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| Question | |
| **Should any non-standard dose, interval or route (e.g. IO or ETT etc.) of epinephrine (adrenaline) vs. to standard dose intravenous epinephrine (adrenaline) (0.01-0.03 mg/kg) at intervals of every 3-5 minutes be used for neonates (of any gestation) ≤ 28 days of age who have no detectable cardiac output or who have asystole or heart rate < 60 bpm despite ventilation and chest compressions?** | |
| **Population:** | neonates (of any gestation) ≤ 28 days of age who have no detectable cardiac output or who have asystole or heart rate < 60 bpm despite ventilation and chest compressions |
| **Intervention:** | any non-standard dose, interval or route (e.g. IO or ETT etc.) of epinephrine (adrenaline) |
| **Comparison:** | to standard dose intravenous epinephrine (adrenaline) (0.01-0.03 mg/kg) at intervals of every 3-5 minutes |
| **Main outcomes:** | Death at hospital discharge; Failure to achieve ROSC; Time to ROSC; Receiving additional dose(s) of epinephrine; |
| **Setting:** |  |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** |  |

# 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 | Large, teaching hospital-based studies indicate that 0.5 to 0.6 per 1000 babies remain asystolic or severely bradycardic despite assisted ventilation {Halling 2017 232; Barber 2006 1028}. Eighty percent of these infants achieved return of spontaneous circulation after administration of epinephrine. There is a need to determine the effects of route of administration, dose, or interval of administration (when multiple doses are required) on efficacy. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know |  | If ET epinephrine is effective, ET administration, when compared with the IV route, could result in a shorter time to provide epinephrine, with the potential for greater efficacy. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know |  | Endotracheal administration of epinephrine could result in a team's decision to delay establishing IV access. If the endotracheal route of administration is ineffective, this could result in lower likelihood of an effective dose of epinephrine being provided in a timely way.  Animal studies suggest that IV epinephrine has a greater efficacy and a better pharmacokinetic profile than ET epinephrine. In asphyxiated term lambs undergoing perinatal transition with asphyxia-induced cardiac arrest, peak plasma epinephrine concentrations were both higher and were achieved earlier after IV epinephrine (right atrium 470±250ng/mL or low umbilical venous cord 450±190ng/mL by 1 minute) when compared to the ET epinephrine peak level of 130±60 ng/mL at 5 minutes (p=0.03), despite a lower IV (0.03 mg/kg) than ET dose (0.1 mg/kg). {Valli 2017 004402}  In the same asphyxiated term lambs undergoing perinatal transition with asphyxia-induced cardiac arrest, using the same doses, IV epinephrine resulted in a shorter median time (interquartile range) to achieve ROSC (2 (1.9-3) than ET epinephrine 4.5 (2.9-7.4) minutes, p=0.02).  In addition, IV epinephrine resulted in higher rates of ROSC (19/22 (86%)) than ET epinephrine 12/22 (54%)). |
| 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 | **Comparison between initial ET vs. initial IV epinephrine**  For the critical outcome of **death before discharge** (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from one observational study {Halling 2017 232} in which 50 neonates were treated with epinephrine (P), that showed no significant benefit or harm of the initial administration of epinephrine via ET (I) when compared with administration via IV (C) (RR, 1.03; 95%CI, 0.62, 1.71; Absolute risk reduction [ARR]; 17 more per 1000 neonates died when epinephrine was administered via ET compared to via IV [95%CI, 209 fewer to 391 more neonates per 1000 neonates died with ET epinephrine]).  For the critical outcome of **failure to achieve ROSC** (which equates to death before neonatal unit admission) (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from two observational studies {Barber 2006 1028; Halling 2017 232} in which 97 neonates were treated with epinephrine (P), that showed no significant benefit or harm of the initial administration of epinephrine via ET (I) when compared to administration via IV (C) (RR, 0.97; 95%CI, 0.38, 2.48; P=0.96; Absolute risk reduction [ARR]; Seven fewer per 1000 neonates died when the epinephrine was administered via ET compared to via IV [95%CI, 135 fewer to 322 more neonates per 1000 neonates died with ET epinephrine]).  For the important outcome of **time to ROSC** (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from one observational study {Halling 2017 232} which compared in 38 neonates time to ROSC after the treatment with epinephrine (P), which showed no significant difference in the time to ROSC after the administration of epinephrine via ET (I) when compared to administration via IV (C) (mean difference 2.00 minutes later when the epinephrine was administered via ET compared to via IV [95%CI, 0.60 minutes earlier to 4.60 minutes later when epinephrine was administered via ET]).  For the important outcome of **receiving an additional dose after the initial epinephrine administration** (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from two observational studies {Barber 2006 1028; Halling 2017 232} in which 97 neonates were treated with epinephrine (P), that showed no significant difference in the receipt of an additional dose after the initial administration of epinephrine via ET (I) when compared with that via IV (C) (RR, 1.94; 95%CI, 0.18, 20.96; P=0.59; Absolute risk reduction [ARR], 654 more neonates per 1000 would receive additional epinephrine dose or doses after the initial epinephrine via ET compared to via IV [95%CI, 570 fewer to 1000 more neonates per 1000 neonates would receive an additional dose or doses after initial epinephrine administration via ET than if the epinephrine was given via IV]).  **Comparison the outcomes of infants receiving initial ET epinephrine at 0.03 versus 0.05mg/kg/dose (post hoc analysis)**  For the critical outcome of **survival at discharge** (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from one observational study {Halling 2017 232} in which 30 neonates were treated with ET epinephrine (P), that showed no significant benefit or harm of ET epinephrine at 0.03mg/kg/dose (I) when compared with 0.05mg/kg/dose (C) (RR, 1.12; 95%CI, 0.50, 2.54; Absolute risk difference [ARD]; 49 more per 1000 neonates survived when the initial dose of epinephrine was administered at 0.03mg/kg compared to 0.05mg/kg [95%CI, 206 fewer to 634 more per 1000 neonates).  For the critical outcome of **No ROSC** (O), we have identified very-low-certainty evidence (downgraded for risk of bias and imprecision) from one observational study {Halling 2017 232} in which 30 neonates were treated with ET epinephrine (P), that showed no significant benefit or harm of ET epinephrine at a 0.03mg/kg/dose (I) when compared with a 0.05mg/kg/dose (C) (RR, 0.52; 95%CI, 0.12, 2.28; Absolute risk difference [ARD]; 149 fewer per 1000 neonates at 0.03mg/kg compared to 0.05mg/kg [95%CI, 259 fewer to 376 more per 1000 neonates).  Except for the comparison between IV vs. ET epinephrine, we did not find any eligible studies comparing **different routes of administration**.  We did not find any eligible studies comparing **different intervals of epinephrine administration.**  We did not find any eligible studies comparing **different doses of IV epinephrine**. |  |
| 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 | A recent study finds agreement on the value of the main outcomes {Strand 2019 316942} |  |
| 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 current evidence from newborn infants is insufficient, but does not favour initial ET over initial IV epinephrine for any important or critical outcome. | The established recommendation is favoured because it is not challenged by available animal evidence which in fact supports present practice.  In asphyxiated term lambs undergoing perinatal transition with asphyxia-induced cardiac arrest IV epinephrine compared to ET epinephrine resulted in a shorter median time (interquartile range) of time to achieve ROSC with 2 (1.9-3) versus 4.5 (2.9-7.4) minutes, p=0.02.  In addition, IV epinephrine compared to ET epinephrine resulted in higher rates of ROSC with 19/22 (86%) versus 12/22 (54%), respectively. {Valli 2017 004402} |
| 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 | No studies have measured the difference in resources required for ET vs IV epinephrine, or any different dose or interval of epinephrine in newborn infants. | Most infants who require epinephrine will require endotracheal intubation and at some point, establishment of intravenous access. Therefore, in terms of disposable equipment, the resources are similar for ET and IV epinephrine.  This recommendation is similar to the previous ILCOR treatment recommendation in 2010. Therefore, there are no new resource implications for implementation. |
| 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 |  | Based on expert opinion, at least one additional resuscitation team member is required to establish IV access. |
| 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 are no studies that examine cost effectiveness of different routes, doses or intervals of administration of epinephrine. |  |
| 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 are no studies that examine the impacts of route, dose or interval of administration of epinephrine for newborn infants on health equity. | Because epinephrine is not currently available in low healthcare resourced settings, equity is not promoted by a recommendation for either the intervention of the comparator. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Either IV or ET administration of epinephrine is acceptable to clinicians. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Either the administration of I V or ET epinephrine is feasible, in well-resourced healthcare settings. {Halling 2017 232; Barber 2006 1028} | The administration of either ET or IV epinephrine is likely only to be feasible in locations with moderate or high healthcare resources. |

# 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 |
| If the heart rate has not increased to > 60 beats per minute after optimizing ventilation and chest compressions, we suggest the administration of intravascular epinephrine (0.01 to 0.03 mg/kg). (Weak recommendation, very low certainty of evidence).  If intravascular access is not yet available, we suggest administering endotracheal epinephrine at a larger dose (0.05 to 0.1 mg/kg). The administration of endotracheal epinephrine should not delay attempts to establish vascular access. (Weak recommendation, very low certainty of evidence).  We suggest the administration of further doses of epinephrine every 3-5 minutes, preferably intravascularly, if the heart rate remains less than 60 beats per minute. (Weak recommendation, very low certainty of evidence).  If the response to endotracheal epinephrine is inadequate, we suggest that an intravascular dose be given as soon as vascular access is obtained, regardless of the interval. (Weak recommendation, very low certainty of evidence). |
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| Justification |
| The very limited human infant evidence does not demonstrate greater efficacy of IV vs ET epinephrine. In term lambs undergoing perinatal transition with asphyxia-induced cardiopulmonary arrest:  · peak plasma epinephrine concentrations were achieved higher and sooner after central venous epinephrine [right atrium 470±250ng/mL or low umbilical venous cord 450±190ng/mL at one minute] than after endotracheal epinephrine of 130±60 ng/mL at 5 minutes (p=0.03), despite lower central venous doses (0.03 mg/kg IV vs. 0.1 mg/kg ET).  · Central venous epinephrine compared to ET epinephrine resulted in a shorter median time (interquartile range) to achieve ROSC with 2 (1.9-3) versus 4.5 (2.9-7.4) minutes, p=0.02, using the same lower central venous doses.  · In addition, central venous epinephrine compared to ET epinephrine resulted in higher rates of ROSC with 19/22 (86%) versus 12/22 (54%) p=0.02, respectively, using the same lower central venous doses. |

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| Subgroup considerations |
| There is no evidence on which to differentiate effects on subgroups of infants. |

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| Implementation considerations |
| This recommendation is similar to the previous ILCOR treatment recommendation in 2010 (Route and Dose of Epinephrine NRP-008A, NRP-008B, NRP-009A, NRP-009B);*“If adequate ventilation and chest compressions have failed to increase the heart rate to > 60 beats per minute, then it is reasonable to use epinephrine despite the lack of human neonatal data. If epinephrine is indicated, a dose of 0.01 to 0.03 mg/kg should be administered intravenously as soon as possible. If adequate ventilation and chest compressions have failed to increase the heart rate to 60 beats per minute and intravenous access is not available, then it is reasonable to administer endotracheal epinephrine. If epinephrine is administered by the endotracheal route, it is likely that a larger dose (0.05 mg/kg to 0.1 mg/kg) will be required to achieve an effect similar to that of the 0.01 mg/kg intravenous dose. Higher intravenous doses cannot be recommended and may be harmful.”* Therefore, there are no new implications for implementation. |

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| Monitoring and evaluation |
| We recommend that health services should monitor the rate of use of epinephrine for newborn resuscitation, together with the outcomes of epinephrine treatment reported in this review. Wherever possible, this monitoring should include the characteristics of the infants, the resuscitation measures they have received before epinephrine, the dose(s), route(s) and treatment intervals and any adverse effects of treatment. The reasons are that there is unlikely to be high certainty evidence from clinical trials on which to base treatment recommendations about epinephrine doses, administration time intervals and delivery routes in the near future. Meanwhile, increasing the number of good quality, published observational studies could offer the best opportunity to validate or improve treatment recommendations. Also, rates of epinephrine administration may reflect the quality of earlier steps in resuscitation and could therefore be a valuable benchmark. |

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| Research priorities |
| The following specific gaps in knowledge were identified:  • Optimal (heart rate) thresholds for administration of epinephrine  • Potential harms of epinephrine (single or multiple doses)  • Optimal dose and interval of epinephrine.  • Optimal route and method of administration of epinephrine.  • Effect of vasoactive drugs other than epinephrine.  Since the decision to administer epinephrine needs to be rapid in newborn resuscitation, and the event is rare and unpredictable, adequate ethical randomized trials of human infants with prior parental informed consent may be difficult. Prospective, multicentre cluster-randomised trials could be a good option.  Newborn animal studies that address pharmacokinetics and pharmacodynamics are needed to determine the optimal dose and route of epinephrine are also needed, in order to inform the optimal design of human infant studies. |

# References Summary

1. Halling C, Sparks JE, Christie L, Wyckoff MH. Efficacy of Intravenous and Endotracheal Epinephrine during Neonatal Cardiopulmonary Resuscitation in the Delivery Room. J Pediatr. 2017 Jun;185:232-236. doi: 10.1016/j.jpeds.2017.02.024. Epub 2017 Mar 10. PubMed PMID: 28285754.

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3. Vali P, Chandrasekharan P, Rawat M, Gugino S, Koenigsknecht C, Helman J, Jusko WJ, Mathew B, Berkelhamer S, Nair J, Wyckoff MH, Lakshminrusimha S. Evaluation of Timing and Route of Epinephrine in a Neonatal Model of Asphyxial Arrest. J Am Heart Assoc. 2017 Feb 18;6(2). pii: e004402. doi: 10.1161/JAHA.116.004402. PubMed PMID: 28214793; PubMed Central PMCID: PMC5523751.

4. Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2019 Mar 29. pii: fetalneonatal-2019-316942. doi:10.1136/archdischild-2019-316942. [Epub ahead of print] PubMed PMID: 30926715.