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| Question | |
| **Should the presence of brain stem reflexes vs. none be used for predicting good neurological outcomes in children after cardiac arrest?** | |
| **Population:** | Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause. |
| **Intervention:** | brain stem reflexes present within 10 days after cardiac arrest |
| **Comparison:** | none |
| **Main outcomes:** | Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2. |
| **Study DESIGN** | Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created. |
| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022. |

# Assessment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | The presence of brain stem reflexes to predict good neurological outcome at intensive care unit or hospital discharge were evaluated in 2 studies [Brooks 2018 324, Topjian 2021 282] which including 118 patients. Evoked response to pain, gag reflex, and cough reflex were assessed at 6-12 hours, and 24h. Predictive sensitivity of presence of pain response at 6-12hours was 100% with a FPR of 67%. A present gag and cough reflex at 24h both predicted a good neurological outcome with a sensitivity of 40% and FPR of 32- 35%, respectively. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | A false positive prediction of a good outcome and continued treatment based on presence of brain stem reflex may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from medication, sedation and neuro-muscular blocking drugs, impairing brain stem assessment. |  |
| 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 | The certainty of evidence from brain stem reflexes is very low for predicting good neurological outcome because of the risk of bias, especially risk of confouding from concurrent medication (sedative drug) use and risk of self-fulfilling prophecy. |  |
| 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 | Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment.  We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest.  A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.  A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological outcome. |  |
| 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 | Considering the moderate sensitivity of brain stem reflex prediction, relatively low false positive rate at all time points but only one study evluating the test, the balance of effects neither favors for or against the use of the test for predicting good neurological outcome |  |
| 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 | Costs for the assessment of brain stem reflexes are negligible. However, no study assessed savings from prognostication based on brain stem reflexes have been included in our review. |  |
| 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 | We did not identify any studies assessing cost assessing of brain stem reflex test. |  |
| 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 | We did not identify any studies addressing cost-effectiveness. . |  |
| 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 | Considering the negligible costs of brain stem reflex testing, a problem of inequity is unlikely. |  |
| Acceptability Is 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 study assessing acceptability, but acceptability is likely. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of brain stem reflex test requires basic training of clinical neurological examination. No additional equipment is required and is therefore feasible in resource limited settings. |  |

# 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 cannot make a recommendation for or against the use of brainstem tests after ROSC for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very-low-certainty evidence).** |
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| Justification |
| The FPR was moderate to high in 2 studies (n=118) for predicting good neurological outcome using presence of brainstem reflexes. The predictive sensitivity of presence of pain response at 6-12h was 100% with a FPR of 67%. A present gag and cough reflex at 24h both predicted a good neurological outcome with a sensitivity of 40% and FPR of 32- 35%, respectively.  Inconsistency in specificity across timepoints raises concern about the heterogenity of studies, patient inclusion and accuracy of this prognostic test. This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions ( e.g. targeted temperature management) or to facilitate ventilation.  No studies reported any assessment of the confounding influence of medication on brain stem reflex test. No studies included blinding of test results from treating clinicians and no study had blinded outcome assessment.    None of the included studies specifically excluded the presence of residual sedation at the time coma score was assessed. Lack of blinding is a major limitation of brain stem reflex test, even if WLST based on coma score only has not been documented in any of the studies included in our review. |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| Brain stem reflex tests are easy clinical assessments; however, the examiner requires knowledge of basic neurological examination. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| Use of brain stem reflex testing, with blinding of test results and outcome from cllinicians making prognostic decisions requires assessment in the paediatric population. |

# References Summary