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REFERENCES:

1. Oskvarek JJ..Pines JM; US Acute Care Solutions Research Group. Opioid Prescription Reduction After Implementation of a Feedback Program in a National Emergency Department Group. Ann Emerg Med. 2022 May;79(5):420-432.
2. Pines JM, et al. The Impact of Advanced Practice Provider Staffing on Emergency Department Care: Productivity, Flow, Safety, and Experience. Acad Emerg Med. 2020 Nov;27(11):1089-1099.
3. Pines JM, et al. Under the Microscope: High Variability and Limited Construct Validity in Emergency Department Patient-Experience Scores. Ann Emerg Med. 2018 May;71(5):545-554.e6.

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Epinephrine for Out-of-hospital Cardiac Arrest

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Summary	Epinephrine increases the probability of Return of Spontaneous Circulation (ROSC) without improving survival or favorable long-term neurological outcome.
Source	Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest (OHCA) really worth it? J Crit Care 2015;30:1376–81.
Benefits in NNT	One in seven adult patients treated with epinephrine for OHCA achieved ROSC prior to hospital arrival. There was no benefit for survival to hospital discharge or survival at 1 month.
Benefits in percentage	Fourteen percent of adult patients treated with epinephrine for OHCA achieved ROSC prior to hospital arrival. There was no benefit for survival to hospital discharge or survival at 1 month.
Harms in NNT	One in 83 adult patients treated with epinephrine for OHCA had a worse long-term neurologic outcome.
Harms in percentage	A total of 1.2% of adult patients treated with epinephrine for OHCA had a worse long-term neurologic outcome.
Color recommendation	Red (no benefits)

EFFICACY ENDPOINT(S)

Prehospital ROSC, survival to hospital discharge, survival at 1 month.

HARM ENDPOINT(S)

Long-term neurologic outcome, defined as cerebral performance category (CPC) score of 1 or 2 (corresponding to independence in Activities of Daily Living).

WHO WAS IN THE STUDIES

A total of 655,853 patients from 13 observational studies and one randomized, controlled trial (RCT) involving patients who experienced out-of-hospital cardiac arrest (OHCA).

NARRATIVE

The original data supporting the use of epinephrine for cardiac arrest is rooted in a poorly controlled canine study[1] from the 1960s. The Advanced Cardiac Life Support (ACLS) recommendation that it "may be reasonable" to use epinephrine in cardiac arrest continues in contemporary practice. Yet, when the ACLS guidelines[2] are read carefully, they state that "for both survival to discharge and survival to discharge with good neurological outcome, there was no benefit" to receiving epinephrine.

Physiologically, epinephrine is theorized to promote peripheral vasoconstriction, thereby increasing diastolic pressure and coronary perfusion. Epinephrine also increases myocardial work and metabolic demand and may worsen tachydysrhythmia. Despite the purported physiologic benefits, it appears that epinephrine use for OHCA increases the rate of ROSC but does not increase the chance of survival (Table 1). Epinephrine may even worsen the neurologic outcome in patients who do survive. Epinephrine use for OHCA may therefore extend suffering and increase end-of-life health care costs due to intensive care and prolonged hospitalization without clear patient-centered, long-term benefits. Patients who survive to hospital discharge

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Table 1
Benefits and Harms Associated With the Use of Epinephrine in Prehospital Cardiac Arrest Between Epinephrine and No Epinephrine Groups*

	Epinephrine	No Epinephrine	Absolute Risk Difference	OR (95% CI)	NNT (or Harm)
Prehospital ROSC	19.7%	5.5%	14.2%	2.84 (2.3–3.5)	7 (NNT)
Survival at 1 month	5.4%	4.5%	0.9%	1.03 (0.79–1.34)	Not applicable (no benefit)
Survival at hospital discharge	5%	4.9%	0.1%	0.82 (0.46–1.48)	Not applicable (no benefit)
Good neurologic outcome (CPC score 1 or 2)	1%	2.2%	1.2%	0.51 (0.31–0.84)	83 (NNH)

*Source: Loomba, et al.[1]
CPC score = cerebral performance category score; NNH = number needed to harm; NNT = number needed to treat.

may be more likely to be dependent on others for care. This presents an obvious ethical quandary, as patient and family preferences may differ greatly with regard to life-prolonging therapies.

CAVEATS

The source meta-analysis[3] incorporated 13 observational studies and only one RCT:[4] Jacobs et al.[4] studied 601 patients and showed that epinephrine for OHCA was effective at increasing rate of ROSC (odds ratio [OR] = 3.4, 95% confidence interval [CI] = 2.0 to 5.6) and survival to hospital admission (OR = 2.3, 95% CI = 1.4 to 3.6) but lacked a statistically significant effect on survival to hospital discharge (OR = 2.2, 95% CI = 0.7 to 6.3). The observational trials included in the meta-analysis[3] attempted to control for potential confounders (i.e., time to cardiopulmonary resuscitation [CPR]) by propensity-matching individual study subjects, although bias can never be fully accounted for in any observational study. Similarly, the use of random-effects methods cannot fully control for heterogeneity when reporting pooled effects in meta-analyses, and three-fourths of reported outcomes had exceedingly high heterogeneity (I^2 = 96%). The source of heterogeneity may be patient characteristics, cointerventions, or trial-level and random-effects methods only attempt to adjust for between-trial variability, which can unintentionally inflate the effect of small studies on the pooled results.[5] Propensity-matched outcomes in individual studies were generally in agreement with the pooled outcomes in this meta-analysis[3] with the exception of survival at 1 month. The pooled results for 1-month survival may be confounded by the negative effect of smaller studies that were in favor of withholding epinephrine.

Specific effect modifiers in the included studies such as the timing and dosing of epinephrine administration may have influenced treatment effects on resuscitation outcomes. Earlier epinephrine administration has been associated with more favorable outcomes.[6–8] The "standard" 1 mg of epinephrine given in cardiac arrest is not weight-based and therefore can have a differential physiologic effect depending on the individual patient.[9] The meta-analysis[3] included some trials that used "high dose" (0.1 to 0.2 mg/kg) epinephrine, which may have contributed negatively to pooled outcome results. Epinephrine administered at higher doses may be harmful[10] and is not recommended by current guidelines.[2]

Loomba et al.[3] defines positive neurologic outcome as a CPC of 1 or 2, which represents mild or moderate cerebral dysfunction but ability to independently perform activities of daily living. This is a validated method of measuring neurologic outcome; however, trials included in the systematic review[3] measured the CPC at different time points (hospital discharge, 1 month, etc.), resulting in significant heterogeneity in the data. The "recovery time" prior to CPC assessment is an important confounder when determining neurologic outcome as are post-ROSC interventions such as targeted temperature management and urgent cardiac catheterization, none of which were adjusted for in the individual trials of this meta-analysis.[3] Therefore, the results of the meta-analysis pertaining to this outcome should be interpreted with caution. The data discussed in Loomba et al.[3] are primarily applicable to cardiac arrests that occur out of hospital, and conclusions may not apply to patients that experience cardiac arrest in the setting of an emergency department, hospital floor, intensive care unit, or operating room. In these more controlled hospital settings, epinephrine is more likely to be given earlier along with prompt defibrillation and high-quality CPR, and therefore its use for in-hospital cardiac arrests may result in different outcomes. Finally, this systematic review[3] analyzed only adult patients, and its conclusions should not be applied to the pediatric population.

Although in the past, there may have been barriers to performing true RCTs that must withhold potentially lifesaving, guideline-recommended, "standard of care" from a control group, a double-blind, RCT (PARAMEDIC-2)[11] was recently published and largely agrees with the meta-analysis.[3] After 8,014 patients were enrolled and followed in pragmatic fashion, PARAMEDIC-2 demonstrated that epinephrine increases survival to hospital admission and 30 days, with an NNT of 112 to prevent one death at 30 days. However, the additional proportion that received epinephrine and survived did so with severe neurologic disability (defined as 4 or 5 on the modified Rankin scale). There was no evidence of benefit in the proportion of patients who survived to hospital discharge with a favorable neurologic outcome (OR = 1.18, 95% CI = 0.86–1.61), and the lack of effect persisted at 3 months. This confirms that the use of epinephrine for OHCA is not patient-centered (as defined by patients and the public in preparation for the PARAMEDIC-2 trial) and will cause prolonged suffering in a severely disabled state.

In summary, we chose a color recommendation of "red" for epinephrine administration in OHCA. There is no patient-centered benefit and probable harm due to increased survival with worse long-term neurologic function.

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References

1. Pearson JW, Redding JS. Epinephrine in cardiac resuscitation. Am Heart J 1963;66:210–4.
2. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132(18 Suppl 2):S444–64.
3. Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? J Crit Care 2015;30:1376–81.
4. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43.
5. Costa BR, Jüni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. Eur Heart J 2014;35:3336–45.
6. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J 2012;76:1639–45.
7. Hubble MW, Johnson C, Blackwelder J, Collopy K, Houston S, Martin M. Probability of return of spontaneous circulation as a function of timing of vasopressor administration in out-of-hospital cardiac arrest. Prehosp Emerg Care 2015;19:457–63.
8. Hansen M, Schmicker RH, Newgard CD, et al. Time to epinephrine administration and survival from non-shockable out-of-hospital cardiac arrest among children and adults. Circulation 2018;137:2032–40.
9. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardiovascular life support: section 6: pharmacology II: agents to optimize cardiac output and blood pressure. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2000;102(Suppl 1):I129–35
10. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol 2014;64:2360–7.
11. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018;379(8):711–21.