**Clinical question.**

In adult patients in cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of vasopressors (epinephrine, norepinephrine, others) or combination of vasopressors (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O).

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<tr>
<th>Is this question addressing an intervention/therapy, prognosis or diagnosis?</th>
<th>Yes, therapy and prognosis</th>
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<tr>
<td>State if this is a proposed new topic or revision of existing worksheet:</td>
<td>New topic</td>
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**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

Pubmed: (adrenaline or noradrenaline or vasopressor) and (heart arrest or cardiac arrest) and therapy

ECC Master library: vasopress (all), epinephrine (all)

Hand review of bibliographies of selected articles

Hand review of C2005 worksheets bibliography

**State inclusion and exclusion criteria**

Inclusions: human studies, controlled trials, meta-analyses or case series

Exclusions: no abstract, abstract only, or non-English abstract, vasopressors without any previous human clinical trials, case reports, reviews, trauma arrest

**Number of articles/sources meeting criteria for further review:**

48
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
<td></td>
<td>(Goetting and Paradis 1991)A-D</td>
<td>(Goetting and Paradis 1989)A</td>
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<td>(Grmec and Mally 2006)A-D</td>
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<td>(Gonzalez, Ornato et al. 1989)E</td>
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<td>(Lindner, Prengel et al. 1996)A-D</td>
<td>(Barton and Callaham 1991)A</td>
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<td>(Matok, Vardi et al. 2007)A-D</td>
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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- *Italicics* = Animal studies
## Evidence Neutral to Clinical Question

| Good                        | (Aung and Htay 2005)A-D  
|                            | (Brown, Martin et al. 1992)A-D  
|                            | (Callaway, Hostler et al. 2006)A-D  
|                            | (Choux, Gueugniaud et al. 1995)A-D  
|                            | (Gueugniaud, David et al. 2008)A-D  
|                            | (Gueugniaud, Mols et al. 1998)A-D  
|                            | (Lindner, Dirks et al. 1997)A-D  
|                            | (Lindner, Ahnefeld et al. 1991)A-C  
|                            | (Olson, Thakur et al. 1989)A-C  
|                            | (Olasveengen, Sunde et al. 2009)A-D  
|                            | (Callaham, Madsen et al. 1992)A-D  
|                            | (Lindner, Ahnefeld et al. 1991) A-C  
|                            | (Patrick, Freedman et al. 1995)A-D  
|                            | (Perondi, Reis et al. 2004)A-C  
|                            | (Sherman, Munger et al. 1997)A-C  
|                            | (Stiell, Hebert et al. 1992)A-D  
|                            | (Stiell, Hebert et al. 2001)A-E  
|                            | (Turner, Parsons et al. 1988)A-D  
|                            | (Wenzel, Krismer et al. 2004)A-D  
|                            | (Carvolth and Hamilton 1996)A-C  |
| Fair                       | (Patterson, Boenning et al. 2005)A-D  
|                            | (Silfast, Saarnivaara et al. 1985)A  
|                            | (Vandycke and Martens 2000)A-D  
|                            | (Takeo, Kosaku et al. 2009)A-D  
|                            | (Carpenter and Stenmark 1997)A-D  |
| Poor                       | (Woodhouse, Cox et al. 1995)A-C  
|                            | (Morris, Derecky et al. 1997) E  
|                            | (Gonzalez, Ornato et al. 1988)E  
|                            | (Dieckmann and Vardis 1995)A-D  
|                            | (Mally, Jelatansev et al. 2007)A-C, E  
|                            | (Callaham, Barton et al. 1991)B-E  
|                            | (Ong, Tan et al. 2007)A-D  |

### Level of Evidence

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*A = Return of spontaneous circulation  
C = Survival to hospital discharge  
B = Survival of event  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*

## Evidence Opposing Clinical Question

| Good                        | (Behringer, Kittler et al. 1998)A,D  |
| Fair                       | (Herlitz, Ekstrom et al. 1995)A-C  |
| Poor                       | (Rivers, Wortsman et al. 1994)A, B, E  
|                            | (Chang, Ma et al. 2007)E  
|                            | (Duncan, Meaney et al. 2009)A-E  |

### Level of Evidence

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*A = Return of spontaneous circulation  
C = Survival to hospital discharge  
B = Survival of event  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
After review of the available human literature regarding the use of vasopressors to improve outcomes during cardiac arrest, we have been able to categorize the data into five topics from which to make assessments:

1. Any vasopressor vs. placebo
2. Vasopressin vs. Epinephrine
3. High Dose Epinephrine (HDE) vs. Standard Dose Epinephrine (SDE)
4. Alternative Vasopressors vs. Epinephrine
5. Vasopressors in Pediatric Arrest

1. Any Vasopressor vs. Placebo:

The most significant work related to this topic has just recently been published (Olasveengen, 2009, 2222). In this prospective study, the authors compare outcomes related to groups receiving intravenous drug administration vs. no intravenous drug administration for out-of-hospital cardiac arrest. They demonstrate improved short term outcomes in the intravenous group (ROSC, survival to hospital admission, survival to ICU admission) when compared to the no intravenous group. However, no significant differences are noted between the groups with regards to survival to hospital discharge or good neurologic outcomes. The individual contribution of vasopressors (epinephrine) to these survival data is not elucidated.

There is one prospective randomized control trial comparing high dose (HDE) and standard dose epinephrine (SDE) to placebo for the treatment of cardiac arrest (Woodhouse, 1995, 243). In the Woodhouse trial, patients were blindly randomized to receive HDE (10mg) or placebo (saline) during the first 5-10 minutes of arrest, followed by 1mg aliquots of epinephrine as per standard ACLS protocols. As there were many protocol violations in which 1mg epinephrine doses were given in place of the blinded drugs (likely due to practitioners fear of the patient receiving placebo), a third study arm was created post-hoc to include this group for comparison. The conclusions state that there were no differences in immediate survival or survival to hospital discharge between treatment groups. However, the study is methodologically flawed and is of overall poor quality. At the conclusion of the study, the patients had not been systematically randomized to a treatment groups, their treatment by clinicians was not truly blinded, and the groups were not treated equally.

There is a retrospective review comparing VF patients treated by EMS personnel authorized to administer epinephrine during ACLS to another group of VF patients treated by EMS personnel unauthorized to use epinephrine (Herlitz, 1995, 195) (N=1203). Those patients with sustained VF after 3 shocks and then treated with epinephrine were more likely to achieve ROSC and survival to admission. There was no difference in rate of hospital discharge in these patients (12/206 vs. 17/145). This conclusion was similar in patients who converted from VF to PEA or asystole (9/246 vs. 6/671). The LOE is fair, with poor confounder control.

One other study exists which examines patient populations before and after the introduction of epinephrine for use by the EMS system in Taiwan (Ong, 2007, 635) (N=1296). The conclusions demonstrated no improvement in ROSC, survival to hospital admission, or survival to discharge with the use of epinephrine. However, the study has methodologic issues including untreated patients in the treatment arm and is ranked LOE3-poor due to poor confounder control and group selection.

In summary, the data on which to draw conclusions related to the use of vasopressors vs. placebo during cardiopulmonary arrest is limited. The most recent and best performed study demonstrates significant improvement in short term survival statistics when using ACLS drugs, including epinephrine, but no improvement to hospital discharge or neurologic outcomes.

2. Vasopressin vs. Epinephrine:

There is a large body of literature related to the use of Vasopressin during cardiac arrest. Studies have documented the physiologic effects of the drug on patients including increased CPP in 4/10 cases after prolonged arrest (Morris, 1997, 878) and increased end-tidal CO2 and mean arterial pressure (MAP) on admission to hospital (Mally, 2007, R39). These parameters are all thought to correlate with improved survival. An early case series (Lindner, 1996, 1061) suggested possible benefit for vasopressin use. Two out-of-hospital randomized trials comparing vasopressin vs. epinephrine as first line therapy in cardiac arrest have been undertaken (Lindner, 1997, 535) (N=40); Wenzel, 2004, 105) (N=1186)), as well as one in-hospital trial (Stiell, 2001, 105) (N=200). Although the small initial study (Lindner, 1997) showed some improvement in survival to hospital admission, the larger studies demonstrated no difference in 1hr survival (Stiell, 2001), no change in survival to hospital admission in patients presenting with VF or PEA (Wenzel, 2004), or survival to hospital discharge (Stiell, 2001). There was noted to be improved rates of hospital admission and discharge in patients presenting with asystole treated with vasopressin vs. epinephrine (Wenzel, 2004). Furthermore, there appears to be some evidence to suggest that patients in refractory arrest treated with vasopressin have improved rates of survival to hospital admission and discharge (Lindner, 1996; Wenzel, 2004).

There is one study (Takeo, 2009, 755(N=336) that compares vasopressin alone vs epinephrine alone as the only vasopressor administered for OOHCA. The authors report no difference between groups with regards to ROSC, 24 hour survival, or survival to discharge. There is incomplete reporting for neurologic outcome data in this study. In this study, time to initial vasopressor dose exceeded 30 minutes for both groups.

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A systematic review and meta-analysis was undertaken (Aung, 2005, 17) using the three randomized control trials discussed (Lindner, 1997, 535; Stiell, 2001, 105; Wenzel, 2004, 105) as well as two studies excluded from our review (one was only presented as an abstract, one is written in Chinese). The meta-analysis revealed no differences in failure of ROSC, death before hospital admission, death within 24 hours, death before hospital discharge, and combination of number of deaths and neurologically impaired survivors. The authors view the improvements seen with vasopressin use in asystole and prolonged arrests, as delineated by Wenzel, cautiously.

Two recent randomized clinical trials have examined the use of vasopressin in combination with epinephrine vs. epinephrine alone as first line vasopressors during cardiac arrest (Callaway, 2006, 1316 (N=325); Gueugniaud, 2008, 21(N=2984)) after some initial supportive data had been reported (Guyette, 2004, 277). Callaway concluded that there was no improvement in ROSC and pulses at hospital arrival between the two treatments arms. Gueugniaud found no difference in ROSC, survival to hospital admission or discharge, 1 year survival, or neurologic outcomes between the two treatments arms.

There is a recent study randomized clinical trial comparing vasopressin, methylprednisolone, and epinephrine vs. epinephrine alone in in-hospital cardiac arrest (Mentzelopoulos, 2009, 15 N=100)). This study reports improved ROSC, survival of event, and survival to hospital discharge in the vasopressin and methylprednisolone group. Neurologic outcomes for this study are not reported. It is unclear whether the treatment benefits are related to vasopressin, methylprednisolone, or a combination of the two medications.

In summary, the use of vasopressin alone or in combination with epinephrine as the first line vaspressors during resuscitation from cardiac arrest offers no benefit related to short- and long-term survival compared to the use of epinephrine alone. However, no detrimental effects were demonstrated.

3. Adult High Dose vs. Standard Dose Epinephrine:

The use of epinephrine as a standard 1 mg dose dates to the 1960s. Animal studies suggested the use of high dose epinephrine (HDE) may improve outcomes over standard dose epinephrine (SDE). Initial human trials suggested improved outcomes with HDE. Improved ROSC, aortic and coronary perfusion pressures were reported (Gonzales, 1989, 920; Barton, 1991, 722; Paradis, 1991, 1139). One study showed improvement in ROSC for asystole with trends toward survival to hospital discharge (Lindner, 1991, 253). Retrospective (Carvolth, 1996, 219) and randomized clinical trials (Brown, 1992, 1051 (N=1280); Choux, 1995, 3 (N=536), Callaham, 1992,2667 (N=816), Gueugniaud, 1998, 1595 (N=3327), Linder, 1991, 253 (N=68), Lipman, 1993,192 (N=35), Sherman, 1997, 242 (N=140) and Stiell, 1992, 1045 (N=650)) were subsequently reported. These trials uniformly show no improvement in survival to hospital discharge and long-term survival with HDE compared to SDE. A meta-analysis of these studies confirmed no benefit in the pooled analysis (Vandycke, 2000, 161).

There is evidence that alterations in oxygen utilization following HDE results in worsened outcomes following resuscitation (Rivers, 1994,1499).

In summary, the data demonstrates that HDE confers no benefit over SDE for survival to hospital discharge and long-term survival.

4. Alternative Adrenergic Vasopressors vs. Epinephrine:

Several alternative vasopressors have been studied in comparison to, or as an adjunct with, the use of epinephrine. Methoxamine has been compared to epinephrine in three randomized clinical trials (Olson, 1989, 250 (N=51); Patrick, 1995,519 (N=145); Turner, 1988, 443 (N=80)). These studies are difficult to compare, as a wide range of doses was used (Olson, 1989: 0.5mg Epi and 5mg Methoxamine; Patrick, 1995: 2mg Epi and 40 mg Methoxamine; Turner, 1988: 1 mg Epi and 10 mg Methoxamine). These studies all demonstrated no benefit with methoxamine compared to epinephrine in ROSC or survival rates. Norepinephrine (NE 11mg) was compared to HDE (15mg) and SDE (1mg); (Callaham, 1992, 2667 (N=816)). Initial ROSC was higher in the NE and HDE groups. There were no significant differences between groups in terms of long term survival or neurologic outcome. A small study (Lindner, 1991, 427 (N=50)) compared SDE 1mg to NE 1 mg. They report improved ROSC with NE but similar rates of hospital discharge.

The addition of a dopamine infusion (15mcg/kg/min) in conjunction with escalating epinephrine boluses (1, 3, 5 mg) was compared to the use of epinephrine boluses alone by Gonzales, 1988, 868 (N=9). The continuous dopamine infusion did not generate additional increases in blood pressure. No other outcome data were collected or recorded during this study.

The alpha agonist phenylephrine 1mg was compared to epinephrine 0.5mg (Silfvast, 1985,610 (N=65)). They report identical rates of ROSC but no longer term data.

In summary, no other reported adrenergic vasopressor has been shown to be more effective than standard dose epinephrine.

5. Vasopressors in Pediatric Arrests:

There is limited human data in the pediatric literature regarding the use of vasopressors in cardiac arrest for this patient population. Six articles are related to the use of HDE vs. SDE in pediatric cardiac arrest (Carpenter, 1997, 403; Dieckmann, 1995, 901; Goetting, 1991, 22; Goetting, 1989, 1258; Patterson, 2005, 227; Perondi, 2004,1722). The articles by Goetting, et.al., describe two case series of patients using HDE after the administration of 2 doses of SDE in a small cohort. They found significant
improvement in ROSC and survival to discharge in those treated with HDE, but the sample size was small (N=40 for the larger study). An out-of-hospital, retrospective study comparing HDE, SDE and NE as the initial vasopressor used in the treatment group demonstrated no improvement in ROSC, survival to admission, survival to discharge, or neurologic outcome between the groups (Dieckmann, 1995). The study population was small (N=40 HDE, N=13 SDE, N=12 NE). The other retrospective review (Carpenter, 1997) examined the use of HDE vs. SDE for in-hospital arrest from all causes. There was no demonstrated difference in ROSC, short-term survival, long-term survival, or neurologic outcome scores between the HDE and SDE treatment groups (N=21 HDE, N=30 SDE). Both inpatient (Perondi 2004, N=68) and outpatient (Patterson 2005, N=154) prospective, randomized clinical trials report the same lack of improvement with HDE compared to SDE.

There is one case-series drawn from the AHA national registry of CPR (Duncan, 2009, 199 (N=1293) in which 64 patients received vasopressin for in-hospital CA and were reported to have worsened outcome related to ROSC, 24 hour survival, survival to discharge and neurologic outcome as compared to the no vasopressin group. The vasopressin group was confounded by longer arrest duration, and more than 98% of this group received epinephrine. The timing of vasopressin administration for the group is lacking.

There is one other pediatric case report on the use of terlipressin, a long-acting analog of vasopressin, in cardiopulmonary arrest after the administration of epinephrine (Matok, 2007, 1161). In seven pediatric patients with asystole and 8 episodes of refractory cardiac arrest treated with epinephrine, the use of terlipressin was associated with ROSC in 6 episodes, and 4 patients survived to hospital discharge without neurologic deficit.

Acknowledgements:

Citation List


Comments: LOE 1; good; neutral; This is a meta-analysis of 5 RCTs demonstrating no difference in outcomes (ROSC, death before hospital admission, death within 24 hours, death before hospital discharge, combined number of deaths and neurologic outcomes) between groups treated with vasopressin vs epinephrine for cardiac arrest. Subgroup analysis revealed no difference in outcomes base on initial rhythm.


Comments: LOE 4; fair; supporting; This is a case series of 10 patients treated with HDE vs 39 patients treated with SDE. ROSC was the main outcome measure. There is a relatively small sample size overall, particularly in the HDE group. This data is confounded by issues including distribution of presenting rhythms and variable medication doses defined as HDE. Relatively few patients in the SDE group received bystander CPR. No further outcomes are reported except a notation that no patients survived to hospital discharge.


Comments: LOE 3, good, opposing; This is a retrospective case series; There was a worsened neurologic outcome associated with a higher epinephrine dose in patients suffering VF cardiac arrest. Groups were well defined and the authors controlled for the main confounder "duration of arrest". Significant differences in CPC was demonstrated with 6 month follow-up included.

Comments: LOE1; good; neutral. This is a large RCT comparing SDE vs HDE for out-of-hospital cardiac arrest. This is a well conducted study reporting outcomes including ROSC, survival of event, survival to discharge, and neurologic outcomes. The neurologic outcome reported is "conscious at hospital discharge" as opposed to a CPC score. The dosing of epinephrine is well-defined in each group.


Comments: LOE 3; poor; neutral. This article is a retrospective analysis of potential complications of epinephrine administration for cardiac arrest comparing patients treated with HDE vs SDE. Potential complications examined include deleterious rhythms, serum laboratory values, hemodynamics, and neurologic status at time of discharge. The definition of HDE was calculated retrospectively, making the group selection appeared biased. Other confounders were poorly controlled.


Comments: LOE1; good; neutral. This is a large RCT comparing patients treated with vasopressin and epinephrine vs epinephrine and placebo for out-of-hospital cardiac arrest. This is a well-performed study with outcomes reported including ROSC, survival to admission, and survival duration. There is non-standardized neurologic outcome data.


Comments: LOE 3; fair, neutral. This is a restropective review examining comparing HDE and SDE for in-patient pediatric cardiac arrest from all causes. There is poor confounder control and follow-up is not done. Repeated arrests in 7 cases are reported as independent events. Outcome measures include ROSC, survival of event, survival to discharge, and scaled neurologic assessment (Pediatric Outcome Measures Category) at discharge.


Comments: LOE 3; good; neutral. This study compares SDE vs HDE for out-of hospital cardiac arrest. It compares outcomes of a prospectively treated HDE group using a retrospective SDE group as a control group. Outcomes reported include ROSC, survival of event, and survival to discharge. There is no neurologic or long-term follow-up reported. The dosing of HDE is standardized in the study but not typical of other studies. No differences in reported outcomes are noted.

Comments: LOE 4; poor, opposing; Case series of examining outcome of postarrest myocardial dysfunction; Patients who received >5mg epinephrine were found to have a lower EF. Neurologic outcome was scored but not part of the conclusion. Confounders for the groups were not controlled. No patient follow-up is recorded.


Comments: LOE1; good, neutral; RCT of HDE vs SDE; Long-term follow-up included.


Comments: LOE 3; poor, neutral; This is a retrospective cohort study in prehospital pediatric arrest; Patients were treated with either SDE, HDE or no epinephrine but were not randomly assigned to a treatment group. There is long-term follow-up but confounders are poorly controlled.


Comments: LOE4; poor, opposing; Pediatric arrest patients from a large national database Compared outcomes between patients who were treated with vasopressin vs those who did not receive vasopressin. No confounder control. Few patients received vasopressin (64 of 1293) for comparison.


Comments: LOE 3; poor, supporting; Small trial of pediatric patients treated with HDE after failure to respond to 2 doses of SDE; retrospective outcome comparison to 20 previous pediatric arrest patients treated with SDE alone. No confounder control; only measured ROSC as outcome.


Comments: LOE 3; good, supporting; Prospective pediatric patients treated with HDE after failure of SDE compared to retrospective control group treated with SDE for cardiac arrest. This study appears to be a continuation of a study previously published by the same authors with an increased number of patients. Outcome measures include ROSC, hospital discharge and neurologic assessment.


Comments: LOE 4; good, supporting; Reports measurement of radial artery blood pressure and end-tidal CO2 after prolonged arrest and repeated doses of epinephrine. Patient serves as own control in this dose-response study (1, 3 and 5mg doses of epinephrine). BP improves with higher dose epinephrine and ETCO2 decreases.

Comments: LOE2; poor, neutral; This is a trial of patients treated with increasing doses of epinephrine with or without simultaneous dopamine for cardiac arrest. Outcome measurement is blood pressure. Patients not randomized to groups and there is a small sample size in each group. No difference is seen with the addition of dopamine.


Comments: LOE 3; good, supporting; Retrospective case control study demonstrating benefit in patients treated with vasopressin for VF and pulseless VT arrest for outcomes of ROSC and 24 hour survival. Not significantly different between groups for survival to hospital discharge or neurologic outcomes but grossly underpowered for the latter assessments.


Comments: LOE1; good, neutral. Large RCT with no difference in outcomes including ROSC, survival to admission, survival to discharge, or neurologic outcomes. One year survival unchanged; no one year neurologic follow-up.


Comments: LOE1; good, neutral; Large RCT HDE vs SDE. Demonstrated improvement to ROSC and survival to hospital admission. No improvement to hospital discharge. Higher inhospital mortality for the HDE group.


Comments: LOE 3; poor, supporting. Retrospective control of out-of-hospital cardiac arrest comparing patients treated with vasopressin and epinephrine vs epinephrine alone. Outcomes include ROSC and pulse in ED, both improved in patients treated with the combination of vasopressin and epinephrine. Small sample size and a large selection bias limit this study.


Comments: LOE2; fair; neutral; opposing. Out-of-hospital cardiac arrest patients treated with epinephrine or no epinephrine by EMS personnel. Study uses nonrandomized concurrent controls. Outcomes of improved ROSC and survival to hospital admission in patients treated with epinephrine. No difference between groups in survival to hospital discharge. Poor confounder control.

Comments: LOE 1; good, neutral. RCT with 50 patients written as a 2 page abstract formula. 25 patients per group. Comparing the epinephrine to the norepinephrine group: 6/25 vs 14/25 had ROSC, 4/25 vs 6/25 to survived to hospital discharge. There is no neurologic outcomes reported.


Comments: LOE1; good, neutral. Includes 68 inpatient and out-of hospital cardiac arrest patients with asystole or PEA. Compared HDE vs SDE with outcomes including ROSC, survival to hospital admission and survival to discharge. ROCS improved for asystole group; no difference in other outcomes.


Comments: LOE1; good, neutral; RCT with small number of patients. Improved ROSC and survival to hospital admission in vasopressin group. Patient numbers too small to demonstrate outcome differences beyond these findings. Survival to hospital discharge and neurologic outcomes included.


Comments: LOE4; good, supporting. Case series of 8 patients who received ACLS including defibrillation and epinephrine without success, then improved after receiving vasopressin. Outcomes including ROSC, survival to hospital admission, survival to hospital discharge, and neurologic assessment at discharge.


Comments: LOE 1; good, neutral; Inhospital arrest study with mostly septic patients on vasopressors at time of arrest, including epinephrine and dobutamine. Outcomes measured include ROSC, survival of event, and discharge from ICU. Outcomes related to death from overwhelming sepsis.


Comments: LOE3; poor, neutral. Prehospital retrospective study of epinephrine vs vasopressin demonstrating improvement in ROSC and survival to admission but no difference in survival. Other endpoints include ETCO2 and Mean arterial pressure. Patient selection bias as vasopressin was intermittently unavailable. Confounders poorly identified.


Comments: LOE 4, fair, supporting. Case series of 8 arrest events in 7 patients from the pediatric ICU using terlipressin (a vasopressin analog) at some point during the arrest. Outcomes measured include ROSC, survival of event, survival to hospital discharge and neurologic outcome. Confounders are poorly controlled.

Comments: LOE1; good, supporting. RCT comparing vasopressin, epinephrine and methylprednisilone treated patients to epinephrine alone for in-hospital cardiac arrest. Outcome measures include ROSC, survival of event, survival to hospital discharge and neurologic outcomes. Other measurements included hemodynamics, number of organ-failure free days, serum markers and central venous oxygenation.


Comments: LOE2; poor, neutral. Study of 10 patients acting as own controls who failed ROSC for out-of-hospital cardiac arrest. Each patient received epinephrine and then vasopressin 5 minutes later after prolonged arrest. Comparison of calculated coronary perfusion pressure was undertaken between the 2 treatments. 4 of 10 patients had improved CPP after vasopressin during prolonged arrest. There were no survivors.


Comments: LOE1, good, neutral. RCT of patients receiving intravenous drugs vs no intravenous drugs for OOHCA. Intravenous drug group with improvement in ROSC, survival to hospital admission, survival to ICU admission. No difference between groups for survival to hospital discharge or good neurologic outcomes. Does not separate influences of individual drugs (vasopressors/antiarrhythmics/vagolytics).


Comments: LOE1; good, neutral. RCT comparing 0.5 mg epinephrine to 5mg methoxamine for prehospital ventricular fibrillation arrest after initial defibrillations. Outcomes include ROSC, survival of event, survival to discharge. Improvement in ROSC noted in epinephrine group, otherwise no differences were noted.


Comments: LOE3, poor, neutral. Prehospital study performed in Taiwan comparing patients treated with epinephrine after it was added to EMS protocols for OOHCA to retrospective control group of OOHCA patients prior to the use of epinephrine by EMS. 44% of treatment group did not receive epinephrine due to a protocol restriction. Outcomes measured include ROSC, survival of event, survival to discharge, and neurologic outcome. Poor group selection and poor confounder control limit the utility of this study.


Comments: LOE2; fair, supporting; Human model of prolonged cardiac arrest with patients serving as own control. Compares calculated coronary perfusion pressures after receiving SDE to coronary perfusion pressures when the patients later received HDE after no response to SDE. Outcome measures include
ROSC, survival of event, survival to discharge, and coronary perfusion pressures. Four of 35 patients had ROSC; there were no survivors to hospital discharge.


Comments: LOE1; good, neutral. RCT with both OOHCA and inhospital witnessed cardiac arrest comparing the use of methoxamine to epinephrine. Outcome measures include ROSC, survival of event, survival to hospital discharge, and neurologic outcomes. No differences are noted.


Comments: LOE1; fair, neutral. Multicenter, prospective, unblinded comparison of HDE vs SDE as initial emergency department dose for out-of-hospital pediatric cardiac arrest. Includes traumatic and nontraumatic arrest. Methodologic issues exist related to randomization into groups. 95/154 nontrauma patients were in the HDE group. Outcome measures include ROSC, survival of event, survival to discharge and neurologic outcomes. No differences in outcome were noted.


Comments: LOE1; good, neutral; RCT of HDE after SDE for inhospital pediatric cardiac arrest. Improved outcomes in 24 hour survival in SDE group, but no differences noted in ROSC, survival to discharge.


Comment: LOE2; poor, opposing; Compares physiologic variables in patients treated with less than 15mg of epinephrine to those receiving more than 15mg epinephrine after ROSC for cardiac arrest. Notes differences in hemodynamic parameters, oxygen indices, mean arterial pressure, and serum laboratory values. There are poor confounder controls and poor selection criteria to define cut-off point for HDE definition.


Comments: LOE1, good, neutral. Compares use of HDE vs SDE after prolonged cardiac arrest. Outcomes include ROSC, survival of event, and survival to discharge. No difference in outcomes were noted, but the study did not achieve the appropriate sample size based on power calculation and the study was terminated early due to a variety of factors.


Comments: LOE1, fair, neutral; RCT comparing epinephrine to phenylephrine for OOHCA. Patients received relatively low epinephrine doses, but there was no difference in ROSC between the groups (28% and 31% ROSC respectively). No other outcomes reported.

**Comments:** LOE1; good, neutral. RCT of both inhospital and out-of-hospital cardiac arrest patients treated with HDE vs SDE. No differences in outcomes were noted including ROSC, survival of event, survival to hospital discharge, or neurologic outcomes.


**Comments:** LOE1; good, neutral. RCT of inhospital and out-of-hospital cardiac arrest patients treated with vasopressin or epinephrine as the initial vasopressor, followed by epinephrine. No differences between the groups were noted including ROSC, survival of event, survival to hospital discharge, or neurologic outcome. Includes analysis of adverse effects of the medication and 30 day survival outcomes.


**Comments:** LOE1; fair, neutral. RCT comparing vasopressin alone vs epinephrine alone as the only vasopressor administered for OOHCA. The authors report no difference between groups with regards to ROSC, 24 hour survival, or survival to discharge. In this study, time to initial vasopressor dose exceeded 30 minutes for both groups. Methods of randomization not included in article.


**Comments:** LOE1; good, neutral. RCT of inhospital and out-of-hospital pulseless electrical activity cardiac arrest patients comparing epinephrine to methoxamine as the vasopressor given throughout the resuscitation. No difference in outcomes were noted including ROSC, survival at multiple time points after the event, and survival to discharge. There was one survivor from the entire cohort with CPC 4 from the epinephrine group.


**Comments:** LOE1; fair, neutral; Meta-analysis of 5 manuscripts comparing HDE vs SDE for the treatment of cardiac arrest. Authors only searched Medline database. Authors did not list excluded articles. No clear PICO question was identified.


**Comments:** LOE1; good, neutral. Large RCT comparing patients treated with vasopressin vs epinephrine as the initial vasopressor in OOHCA. Using logistic regression analysis, no differences in outcomes were noted for patients with ventricular fibrillation orPEA arrest including ROSC, survival to hospital admission, survival to hospital admission, or neurologic outcome. There is a possible improvement in ROSC, survival to hospital admission and survival to hospital discharge for asystolic arrest in the vasopressin group based on subgroup analysis.

Comments: LOE1; poor, neutral; RCT to initial evaluate HDE vs placebo for OOHCA. In this study, there were many protocol violations in which 1mg epinephrine doses were given in place of the blinded drugs (likely due to practitioners fear of the patient receiving placebo). A third study arm was created post-hoc to include this group for comparison. The conclusions state that there were no differences in immediate survival or survival to hospital discharge between treatment groups. However, the study is methodologically flawed and is of overall poor quality. At the conclusion of the study, the patients had not been systematically randomized to a treatment groups, their treatment by clinicians was not truly blinded, and the groups were not treated equally.