tr>
<tr>
<td>Toma (2006)</td>
<td>random</td>
<td>54</td>
<td>Term infants with HR &lt; 100 bpm, apnea</td>
</tr>
<tr>
<td>Toma (2006)</td>
<td>random</td>
<td>44</td>
<td>GA ≥ 34 weeks with HR &lt; 100 bpm, apnea</td>
</tr>
<tr>
<td>Toma (2007)</td>
<td>random</td>
<td>56</td>
<td>Term infants with HR &lt; 100 bpm, apnea</td>
</tr>
</tbody>
</table>
### Oxygen in the Delivery Room: Evidence in Term Infants

#### Oxygen in the Resuscitation of Term Infants: Effect on Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
<th>Risk ratio M-H, fixed, 95% CI</th>
<th>Risk ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>events</td>
<td>total</td>
<td>events</td>
<td>total</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toma, 2006 [15]</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>27</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Toma, 2006 [16]</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>24</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Toma, 2007 [17]</td>
<td>1</td>
<td>30</td>
<td>2</td>
<td>26</td>
<td>0.43 (0.04, 4.51)</td>
</tr>
<tr>
<td>Vento, 2001 [9]</td>
<td>1</td>
<td>300</td>
<td>7</td>
<td>237</td>
<td>0.11 (0.01, 0.91)</td>
</tr>
<tr>
<td>Vento, 2003 [10]</td>
<td>1</td>
<td>55</td>
<td>2</td>
<td>51</td>
<td>0.46 (0.04, 4.96)</td>
</tr>
<tr>
<td>Vento, 2005 [13]</td>
<td>2</td>
<td>17</td>
<td>4</td>
<td>22</td>
<td>0.65 (0.13, 3.13)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>5</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>449</td>
<td>387</td>
<td>11.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 1.87$, d.f. = 3 ($p = 0.60$), $I^2 = 0$

**Test for overall effect:** $Z = 2.30$ ($p = 0.02$)

<table>
<thead>
<tr>
<th>Quasi-randomized trials</th>
<th>Treatment events</th>
<th>Control events</th>
<th>Weight</th>
<th>Risk ratio M-H, fixed, 95% CI</th>
<th>Risk ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bajaj, 2005 [14]</td>
<td>17</td>
<td>107</td>
<td>17</td>
<td>97</td>
<td>0.91 (0.49, 1.67)</td>
</tr>
<tr>
<td>Ramji, 1993 [7]</td>
<td>3</td>
<td>42</td>
<td>4</td>
<td>42</td>
<td>0.75 (0.18, 3.15)</td>
</tr>
<tr>
<td>Ramji, 2003 [11]</td>
<td>24</td>
<td>204</td>
<td>39</td>
<td>214</td>
<td>0.65 (0.40, 1.03)</td>
</tr>
<tr>
<td>Saugstad, 1998 [8]</td>
<td>40</td>
<td>280</td>
<td>60</td>
<td>311</td>
<td>0.74 (0.51, 1.07)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>84</td>
<td>633</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1,082</td>
<td>1,051</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 0.74$, d.f. = 3 ($p = 0.86$), $I^2 = 0$

**Test for overall effect:** $Z = 2.35$ ($p = 0.02$)

**Relative risk 0.69 (95% CI 0.54 to 0.88)**
Oxygen in the Resuscitation of Term Infants: Effect on Hypoxic Ischemic Encephalopathy (stages 2 or 3)

Relative risk 0.88 (95% CI 0.72 to 1.08)
Air/Oxygen: Term babies.

In term infants receiving respiratory support at birth with positive pressure ventilation (PPV), it is best to begin with air (21%) as opposed to 100% oxygen.

If, despite effective ventilation, there is no increase in heart rate or oxygenation (guided by oximetry wherever possible) remains unacceptable, use a higher concentration of oxygen to achieve an adequate preductal oxygen saturation.

High concentrations of oxygen are associated with an increased mortality and delay in time of onset of spontaneous breathing, therefore, if increased oxygen concentrations are used they should be weaned as soon as possible.
# Oxygen in the Resuscitation of Term Infants: Follow-up Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible N</th>
<th>Evaluated N</th>
<th>Abnormal N (%)</th>
<th>Eligible N</th>
<th>Evaluated N</th>
<th>Abnormal N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saugstad 2003</td>
<td>147</td>
<td>91</td>
<td>14 (15.4)</td>
<td>176</td>
<td>122</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>Bajaj 2005</td>
<td>90</td>
<td>77</td>
<td>6 (7.8)</td>
<td>80</td>
<td>70</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Toma 2008</td>
<td>27</td>
<td>27</td>
<td>5 (18.5)</td>
<td>27</td>
<td>27</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>264</strong></td>
<td><strong>195</strong></td>
<td><strong>25 (12.8)</strong></td>
<td><strong>283</strong></td>
<td><strong>219</strong></td>
<td><strong>23 (10.5)</strong></td>
</tr>
</tbody>
</table>
Follow-up studies of oxygen in the resuscitation of term infants lack precise estimates!

<table>
<thead>
<tr>
<th>Method</th>
<th>Pooled Relative Risk</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete case</td>
<td>1.24</td>
<td>(0.73, 2.10)</td>
</tr>
<tr>
<td>Extreme favors air</td>
<td>0.33</td>
<td>(0.22, 0.50)</td>
</tr>
<tr>
<td>Extreme favors 100% O₂</td>
<td>4.09</td>
<td>(2.63, 6.38)</td>
</tr>
<tr>
<td>Best/Worse Case</td>
<td></td>
<td>(0.22, 6.38)</td>
</tr>
<tr>
<td>Uncertainty</td>
<td></td>
<td>(0.41, 2.28)</td>
</tr>
</tbody>
</table>
We lack real evidence that room air resuscitation is safe for term infants....
Evidence for use of oxygen in infants receiving cardiac compressions...


Oxygen Delivery During CPR (Neonatal) - Intervention (NRP 738)

In neonates receiving cardiac compressions (P), does 100% O2 as the ventilation gas (I), compared with lower concentrations of oxygen (C), increase survival rates, improve neurologic outcomes, decrease time to ROSC, or decrease oxidative injury (O)?

Oxygen Delivery During CPR (Neonatal) - Intervention (NRP 738)

Neonatal resuscitation has historically focused on achieving adequate oxygenation as quickly as possible. Recently, it has been recognized that excessive oxygen administration can be toxic.

Current guidelines recommend starting resuscitation with low inspired oxygen and then increasing inspired oxygen as necessary as guided by pulse oximetry. However, once the resuscitation has reached the need for chest compressions, it has been suggested to increase the Fio2.

Oxygen in the Delivery Room: Evidence in Term Infants
Oxygen Delivery During CPR (Neonatal) - Intervention (NRP 738)

Treatment Recommendation

There are no human data to inform this question.

Despite animal evidence showing no advantage to the use of 100% oxygen, by the time resuscitation of a newborn baby has reached the stage of chest compressions, the steps of trying to achieve ROSC using effective ventilation with low-concentration oxygen should have been attempted. Thus, it would seem prudent to try increasing the supplementary oxygen concentration (Good Practice Guidance).

If used, supplementary oxygen should be weaned as soon as the heart rate has recovered (weak recommendation, very-low-quality evidence).

Oxygen in the Delivery Room: Evidence in Preterm Infants
Oxygen Concentration for Resuscitating Premature Newborns - Intervention (NRP 864)

Among preterm newborns (less than 37 weeks of gestation) who receive PPV in the delivery room (P), does the use of high O2 (50% to 100%) as the ventilation gas (I), compared with low concentrations of O2 (21% to 30%) (C), decrease mortality, decrease bronchopulmonary dysplasia, decrease retinopathy, decrease IVH (O)?
Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease.


FiO$_2$ received by ELGANS in the low vs. high oxygen group.

Vento. Pediatrics 2009
Biomarkers of oxidative stress in the low vs. high oxygen group

Vento. Pediatrics 2009
Association of oxidative stress markers with BPD

Vento. Pediatrics 2009
Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤ 32 weeks.

Saugstad OD, Aune D, Aguar M, Kapadia V, Finer N, Vento M.

**AIM:** The optimal initial fraction of oxygen (iFiO2) for resuscitating/stabilizing premature infants is not known. We aimed to study currently available information and provide guidelines regarding the iFiO2 levels needed to resuscitate/stabilize premature infants of ≤ 32 weeks' gestation.

**METHODS:** Our systematic review and meta-analysis studied the effects of low and high iFiO2 during the resuscitation/stabilization of 677 newborn babies ≤ 32 weeks' gestation.

**RESULTS:** Ten randomized studies were identified covering 321 infants receiving low (0.21-0.30) iFiO2 levels and 356 receiving high (0.60-1.0) levels. Relative risk for mortality was 0.62 (95% CI: 0.37-1.04, I(2) = 0%, p(heterogeneity) = 0.88) for low versus high iFiO2; for bronchopulmonary dysplasia, it was 1.11 (95% CI: 0.73-1.68, I(2) = 46%, p (heterogeneity) = 0.06); and for intraventricular hemorrhage, it was 0.90 (95% CI: 0.53-1.53, I(2) = 9%, p (heterogeneity) = 0.36).

**CONCLUSION:** These data show that reduced mortality approached significance when a low iFiO2 (0.21-0.30) was used for initial stabilization, compared to a high iFiO2 (0.60-1.0). There was no significant association for bronchopulmonary dysplasia or intraventricular hemorrhage when comparing low and high iFiO2. Based on present data, premature babies ≤ 32 weeks' gestation in need of stabilization in the delivery room should be given an iFiO2 of 0.21-0.30.

Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤ 32 weeks.

<table>
<thead>
<tr>
<th>Study</th>
<th>Blinded</th>
<th>GA weeks</th>
<th>Low FiO(_2)</th>
<th>High FiO(_2)</th>
<th>Mortality definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lundstrøm (6)</td>
<td>No</td>
<td>24–32</td>
<td>0.21</td>
<td>0.80</td>
<td>Before discharge</td>
</tr>
<tr>
<td>Vento (10)</td>
<td>No</td>
<td>24–28</td>
<td>0.30</td>
<td>0.90</td>
<td>&lt;28 days</td>
</tr>
<tr>
<td>Wang (8)</td>
<td>Yes</td>
<td>23–32</td>
<td>0.21</td>
<td>1.0</td>
<td>&lt;28 days</td>
</tr>
<tr>
<td>Rabi (14)</td>
<td>Yes</td>
<td>≤32</td>
<td>0.21</td>
<td>1.0</td>
<td>Before discharge</td>
</tr>
<tr>
<td>See (22)</td>
<td>No</td>
<td>&lt;31</td>
<td>0.21</td>
<td>1.0</td>
<td>Before discharge</td>
</tr>
<tr>
<td>Rook (21)</td>
<td>Yes</td>
<td>&lt;32</td>
<td>0.30</td>
<td>0.65</td>
<td>&lt;36 weeks' postconceptional age</td>
</tr>
<tr>
<td>Amanian (13)</td>
<td>No</td>
<td>29–34</td>
<td>0.30</td>
<td>1.0</td>
<td>Not specified</td>
</tr>
<tr>
<td>Kumar (23)</td>
<td>Yes</td>
<td>&lt;32</td>
<td>0.21</td>
<td>1.0</td>
<td>&lt;28 days</td>
</tr>
<tr>
<td>Aguar (24)</td>
<td>Yes</td>
<td>&lt;30</td>
<td>0.30</td>
<td>0.60</td>
<td>Before discharge</td>
</tr>
<tr>
<td>Kapadia (15)</td>
<td>No</td>
<td>&lt;35</td>
<td>0.21</td>
<td>1.0</td>
<td>Before discharge</td>
</tr>
<tr>
<td>Excluded studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasling (11)</td>
<td>No</td>
<td>&lt;31</td>
<td>0.50</td>
<td>1.0</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ezaki (12)</td>
<td>Yes</td>
<td>&lt;35</td>
<td>Unknown</td>
<td>1.0</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

GA = Gestational age.

Only enrolled infants with a gestational age <33 weeks are included in this review from studies referenced (12,13) and (15).

Lower (0.21 to 0.30) vs. Higher (0.60 to 1.00) Oxygen Concentration for Delivery Room Stabilization of Preterm Neonates ≤ 32 weeks
Effect on Mortality

Typical risk ratio 0.62, 95% CI 0.37 to 1.04

Lower (0.21 to 0.30) vs. Higher (0.60 to 1.00) Oxygen Concentration for Delivery Room Stabilization of Preterm Neonates ≤ 32 weeks
Effect on Chronic Lung Disease

Typical risk ratio 1.11, 95% CI 0.76 to 1.68

Oxygen Concentration for Resuscitating Premature Newborns - Intervention (NRP 864)

Treatment Recommendations

We recommend against initiating resuscitation of preterm newborns (less than 35 weeks of gestation) with high supplementary oxygen concentrations (65% to 100%).

We recommend initiating resuscitation with a low-oxygen concentration (21% to 30%) (strong recommendation, moderate quality evidence).

Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

Ju Lee Oei, Ola D. Saugstad, Kei Lui, Ian M. Wright, John P. Smyth, Paul Craven, Yueping Alex Wang, Rowena McMullan, Elisabeth Coates, Meredith Ward, Parag Mishra, Koert De Waal, Javeed Travadi, Kwee Ching See, Irene G.S. Cheah, Chin Theam Lim, Yao Mun Choo, Azanna Ahmad Kamar, Fook Choe Cheah, Ahmed Masoud, William Tarnow-Mordi


BACKGROUND AND OBJECTIVES: Lower concentrations of oxygen (O2)(≤ 30%) are recommended for preterm resuscitation to avoid oxidative injury and cerebral ischemia. Effects on long-term outcomes are uncertain. We aimed to determine the effects of using room air (RA) or 100% O2 on the combined risk of death and disability at 2 years in infants <32 weeks’ gestation.

METHODS: A randomized, unmasked study designed to determine major disability and death at 2 years in infants <32 weeks’ gestation after delivery room resuscitation was initiated with either RA or 100% O2 and which were adjusted to target pulse oximetry of 65% to 95% at 5 minutes and 85% to 95% until NICU admission.
Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

RESULTS: Of 6291 eligible patients, 292 were recruited and 287 (mean gestation: 28.9 weeks) were included in the analysis (RA: n = 144; 100% O2: n = 143). Recruitment ceased in June 2014, per the recommendations of the Data and Safety Monitoring Committee owing to loss of equipoise for the use of 100% O2. In non-prespecified analyses, infants < 28 weeks who received RA resuscitation had higher hospital mortality (RA: 10 of 46 [22%]; than those given 100% O2: 3 of 54 [6%]; risk ratio: 3.9 [95% confidence interval: 1.1–13.4]; P = .01). Respiratory failure was the most common cause of death (n = 13).

CONCLUSIONS: Using RA to initiate resuscitation was associated with an increased risk of death in infants < 28 weeks’ gestation. This study was not a prespecified analysis, and it was underpowered to address this post hoc hypothesis reliably. Additional data are needed.

# Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All infants RR (95% CI)</th>
<th>Infants &lt; 28 weeks RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Deaths</td>
<td>2.3 (0.9 to 5.7)</td>
<td>2.9 (0.9 to 8.7)</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>3.1 (0.9 to 11.1)</td>
<td>3.1 (0.9 to 11.1)</td>
</tr>
<tr>
<td>Death before hospital discharge</td>
<td>2.6 (0.9 to 7.1)</td>
<td>3.9 (1.1 to 13.4)</td>
</tr>
</tbody>
</table>

Higher or lower oxygen for delivery room resuscitation of preterm infants below 28 completed weeks gestation: a meta-analysis

Ju Lee Oei, Maximo Vento, Yacov Rabi, Ian Wright, Neil Finer, Wade Rich, Vishal Kapadia, Dagfinn Aune, Denise Rook, William Tarnow-Mordi, Ola D Saugstad

Arch Dis Child 2016

**Objective:** To systematically review outcomes of infants ≤ 28+6 weeks gestation randomized to resuscitation with low (≤ 0.3) vs high (≥ 0.6) fraction of inspired oxygen (FiO2) at delivery.

**Design:** Systematic review of randomized controlled trials of low (≤ 0.3) vs high (≥ 0.6) FiO2 resuscitation. Information was obtained from databases (Medline/Pub Med, EMBASE, ClinicalTrials.gov, Cochrane) and meeting abstracts between 1990 to 2015. Search index terms: preterm/resuscitation/oxygen. Data for infants ≤ 28 +6 weeks gestation were independently extracted and pooled using a random effects model. Analyses were performed with Revman V.5.

**Main outcome measures:** Death in hospital, bronchopulmonary dysplasia (BPD), retinopathy of prematurity > stage 2 (ROP), intraventricular hemorrhage > grade 2 (IVH), patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).
Higher or lower oxygen for delivery room resuscitation of preterm infants below 28 completed weeks gestation: a meta-analysis

Ju Lee Oei, Maximo Vento, Yacov Rabi, Ian Wright, Neil Finer, Wade Rich, Vishal Kapadia, Dagfinn Aune, Denise Rook, William Tarnow-Mordi, Ola D Saugstad

Arch Dis Child 2016

Results: A total of 251 and 253 infants were enrolled in 8 studies (6 masked, 2 unmasked) in the lower and higher oxygen groups, respectively, (mean gestation 26 weeks) between 2005 and 2014. There were no differences in BPD (relative risk, 95% CIs 0.88 (0.68 to 1.14)), IVH (0.81 (0.52 to 1.27)), ROP (0.82 (0.46 to 1.46)), PDA (0.95 (0.80 to 1.14)) and NEC (1.61 (0.67 to 3.36)) and overall mortality (0.99 (0.52 to 1.91)). Mortality was lower in low oxygen arms of masked studies (0.46 (0.23 to 0.92), p=0.03) and higher in low oxygen arms of unmasked studies (1.94 (1.02 to 3.68), p=0.04).

Conclusions: There is no difference in the overall risk of death or other common preterm morbidities after resuscitation is initiated at delivery with lower (≤ 0.30) or higher (≥ 0.6) FiO2 in infants ≤ 28+6 weeks gestation. The opposing results for masked and unmasked trials may represent a Type I error, emphasizing the need for larger well designed studies.
**Meta Analysis**

Low vs Higher Oxygen in DR – Mortality

*Infants < 28 weeks*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Low oxygen Events</th>
<th>Low oxygen Total</th>
<th>High oxygen Events</th>
<th>High oxygen Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2008</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>1.4%</td>
<td>4.33 [0.20, 94.83]</td>
</tr>
<tr>
<td>Rabi 2011</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>15</td>
<td>4.5%</td>
<td>0.44 [0.02, 9.98]</td>
</tr>
<tr>
<td>Kapadla 2012</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>17</td>
<td>7.1%</td>
<td>0.50 [0.05, 4.94]</td>
</tr>
<tr>
<td>Escrig 2008</td>
<td>4</td>
<td>19</td>
<td>3</td>
<td>22</td>
<td>9.6%</td>
<td>1.61 [0.41, 6.34]</td>
</tr>
<tr>
<td>Aguar 2013</td>
<td>4</td>
<td>37</td>
<td>3</td>
<td>40</td>
<td>10.0%</td>
<td>1.48 [0.35, 6.17]</td>
</tr>
<tr>
<td>Vento 2009</td>
<td>4</td>
<td>34</td>
<td>7</td>
<td>41</td>
<td>28.0%</td>
<td>0.44 [0.14, 1.34]</td>
</tr>
<tr>
<td>Rook 2014</td>
<td>6</td>
<td>53</td>
<td>10</td>
<td>63</td>
<td>39.4%</td>
<td>0.48 [0.19, 1.20]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Total events: 20 (Low) vs 26 (High)
- Weight: 100.0%
- Risk Ratio: 0.73 [0.44, 1.22]

Heterogeneity: Chi² = 5.34, df = 6 (P = 0.50); I² = 0%

Test for overall effect: Z = 1.19 (P = 0.23)

Typical risk ratio 0.73, 95% CI 0.44 to 1.22
Mortality (all studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Low oxygen</th>
<th>High oxygen</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguar</td>
<td>4</td>
<td>7</td>
<td>17.2%</td>
<td>0.44 [0.14, 1.34]</td>
</tr>
<tr>
<td>Rabi</td>
<td>0</td>
<td>1</td>
<td>3.9%</td>
<td>0.44 [0.02, 9.98]</td>
</tr>
<tr>
<td>Rook</td>
<td>6</td>
<td>10</td>
<td>20.4%</td>
<td>0.48 [0.19, 1.20]</td>
</tr>
<tr>
<td>Kapadia</td>
<td>1</td>
<td>2</td>
<td>6.6%</td>
<td>0.50 [0.05, 4.94]</td>
</tr>
<tr>
<td>Vento</td>
<td>4</td>
<td>3</td>
<td>13.1%</td>
<td>1.48 [0.35, 6.17]</td>
</tr>
<tr>
<td>Wang</td>
<td>1</td>
<td>1</td>
<td>5.3%</td>
<td>1.50 [0.11, 20.68]</td>
</tr>
<tr>
<td>Escrig</td>
<td>4</td>
<td>3</td>
<td>13.8%</td>
<td>1.61 [0.41, 6.34]</td>
</tr>
<tr>
<td>Oei</td>
<td>14</td>
<td>5</td>
<td>19.7%</td>
<td>3.18 [1.20, 8.40]</td>
</tr>
</tbody>
</table>

Total (95% CI) 251 258 100.0% 0.99 [0.52, 1.91]

Total events 34 32
Heterogeneity: Tau² = 0.32; Chi² = 11.52, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 0.02 (P = 0.98)

Oei and colleagues. Arch Dis Child 2016
Mortality (masked studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Low oxygen Events</th>
<th>Low oxygen Total</th>
<th>High oxygen Events</th>
<th>High oxygen Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabi</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>15</td>
<td>5.0%</td>
<td>0.44 [0.02, 9.98] 2011</td>
</tr>
<tr>
<td>Aguar</td>
<td>4</td>
<td>34</td>
<td>7</td>
<td>26</td>
<td>38.8%</td>
<td>0.44 [0.14, 1.34] 2013</td>
</tr>
<tr>
<td>Rook</td>
<td>6</td>
<td>53</td>
<td>10</td>
<td>42</td>
<td>56.2%</td>
<td>0.48 [0.19, 1.20] 2014</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>96</strong></td>
<td><strong>83</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.46 [0.23, 0.92]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 10 18

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)

Mortality (unmasked studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Low oxygen Events</th>
<th>Low oxygen Total</th>
<th>High oxygen Events</th>
<th>High oxygen Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>12</td>
<td>6.0%</td>
<td>1.50 [0.11, 20.68]</td>
</tr>
<tr>
<td>Kapadia</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>7.9%</td>
<td>0.50 [0.05, 4.94]</td>
</tr>
<tr>
<td>Vento</td>
<td>4</td>
<td>37</td>
<td>3</td>
<td>41</td>
<td>20.2%</td>
<td>1.48 [0.35, 6.17]</td>
</tr>
<tr>
<td>Escrig</td>
<td>4</td>
<td>19</td>
<td>3</td>
<td>23</td>
<td>22.1%</td>
<td>1.61 [0.41, 6.34]</td>
</tr>
<tr>
<td>Oei</td>
<td>14</td>
<td>74</td>
<td>5</td>
<td>84</td>
<td>43.8%</td>
<td>3.18 [1.20, 8.40]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>153</strong></td>
<td><strong>175</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.94 [1.02, 3.68]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 24 14

Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Bronchopulmonary dysplasia (survivors only)

Oei and colleagues. Arch Dis Child 2016
Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth.

Lui K, Foster JP, Osborn DA, Jones LJ, Davis PG, Oei JL, Ching SK.


Updated 2017
Mortality near term corrected age or discharge
**Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions**


**BACKGROUND AND OBJECTIVES:** Stabilization of preterm infants after birth frequently requires oxygen supplementation. At present the optimal initial oxygen inspiratory fraction (Fio2) for preterm stabilization after birth is still under debate. We aimed to compare neurodevelopmental outcomes of extremely preterm infants at 24 months corrected age randomly assigned to be stabilized after birth with an initial Fio2 of 0.3 versus 0.6 to 0.65 in 3 academic centers from Spain and the Netherlands.

**METHODS:** Randomized, controlled, double-blinded, multicenter, international clinical trial enrolling preterm infants <32 weeks’ gestation assigned to an initial Fio2 of 0.3 (Lowox group) or 0.6 to 0.65 (Hiox group). During stabilization, arterial pulse oxygen saturation and heart rate were continuously monitored and Fio2 was individually titrated to keep infants within recommended ranges. At 24 months, blinded researchers used the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) to assess visual acuity, neurosensory deafness, and language skills.
Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions

**RESULTS:** A total of 253 infants were recruited and 206 (81.4%) completed follow-up. No differences in perinatal characteristics, oxidative stress, or morbidities during the neonatal period were assessed. Mortality at hospital discharge or when follow-up was completed didn’t show differences between the groups. No differences regarding Bayley-III scale scores (motor, cognitive, and language composites), neurosensorial handicaps, cerebral palsy, or language skills between groups were found.
Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions

Overall Rates of Disabilities in Preterm Infants Resuscitated with an Initial FiO2 of 0.3 (Lowox) vs. 0.6 to 0.65 (Hiox) At 24 months corrected age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lowox Total, n (%)</th>
<th>Hiox Total, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disability</td>
<td>67 (75.3)</td>
<td>61 (71.8)</td>
<td>1.17 (0.60–2.30)</td>
<td>.64</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (15.7)</td>
<td>16 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (6.7)</td>
<td>7 (8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (2.3)</td>
<td>1 (1.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outcome of preterm infants following the introduction of room air resuscitation

Resuscitation 2015; 96: 252-59

✓ In 2006 most NICUs in Canada introduced room air resuscitation for babies at term and changed their practice for preterm babies – previously 100% O2, to either starting in 21% or at some intermediate concentration i.e. 40%.

✓ Reviewed CNN database for babies between 23 and 27 weeks gestation,

✓ Evaluated occurrence of death or a severe brain injury (grade 3 or 4 IVH or PVL), for the 2 years up to their change in practice, and for 2 years after following 1 year washout
Outcome of preterm infants following the introduction of room air resuscitation

Canadian evidence raises concerns about lower initial FiO2 in preterm infants.

- Cohort of 2,326 infants ≤ 27 weeks gestation in 17 NICUs in 2004-2009.
- Initial FiO2 was reduced in 2006 from 100% to 21-40%.
- Mean SNAP illness severity score decreased from 17 to 14 (P<0.01).
- Death or severe neurologic injury increased – AOR 1.36 (1.11 to 1.66).

Resuscitation 2015; 96: 252-59
Clinicians in 25 countries prefer to use lower levels of oxygen to resuscitate preterm infants at birth


AIM: This study determined current international clinical practice and opinions regarding initial fractional inspired oxygen (FiO2) and pulse oximetry (SpO2) targets for delivery room resuscitation of preterm infants of less than 29 weeks of gestation.

METHODS: An online survey was disseminated to neonatal clinicians via established professional clinical networks using a web-based survey program between March 9 and June 30, 2015.

RESULTS: Of the 630 responses from 25 countries, 60% were from neonatologists. The majority (77%) would target SpO2 between the 10th to 50th percentiles values for full-term infants. The median starting FiO2 was 0.3, with Japan using the highest (0.4) and the UK using the lowest (0.21). New Zealand targeted the highest SpO2 percentiles (median 50%).

CONCLUSION: Clinicians currently favor lower SpO2 targets for preterm resuscitation, despite acknowledging the lack of evidence for benefit or harm, and 65% would join a clinical trial.

Oxygen Concentration for Resuscitating Premature Newborns - Intervention (NRP 864)

Knowledge Gaps

The most appropriate time-specific oxygen targets for premature newborns need to be defined.

Neurodevelopmental outcomes for preterm newborns resuscitated with low- and high-oxygen concentrations need to be determined.

Guest Discussant

Neil Finer, M.D
Emeritus Professor
University of California, San Diego

What does this mean?
Knowledge Gaps

• Do preterm infants meet $\text{SpO}_2$ targets in:
  1. Randomized controlled trials
  2. Guidelines

• What happens to babies who do not reach $\text{SpO}_2$ targets?
• No studies comparing outcomes using different targets!!
Achievement of Target SpO2 during Resuscitation – Oei et al. – EAPS 2017

Hypothesis

• Preterm babies (regardless of starting FiO2) who do not reach SpO2 of 80% at 5 minutes of age are at an increased risk of death and/or major intraventricular hemorrhage (IVH)
Oei et al. Achievement of Target SpO2

- Individual patient data from 8 randomized controlled studies of lower ($\leq 30\%$) vs. higher ($\geq 60\%$) oxygen for preterm infants resuscitation
- Infants categorized according to $5 \text{ min } \text{SpO}_2$ readings as:
  - Met goal saturation (80 to 85%)
  - Did not reach (< 80%)
  - Overshot (> 85%)
| Studies |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Year** | **Low Fio2** | **High Fio2** | **Masked** | **5 min SpO2 Targets** |
| Wang | 2005 | 21% | 100% | No | 80-95 |
| Aguar | 2010 | 30% | 60% | Yes | 80-85 |
| Escrig | 2005 | 30% | 90% | No | 75 |
| Vento | 2007 | 30% | 90% | No | 75 |
| Kapadia | 2010 | 21% | 100% | No | 80-85 |
| Rook | 2008 | 30% | 65% | Yes | 88-94 |
| Oei | 2009 | 21% | 100% | No | 80-95 |
| Rabi | 2005 | 21% | 100% | Yes | 85-92 |
<32 weeks
N = 768

5 min SpO₂
706 (92%)

FiO₂ 21%
N = 184

FiO₂ 30%
N = 168

FiO₂ 60-65%
N = 97

FiO₂ 90-100%
N = 257
### Patient Demographics

#### Trial Targets

<table>
<thead>
<tr>
<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
</tr>
</thead>
<tbody>
<tr>
<td>343 (49%)</td>
<td>159 (23%)</td>
<td>204 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestation</th>
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<th>Met</th>
<th>Overshot</th>
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</tr>
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<tbody>
<tr>
<td>27.2 (2.0)*</td>
<td>28.0 (2.1)</td>
<td>28.2 (1.9)</td>
<td>27.7 (2.1)</td>
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<table>
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<th>&lt; 29 weeks</th>
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<th>Met</th>
<th>Overshot</th>
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<tbody>
<tr>
<td>86 (25%)</td>
<td>68 (43%)</td>
<td>95 (47%)</td>
<td>249 (35%)</td>
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</table>

<table>
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<tr>
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<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
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<tbody>
<tr>
<td>153 (44.6%)</td>
<td>52 (33%)</td>
<td>30 (15%)</td>
<td>235 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>21%</th>
<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
</tr>
</thead>
<tbody>
<tr>
<td>105 (31%)</td>
<td>50 (31%)</td>
<td>29 (14%)</td>
<td>184 (26%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30%</th>
<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
</tr>
</thead>
<tbody>
<tr>
<td>119 (35%)</td>
<td>36 (23%)</td>
<td>11 (5.4%)</td>
<td>166 (23.5%)</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>60-65%</th>
<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (15.5%)</td>
<td>25 (15.7%)</td>
<td>21 (10.3%)</td>
<td>99 (14.0%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>90-100%</th>
<th>Did not meet</th>
<th>Met</th>
<th>Overshot</th>
<th>Total N = 706</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (19.2%)</td>
<td>48 (30.2%)</td>
<td>143 (70.1%)</td>
<td>257 (36.4%)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001
SpO$_2$ in 1$^{st}$ 10 minutes – All Babies
>29 weeks
<28 weeks

American Heart Association

European Resuscitation Council

SpO2 % (mean)

Minutes

21%
30%
60-65%
90-100%
Outcomes of Babies Who Do Not Reach SpO₂ 80% at 5 minutes

- Dead: OR 2.4 (1.3-4.4)
- IVH > grade 3: OR 4.5 (2.1-9.8)
- BPD*: OR 4.5 (2.1-9.8)

Legend:
- Blue: <80%
- Orange: 80-85%
- Gray: >85%
Time To Reach $\text{SpO}_2$ 80% - Death

- $\geq 29$ weeks gestation
- $< 28+6$ weeks gestation
Time To Reach $\text{SpO}_2$ 80% - IVH

- $>29$ weeks gestation
- $\leq 28+6$ weeks gestation
Does Lower $\text{SpO}_2$ Lead to Adverse Outcomes?

Babies may not have met target $\text{SpO}_2$ because:

1. Very sick
2. Given less oxygen

- Similar outcomes noted in:
  - Retrospective review of Canadian infants – *increased death and neurological morbidity* after change in resuscitation policy from 100% oxygen to air/titrated oxygen
  - Torpedo study – largest RCT showed that air was associated with OR 3.9 increased death compared to 100% oxygen for preterms < 29 weeks gestation

Limitations

- Data collected over long period
- Each study had different methodologies
Conclusions

• Almost 50% of infants < 32 weeks do not reach SpO$_2$ study targets at 5 minutes of age

• Those who do not reach SpO$_2$ 80% by 5 minutes are at increased risk of death and IVH especially when compared to those who exceed the target

• Is the current 5 min target too Low??

• Do we need more oxygen initially??

• Larger well designed randomised controlled studies are needed to review current oxygen management strategies and outcomes!!

• These include studies of different target levels!!
Guest Discussant

William Tarnow-Mordi, BA, MBChB, MRCP (UK), DCH, FRCPCH
Professor of Neonatal Medicine, Sydney Medical School
Director, Neonatal and Perinatal Trials, NHMRC Clinical Trials Centre

Directions Forward?
Study question: $\text{SpO}_2$ targets or initial $\text{FiO}_2$?

Individual consent

Cluster randomized trials

Parent’s role in designing research
Randomized trials of different oxygen saturation (SpO$_2$) targets for preterm infants at delivery

1. We certainly need RCTs of survival or morbidity in infants assigned to lower vs higher ranges of oxygen saturation from birth to NICU admission.

2. But first, we need **reliable methods to target relatively narrow ranges of oxygen saturation**, e.g. the 25$^{th}$-50$^{th}$ vs the 75$^{th}$-90$^{th}$ Dawson centile curves.

3. These methods will ensure minimal overlap between assigned target ranges, thus maximising study power.
The Transitional Oxygen Targeting System (TOTS) shows SpO₂ values against the 10th and 50th Dawson centiles as a visual target.

Staff manually adjust FiO₂ guided by the real time TOTS display.

In a before-after cohort study, 20 infants spent 37% of the time within target before TOTS was introduced. 20 infants spent 52% of the time within target after TOTS was introduced (P=0.03).
In this study in 22 lambs, time in the target range (25th – 75th Dawson centiles) did not differ significantly between manual (41.4%) or automated (44.3%) FiO₂ control during resuscitation.

The authors suggested further trials to improve closed loop equipment.

Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support

Gemma K Plottier,1,2 Kevin I Wheeler,3 Sanoj K M Ali,1,2 Omid Sadeghi Fathabadi,4 Rohan Jayakar,4 Timothy J Gale,4 Peter A Dargaville1,5

A novel, rapidly responsive proportional-integral-derivative (PID) algorithm for automated oxygen control in 20 non-intubated infants.

Automated control achieved 25% more time within target range than manual control [81% vs 56% manual, P<0.001].

The team plan to develop a rapidly adapting algorithm for automated oxygen control during resuscitation of preterm infants.

In this Cochrane Review of 15 RCTs in 738 infants, delaying clamping by 30 to 120 seconds improved four secondary outcomes (i) need for transfusion, (ii) BP, (iii) all grades of IVH and (iv) NEC.

Data were insufficient for reliable conclusions about the primary outcomes: death, grade 3 or 4 IVH, periventricular leukomalacia.

The review was last assessed as up to date on 1 Nov 2011.

If updated evidence supports delayed clamping of 30-120 sec, oxygen saturation readings may be delayed. This would make the choice of initial FiO₂ even more important.

The PROMOTION Project includes 2 RCTs in infants ≤ 28 weeks.

Study interventions and outcomes are identical in both RCTs.

Expressions of interest are invited in either study.

1. **US TORPIDO2** is an individual patient RCT in ~ 3,000 infants
2. **HiLo** is a crossover cluster RCT in up to 66 NICUs
3. Both, when completed, will be combined in a **PROspective Meta analysis Of Trials of Initial Oxygen in preterm Newborns.**
4. The PROMOTION Project will have > 80% power to show a 16% reduction in relative risk of death, from 15% to 12.6%. 
2nd study of Targeted Oxygen in Respiratory care of Premature Infants at Delivery: effects on Outcome

**Patients:** Infants born ≤28 weeks

**Intervention:** Initial stabilization in the delivery room

**Comparators:** Randomized to initial FiO₂ 0.6 vs 0.3 with a common 5 min target SpO₂ 80-85%

**Outcomes**

**Primary:** Survival to hospital discharge

**Secondary:** BPD, Brain injury, severe ROP, NEC, Late onset sepsis, Developmental delay
US TORPIDO2

2nd study of Targeted Oxygen in Respiratory care of Premature Infants at Delivery: effects on Outcome

- **US TORPIDO2** is an individual patient trial in 3,160 very preterm infants in the United States and in NICUs with comparable mortality rates and levels of care in North and South America, Europe, Australia, New Zealand and SE Asia.
- This yields > 80% power to demonstrate a decrease from 15% to 11.25% in death with a 2 tailed P value <0.05.
- This is a 25% reduction in relative risk (RRR) of death
US TORPIDO2

2nd study of Targeted Oxygen in Respiratory care of Premature Infants at Delivery: effects on Outcome

• Funding:
  An application is being submitted to PCORI, the Patient Centered Outcomes Research Institute, Washington, DC for ∼US$1,500 per patient to support local recruitment

• Expressions of interest:
  – To request more information or to lodge an expression of interest in joining the US TORPIDO2 study, contact: torpedo2@ctc.usyd.edu.au
<table>
<thead>
<tr>
<th>Randomize NICUs</th>
<th>12 – 18 months</th>
<th>12 weeks changeover (no data capture)</th>
<th>12 – 18 months</th>
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<tbody>
<tr>
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HiLo Crossover Cluster RCT of initial FiO₂ 0.6 vs 0.3 in infants ≤28⁶ weeks
HiLo Crossover Cluster RCT of initial FiO₂ 0.6 vs 0.3 in infants ≤28⁶ weeks

• Neither initial FiO₂ 0.6 or 0.3 is associated with known harm.

• Half the NICUs are allocated to use initial FiO₂ 0.6 as standard care for 12-18 months, then initial FiO₂ 0.3 as standard care for 12-18 months.

• The other half are allocated in reverse order to initial FiO₂ 0.3 for 12-18 months, then initial FiO₂ 0.6 for 12 or 18 months.

• Throughout both periods, the common target for SpO₂ at 5 minutes is 80-85%.

• We plan a crossover cluster randomized trial in up to 66 NICUs worldwide of up to 7,500 infants of ≤ 28⁶ weeks gestation.

• This could detect a 25% relative risk reduction in hospital mortality with > 90% power and two sided P<0.05.
HiLo Crossover Cluster RCT of initial FiO₂ 0.6 vs 0.3 in infants ≤28⁶ weeks

• **Funding:**
  An application is being submitted to PCORI, the Patient Centered Outcomes Research Institute, Washington, DC for ~US$200 per patient to support local co-ordination.

• **Expressions of interest:**
  – To request more information or to lodge an expression of interest in joining the HiLo Prem-Parent study contact:
  
  **hilo@ctc.usyd.edu.au**

  visit **hilo@org.au**

  or email: **Elizabeth.coates@ctc.usyd.edu.au**
Crossover cluster RCTs of low risk treatments in the delivery room can:

• Meet international criteria for opt out or waiver of consent
• Enrol representative samples, including infants at highest risk
• Reduce the burden of prior consent on parents and staff
• Recruit larger populations faster than individual patient RCTs
• Be conducted simultaneously with individual patient RCTs of other interventions, thus helping prevent “trial bottleneck”
• Halve the number of NICUs needed in a standard cluster RCT
Information for parents

Key points

- 0.3 and 0.6 FiO₂ are routinely used for preterm resuscitation worldwide.
- Both levels of FiO₂ are within standard care.
- There is no known additional risk for babies of being in this study.
- Data are anonymous. No baby or family will ever be identified.
- The baby’s clinical need will always take precedence over the study. Babies needing more support will receive it, regardless of allocated group.

- A single Data and Safety Monitoring Committee will oversee both US TORPIDO2 and HiLO
- It will recommend early stopping if a clear result is beyond reasonable doubt in either study.
- Each study has been designed with advice from parents of previous premature infants.
- The committee running the trials have parents as part of the team.
- Parents helped write the leaflets for parents used by hospitals and have contributed to the overall design of the study.
Parents will be on every key committee

- No document will go forward until parents have approved it
- Groups of parents will be engaged in a sub-study, PACER (Parent Attitudes to Comparative Effectiveness Research)
- **PACER** will address parents’ preferences about approaches to consent, whether parents find study processes acceptable and which secondary outcomes they would like measured.
Questions/Discussion?
TEACH MY TONGUE TO SAY I DO NOT KNOW AND THOU SHALT PROGRESS.
Housekeeping details!

CME credit?


Next web seminar?

Prevention of Intraventricular Hemorrhage: Evidence from systematic reviews

June 28th 2017