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| Question | |
| **Should No vasopressor vs. vasopressor use be used for cardiac arrest in children?** | |
| **Population:** | Cardiac arrest in children |
| **Intervention:** | Vasopressor use |
| **Comparison:** | No vasopressor |
| **Main outcomes:** | Pre-hospital ROSC; 1-month survival; Favorable neurological outcome at 1-month; Survival to Hospital Discharge; Favorable neurological outcome at hospital discharge |
| **Setting:** | Any |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | Nil |

# 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 | Administration of epinephrine in pediatric cardiac arrest has been traditionally taught as a fundamental part of advanced life support despite a lack of evidence that it improves patient-centered outcomes such as long-term neurological outcomes. | A randomized trial of epinephrine in out-of-hospital cardiac arrest in adults demonstrated that administration of epinephrine increased 30-day survival rates, although a larger proportion of patients in the epinephrine group were more significantly neurologically impaired6. |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | The systematic review reported 2 pre-hospital retrospective, propensity-score matched cohort studies that addressed our PICOST1,4.  ***Favorable neurological survival at 1-month (Cerebral Performance Category)***  For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children 8 to 17 years old4 , involving 608 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (10 more patients with favorable neurological survival at 1-month per 1,000 resuscitations; 95 CI%: 20 fewer to 40 more).  ***Favorable neurological survival at hospital discharge (Modified Rankin Score)***  For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children less than 18 years old1 , involving 1432 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (20 more patient with favorable neurological survival at hospital discharge per 1,000 resuscitations; 95 CI%: 10 fewer to 40 more).  ***Survival at 1-month***  For this critical outcome, we identified low certainty data (downgraded for serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children 8 to 17 years old4 , involving 608 patients which showed no significant difference associated when epinephrine was administered compared to when no epinephrine was administered (20 more survivors per 1,000 resuscitations; 95 CI%: 20 fewer to 70 more).  ***Survival to hospital discharge***  For this critical outcome, we identified low certainty data (downgraded serious risk of bias, and serious indirectness), from 1 cohort study which was propensity score matched for children less than 18 years old1 , involving 1432 patients which showed no significant difference associated with survival at hospital discharge when epinephrine was administered compared to when no epinephrine was administered (20 more survivor per 1000 resuscitations; 95 CI%: 0 fewer to 50 more).  ***Pre-hospital Return of spontaneous circulation (ROSC)***  For this important outcome, we identified very low certainty data (downgraded for serious risk of bias, very serious inconsistency, and serious indirectness), from the 2 cohort studies1,4 , involving 2038 patients less than 18 years old, which showed significant negative associations with ROSC when epinephrine was administered, compared to when no epinephrine was administered (60 more patients with ROSC per 1,000 resuscitations; 95 CI%: 30 more to 90 more). | While return of spontaneous circulation may not be a patient-centered outcome, the need for additional considerations of maintaining organ viability for potential organ donation needs to be addressed.  The 2 pediatric studies did not report less favorable neurological outcomes from the administration of epinephrine. There were consistent signals but non-significant associations with the use of epinephrine (versus when not given) with comparatively more short-term survival and favorable neurological outcomes.  Further studies are needed to evaluate long term neurological outcomes of pre-hospital administration of epinephrine for pediatric out-of-hospital cardiac arrest. These patient-centered clinical outcomes should be studied7. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know | While there are no direct undesirable anticipated effects that were reported in the included studies, the resources that may be needed for additional equipment, training and maintenance of skillsets of EMS personnel to enable the administration of epinephrine in pediatric out-of-hospital cardiac arrests may be substantial.  These advanced interventions should be evaluated against other priorities of healthcare systems in committing significant resources to implement pre-hospital administration of epinephrine in pediatric cardiac arrest, especially in resource-limited settings.  The 2 included studies were from advanced EMS systems that could provide pre-hospital advanced pediatric life support1,4. | There are some potential drawbacks in epinephrine administration in an out-of-hospital setting. A recent cohort study highlighted that among pediatric out-of-hospital cardiac arrest treated by emergency medical service in the United States, there was at least one severe adverse safety event (eg, failure to give an indicated medication, 10-fold medication overdose) occurred in 610/1019 (60%) patients, and 310/1019 (30%) patients had 2 or more adverse events2. The only factor associated with severe adverse safety events was young age. |
| 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 systematic review reported 2 pre-hospital retrospective, propensity-score matched cohort studies that addressed our PICOST. Based on the 2 included observational studies, the use of epinephrine in the out-of-hospital setting did demonstrate an improved ROSC rate in both studies1,4.  The 2 identified studies provided low certainty of evidence with the critical outcomes (downgraded for serious risk of bias and serious indirectness) and very low certainty of evidence with the important outcomes (downgraded for serious risk of bias, very serious inconsistency, and serious indirectness). |  |
| 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 | There may be variability in the perceived clinical value of pre-hospital return of spontaneous circulation. | While return of spontaneous circulation may not be a patient-centered outcome, the need for additional considerations of maintaining organ viability for potential organ donation needs to be considered. |
| 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 | The evidence is supportive of the administration of epinephrine in pediatric out-of-hospital cardiac arrest to significantly improve ROSC rates.  In any healthcare system that has advanced EMS life support teams that are trained and have the necessary resources to administer epinephrine for pediatric cardiac arrest patients in the out-of-hospital setting, these would likely result in similar clinical outcomes.  Future specific research will need to focus on the prospective evaluation of the use of epinephrine in advanced EMS systems that are able to provide advanced life support to pediatric cardiac arrest patients in the pre-hospital setting. These should include patient-centered clinical outcomes, especially long-term neurological outcomes7.  The task force acknowledges that randomized controlled trials on its use in pediatric cardiac arrest would unlikely be studied in the near future. | In EMS systems that can provide advanced pediatric life support, the administration of epinephrine in pediatric out-of-hospital cardiac arrests should still recommended.  The cost-effectiveness of healthcare systems committing significant resources to train and maintain skillsets in developing EMS systems or in resource-limited settings, so that EMS personnel may be able to obtain vascular access for the administration of epinephrine in the pre-hospital setting is still unknown. |
| Resources required | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know | There is paucity of studies looking at resources required to train, maintain skillsets and provide the necessary equipment and drugs need for EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests.  There are no studies looking at the health economic impact and benefits of EMS to be able to deliver vasopressors in pediatric out-of-hospital cardiac arrests in resource-rich healthcare systems, but also in resource-limited countries.  However, the resources needed are likely to be substantial in developing EMS systems while probably not significant in mature EMS systems that currently provide advanced pediatric life support. | The advocacy to administer epinephrine in pediatric out-of-hospital cardiac arrests should consider additional training and resources in different healthcare settings to provide these advanced life support measures. |
| 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 | It is of note that these 2 observational studies were from healthcare settings with advanced EMS systems.  There were no studies identified that evaluated the resources required to train, maintain skillsets and provide the necessary equipment and drugs needed for EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests. |  |
| 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 | There were no studies identified that evaluated the cost-effectiveness of enabling EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests. |  |
| 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 | There were no studies identified that looked directly at the health economic impact and benefits of EMS to be able to deliver vasopressors in pediatric out-of-hospital cardiac arrests in all settings, including in resource-limited countries.  Further studies should look not only in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries. When powered with more analyzable data, these should be stratified by resource-availability e.g. Gross National Income or Sociodemographic Index status of the country. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know | There was sufficient evidence to support administering epinephrine in advanced EMS systems that can or already provide advanced pediatric life support in pediatric out-of-hospital cardiac arrest.  In developing EMS systems or healthcare settings with significant resources limitations, the feasibility of administrating epinephrine in pediatric out-of-hospital cardiac arrests is unknown due to lack of studies on its cost effectiveness. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○  No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know | In advanced EMS systems that can provide advanced pediatric life support for pediatric out-of-hospital cardiac arrests, the evidence suggests that administration of epinephrine improved outcomes of ROSC; favouring the intervention.  In developing EMS systems or countries with significant resource limitations, the feasibility of administrating epinephrine in pediatric out-of-hospital cardiac arrests is unknown due to lack of studies. |  |

# 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 |
| We suggest to use epinephrine in pediatric out-of-hospital cardiac arrest. [weak recommendation, very low-quality evidence].  There is insufficient evidence to generate a treatment recommendation for the use of epinephrine in pediatric in-hospital cardiac arrest.  However, the task force considers the indirect evidence from OHCA to *support the administration of epinephrine in pediatric in-hospital cardiac arrest. [Good practice statement]* |
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| Justification |
| In EMS systems that are already providing or planning to provide advanced pediatric life support while ensuring high quality basic life support, the current evidence while very low-quality, suggest using epinephrine in pediatric out-of-hospital cardiac arrest.  The taskforce acknowledged that the included studies were from settings with advanced Emergency Medical Services. In similar settings, the administration of epinephrine as part of advanced pediatric life support for pediatric out-of-hospital cardiac arrest should be continued but also further evaluated.  However, there is paucity of studies looking at resources required to train, maintain skillsets and provide the necessary equipment for EMS systems to administer epinephrine in pediatric out-of-hospital cardiac arrests. Future studies should be undertaken to evaluate the ability of EMS systems to provide advanced care in pediatric out-of-hospital cardiac arrest, to better inform equity issues of such systems in both resource-rich healthcare but also in resource-limited countries. |

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| Subgroup considerations |
| · Age-subgroups: infants, children and adolescents in out-of-hospital cardiac arrest  · Early versus Late epinephrine in shockable rhythms  · Non-shockable rhythms – asystole versus PEA (versus ?bradycardia)  · LMICs versus Non-LMICs  · Single-tiered versus Tiered EMS response (BLS/ALS) systems |

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| Implementation considerations |
| · Resourcing  · Feasibility  · Cost-effectiveness  · Equity and Acceptability |

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| Monitoring and evaluation |
| Evidence updates will be reviewed annually for the PICOST |

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| Research priorities |
| · Future studies should include patient-centered outcomes such as long-term survival and neurological outcomes7.  · Further studies should address if specific sub-populations might potentially benefit from administration of epinephrine in the pre-hospital settings  · Cost-effectiveness and feasibility on the provision of advanced pediatric life support in the pre-hospital settings to facilitate administration of epinephrine, in pediatric out-of-hospital cardiac arrest while ensuring high quality basic life support, should be explored in all healthcare settings, including in LMICs.  · There were no inpatient studies identified. Future studies should include evaluation of use of vasopressors in the inpatient setting, especially in the context of initial resuscitation of pediatric cardiac arrest patients prior to extracorporeal cardiopulmonary resuscitation (ECPR)3,5. |

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Vasopressor use** | **no vasopressor** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Favorable neurological outcome at 1-month** | | | | | | | | | | | | |
| 1 | non-randomised studies | seriousa | not serious | seriousc,d | not serious | none | 11/304 (3.6%) | 8/304 (2.6%) | **RR 1.38** (0.56 to 3.37) | **10 more per 1,000** (from 20 fewer to 40 more) | ⨁⨁◯◯ Lowa,c,d | CRITICAL |
| **Favorable neurological outcome at hospital discharge** | | | | | | | | | | | | |
| 1 | non-randomised studies | seriousa | not serious | seriousc | not serious | none | 35/716 (4.9%) | 24/716 (3.4%) | **RR 1.46** (0.88 to 2.43) | **20 more per 1,000** (from 10 fewer to 40 more) | ⨁⨁◯◯ Lowa,c | CRITICAL |
| **1 month survival** | | | | | | | | | | | | |
| 1 | non-randomised studies | seriousa | not serious | seriousc,d | not serious | none | 31/304 (10.2%) | 24/304 (7.9%) | **RR 1.29** (0.78 to 2.15) | **20 more per 1,000** (from 20 fewer to 70 more) | ⨁⨁◯◯ Lowa,c,d | CRITICAL |
| **Survival to Hospital Discharge** | | | | | | | | | | | | |
| 1 | non-randomised studies | seriousa | not serious | seriousc | not serious | none | 45/716 (6.3%) | 29/716 (4.1%) | **RR 1.55** (0.98 to 2.45) | **20 more per 1,000** (from 0 fewer to 50 more) | ⨁⨁◯◯ Lowa,c | CRITICAL |
| **Pre-hospital ROSC** | | | | | | | | | | | | |
| 2 | non-randomised studies | seriousa | very seriousb | seriousc | not serious | none | 156/1018 (15.3%) | 95/1020 (9.3%) | **RR 1.65** (1.30 to 2.09) | **60 more per 1,000** (from 30 more to 90 more) | ⨁◯◯◯ Very lowa,b,c | IMPORTANT |

**CI:** confidence interval; **RR:** risk ratio

#### Explanations

a. Due to missing data

b. Difference in study population (age)

c. Not a direct comparison

d. The population is limited to children greater than 8 years old

# References Summary

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