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| Question | |
| **Should absence of a benign (continuous) EEG pattern or presence of malignant background (attenuated or burst suppression) EEG pattern vs. presence or absence be used for predicting poor 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:** | Absence of a continuous or normal background EEG, or Presence of 1) attenuated, isoelectric or flat EEG background or 2) burst suppression, burst attenuation or generalized periodic epileptiform discharges (GPEDS) on EEG background |
| **Comparison:** | Absence of these features |
| **Main outcomes:** | Prediction of death or survival with poor neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of >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). |
| **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 Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded.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| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded.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 Aug 27th 2024. |

# 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, it has a low rate of survival and high chance of neurological injury. Prediction of 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 | **Absence of continuous or normal background EEG**  The absence of a normal/continuous EEG background pattern (defined as normal, continuous and reactive, continuous and unreactive, and nearly continuous by ACNS definitions1) was reported in 14 studies at 6 different time points, and included 563 patients.2-15 There was a wide variability of FPR and sensitivity reported across all timepoints for predicting poor neurological outcome. Only 4/14 studies identified a FPR <10%. The range of FPR across studies was 0-90%. Sensitivity ranged 7 to 96% with 4 studies having a sensitivity >90%. Overall, absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome.  **Presence of attenuated, isoelectric or flat EEG background**  The presence of an attenuated, isoelectric, or flat EEG was reported in 12 studies including up to 526 patients (although there was a risk of some patients appearing in multiple studies).2-15 In 7/9 studies, which reported prediction of poor neurological at 24 hours to 6 days, there was a FPR <10% (95%CI upper limit ranges 4-52%) and sensitivity of 18-58%.2-4,7-10 In 4/9 studies, the FPR was <1% (95%CI upper limit ranges 4-52%).3,4,9,10 At time points earlier than 24 hours, FPR was much higher (ranged 10-90%).6,7,13,14 Therefore, the absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome.  **Presence of burst suppression, burst attenuation or generalized periodic epileptiform discharges (GPEDS) on EEG background**  Presence of burst suppression, burst attenuation or GPEDS was reported in 7 studies including 395 patients.2,3,6,10,13-15 Prior to 24 hours, in 4 studies, the FPR ranged 0-19% and sensitivity 9-30%. From 24 hours onwards, the accuracy improved. A FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.3,11,15 Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours. |  |
| 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 poor outcome and discontinuing treatment based on electrophysiological tests may lead to inappropriate treatment withdrawal in a patient with a good neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from sedation and medication affects of electrophysiological parameters. |  |
| 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 clinical and electrophysiological tests is very low because of the risk of bias, lack of blinding, imprecision and 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).16 However, tools and definitions to measure poor neurological outcome in our studies were the PCPC >2 and >3, or >1 change in PCPC and the VABS II <70. Change from baseline neurological status may be more important than the neurological functional level, especially in infants and children with pre-existing neurological impairment.  We defined poor neurological outcome prediction as imprecise when the false positive rate (FPR) was >1%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. We defined the reliability of the evidence as reliable if the FPR was <1% and the upper 95% confidence intervals <10%) and moderately reliable if FPR was <1% with without a restriction on width of 95% confidence interval.  A low false positive rate means that a low proportion of patients, predicted to have a poor outcome will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). The task force felt that when focused on accuracy of predicting a poor outcome - a low false positive rate (e.g. <1%) is more desirable to avoid falsely pessimistic prediction than a high sensitivity. The cut off of <1% FPR (equivalent to 99% specificity) was chosen as the consequences of false pessimism is substantial. False pessimism may result in discontinuation of life sustaining therapy in a patient who will eventually have a good outcome.  Continuing treatment may involve increased resources; however, this may also allow more time for further prognostic evaluation and further additional tests. 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. |  |
| 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 | Overall, absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome. The absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome. However, for absence of burst suppression, burst attenuation or GPEDS a FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.3,11,15 Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours. |  |
| 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 | We did not identify any specific studies assessing costs of assessing background EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings. |  |
| 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 specifically assessing costs of performing continuous or intermittent electroencephalography for assessing background EEG. |  |
| 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 | The specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity. |  |
| 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 | Feasibility was not specifically addressed in any of the studies included in this review. Evaluating background EEG pattern on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day. |  |

# 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  (continuous or normal background EEG) | Conditional recommendation for either the intervention or the comparison  (presence of attenuated, isoelectric or flat EEG) | Conditional recommendation for the intervention  (presence of burst suppression, burst attenuation or GPEDs) | Strong recommendation for the intervention |
| ○ | **●** | **●** | **●** | ○ |

# Conclusions

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| Recommendation |
| * **We recommend that no single electrophysiology test be used in isolation to predict poor neurological outcome in children after cardiac arrest at any time point (strong recommendation, very-low certainty evidence).** * **Clinicians should consider using multiple tests in combination for poor neurological outcome prediction (good practice statement).** * **The presence of burst suppression, burst attenuation or GPEDs between 24-72 hours after ROC, had moderate reliability and may be considered as part of multi-modal testing to predict poor neurological outcome in children after cardiac arrest (good practice statement).** * **We suggest against using the following EEG features for predicting poor neurological outcome: absence of continuous or normal background EEG at any time point (weak recommendation, very-low-certainty evidence).** * **There was insufficient evidence to make a recommendation for or against the use of presence of attenuated, isoelectric or flat EEG to predict poor neurological outcome in children after cardiac arrest at any time point.** |
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| Justification |
| **Overall justification**  Overall, absence of a continuous EEG was an inaccurate and unreliable method for predicting poor neurological outcome. The absence of an attenuated, isoelectric, or flat EEG FPR was imprecise (at the FPR<1% cut off) in more than 50% of included studies to predict a poor neurological outcome. However, for absence of burst suppression, burst attenuation or GPEDS a FPR <1% (95%CI upper limit range 16-54%) was reported in 3 of 4 studies at 24, 48 and 72 hours with a sensitivity of 0-67%.3,11,15 Therefore, prediction of poor neurological outcome was moderately reliable from 24 to 72 hours.  **Detailed justification**  *Certainty of evidence*  None of the studies adjusted for the confounding effect of sedation or targeted temperature management on background EEG.  *Resources required*  Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.  *Equity*  Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.  The available scientific evidence had a high risk of bias based on high heterogeneity across studies, small number of studies and small number of patients included in addition to lack of blinding, variation in test assessment and performance, and variability in outcome measurement. Therefore, no meta-analysis was performed. Overall assessment of test performance was based on visual assessment of forest plots.  In addition to providing prognostic information, electrophysiology monitoring may allow identification of reversible events e.g. seizures. Treatment of seizures may prevent additional secondary injury following a hypoxic-ischemic insult. The role of electrophysiology monitoring was not assessed for this purpose.  American Clinical Neurophysiology Society (ACNS) definitions for background EEG patterns were followed in some studies. EEG and SSEP prognostic criteria require clear and reproducible definitions and require validation in the pediatric ICU environment. |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| Electrophysiology tests for prognostication after cardiac arrest appear promising but more research is required in infants and children.  More research is required on type of monitoring, intermittent or continuous EEG, use of reduced channel monitoring, quantitative EEG systems, duration and timing of prognostic assessment.  Validation of ACNS or other international definitions of EEG indices within the pediatric ICU environment for infants and children after cardiac arrest.  Further work on multi-modal prognostication, timing, definitions of testing, accurate outcome timing and definition.  We encourage wider research and consultation with patients, children, parents, guardians and caregivers, health care professionals and members of the wider society on understanding survivorship after pediatric cardiac arrest to inform correct definitions and framework of good neurological outcome for prediction research. Status epilepticus represents increased seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.  Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions. |

# References Summary

1. Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol*. 2021;38:1-29. doi: 10.1097/wnp.0000000000000806

2. Bach AM, Kirschen MP, Fung FW, Abend NS, Ampah S, Mondal A, Huh JW, Chen SL, Yuan I, Graham K, et al. Association of EEG Background With Diffusion-Weighted Magnetic Resonance Neuroimaging and Short-Term Outcomes After Pediatric Cardiac Arrest. *Neurology*. 2024;102:e209134. doi: 10.1212/wnl.0000000000209134

3. Brooks GA, Park JT. Clinical and Electroencephalographic Correlates in Pediatric Cardiac Arrest: Experience at a Tertiary Care Center. *Neuropediatrics*. 2018;49:324-329.

4. Ducharme-Crevier L, Press CA, Kurz JE, Mills MG, Goldstein JL, Wainwright MS. Early presence of sleep spindles on electroencephalography is associated with good outcome after pediatric cardiac arrest. *Pediatric Critical Care Medicine*. 2017;18:452-460.

5. Fink EL, Berger RP, Clark RSB, Watson RS, Angus DC, Richichi R, Panigrahy A, Callaway CW, Bell MJ, Kochanek PM. Serum biomarkers of brain injury to classify outcome after pediatric Cardiac Arrest\*. *Critical Care Medicine*. 2014;42:664-674.

6. Fung FW, Topjian AA, Xiao R, Abend NS. Early EEG Features for Outcome Prediction After Cardiac Arrest in Children. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*. 2019;36:349-357.

7. Kessler SK, Topjian AA, Gutierrez-Colina AM, Ichord RN, Donnelly M, Nadkarni VM, Berg RA, Dlugos DJ, Clancy RR, Abend NS. Short-term outcome prediction by electroencephalographic features in children treated with therapeutic hypothermia after cardiac arrest. *Neurocrit Care*. 2011;14:37-43. doi: 10.1007/s12028-010-9450-2

8. Kirschen MP, Licht DJ, Faerber J, Mondal A, Graham K, Winters M, Balu R, Diaz-Arrastia R, Berg RA, Topjian A, et al. Association of MRI brain injury with outcome after pediatric out-of-hospital cardiac arrest. *Neurology*. 2021;96:e719-e731.

9. Mazzio EL, Topjian AA, Reeder RW, Sutton RM, Morgan RW, Berg RA, Nadkarni VM, Wolfe HA, Graham K, Naim MY, et al. Association of EEG characteristics with outcomes following pediatric ICU cardiac arrest: A secondary analysis of the ICU-RESUScitation trial. *Resuscitation*. 2024;201:110271. doi: 10.1016/j.resuscitation.2024.110271

10. Ostendorf AP, Hartman ME, Friess SH. Early electroencephalographic findings correlate with neurologic outcome in children following cardiac arrest. *Pediatric Critical Care Medicine*. 2016;17:667-676.

11. Oualha M, Gatterre P, Boddaert N, Dupic L, De Saint Blanquat L, Hubert P, Lesage F, Desguerre I. Early diffusion-weighted magnetic resonance imaging in children after cardiac arrest may provide valuable prognostic information on clinical outcome. *Intensive Care Medicine*. 2013;39:1306-1312.

12. Smith AE, Ganninger AP, Mian AY, Friess SH, Guerriero RM, Guilliams KP. Magnetic resonance imaging adds prognostic value to EEG after pediatric cardiac arrest. *Resuscitation*. 2022;173:91-100. doi: doi:<https://dx.doi.org/10.1016/j.resuscitation.2022.02.017>

13. Topjian AA, Sanchez SM, Shults J, Berg RA, Dlugos DJ, Abend NS. Early Electroencephalographic Background Features Predict Outcomes in Children Resuscitated from Cardiac Arrest. *Pediatric Critical Care Medicine*. 2016;17:547-557.

14. Topjian AA, Zhang B, Xiao R, Fung FW, Berg RA, Graham K, Abend NS. Multimodal monitoring including early EEG improves stratification of brain injury severity after pediatric cardiac arrest. *Resuscitation*. 2021;167:282-288. doi: 10.1016/j.resuscitation.2021.06.020

15. Yang D, Ryoo E, Kim HJ. Combination of early EEG, brain CT, and ammonia level is useful to predict neurologic outcome in children resuscitated from cardiac arrest. *Frontiers in Pediatrics*. 2019;7:223.

16. Topjian AA, Scholefield BR, Pinto NP, Fink EL, Buysse CMP, Haywood K, Maconochie I, Nadkarni VM, de Caen A, Escalante-Kanashiro R, et al. P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) in Children: An Advisory Statement From the International Liaison Committee on Resuscitation. *Resuscitation*. 2021;162:351-364. doi: 10.1016/j.resuscitation.2021.01.023