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| Question |
| **IV VS. IO ADMINISTRATION OF DRUGS DURING CARDIAC ARREST - NEONATES** |
| **Population:** | Neonates in any setting (in-hospital or out-of-hospital) with cardiac arrest (includes severe bradycardia and inadequate perfusion requiring chest compressions). |
| **Intervention:** | Placement of an intraosseous (IO) cannula and drug administration through this IO during cardiac arrest |
| **Comparison:** | Placement of an intravenous (IV) cannula (umbilical vein in newly born infants) and drug administration through this IV during cardiac arrest. |
| **Main outcomes:** | * Death during event, within 24 hours and before hospital discharge
* Long term neurodevelopmental outcomes
* Return of spontaneous circulation (ROSC): any signs of cardiac output with HR > 60bpm, and time to ROSC
* Brain Injury [HIE stage 2-3 Sarnat (term only), IVH Grades III-IV, PVL (preterm only)];
* Time to secure access
* Morbidity related to IO (osteomyelitis, fracture, epiphyseal plate injury, compartment syndrome, amputation) or to IV (extravasation, embolic phenomenon, phlebitis)
 |
| **Setting:** | In-hospital (delivery room and neonatal unit) or out-of-hospital |
| **Perspective:** | Population |
| **Background:** | When severe bradycardia (< 60bpm) persists at birth, once ongoing aeration of the lungs is established and chest compressions are coordinated with ventilation, adrenaline and/or volume expansion should be given rapidly to increase myocardial blood flow and ensure the best possible chance of return of spontaneous circulation (ROSC). Approximately 1/1000 newly born infants receive medications in the delivery room (Perlman 1995, 20), and about 75% of the patients achieve ROSC after intravenous adrenaline via the umbilical vein at birth (Barber 2006, 1028; Halling 2017, 232). In addition, sick newborns presenting in extremis due to sepsis or congenital heart disease pose a challenge for healthcare practitioners to secure a reliable site to provide life-saving medications and fluids. In 2010, ILCOR recommended that temporary intraosseous access to provide fluids and medications to resuscitate critically ill neonates may be indicated following unsuccessful attempts to establish intravenous vascular access or when caregivers are more skilled at securing intraosseous access (Perlman 2010, S516). In 2015, the use of IV route for newborn resuscitation was not reviewed by ILCOR Neonatal Taskforce (Perlman 2015, S204).IO administration of drugs, fluids or blood may be the only option in intensive care neonatal units, when peripheral IV access in emergencies is not possible, or umbilical vein is closed, as published in one case series with 27 neonates (Ellemunter 1999, F74), and 15 neonatal case reports (Ghirga 1992, 377; Kelsall 1993, 324; Martino Alba 1994, 529; Kakhandki 1997, 748; Nasimi 1998, 414; Ramet 1998, 327; Lake 2003, F409; Singh Tomar 2006, 202; Heyder-Musolf 2011, 654), but with morbidity related to IO access (Vidal 1993, 1201; Katz 1994, 258; Carreras-Gonzales 2012, 233; Oesterlie 2014, 413; Suominen 2015, 1389). In the neonatal simulation setting, IO access is easier and faster than IV access by umbilical vein (Abe 2000,126; Rajani 2011, e954; Schwindt 2018, 468). |
| **Conflict of interests:** | None |

# ASSESSEMENT

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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 | Drugs are rarely indicated in resuscitation of the newly born infant. Approximately 1/1000 newly born infants receive medications in the delivery room (Perlman 1995, 20), and about 75% of patients achieve return of spontaneous circulation after adrenaline by umbilical vein at birth (Barber 2006, 1028; Halling 2017, 232).In addition, sick newborns presenting in extremis due to sepsis or congenital heart disease pose a challenge for healthcare practitioners to secure a reliable site to provide life-saving medications and fluids.  |  |

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| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○  Small● Moderate○  Large○  Varies○ Don't know | When severe bradycardia (< 60bpm) persists at birth, once ongoing aeration of the lungs is established and chest compressions are coordinated with ventilation, adrenaline and/or volume expansion should be given rapidly to increase myocardial blood flow and ensure the best possible chance of return of spontaneous circulation (ROSC). IO administration of drugs, fluids or blood may be the only option, when peripheral IV access in emergencies is not possible, umbilical vein is closed or the cord stump is dry, making IV administration by umbilical vein almost impossible. Delay in initiating administration of drugs by umbilical vein, especially when the provider is unable to rapidly reach the central venous circulation, may negatively impact critical outcome (i.e. death). If there is a finding of benefit of the IO administration, this could be a benefit for the individual, family, and population. |  |

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| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large● Moderate○ Small○ Trivial○ Varies○ Don't know | IO access in neonates is associated with adverse effects. Pharmacokinetics and pharmacodynamics of neonatal resuscitation drugs delivered by IO access have not been established. | IO access in neonates is associated with severe complications, including tibial fractures, extravasation of fluid and medications resulting in compartment syndrome and amputation (Vidal 1993, 1201; Katz 1994, 258; Ellemunter 1999, F74; Carreras-Gonzales 2012, 233; Oesterlie 2014, 413; Suominen 2015, 1389). IO pharmacokinetics and plasma availability of drugs might be not as effective as IV administration.  |
| 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 | The certainty of evidence cannot be established due to the absence of clinical trials or cohort studies with neonates during resuscitation that received IO vs IV administration regarding any outcome. No published studies are available on IO administration in neonatal resuscitation in the delivery room.  |  |
| **Values**Is there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement |  | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | Parents and providers are likely to value the outcomes included in this systematic review (Strand 2019 [Epub ahead of print])  |  |
| 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 | The balance between desirable and undesirable effects could not be ascertained due to the absence of clinical trials or cohort studies with neonates during resuscitation that received IO vs IV administration regarding any outcome.  | Case reports suggest that intraosseous lines have the potential for serious complications which include amputation and frequent misplacement (Fuchs 2018, 79; Maxien 2019, 1)  |
| 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 specifically comparing resources including costs between the two interventions.  |  |
| 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 did not identify any studies comparing resources including costs between the two interventions. |  |
| 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 comparing cost-effectiveness between the two interventions. |  |
| 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 did not identify any studies addressing health equity. |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | Emergency umbilical vein access has been accepted as standard of care for many years in neonatal resuscitation.  | In a variety of neonatal simulation settings, IO placement was faster than umbilical venous access (Abe 2000,126; Rajani 2011, e954; Schwindt 2018, 468), but there was no assessment of training level in these settings. The relevance to the clinical setting is unknown. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes●  Varies○ Don't know | We did not identify any studies addressing feasibility in neonatal resuscitation.  | There are case reports of successful emergent IO placement for neonatal resuscitation. |

# 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 suggest umbilical venous catheterization as the preferred vascular access during newborn resuscitation (weak recommendation, very low certainty of evidence).If umbilical venous access is not feasible, the intraosseous route as vascular access during newborn resuscitation is a reasonable alternative (weak recommendation, very low certainty of evidence). |
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| Justification |
| In making this recommendation we recognize the absence of data from human neonatal studies supporting any advantage of intraosseous over umbilical venous access. There are a number of case reports of serious adverse effects of intraosseous access in neonates (Vidal 1993, 1201; Katz 1994, 258; Ellemunter 1999, F74; Carreras-Gonzales 2012, 233; Oesterlie 2014, 413; Suominen 2015, 1389). The rate of adverse effects attributable to emergency umbilical venous catheterization is unknown. The actual route used may depend on availability of equipment, training and experience. |

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| Subgroup considerations |
| No data available in neonatal resuscitation.  |

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| Implementation considerations |
| Although rarely used, training and maintenance of skills for both emergency umbilical venous catheter and intraosseous placement are important.  |

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| Monitoring and evaluation |
| Adverse events should be monitored and reported. |

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| Research priorities |
| KNOWLEDGE GAPSThere are many gaps related to IO access and umbilical vein access in newborn during resuscitation due to the absence of clinical trials, cohort studies and case-control studies. Even case series or case reports are not available on IO administration in neonatal resuscitation in the delivery room.Specific research is required in preterm and term neonates:* Determination time from start of CPR to achieve successful IO placement;
* Determination time from start of CPR to achieve successful IV umbilical vein placement;
* Optimal IO device suitable for newly born infants;
* Position of IO device (head of humerus, proximal tibia, other) to successful IO access;
* Short and long-term safety of IO placement during newborn resuscitation;
* Complications related to emergency umbilical venous catheterization;
* Pharmacokinetics and plasma availability of IO compared to IV administration of drugs;
* Training for IO placement and IV umbilical vein placement during neonatal resuscitation;
* How to best secure and maintain any emergency vascular access devices;
* Optimal method to determine correct placement of any emergency vascular access device;
* Do animal and simulation models translate to clinical practice?
* IO access during neonatal resuscitation outside the delivery room.
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