QUESTION

Should Low FiO2 vs. High FiO2 be used for Pre-Term Neonatal Resuscitation?

POPULATION:	Pre-Term Neonatal Resuscitation
INTERVENTION:	Low FiO2
COMPARISON:	High FiO2
MAIN OUTCOMES:	Mortality - RCT Short-term Mortality; Mortality (RCT)- Long-Term Mortality (1-3 Years); Mortality - Cohort Short-term Mortality; Mortality - Cohort Long-Term Mortality (1-3 years); Neurodevelopmental Impairment - RCT NDI (1-3 Years); Neurodevelopmental Impairment - Cohort NDI (1-3 Years); Retinopathy of Prematurity - RCT RoP; Retinopathy of Prematurity - Cohort RoP; Necrotizing Enterocolitis - NEC RCT; Necrotizing Enterocolitis - NEC Cohort; Major intra-ventricular hemorrhage (grade III/IV) - IVH RCT; Major intra-ventricular hemorrhage (grade III/IV) - IVH Cohort; Bronchopulmonary Dysplasia - BPD RCT; Bronchopulmonary Dysplasia - BPD Cohort;
SETTING:	Delivery Room
PERSPECTIVE:	Patient
BACKGROUND:	Important issue that effects large numbers of infants worldwide each year.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ○ Trivial
- ○ Varies
- ● Don't know

RESEARCH EVIDENCE

Outcomes	With High FiO2	With Low FiO2	Difference	Relative effect (95% CI)
Mortality - RCT Short-term Mortality	87 per 1,000	**72 per 1,000** (44 to 119)	**15 fewer per 1,000** (44 fewer to 32 more)	**RR 0.83** (0.50 to 1.37)

ADDITIONAL CONSIDERATIONS

For the all the important outcomes assessed in the meta analyses of RCTs, the 95% confidence intervals of relative risks (RR) were wide enough to include both potential harm as well as potential benefit. Furthermore, the direction of effect differs between outcomes. Therefore, it is unclear whether the intervention of interest (initial low oxygen concentration) has any undesirable effect.

Mortality (RCT)-Long-Term Mortality (1-3 Years)	104 per 1,000	**109 per 1,000** (33 to 352)	**5 more per 1,000** (71 fewer to 248 more)	**RR 1.05** (0.32 to 3.39)
Neurodevelopmental Impairment - RCT NDI (1-3 Years)	192 per 1,000	**219 per 1,000** (150 to 321)	**27 more per 1,000** (42 fewer to 129 more)	**RR 1.14** (0.78 to 1.67)
Retinopathy of Prematurity - RCT RoP	72 per 1,000	**53 per 1,000** (30 to 91)	**19 fewer per 1,000** (42 fewer to 19 more)	**RR 0.73** (0.42 to 1.27)
Necrotizing Enterocolitis - NEC RCT	35 per 1,000	**47 per 1,000** (22 to 100)	**12 more per 1,000** (13 fewer to 65 more)	**RR 1.34** (0.63 to 2.84)
Major intra-ventricular hemorrhage (grade III/IV) - IVH RCT	83 per 1,000	**79 per 1,000** (50 to 125)	**3 fewer per 1,000** (32 fewer to 42 more)	**RR 0.96** (0.61 to 1.51)
Bronchopulmonary Dysplasia - BPD RCT	267 per 1,000	**267 per 1,000** (190 to 374)	**0 fewer per 1,000** (77 fewer to 107 more)	**RR 1.00** (0.71 to 1.40)

a. The effect of initial FiO2 may vary based upon gestational age subgroups, and thus this combined analysis may not apply to each subgroup.
b. 95% CI of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect).
c. Four out of ten studies have high risk of "Blinding for patients and personnel". This risk influences the outcome.
d. The effect of initial FiO2 may vary based upon gestational age subgroups, and thus this combined analysis may not apply to each subgroup.
e. There is high heterogeneity among four studies (I2=81%).
f. 95% CI of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect).
g. High risk of "Incomplete outcome data" affect outcome.
h. The only included study that was a combination of 2 studies in two

	countries with very similar methods was scored as "unclear" risk of bias. i. There's only 1 study, there's no chance to find inconsistency. j. We have only one RCT and these results are the combination of 2 studies. 95% confidence intervals of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect). k. 95% confidence intervals of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect). l. Three out of seven have high risk of "Blinding for patients and personnel" and five out of seven have unclear of "Blinding for outcome assessor". The latter risk is strongly associated with outcome. m. Four out of eight have high risk of "Blinding for patients and personnel" and three out of eight have unclear of "Blinding for outcome assessor". The latter risk is especially strongly associated with outcome. n. 95% confidence intervals of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect). o. 95% confidence intervals of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect). p. Four out of seven have high risk for "Blinding for patients and personnel". q. Two out of eight have unclear for "Allocation concealment", three out of eight have high risk for "Blinding for patients and personnel", and two out of eight have unclear for "Blinding for assessor". These domains would lead to high risk of bias. r. There is moderate heterogeneity among seven studies (I2=47%). s. 95% confidence intervals of RR include both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) as well as 1.00 (absolute effect).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See research evidence for Undesirable Effects (above)	We considered the overall certainty of evidence as very low because, for the all the critical and important outcomes assessed in the meta_analyses of RCTs, there was serious risk of bias and very serious imprecision with very wide 95% confidence intervals for relative risks (RR). Therefore, there is potential for either benefit (RR = 0.73) or harm (RR = 1.35). However, evidence of effect in term infants and animal studies suggests harm when initial high oxygen is used.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Strand M, Simon W, Wyllie J, Wyckoff M, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. In: Pediatric Academic Societies Meeting: 2018 May 5-8; Toronto, Canada. Webbe J, et al. Parent, patient and clinician perceptions of outcomes during and following neonatal care: a systematic review of qualitative research BMJ Paediatrics Open 2018;2:e000343. doi:10.1136/bmjpo-2018-000343	Mortality and neurodevelopmental impairment were deemed critical by the neonatal task force and a larger group of neonatal resuscitation experts who ranked the importance of the outcomes (see abstract). In addition, parents emphasize the importance of these outcomes (see Strand et al and Webbe et al.).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Low initial oxygen for resuscitation of term and late preterm newborns is the intervention for this PICOST and reduces the critical outcome of mortality.	The systematic review found no difference in any critical or important outcomes assessed in the meta-analysis of all RCTs. We place value on not exposing preterm newborns to additional oxygen without proven benefit. Animal and human data demonstrate that hyperoxia can cause injury to the lungs, eyes, and brain in newborns.

Outcomes	With High FiO2	With Low FiO2	Difference	Relative effect (95% CI)
Mortality - RCT Short-term Mortality	87 per 1,000	**72 per 1,000** (44 to 119)	**15 fewer per 1,000** (44 fewer to 32 more)	**RR 0.83** (0.50 to 1.37)

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Although there are no published cost data, it is likely that use of low FiO2 compared to high FiO2 does not use any additional resources.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No data available	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No data available	Although there are no published cost data, it is likely that use of low FiO2 compared to high FiO2 does not add cost. In highly resourced delivery populations, regardless of the starting oxygen concentration, the cost of pulse oximetry, blenders, and gas lines would be the same whether low or high FiO2 is used initially. True cost effectiveness cannot be calculated as there is no cost information or long-term outcome data.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No data	Because none of these studies have been done in low resourced settings we cannot determine the impact of initial low oxygen on health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Oei JL, Ghadge A, Coates E, Wright IM, Saugstad OD, et al. Clinicians in 25 countries prefer to use lower levels of oxygen to resuscitate preterm infants at birth. Acta Paediatr. 2016 Sep;105(9):1061-6. doi: 10.1111/apa.13485. Epub 2016 Jun 24. PubMed PMID: 27228325.	We acknowledge that there is unease in the neonatal community as to what the balance of benefits and harms is of low versus high initial oxygen. Reasons include 1. the very low level of evidence 2. the initial FiO2 is only one small component of the stabilization of the preterm newborn. 3. whilst there is a general view that very high FiO2 is more likely to be harmful, the optimal starting FiO2 for most preterm infants is unknown. The optimal starting FiO2 for most infants could lie between the levels studied in the clinical trials. An international survey demonstrated that the majority of respondents are currently avoiding a high oxygen strategy during preterm newborn stabilization (Oei et al.).

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Use of 21-30% is feasible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We **suggest** starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence).

Justification

Balancing the benefits and serious potential harm of low versus high oxygen concentrations in neonatal care is a ubiquitous concern, particularly for preterm infants as decades of research demonstrate that oxygen exposure is a determinant of critical neonatal outcomes in preterm infants. Concern remains that the oxygen concentrations to which preterm infants are first exposed if they need resuscitation immediately after birth may be a critical contributor to outcomes regardless of subsequent oxygen exposure. Both parents and clinicians rate the outcomes assessed in this systematic review as either critical or important. For all the critical outcomes assessed in the meta-analyses of RCTs, the 95% confidence intervals of relative risks were wide enough to include both potential harm as well as potential benefit. Thus, it is unclear whether initial low (or high) oxygen concentrations may have undesirable effects. In still suggesting to start with low oxygen concentrations, we place value on avoiding exposure of preterm babies to additional oxygen without proven benefit for critical or important outcomes, as we are cognizant of harms in preterm animals and increased neonatal mortality in term infants exposed to high initial O2 concentration.

We recognize that no studies have compared the safety or efficacy of commencing resuscitation in 21% versus intermediate concentrations such as 30% oxygen; however, nearly all preterm babies whose respiratory support was initiated with 21% oxygen subsequently received additional oxygen (30-40%) to meet empiric oxygen saturation targets. We emphasize that the included studies only measured the effect of varying initial inspired oxygen concentrations and were not designed to assess the safety or efficacy of different oxygen saturation targets.

The feasibility and acceptability among clinicians of initiating resuscitation with 21-30% oxygen has been demonstrated: most respondents to a recent international survey were already avoiding a high initial oxygen concentration strategy (such as 100% oxygen) during preterm newborn resuscitation and stabilization. Although there are no published economic analyses, it is likely that use of low FiO2 does not add cost. In well-resourced perinatal care settings, the cost of pulse oximetry, blenders, and gas lines would probably be the same regardless of the initial oxygen concentration. However, in poorly resourced settings, it is the availability of human resources, gases, and equipment that will determine the immediate financial impact of this suggestion/recommendation. The overall cost-effectiveness of this suggestion/recommendation cannot currently be estimated as there is no evidence in relation to long-term outcomes and their cost.

Subgroup considerations

Very few of the very lowest gestation age infants (22-23 weeks EGA) have been included in any studies

Implementation considerations

21% oxygen is available everywhere. Where resources permit, compressed air and oxygen source, blender and pulse oximeter should be available to guide adjustments in oxygen concentration

Monitoring and evaluation

Whenever an intervention that impacts critical outcomes is introduced, monitoring of process and outcomes is encouraged.

Research priorities

- As the 95% CI for the primary outcome includes both harm and benefit, further, high quality studies are needed to determine the effect size more precisely.
- Need long term NDI outcomes from more randomized studies.
- Current studies have not adequately addressed the possible oxygen requirements for specific gestational age groups
- Oxygen targets for preterm infants remain unknown
- How to best titrate oxygen in the delivery room for preterm infants is unknown
- Information regarding how cord clamping management impacts oxygen use following birth is needed