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| Question |
| **Should one pharmacological strategy for seizure treatment vs. another pharmacological strategy or no seizure treatment be used for patients with ROSC after cardiac arrest?** |
| **Population:** | Children with ROSC after cardiac arrest |
| **Intervention:** | One strategy for prophylactic anti-seizure medication OR seizure treatment |
| **Comparison:** | Another strategy or no prophylactic anti-seizure medication OR seizure treatment |
| **Main outcomes:** | Good neurological outcome or survival as per Pediatric Core Outcome Set for Cardiac Arrest (1) |
| **Setting:** | In-hospital or out-of-hospital cardiac arrest |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | None declared |

# 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, both in the out-of-hospital and in-hospital setting, is relatively common and has a very high mortality, with hypoxic-ischemic brain injury as a common cause of death. Seizures including suspected clinical seizures, electroclinical and electrographic seizures with EEG correlation are common manifestations of post-cardiac arrest brain injury in children with approximate incidence of 10-40% (Brooks and Park, 2018, 324, Fung et al., 2019, 349, Abend et al., 2011, 141). Seizures and abnormalities on EEG post cardiac arrest are associated with poor neurological outcome in children (Fung et al., 2019, 349, Lin et al., 2020, 534, Ostendorf et al., 2016, 667, Topjian et al., 2016, 547). It is unclear if prophylactic anti-seizure medication to prevent seizures and treatment of seizures when they are identified improves outcome. There are no existing ILCOR recommendations for children.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | ***Prophylactic Anti-Seizure Medication***For the critical outcome of survival with favourable neurological outcome at discharge/30 days or longer, no pediatric RCTs nor non-randomized comparative studies were identified.Indirect evidence from adult patients was identified. For the critical outcome of survival with favourable neurological outcome at discharge; Two prospective RCTs (BRCT Study Group 1986, 397; Longstreth 2002 506)involving a total of 562 comatose adults post-arrest provided very low-certainty evidence (downgraded for risk of bias, indirectness and imprecision) of no benefit from prophylactic anti-seizure medication administration. For the BRCT study, good neurological outcome for treatment with thiopentone vs standard care (no prophylactic anti-seizure medication) had a RR of 1.3 [95% CI 0.76 to 2.21; 46 more survivors per 1,000 patients [95% CI from 37 fewer to 185 more). For the Longstreth study: for treatment with intravenous magnesium versus placebo, RR for improved outcome was 1.37 [95% CI 0.83 to 2.25]; 94 more survivors per 1,000 patients [95% CI from 43 fewer to 317 more]; for treatment with intravenous diazepam versus placebo, RR for improved outcome was 0.68 [95% CI 0.36 to 1.28]; 81 fewer survivors per 1,000 patients [95% CI from 162 fewer to 71 more]; for treatment with intravenous magnesium *and* diazepam versus placebo, RR for improved outcome was 0.68 [95% CI 0.36 to 1.28]; 81 fewer survivors per 1,000 patients [95% CI from 162 fewer to 71 more].One non-randomized prospective clinical trial (Monsalve 1987, 244)with 107 adults compared patients who received a bolus and continuous infusion of thiopentone and phenobarbital compared to historic controls, provided very low-certainty evidence (downgraded for risk of bias, indirectness, and imprecision) of no benefit (RR 1.41 [95% CI 0.88 to 2.27]; 137 more survivors per 1,000 adults [95% CI from 40 fewer to 423 more]).For the critical outcome of survival to hospital discharge/30 days or longer, one non-randomized prospective clinical trial (Monsalve 1987, 244)with 107 adults compared patients who received a bolus and continuous infusion of thiopentone and phenobarbital compared to historic controls, provided very low-certainty evidence (downgraded for risk of bias, indirectness, and imprecision) of no benefit (RR 1.40 [95% CI 0.83 to 2.36]; 119 more survivors per 1,000 patients [95% CI from 50 fewer to 403 more].***Treatment of Seizures***For the critical outcome of survival with favourable neurological outcome at discharge/30 days or longer, no pediatric RCTs or non-randomized comparative studies were identified.Indirect evidence from adults were identified.For the critical outcome of survival with favourable neurological outcome at discharge/30 days or longer; One RCT (Ruijter 2022, 724) that addressed the effect of treatment of rhythmic and periodic discharges with anti-seizure medications in 172 comatose adults post-cardiac arrest, compared with no seizure treatment on the critical outcome of survival with favourable neurological outcome at 3 months (CPC score 1 or 2). This study provided low level certainty evidence (downgraded for imprecision and indirectness) of no significant difference for the intervention (administration of anti-seizure medications for rhythmic and periodic EEG patterns) compared with standard care (RR 1.21 [95% CI 0.47 to 3.10; 2 more survivors per 100 patients, [95% CI from 7 fewer to 11 more]). For the critical outcome of survival to 3 months, we identified low certainty evidence (downgraded for imprecision, indirectness) from one RCT (Ruijter 2022, 724)for no significant effect of treatment of rhythmic and periodic EEG patterns in 172 comatose adults post-cardiac arrest, compared with no seizure treatment (RR 0.14 [95% CI 0.62 to 2.12; 3 more survivors per 100 adults, [95% CI from 9 fewer to 14 more]. | The TF also discussed that high seizure burden in children has been associated with poor neurological outcome (Payne 213, 1429, Srinivasakumar 2015, e1302). There are safe and effective anti-seizure medications that can reduce seizure burden which in turn is likely to benefit longer term outcomes (Lyttle, 2019, 2125). Therefore, the Task Force decided to make the Good Practice Statement suggesting for the treatment of seizures in children post-cardiac arrest.  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | There is no direct evidence of undesirable effects of anti-seizure medications in children post-cardiac arrest survivors. Treatment with sedatives and conventional antiseizure medications in high doses has the potential to delay awakening, prolong the need for mechanical ventilation, and increase critical care days. The task force also discussed the potential cost of delayed neurological prognostication and prolonged ICU care associated with active treatment of seizures because of the need to continue sedation.  |  |
| 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 | Overall evidence is of very low certainty. No evidence in the pediatric population was found.Indirect evidence for adults after cardiac arrest, both anti-seizure medication use and in treatment of seizures was identified but downgraded for indirectness, and imprecision.  |  |
| 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 at discharge/30 days or longer are generally accepted as critical outcomes (Topjian P-COSCA). Similar outcomes were identified in the adult studies.  |  |
| 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 | No pediatric studies were identified The TELSTAR study suggests that there is little improvement in outcome with treatment compared with no treatment, of rhythmic and periodic EEG discharges in adult patients who are post- cardiac arrest.  | Detecting seizures post cardiac arrest can be difficult unless the patient has continuous video EEG (cEEG)I monitoring. This is not available at many centres and is complicated, requiring availability of experts to interpret the recordings. Intermittent EEG recording has been shown to detect less episodes of seizure-like activity than cEEG - but if Rx of abnormal EEG activity doesn’t alter patient outcome, there is less reason to do it, suggesting time and resources routinely invested in cEEG monitoring may not be worthwhile. However, research comparing testing modalities is warranted as there is no current evidence. |
| 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 a sedating agents and conventional anti-seizure medication in post-cardiac arrest patients. Cost is variable depending on type and number of agents used. Continuous EEG monitoring is used to assess prognosis and to diagnose seizures and monitor response to therapy. It is labor intensive and likely to add significant cost to patient care. The net cost-effectiveness of this approach is controversial and may depend substantially on the organization. There is also the potential cost of delayed neurologic prognostication and prolonged ICU care. | We need to understand the efficacy of continuous vs intermittent EEG monitoring in post arrest patients prior to calculating required resources and cost effectiveness metrics |
| 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 have not identified studies evaluating the cost of sedating agents and conventional anti-seizure medication in this patient population.  |  |
| 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 of post-cardiac arrest seizure treatment.  | We need to understand the efficacy of continuous vs intermittent EEG monitoring in post arrest patients prior to calculating required resources and cost effectiveness metrics |
| 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 identified no studies that addressed health equity. Disparities in the availability of anti-seizure medication therapy in various settings was not investigated. However, it is likely that the availability of specific agents will vary with setting and region. The availability of conventional and continuous EEG monitoring is likely to be limited in low resourced environments. |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes○ Varies● Don't know | We identified no research that assessed acceptability.  |  |
| 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, treatment for seizures with anti-seizure medication is routine in pediatric practice. |  |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Trivial | Small | Moderate | Large |  | 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 |
| ***Prophylactic Anti-Seizure Medication***There is insufficient evidence to make a *treatment recommendation* for or against the use of prophylactic anti-seizure medicationin children post-cardiac arrest.We suggest against the routine use of prophylactic anti-seizure medications in children post-cardiac arrest (Good Practice Statement).***Seizure Treatment***There is insufficient evidence to make a *treatment recommendation* for or against the treatment of seizures in children post-cardiac arrest.We suggest for the treatment of seizures in children post-cardiac arrest (Good Practice Statement).  |
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| Justification |
| ***Prophylactic Anti-Seizure Medication***Due to the lack of direct evidence in children post-cardiac arrest, and very low certainty of the indirect evidence from adults, the Task Force was unable to make a treatment recommendation. The Task Force decision to provide a Good Practice Statement suggesting against post-cardiac arrest prophylactic anti-seizure medication was based on the absence of in-direct evidence from adult comatose cardiac arrest survivors that prophylactic therapy with anti-seizure medication prevents seizures or improves important outcomes. However, the Task Force did recognize the very low certainty of the evidence from RCTs. The Task Force also considered that the administration of prophylactic anti-seizure medication in other forms of acute brain injury (e.g. neonatal hypoxic-ischemic encephalopathy) (Young 2016, 1) is not associated with improved long-term outcomes. Although prophylactic anti-seizure medication is recommended following traumatic brain injury in children (Kochanek 2019, 1172), the evidence of benefit for early seizure prevention is very-low certainty and there is no evidence of improved long-term outcomes (7) (Liesemer 2011, 755)The medications used for anti-seizure prophylaxis in the included trials (e.g. barbiturates) can have significant side effects although the cardiac side-effects seen in adults may be less common in children. The Task Force acknowledged that newer anti-seizure medications have not been evaluated and their efficacy and side effect profile may differ. Further evaluation is encouraged.***Seizure Treatment***No direct pediatric evidence of the effects of treating seizures in children after cardiac arrest was identified and the Task Force was unable to make a treatment recommendation. High seizure burden in children has been associated with poor neurological outcome (Payne 213, 1429, Srinivasakumar 2015, e1302). There are safe and effective anti-seizure medications that can reduce seizure burden which in turn is likely to benefit longer term outcomes (Lyttle, 2019, 2125). Therefore, the Task Force decided to make the Good Practice Statement suggesting for the treatment of seizures in children post-cardiac arrest. There is insufficient evidence to suggest for or against the treatment of rhythmic and periodic EEG patterns in children post-cardiac arrest. One adult RCT (Ruijter 2022 724)did not find a difference in the primary outcome with one therapeutic approach to treatment of rhythmic and periodic EEG patterns. However, no significant harm was noted in the treatment or control arm. Further research is required in children to evaluate the impact on treating specific EEG patterns and electrographic seizures. Medication for sedation (e.g. benzodiazepines and propofol) and targeted temperature management use after cardiac arrest may also affect seizure thresholds. Evaluation of the use of prophylactic anti-seizure medication and seizure treatment in the context of these therapies is important.  |

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| Subgroup considerations |
| No subgroups were considered due to lack of pediatric data.  |

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| Implementation considerations |
| The Task Force acknowledges the challenge of seizure diagnosis and the important role of confirmatory electroencephalographic (EEG) in addition to clinical signs of seizure to increase certainty of diagnosis. The potential risk of treating suspected seizures in settings without access to EEG confirmation needs to be balanced with potential harm of anti-seizure medications. EEG confirmation remains the gold-standard approach for seizure diagnosis; however, EEG may not be available in many clinical settings as it requires significant resources, including neuro-physiology equipment, training and expertise. Continuous EEG monitoring is labor intensive and likely to add significant cost to patient care. The cost-effectiveness of this approach is controversial and may depend on the setting. The relative benefit of continuous EEG compared with intermittent EEG monitoring was not reviewed. |

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| Research priorities |
| There is no pediatric data for the use of prophylactic anti-seizure medication post-cardiac arrest. We encourage the assessment of newer anti-seizure medications and the role of sedative medications with anti-seizure properties used in the post-cardiac arrest period. There is no pediatric data for the use of anti-seizure medications to treat seizures on important clinical outcomes post-cardiac arrest. We encourage research in this field. EEG diagnosis remains the gold standard for seizure diagnosis. Risks and benefits of treating seizures without EEG and the importance of EEG monitoring post-cardiac arrest is a high priority with an important focus on cost effectiveness. This includes the role of continuous EEG, quantitative EEG and intermittent EEG.  |

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