Mortality and morbidity in acutely ill adults treated with liberal vs. conservative oxygen therapy: systematic review and meta-analysis

John D. Neary MD FRCPC, for the IOTA group
McMaster University
CSIM Annual Meeting 2018
The following presentation represents the views of the speaker at the time of the presentation. This information is meant for educational purposes, and should not replace other sources of information or your medical judgment.

Learning Objectives:
1. Understand the evidence for benefit of conservative oxygen therapy relative to liberal oxygen therapy in acute medical inpatients
2. Translate this evidence into improvement in everyday medical practice
Definition: A Conflict of Interest may occur in situations where the personal and professional interests of individuals may have actual, potential or apparent influence over their judgment and actions.

“I have no conflicts to declare”
Some of the drugs, devices, or treatment modalities mentioned in this presentation are:

Oxygen \((O_2 \text{ or } O=O)\)
Some of the drugs, devices, or treatment modalities mentioned in this presentation are:

Oxygen \( (O_2 \text{ or } O=O) \)
Room air \( (78\% \text{ N}_2 / 21\% \text{ O}_2 / 1\% \text{ Ar} / 0.03\% \text{ CO}_2) \)
October 10
Take Home Message

“You best not interfere with something that ain’t botherin’ you none”

1. Too much 02 is harmful
2. Aim for lowest safest Fi02
Case

- 53F presenting with **severe Legionella** CAP
- T 39, HR 120, BP 90/54, RR 30, SpO$_2$ 75% on RA
- Na 115, Hgb 90
Case

- 53F presenting with severe Legionella CAP
- T 39, HR 120, BP 90/54, RR 30, SpO₂ 75% on RA
- Na 115, Hgb 90

- Which abnormalities confer negative prognosis?
- Which should we try to immediately normalize?
### Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Outcome - Direction of effect</th>
<th>Magnitude</th>
<th>Quality</th>
<th>Evidence source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Care</td>
<td>Mortality - Harm</td>
<td>Small</td>
<td>☑☑☑ ☑ LOW</td>
<td>RCT</td>
</tr>
<tr>
<td>Perioperative</td>
<td>Mortality - No benefit, potential harm</td>
<td>Small</td>
<td>☑☑☑ ☑ LOW</td>
<td>RCT</td>
</tr>
<tr>
<td>Stroke</td>
<td>Mortality - No benefit, potential harm</td>
<td>Small</td>
<td>☑☑☑ ☑ LOW</td>
<td>RCT (1 large)</td>
</tr>
<tr>
<td>ACS</td>
<td>Arrhythmia, recurrent MI, infarct size - Harm</td>
<td>Moderate</td>
<td>☑☑☑ ☑ MOD</td>
<td>RCT (AVOID)</td>
</tr>
<tr>
<td></td>
<td>Mortality - Uncertain risk/benefit</td>
<td>Moderate</td>
<td>☑☑☑ ☑ V.LOW</td>
<td>RCT (n=4)</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>Mortality, poor neurologic outcome - Harm</td>
<td>Small</td>
<td>☑☑☑ ☑ V.LOW</td>
<td>Observational</td>
</tr>
</tbody>
</table>

- Implications for EMS, RN/RPN, RT and MD education and practice?
- How to empirically treat undifferentiated patients? Code blues?
- Future research? Knowledge translation and improve quality?
Faculty contribution

“Derek, you are [CENSORED] insane if you don’t put all this together as ‘acute illness’ and pitch it to a top general journal”
Inclusion Criteria

- Acutely III Hospitalized Patients
- Compared Liberal vs. Conservative Oxygen Strategies
- Reported One or More Outcomes of Interest

Study Selection
- Database searches Inception to Oct 25, 2017
  1784 Records
- 1150 Records screened
- 67 Full-text records assessed for eligibility
- 25 Trials Included (26 Records, 16,037 patients)
Acutely Ill Hospitalized Patients

Critical Illness
Stroke
MI
Cardiac Arrest
Emergency Surgery

Inclusion Criteria

Reported One or More Outcomes of Interest
Compared Liberal vs. Conservative Oxygen Strategies

Study Selection

Database searches Inception to Oct 25, 2017 1784 Records
1150 Records screened
67 Full-text records assessed for eligibility
25 Trials Included (26 Records, 16,037 patients)
Compared Liberal vs. Conservative Oxygen Strategies

Inclusion Criteria

- Acutely III Hospitalized Patients
- Reported One or More Outcomes of Interest
- Compared Liberal vs. Conservative Oxygen Strategies

Study Selection

- Database searches Inception to Oct 25, 2017
  1,784 Records
- 1,150 Records screened
- 67 Full-text records assessed for eligibility
- 25 Trials Included (26 Records, 16,037 patients)
Reported One or More Outcomes of Interest

Hospital-acquired pneumonia
Hospital-acquired infection
Length of stay
Mortality
Disability

Acutely Ill Hospitalized Patients

Compared Liberal vs. Conservative Oxygen Strategies

Study Selection

Database searches Inception to Oct 25, 2017
1784 Records

1150 Records screened

67 Full-text records assessed for eligibility

25 Trials Included (26 Records, 16,037 patients)
Database searches
Inception to Oct 25, 2017
1784 Records

1150 Records screened
67 Full-text records assessed for eligibility
25 RCTs included
(26 Records, 16,037 patients)
Survival Curve

HR 1.11 (95% CI 1.00-1.24)

Number at risk

<table>
<thead>
<tr>
<th>Conservative</th>
<th>Liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>6900</td>
<td>6943</td>
</tr>
<tr>
<td>6484</td>
<td>6450</td>
</tr>
<tr>
<td>6372</td>
<td>6345</td>
</tr>
<tr>
<td>6130</td>
<td>6119</td>
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<td>3542</td>
<td>3564</td>
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<td>3527</td>
<td>3554</td>
</tr>
<tr>
<td>3507</td>
<td>3539</td>
</tr>
<tr>
<td>3372</td>
<td>3402</td>
</tr>
<tr>
<td>3361</td>
<td>3390</td>
</tr>
<tr>
<td>3352</td>
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<td>3345</td>
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<tr>
<td>3344</td>
<td>3365</td>
</tr>
<tr>
<td>3334</td>
<td>3351</td>
</tr>
</tbody>
</table>
## Mortality at Longest Follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, Liberal</th>
<th>n/N, Conservative</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali 2014</td>
<td>1.06 (0.64, 1.78)</td>
<td>26/155</td>
<td>23/146</td>
<td>2.96</td>
</tr>
<tr>
<td>Asfar 2017</td>
<td>1.15 (0.94, 1.42)</td>
<td>107/223</td>
<td>91/219</td>
<td>18.01</td>
</tr>
<tr>
<td>Butler 1987</td>
<td>0.43 (0.10, 1.88)</td>
<td>2/17</td>
<td>6/22</td>
<td>0.36</td>
</tr>
<tr>
<td>Girardis 2016</td>
<td>1.33 (1.00, 1.88)</td>
<td>80/244</td>
<td>58/236</td>
<td>9.49</td>
</tr>
<tr>
<td>Hofmann 2017</td>
<td>0.99 (0.80, 1.22)</td>
<td>166/3311</td>
<td>168/3318</td>
<td>17.87</td>
</tr>
<tr>
<td><strong>ACS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khoshnood 2015</td>
<td>0.88 (0.18, 4.24)</td>
<td>3/85</td>
<td>3/75</td>
<td>0.32</td>
</tr>
<tr>
<td>Kuisima 2006</td>
<td>1.00 (0.31, 3.23)</td>
<td>4/14</td>
<td>4/14</td>
<td>0.57</td>
</tr>
<tr>
<td>Mazdeh 2015</td>
<td>1.60 (0.43, 6.01)</td>
<td>5/26</td>
<td>3/25</td>
<td>0.45</td>
</tr>
<tr>
<td>Nutbeam 2015</td>
<td>1.50 (0.48, 4.68)</td>
<td>6/25</td>
<td>4/25</td>
<td>0.60</td>
</tr>
<tr>
<td>Padma 2010</td>
<td>0.20 (0.01, 3.92)</td>
<td>0/20</td>
<td>2/20</td>
<td>0.09</td>
</tr>
<tr>
<td>Panwar 2016</td>
<td>0.94 (0.58, 1.53)</td>
<td>19/51</td>
<td>21/53</td>
<td>3.29</td>
</tr>
<tr>
<td>Ranchord 2012</td>
<td>0.53 (0.05, 5.70)</td>
<td>1/72</td>
<td>2/76</td>
<td>0.14</td>
</tr>
<tr>
<td>Rawles 1976</td>
<td>2.71 (0.76, 9.73)</td>
<td>9/105</td>
<td>3/95</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roffe 2017</td>
<td>1.05 (0.89, 1.23)</td>
<td>268/2668</td>
<td>256/2668</td>
<td>29.50</td>
</tr>
<tr>
<td>Ronning 1999</td>
<td>1.15 (0.88, 1.49)</td>
<td>91/292</td>
<td>70/258</td>
<td>11.31</td>
</tr>
<tr>
<td>Schietroma 2016</td>
<td>0.50 (0.09, 2.70)</td>
<td>2/119</td>
<td>4/120</td>
<td>0.28</td>
</tr>
<tr>
<td>Singhal 2005</td>
<td>0.78 (0.14, 4.23)</td>
<td>2/9</td>
<td>2/7</td>
<td>0.27</td>
</tr>
<tr>
<td>Singhal 2007</td>
<td>2.37 (1.10, 5.13)</td>
<td>17/43</td>
<td>7/42</td>
<td>1.31</td>
</tr>
<tr>
<td>Stub 2012</td>
<td>0.78 (0.39, 1.54)</td>
<td>14/312</td>
<td>18/312</td>
<td>1.69</td>
</tr>
<tr>
<td>Ukholkina 2005</td>
<td>4.07 (0.53, 98.15)</td>
<td>1/58</td>
<td>0/79</td>
<td>0.08</td>
</tr>
<tr>
<td>Young 2014</td>
<td>1.11 (0.45, 2.75)</td>
<td>5/9</td>
<td>4/8</td>
<td>0.95</td>
</tr>
<tr>
<td>Sattavan 2016</td>
<td>(Excluded)</td>
<td>0/30</td>
<td>0/30</td>
<td>0.00</td>
</tr>
<tr>
<td>Shi 2017</td>
<td>(Excluded)</td>
<td>0/9</td>
<td>0/9</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1.10 (1.00, 1.20)</td>
<td>828/7897</td>
<td>749/7857</td>
<td>100.00</td>
</tr>
</tbody>
</table>

More oxygen better More oxygen worse
# Mortality In-Hospital

<table>
<thead>
<tr>
<th>RCT</th>
<th>RR (95% CI)</th>
<th>n/N, Liberal</th>
<th>n/N, Conservative</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali 2014</td>
<td>1.18 (0.32, 4.30)</td>
<td>5/155</td>
<td>4/146</td>
<td>1.57</td>
</tr>
<tr>
<td>Butler 1987</td>
<td>3.83 (0.17, 88.62)</td>
<td>1/17</td>
<td>0/22</td>
<td>0.27</td>
</tr>
<tr>
<td>Girardis 2016</td>
<td>1.33 (1.00, 1.78)</td>
<td>80/243</td>
<td>58/235</td>
<td>32.14</td>
</tr>
<tr>
<td>Hofmann 2017</td>
<td>1.21 (0.81, 1.80)</td>
<td>53/3311</td>
<td>44/3318</td>
<td>16.75</td>
</tr>
<tr>
<td>Khoshnoood 2015</td>
<td>0.88 (0.18, 4.24)</td>
<td>3/85</td>
<td>3/75</td>
<td>1.07</td>
</tr>
<tr>
<td>Kuiisma 2006</td>
<td>1.00 (0.31, 3.23)</td>
<td>4/14</td>
<td>4/14</td>
<td>1.92</td>
</tr>
<tr>
<td>Nutbeam 2015</td>
<td>1.50 (0.27, 8.22)</td>
<td>3/25</td>
<td>2/25</td>
<td>0.91</td>
</tr>
<tr>
<td>Panwar 2016</td>
<td>0.96 (0.48, 1.90)</td>
<td>12/51</td>
<td>13/53</td>
<td>5.64</td>
</tr>
<tr>
<td>Rawles 1976</td>
<td>2.71 (0.76, 9.73)</td>
<td>9/105</td>
<td>3/95</td>
<td>1.62</td>
</tr>
<tr>
<td>Roffe 2017</td>
<td>1.11 (0.75, 1.66)</td>
<td>50/2668</td>
<td>45/2668</td>
<td>16.56</td>
</tr>
<tr>
<td>Ronning 1999</td>
<td>1.18 (0.74, 1.89)</td>
<td>36/292</td>
<td>27/258</td>
<td>11.94</td>
</tr>
<tr>
<td>Schietroma 2016</td>
<td>0.50 (0.09, 2.70)</td>
<td>2/119</td>
<td>4/120</td>
<td>0.94</td>
</tr>
<tr>
<td>Singhal 2005</td>
<td>0.27 (0.01, 5.70)</td>
<td>0/9</td>
<td>1/7</td>
<td>0.28</td>
</tr>
<tr>
<td>Singhal 2007</td>
<td>3.42 (1.22, 9.54)</td>
<td>14/43</td>
<td>4/42</td>
<td>2.50</td>
</tr>
<tr>
<td>Stub 2012</td>
<td>0.45 (0.16, 1.29)</td>
<td>5/312</td>
<td>11/312</td>
<td>2.41</td>
</tr>
<tr>
<td>Ukholkina 2005</td>
<td>4.07 (0.17, 98.10)</td>
<td>1/58</td>
<td>0/79</td>
<td>0.26</td>
</tr>
<tr>
<td>Young 2014</td>
<td>1.11 (0.45, 2.75)</td>
<td>5/9</td>
<td>4/8</td>
<td>3.21</td>
</tr>
<tr>
<td>Sattavan 2016</td>
<td>(Excluded)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shi 2017</td>
<td>(Excluded)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall (19 RCTs, I²=0%, p=0.020)</strong></td>
<td><strong>1.21 (1.03, 1.43)</strong></td>
<td><strong>283/7555</strong></td>
<td><strong>227/7516</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

More oxygen better  More oxygen worse
### Mortality at 30 days

<table>
<thead>
<tr>
<th>RCT</th>
<th>RR (95% CI)</th>
<th>n/N, Liberal</th>
<th>n/N, Conservative</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali 2014</td>
<td>1.11 (0.52, 2.41)</td>
<td>13/155</td>
<td>11/146</td>
<td>2.39</td>
</tr>
<tr>
<td>Asfar 2017</td>
<td>1.20 (0.95, 1.51)</td>
<td>95/223</td>
<td>78/219</td>
<td>25.88</td>
</tr>
<tr>
<td>Buller 1987</td>
<td>0.26 (0.03, 2.01)</td>
<td>1/17</td>
<td>5/22</td>
<td>0.34</td>
</tr>
<tr>
<td>Girardis 2016</td>
<td>1.42 (0.99, 2.02)</td>
<td>60/244</td>
<td>41/236</td>
<td>11.31</td>
</tr>
<tr>
<td>Hofmann 2017</td>
<td>1.09 (0.79, 1.52)</td>
<td>73/3311</td>
<td>67/3318</td>
<td>13.21</td>
</tr>
<tr>
<td>Panwar 2016</td>
<td>1.10 (0.64, 1.88)</td>
<td>18/51</td>
<td>17/53</td>
<td>4.88</td>
</tr>
<tr>
<td>Ranchord 2012</td>
<td>0.53 (0.05, 5.70)</td>
<td>1/72</td>
<td>2/76</td>
<td>0.25</td>
</tr>
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<td>Roffe 2017</td>
<td>0.99 (0.78, 1.24)</td>
<td>138/2668</td>
<td>140/2668</td>
<td>27.23</td>
</tr>
<tr>
<td>Ronning 1999</td>
<td>1.28 (1.88, 1.87)</td>
<td>55/292</td>
<td>38/258</td>
<td>9.95</td>
</tr>
<tr>
<td>Schietroma 2016</td>
<td>0.50 (0.09, 2.70)</td>
<td>2/119</td>
<td>4/120</td>
<td>0.50</td>
</tr>
<tr>
<td>Singhal 2005</td>
<td>0.78 (0.06, 10.37)</td>
<td>1/9</td>
<td>1/7</td>
<td>0.21</td>
</tr>
<tr>
<td>Singhal 2007</td>
<td>3.42 (0.22, 9.54)</td>
<td>14/43</td>
<td>4/42</td>
<td>1.35</td>
</tr>
<tr>
<td>Stub 2012</td>
<td>0.86 (0.40, 1.82)</td>
<td>12/312</td>
<td>14/312</td>
<td>2.49</td>
</tr>
<tr>
<td>Sattavan 2016</td>
<td>(Excluded)</td>
<td>0/30</td>
<td>0/30</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Overall (14 RCTs, I^2=0%, p=0.033)</strong></td>
<td><strong>1.14 (1.01, 1.28)</strong></td>
<td><strong>484/7546</strong></td>
<td><strong>422/7507</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

More oxygen better: 0.2, 0.5, 1, 2, 5
More oxygen worse:
Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial

Pierre Asfar, Frédérique Schortgen, Julie Boisramé-Helms, Julien Charpentier, Emmanuel Guérot, Bruno Megarbane, David Grimaldi, Fabien Grelon, Nadia Anguel, Sigismond Lasocki, Matthieu Henry-Lagarrigue, Frédéric Gonzalez, François Legay, Christophe Guittton, Maleka Schenck, Jean Marc Doise, Jérôme Devaquet, Thierry Van Der Linden, Delphine Chatellier, Jean Philippe Rigaud, Jean Dellamonica, Fabienne Tamion, Ferhat Meziani, Alain Mercat, Didier Dreyfuss, Valérie Seeers, Peter Radermacher, for the HYPERS2S Investigators* and REVA research network

Lancet Resp Med 2017;5:180-190
Asfar 2017

- 2x2 factorial RCT
- Patients: French adults with septic shock (n=442)
- Interventions
  - Fluids: 3% vs 0.9% NaCl x72h
  - Oxygen: $\text{FiO}_2$ 100% vs target $\text{SpO}_2$ 88-95% x24h
- Outcome: mortality at 28d
- Stopped early for harm with liberal oxygen
Asfar 2017

At 28 days: HR 1.27 (95% CI 0.94-1.72); p=0.12
At 90 days: HR 1.23 (95% CI 0.93-1.63); p=0.16

Number at risk
Normoxia 217 140 129 127
Hyperoxia 217 125 116 113
Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial

Massimo Girardis, MD; Stefano Busani, MD; Elisa Damiani, MD; Abele Donati, MD; Laura Rinaldi, MD; Andrea Marudi, MD; Andrea Morelli, MD; Massimo Antonelli, MD; Mervyn Singer, MD, FRCA
Girardis 2016

- Patients: Italians in a medical/surgical ICU (n=480)
- Interventions (mean ICU LOS 6d):
  - \( \text{PaO}_2 \) up to 150 or \( \text{SpO}_2 \) 97-100%
  - \( \text{PaO}_2 \) 70-100 or \( \text{SpO}_2 \) 94-98%
- Outcomes: ICU mortality
- Stopped early for earthquake
Figure 2. Probability of Survival From Study Inclusion (Day 0) Through Day 60 for Patients in the Conservative and Conventional Oxygen Strategy Groups

No. at risk
Conservative oxygen therapy: 216, 201, 188, 181, 173, 170, 169
Conventional oxygen therapy: 218, 189, 172, 163, 158, 152, 152

Log-rank $P = .02$
Should Stroke Victims Routinely Receive Supplemental Oxygen?
A Quasi-Randomized Controlled Trial

Ole Morten Rønning, MD; Bjørn Guldvog, MD, PhD
Rønning 1999

- Patients: Norwegians with stroke (n=550)
- Interventions (x24 hr):
  - FiO$_2$ 100%
  - Room air
- Outcomes: 1-year survival
- Not stopped early!
Figure 2. Kaplan-Meier estimated time of survival, by treatment group (n=550). The solid line indicates the oxygen group; the dashed line, the control group.
Mortality at Longest-Follow-up

Funnel plot with pseudo 95% confidence limits

Egger’s test, $P = 0.831$
Discussion

- Not driven by one study or one treatment setting
- No subgroup differences (surgical vs medical, ICU vs non-ICU)
- Robust to sensitivity analyses
- Major threat to validity: reporting bias (of meta-analyses, not primary studies)
Further studies

#ICUROXtrial has finished as of right now.

Patient #1000 enrolled at Austin Hospital. #1 recruiter DCCM, Auckland.

Thanks very much RCs, PIs, patients, @DianeMackle @ANZICS_CTG

4:05 PM - 28 May 2018
Improved oxygen therapy on the way for the sickest of the sick. Less than 2000 ICU pt's to go in #HOTICU trial @CRIC_Int_Care
cric.nu/hot-icu/
Take home

- Don’t use more oxygen that you have to
- Every once in a while, a meta-analysis actually can make chicken salad out of chicken 💩💩💩💩
- Encourage your residents. They’re smarter than you
- We need more large pragmatic trials in the inpatient GIM setting
Thank you

On behalf of The Improving Oxygen Therapy in Acute-illness [IOTA] GUIDE group

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Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Chu, Derek K et al. The Lancet, Volume 391, Issue 10131, 1693-1705
Additional Slides
“This systematic review and meta-analysis of more than 16 000 acutely ill adults provides high-quality evidence that liberal supplemental oxygen is harmful.”

See Articles page 1693
Definitions

- **Liberal oxygen strategy:**
  - The treatment arm with the higher oxygen target (measured in any one of fraction of inhaled oxygen ($\text{FiO}_2$), arterial partial pressure of oxygen [$\text{PaO}_2$], arterial oxygen saturation [$\text{SaO}_2$], or arterial oxygen saturation measured by a pulse oximeter [$\text{SpO}_2$])

- **Conservative oxygen strategy:**
  - The arm with the lower oxygen target (including room air)
Inclusion & Exclusion

- Inclusion criteria:
  - RCT enrolling acutely ill adults, comparing liberal versus conservative oxygenation strategies, and reporting an outcome of interest

- Exclusion criteria:
  - Studies limited to patients with chronic respiratory diseases, psychiatric disease, extracorporeal life support, hyperbaric oxygen therapy, elective surgery, patients less than 18 years of age, and pregnant patients
  - Observational and preclinical studies.
  - Studies solely comparing different oxygen delivery modalities (e.g. nasal prongs vs. facemask).
Mechanisms of Harm

Adapted from Sepehrvand, N. et al., 2016

- Hyperoxia
  - Permeability edema
  - ROS Production
- CNS Toxicity
- Cerebral blood flow
- Cell Damage/death
- Vasoconstriction
- Atelectasis
- BP
- afterload
- CO
- Coronary blood flow (↓10-30%)

(Adapted from Sepehrvand, N. et al., 2016)
Oxyhemoglobin Curve

(Haldane effect: $O_2$ displaces $CO_2$ from Hb)

(Bohr effect: $CO_2$, ↓ pH)

↑ pH
↓ DPG
↓ Temp

↑ pH
↑ DPG
↑ Temp

Oxyhaemoglobin (% Saturation)

PO$_2$ (mmHg)
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<td>Interaction, p = 0.97</td>
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Sensitivity Analysis

1. Worst-case or various plausible scenarios for missing participants
2. Disregarding excluded participants or those lost post-randomisation
3. Reweighing trials using fixed-effect analysis
4. Excluding unpublished trials
5. Excluding trials with data-driven early termination for apparent benefit or harm
6. Penalising trials terminated early by reducing their effect size
   1. About 30%
7. Using the more conservative Knapp-Hartung-Sidik-Jonkman random effects meta-analytic method
### 4. Subgroup and Sensitivity analyses (Risk Ratio displayed)

| Risk ratio (95%CI) | Mortality | Disability | | | | | |
|-------------------|-----------|------------|----------------|----------------|----------------|----------------|
|                   | Inhospital| 30 days    | Longest F/U    | Odds ratio     | Infections     | HAP            | LOS (days)    |
| High (1.28)       | (0.56-2.91) | (0.95-1.57) | (0.95-1.39)    | (0.17-9.47)    | (0.91-1.16)    | (0.69-1.37)    | -0.51 (-1.36 to 0.34) |
| Low (1.20)        | (1.00-1.43) | (0.93-1.27) | (0.96-1.19)    | (0.75-0.46)    | (0.18-0.46)    | (21.94)        | 0.02 (-0.44 to 0.47) |
| Interaction       | P=0.88    | P=0.43     | P=0.53         | P=0.84         | P=0.23         | P=0.56         | P=0.29        |

#### Subgroup analyses

- **Risk of Bias subgroup analysis**
  - **High**
    - Inhospital: 1.28 (0.56-2.91)
    - 30 days: 1.22 (0.95-1.57)
    - Longest F/U: 1.15 (0.95-1.39)
    - Odds ratio: 1.26 (0.17-9.47)
    - Infections: 1.03 (0.91-1.16)
    - HAP: 0.97 (0.69-1.37)
    - LOS: -0.51 (-1.36 to 0.34)
  - **Low**
    - Inhospital: 1.20 (1.00-1.43)
    - 30 days: 1.09 (0.93-1.27)
    - Longest F/U: 1.07 (0.96-1.19)
    - Odds ratio: 1.12 (0.75-0.46)
    - Infections: 0.75 (0.46-0.46)
    - HAP: 2.00 (0.18-0.46)
    - LOS: 0.02 (-0.44 to 0.47)

- **Interaction**
  - P=0.88
  - P=0.43
  - P=0.53
  - P=0.84
  - P=0.23
  - P=0.56
  - P=0.29

#### Admission type subgroup analysis

- **Medical**
  - Inhospital: 1.22 (1.03-1.43)
  - 30 days: 1.15 (1.02-1.29)
  - Longest F/U: 1.10 (1.01-1.20)
  - Odds ratio: N/A
  - Infections: 1.03 (0.92-1.15)
  - HAP: 1.08 (0.79-1.48)
  - LOS: 0.07 (-0.48 to 0.62)

- **Surgical**
  - Inhospital: 0.89 (0.15-5.28)
  - 30 days: 0.39 (0.11-1.41)
  - Longest F/U: 0.46 (0.13-1.39)
  - Odds ratio: N/A
  - Infections: 0.50 (0.36-0.69)
  - HAP: 0.54 (0.22-1.31)
  - LOS: 0.64 (-1.42 to 0.14)

- **Interaction**
  - P=0.73
  - P=0.10
  - P=0.12
  - N/A
  - P<0.0001
  - P=0.15
  - P=0.14

#### Delivery method subgroup analysis

- **Nasal prongs**
  - Inhospital: 1.15 (0.86-1.55)
  - 30 days: 1.07 (0.88-1.29)
  - Longest F/U: 1.08 (0.94-1.23)
  - Odds ratio: 1.02 (0.93-1.12)
  - Infections: 0.99 (0.87-1.13)
  - HAP: N/A
  - LOS: -0.10 (-1.20 to 1.00)

- **Face mask**
  - Inhospital: 1.32 (0.78-2.22)
  - 30 days: 1.10 (0.67-1.83)
  - Longest F/U: 1.08 (0.82-1.43)
  - Odds ratio: 1.23 (0.82-1.43)
  - Infections: 1.36 (0.82-2.23)
  - HAP: 2.00 (0.18-21.94)
  - LOS: 0.04 (-0.18 to 0.26)

- **Invasive mechanical ventilation**
  - Inhospital: 1.22 (0.95-1.56)
  - 30 days: 1.22 (1.02-1.46)
  - Longest F/U: 1.17 (0.97-1.37)
  - Odds ratio: 0.28 (0.11-0.47)
  - Infections: 0.77 (0.47-1.37)
  - HAP: 0.97 (0.69-1.37)
  - LOS: -1.33 (-2.56 to -0.10)

- **Interaction**
  - P=0.90
  - P=0.59
  - P=0.74
  - P=0.22
  - P=0.29
  - P=0.56
  - P=0.10

**Similar results if nasal prongs and face mask subgroups collapsed**
Trial Characteristics

• 43% of critical illness and sepsis admitted for a surgical diagnosis

• Ten of 25 trials excluded patients with baseline hypoxemia

• Median follow-up: three months

• Liberal oxygen supplementation: median FiO₂ 0.6 for median of 8 hours

• Conservative supplementation: median FiO₂ 0.21

• 18 RCTs at low risk of bias & 7 at high risk of bias
  Primarily due to data driven early termination
  • 1 RCT for quasi-randomization
  • 1 RCT for missing outcome data
SSI

- The CDC guideline in JAMA (August 2017) and WHO guideline in the Lancet (December 2016)
  - For patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation, administer increased FIO2 during surgery and after extubation in the immediate postoperative period.
    - (Category IA–strong recommendation; moderate-quality evidence.)
  - …adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen (FiO2) intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h, to reduce the risk of SSI
    - (strong recommendation, moderate quality of evidence)
CDC
- 2/13 acute surgery

Primarily driven by elective or mixed acuity surgeries (15 RCTs)
- 13 of these RCTs are made of elective surgeries, C-section, and mixed acuity surgery (>80% participants receiving elective surgery)

Database search up to 2014
- Many large scale RCTs were published after this date which were not included in this search

All records included in the guideline were captured by our search strategies
- But included only emergent surgeries:
  - Bickel
  - Schietroma 2016
• Subgroup in our study:
  • Liberal oxygen therapy was associated with a decreased risk of infection among emergency surgical patients (low quality)

• The PROXI trial (n=1400):
  • Mixed acuity
  • Similar rates of SSI
  • Increased mortality at 30 days

• Needs high quality evidence for effects of liberal oxygen strategy in surgical patients – esp. urgent and emergent surgeries
Meyhoff 2009

- 14 Hospitals in Denmark, N = 1386 intention to treat analysis
- Acute or elective laparotomy
- Indications: (# of patients/1386)
  - Cancer: 714 (51.5%), Benign neoplasm: 108 (7.8%)
  - Appendicitis: 121 (8.7%)
  - Intestinal obstruction due to benign disease: 124 (8.9%)
  - Inflammatory bowel disease: 79 (5.7%)
  - Diverticulitis: 57 (4.1%)
  - Other: 183 (13.2%)

- Mortality: at 30 days
  - Intervention: 30/685 (4.4%)
  - Control: 20/701 (2.9%)
  - p=0.15

- SSI
  - Intervention: 122/555 (22.0%)
  - Control: 116/526 (22.1%)
  - p=0.98
Further Results

- No other significant morbidity outcome differences observed
- Absolute risk increase for in-hospital mortality 1.1%
- Threshold of harm *may* span the SpO₂ range of 94-96%
- Possible dose response relationship with incremental increase in SpO₂ translating into increase in mortality
- Robust to sensitivity analyses & supported by TSA and survival curve
- No significant other subgroup differences:
  - Study population by diagnosis (MI vs. Stroke vs. ICU)
  - Oxygen delivery method (Mechanical ventilation vs Non-mechanical ventilation)
In-Hospital Mortality, 19 RCTs, Overall (I² = 0%, p = 0.020) 1.21 (1.03, 1.43) 283/7555 227/7516

30-day Mortality, 14 RCTs, Overall (I² = 0%, p = 0.033) 1.14 (1.01, 1.28) 484/7546 422/7507

Mortality at Longest Follow-up, 23 RCTs, Overall (I² = 0%, p = 0.044) 1.10 (1.00, 1.20) 828/7897 749/7857

More oxygen better

More oxygen worse