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| Question |
| **Oxygenation strategy after return of spontaneous circulation (ROSC) in children with cardiac arrest** |
| **Population:** | Children with cardiac arrest in any setting who have attained ROSC |
| **Intervention:** | A specific oxygenation strategy |
| **Comparison:** | An alternative oxygenation strategy or no specific oxygenation strategy |
| **Main outcomes:** | Survival to hospital discharge, 3 months or longer; survival to hospital discharge, 3 months or longer with favorable neurologic outcome. |
| **Setting:** | Pre-hospital or in the hospital setting |

# ASSESsment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest in children is a high morbidity and mortality event, and neurologic injury is common in those who do survive. Both hypoxemia and hyperoxia have been thought to possibly be associated with worse outcome in post-arrest patients previously. Hypoxemia may worsen ischemic brain injury and injury to other organs, while hyperoxia may lead to increased oxidative stress and organ damage after reperfusion. Several new adult studies, both observational and randomized trials, have been published since this topic was last updated in 2015. There have been no pediatric studies investigating this question since 2015. |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○  Small○  Moderate○ Large○ Varies●  Don't know | The three pediatric studies {Del Castillo 2012, Bennet 2013, Van Zellem 2015} deemed to have only serious risk of bias all found no significant association between hyperoxia and outcomes. Only one of these {Del Castillo 2012} looked at hypoxia, and also found no association with outcome. One larger registry-based study {Ferguson 2012} did find that hyperoxia was associated with higher mortality, but although this study was much larger than the others it was deemed at critical risk of bias. This was due to high concern for both residual confounding due to the lack of adjustment for cardiac arrest characteristics, and selection bias. There is therefore no convincing evidence from clinical studies demonstrating harm from hyperoxia in children. The evidence on the effect of hyperoxia on survival and neurologic outcome in adults is very mixed, with many inconsistencies in methodology and results across studies. Randomized trials done in adults to date are very small and the observational studies are all at serious or critical risk of bias. Within these limitations studies have reported a mix of positive and negative results, leaving true uncertainty. Randomized trials and observational studies have generally found either no effect or a possible benefit from normoxia compared to hyperoxia. The recent adult RCT that included a subgroup of post-arrest patients (larger than any of the RCTs done previously) found a benefit in the conservative (lower) oxygen group. GRADE TABLES FOR LOWER OXYGEN STRATEGY COMPARED TO HIGHER OXYGEN STRATEGY IN THE ICU (all studies are in adults, downgraded additionally for indirectness for pediatrics)

| **№ of studies** | **Study design** | **lower % oxygen** | **higher % oxygen** | **Relative(95% CI)** | **Absolute(95% CI)** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Survival to discharge-Young** |
| 1  | randomised trials  | 4/8 (50.0%)  | 4/9 (44.4%)  | **RR 1.13**(0.41 to 3.08)  | **58 more per 1,000**(from 262 fewer to 924 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **Survival to discharge-Jakkula** |
| 1  | randomised trials  | 43/61 (70.5%)  | 39/59 (66.1%)  | **RR 1.07**(0.84 to 1.36)  | **46 more per 1,000**(from 106 fewer to 238 more)  | ⨁⨁◯◯LOW  | CRITICAL |
| **3 month survival-ICU-ROX** |
| 1  | randomised trials  | 49/86 (57.0%)  | 32/78 (41.0%)  | **RR 1.39**(1.01 to 1.92)  | **160 more per 1,000**(from 4 more to 377 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **Discharge to home-Young**  |
| 1  | randomised trials  | 2/8 (25.0%)  | 4/9 (44.4%)  | **RR 0.56**(0.14 to 2.29)  | **196 fewer per 1,000**(from 382 fewer to 573 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |
| **CPC 1-2 at 6 months-Jakkula** |
| 1  | randomised trials  | 42/61 (68.9%)  | 36/59 (61.0%)  | **RR 1.13**(0.87 to 1.47)  | **79 more per 1,000**(from 79 fewer to 287 more)  | ⨁⨁◯◯LOW  | CRITICAL |
| **Favorable GOSE at 6 months-ICU-ROX** |
| 1  | randomised trials  | 35/78 (44.9%)  | 23/72 (31.9%)  | **RR 1.40**(0.93 to 2.13)  | **128 more per 1,000**(from 22 fewer to 361 more)  | ⨁◯◯◯VERY LOW  | CRITICAL |

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| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial● Varies○  Don't know | Although the evidence is of low certainty, it is likely that the undesirable effects of hypoxia are significant. The undesirable effects on neurologic outcome of hyperoxia are very uncertain based on inconsistency of study results. |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ● Very low○ Low○ Moderate○ High○ No included studies |  The certainty of evidence varies across the included studies from very low to low (see tables and summary of observational data above).  |  |
| ValuesIs 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 | Survival with favorable neurologic outcome and survival are generally accepted as critical outcomes. |  |
| Balance of effectsDoes 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 | For hyperoxia, pediatric and adult studies generally show either association with harm or no association, but do not generally show association with benefit. The balance of evidence therefore slightly favors avoiding hyperoxia, although it should be noted that the only pediatric studies finding association with harm were deemed at critical risk of bias. For hypoxemia, limited evidence favors avoiding hypoxemia in adults, although this is not supported by data in pediatrics.  |  |
| Resources requiredHow 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 | We did not identify any studies evaluating the cost of an oxygen strategy targeting a specific/lower oxygen saturation. However, as it is the current standard of care to measure an oxygen saturation continuously in post-arrest, critically-ill patients, and since a titrated oxygen approach would lead the same or decreased oxygen use, it is likely that an intervention to avoid hyperoxia would not incur significant cost. For EMS systems, many are not equipped to titrate oxygen, so providing titratable systems would incur additional resource costs. |  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | We did not identify any studies specifically comparing resources including costs between the two interventions.  |  |
| Cost effectivenessDoes 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 | We did not identify any studies addressing cost-effectiveness.  |  |
| EquityWhat 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 | We did not identify any studies addressing health equity regarding this topic.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We have not identified any research that assessed acceptability, but these TRs do not include any substantial changes compared to 2015. | Although we did not identify any studies addressing acceptability, it is common practice to decrease FiO2 for other critically ill patients and would likely be acceptable to those treating post-arrest patients. The TR for carbon dioxide targets is also in line with current clinical practice for other critically ill patients.  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | Feasibility was not specifically addressed by this review. However, avoiding hyperoxia should be feasible in most ICU settings where patients are continually monitored. Decreasing FiO2 in the pre-hospital setting or in the immediate post-arrest period may be less feasible as oxygen saturations may be hard to obtain reliably.  |  |

# Summary of judgements

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | **Small** | Moderate | Large |  | Varies | **Don't know** |
| **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

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| 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

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| Recommendation |
| We suggest that rescuers measure PaO2 after ROSC and target a value appropriate to the specific patient condition. In the absence of specific patient data, we suggest rescuers target normoxemia after ROSC (weak recommendation, very-low-quality evidence). Given the availability of continuous pulse oximetry, targeting an oxygen saturation of 94-99% may be a reasonable alternative to measuring PaO2 and titrating oxygen when feasible to achieve normoxia. |

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| Justification |
|  One large observational study at critical risk of bias found harm associated with hyperoxia in children after cardiac arrest, and 3 much smaller studies at serious risk of bias found no association. Given the lack of association with benefit and the suggestion of possible harm, it seems most reasonable to avoid hyperoxia.  |

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| Subgroup considerations |
|  There is insufficient evidence to evaluate whether particular subgroups, such as children with chronic hypoxemia due to congenital heart disease, would benefit from a different oxygen target. |

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| Implementation considerations |
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| Monitoring and evaluation |
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| Research priorities |
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