QUESTION

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

POPULATION:	Term Neonatal Resuscitation
INTERVENTION:	Low FiO2
COMPARISON:	High FiO2
MAIN OUTCOMES:	Mortality - Short-term Mortality; Neurodevelopmental Impairment - Long-Term NDI (1-3 Years); Hypoxic-Ischemic Encephalopathy (Sarnat Grade II/III) - HIE (Grade II/III);
SETTING:	Delivery Room
PERSPECTIVE:	Patient
BACKGROUND:	The last ILCOR analysis of initial oxygen use for term neonatal resuscitation was completed in 2010 before the adoption of the GRADE methodology for ILCOR reviews. The question of the what oxygen concentration to start resuscitation following birth impacts an enormous number of lives 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

The pooled estimate for short term mortality demonstrated a reduction with 21% oxygen compared to 100% for initiation of resuscitation RR=0.73. 95%CI 0.57-0.94, I2=0% . NNT=22.

Outcomes	With High FiO2	With Low FiO2	Difference	Relative effect (95% CI)
Mortality - Short-term Mortality	170 per 1,000	**124 per 1,000** (97 to 159)	**46 fewer per 1,000** (73 fewer to 10 fewer)	**RR 0.73** (0.57 to 0.94)

ADDITIONAL CONSIDERATIONS

No undesirable effects from initial use of lower oxygen identified. Large undesirable effect on short term mortality from use of higher initial oxygen.

Mostly babies in under-resourced regions studied, long term follow-up isn't very long or detailed, and loss to follow up in the available studies impacts our confidence that we know all desirable or undesirable effects.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

○ Very low
● Low
○ Moderate
○ High
○ No included studies

RESEARCH EVIDENCE

From the GRADE evidence table, our certainty is low for our primary outcome of mortality and secondary outcome of HIE. Our certainty is very low for the outcome of long term NDI.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Low FiO2	With Low FiO2	Difference		
Mortality - Short-term Mortality № of participants: 1469 (7 RCTs)	**RR 0.73** (0.57 to 0.94)	Study population			⨁⨁◯◯ LOW[a,b,c]	
		17.0%	**12.4%** (9.7 to 15.9)	**4.6% fewer** (7.3 fewer to 1 fewer)		
Neurodevelopmental Impairment - Long-Term NDI (1-3 Years) № of participants: 360 (2 RCTs)	**RR 1.41** (0.77 to 2.60)	Study population			⨁◯◯◯ VERY LOW[d,e,f]	
		8.9%	**12.5%** (6.8 to 23.0)	**3.6% more** (2 fewer to 14.2 more)		

ADDITIONAL CONSIDERATIONS

The task force considered the certainty of evidence to be low due to

methodologic problems such as lack of allocation concealment, lack of blinding and risk of publicaton bias as well as insufficient numbers studied to reach optimal sample size. Also the studies were done in populations or settings in which pulse oximetry and titration were not available and may not be generalizable to all settings.

Hypoxic-Ischemic Encephalopathy (Sarnat Grade II/III) - HIE (Grade II/III) № of participants: 1359 (5 RCTs)	**RR 0.90** (0.71 to 1.14)	Study population			⊕⊕◯◯ LOW[g,h,i]	
		19.6%	**17.7%** (13.9 to 22.4)	**2.0% fewer** (5.7 fewer to 2.7 more)		

a. Five out of seven studies have a high risk of "Allocation sequence", "Allocation concealment", and "Blinding". These domains may influence the outcome.
b. Total number of patients (1469) include in the SR was less than OIS (2146).
c. The funnel plot was not symmetric. This would be an indication for publication bias.
d. The funnel plot was not symmetric. This would be an indication for publication bias.
e. 95% CI of RR included both benefit and harm (RR of under 0.75 or over 1.25 as a rough guide) would downgrade.
f. Both studies have high risk of "Allocation sequence", "Allocation concealment", and "Blinding". NDI should be ideally assessed by a blinded assessor but "Blinding of data collectors" was unclear. And the follow-up rate (Saugstad 2003) was extremely low (only approximately 2/3 of patients).
g. All studies have the high risk of "Allocation concealment" and "Blinding" affecting the outcome.
h. 95% CI includes 1,0 (absolute effect) although CI relatively narrow.
i. The funnel plot was not symmetric. This would be an indication for publication bias.

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-	Mortality, Neurodevelopment Impairment and HIE 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.

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Balance of effects

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

JUDGEMENT

○ 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

RESEARCH EVIDENCE

Low initial oxygen for resuscitation of term and late preterm newborns is the intervention for this PICOST and reduces the critical outcome of mortality.

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
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a. Five out of seven studies have a high risk of "Allocation sequence", "Allocation concealment", and "Blinding". These domains may influence the outcome.
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c. The funnel plot was not symmetric. This would be an indication for publication bias.

The comparator of 100% oxygen is associated with increased childhood cancer, and more heart, kidney and brain injury after asphyxial injury (observational data not included in this systematic review) and increased oxidative stress markers.

ADDITIONAL CONSIDERATIONS

The large reduction in the primary outcome of short term mortality (NNT=22) with no demonstrated adverse effects when 21% oxygen is used favors its use, although the certainty of the evidence is low.

When you consider the additional observational evidence (not included in this review) of the association of delivery room oxygen exposure and increased childhood cancer, worse heart, kidney and neurologic injury after asphyxial brain injury and increased evidence of oxidative stress, the possible harms from 100% also tip the balance in favor of starting with 21% oxygen.

	Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA. Childhood cancer following neonatal oxygen supplementation. *J Pediatr.* 2005;147(1)27-31. Naumburg E, Bellococco R, Cnattingius S, et al. Supplementary oxygen and risk of childhood lymphatic leukemia. *Acta Paediatr.* 2002;91(12):1328-33 Vento M, Sastre J, Asensi MA et al. Room-air resuscitation causes less damage to heart and kideny than 100% oxygen. *Am J Respir Crit Care Med.* 2005;172(11)1393-1398. Kapadia VS, Chalak LF, DuPont TL, et al. Perinatal asphyxia with hyperoxemia within the first hour of life is associated with moderate to severe hypoxic-ischemic encephalopathy. *J Pediatr.* 2013;163(4):949-954. Vento M, Asensi M, SatreJ, et al. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. J Pediatr. 2003;142(3):240-246.	

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	No published studies on air versus 100% oxygen costs.	Although there is no published cost data, common sense would suggest use of 21% oxygen (air) alone does not add cost. In fact there would likely be cost savings compared to 100% oxygen which mandates a compressed gas source.

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		Although there is no published cost data, common sense would suggest use of 21% oxygen alone does not add cost. In fact there would likely be cost savings compared to 100% oxygen which mandates a compressed gas source. Given the benefits at relatively no additional cost, the cost effectiveness likely favors initiaton of resuscitation with 21% oxygen. In a highly resourced delivery populations, regardess of the starting oxygen concentration, the cost of pulse oximetry, blenders and gas lines would be the same whether you used either 21% or 100%. True cost effectiveness can not be calculated as we don't have cost information or long term outcome data

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced		Use of initial 21% oxygen for resuscitation is available in

○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		resource limited areas. Much of the data came from resource limited settings and showed benefit in reducing mortality. There are plausible reasons to anticipate that using 21% oxygen compared to 100% oxygen is of greater benefit in low resource settings.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Use of 21% oxygen for initiation of resuscitation in term and late preterm newborns has been well accepted in the neonatal community since 2005 in Europe and Canada and the rest of the world since 2010.

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% oxygen is feasible as it is available everywhere. For deliveries in highly resourced regions, implementation of initiaton of resuscitation with 21% oxygen and subsequent titration to meet saturation goals requires separate gas lines, blenders, and pulse oximetry to meet saturaton goals. This would also be needed if 100% was used initially.

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

	JUDGEMENT						
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

For term and late preterm newborns (≥ 35 weeks gestation) receiving respiratory support at birth, we **suggest** starting with 21% oxygen (**weak** recommendation, low certainty evidence). We **recommend against** starting with 100% oxygen (**strong** recommendation, low certainty evidence).

Justification

Parents and clinicians rate mortality as a critical outcome. Despite low certainty of the evidence, the large reduction in the primary outcome of short term mortality (NNT=22) with no demonstrated adverse effects favors use of 21% oxygen as the initial gas for resuscitation in term and late preterm newborns. Although there are no published cost data, it is likely that initiating resuscitation with 21% oxygen does not add cost and might result in cost savings compared to initial 100% oxygen in some settings. Babies born in low resource settings are disadvantaged by increased mortality and morbidity. Therefore, it is plausible that using 21% oxygen compared to 100% oxygen has greater impact in low resource settings. Use of 21% oxygen for initial resuscitation is universally feasible and is now accepted by the neonatal community world-wide.

Subgroup considerations

Relatively few late preterm (35-36 week gestation) infants were included in the studies. The confidence in our recommendations for this gestational age group is low.

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

KNOWLEDGE GAPS

There were relatively few late preterm (35-36 week gestation) infants in the studies. The confidence in our recommendations for this gestational age group is low. More studies are needed regarding this population

Does titration of oxygen to SpO2 targets impact conclusions?

Need data comparing intermediate oxygen concentrations

Does delayed cord clamping have any effect on the impact of oxygen exposure?