

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**Worksheet author(s)**

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Date Submitted for review: 27 August 2009**Clinical question.**

In adult and pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) (P), does the use of vasopressin or vasopressin + epinephrine (I) compared with standard treatment recommendations (C), improve outcome (eg, ROSC, survival to hospital discharge, or survival with favorable neurologic outcome) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet:

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).

Search Strategy A: "cardiac arrest" AND "vasopressin" AND NOT "animal"
Search Strategy B: "cardiac arrest" AND "vasopressin" AND "animal"

By reviewing titles/abstracts resulting from each search and using inclusion/exclusion criteria, references were selected for more detailed review. Manually reviewed references contained in the selected articles and in selected comprehensive reviews to find other relevant studies.

ENDNOTE X ECC Master Library 24 March 2008

Search Strategy A: 64 references: After exclusions → 10 references (1 ped case/1 ped case series / 8 adult studies)

Search Strategy B: 62 references: After exclusions → 2 ped animal references; 15 adult animal references

PUBMED (NLM) August 2009

Search A: 124 references: After exclusions → 18 references (3 ped/15 adult)

Search B: 123 references: After exclusions → 2 ped animal references; 15 adult animal references

EMBASE (Oct 2009)

Search Strategy A: "heart arrest" AND "vasopressin" AND (article OR article in press OR review) AND (geriatric or internal medicine or pediatrics or preventive health) AND humans → 108 references.

Search Strategy B: "heart arrest" AND "vasopressin" AND (article OR article in press OR review) AND animals → 34 references

Neither strategy revealed new references from those found by using PUBMED or ENDNOTE X ECC Master Library

COCHRANE Review August 2009

Searched with MESH terms: heart arrest AND vasopressin → 2 structured abstract reviews

1) Does Vasopressin improve survival. (Pellegrino, AM. Emergency Medical Services 2006; 35(3) 86-92

2) Vasopressin for cardiac arrest: a systematic review and meta-analysis. (Aung K, Htay T; Archives of Internal Medicine 2005; 165 (1): 17-24

Combining Endnote X, PubMed and Cochrane Review Searches and eliminating duplicates, the results for further detailed review were:

- 1) 4 Pediatric references including 1 case report
- 2) 15 Adult references (3 were either systematic reviews or dealt with changes in physiologic parameters as primary outcomes)
- 3) 17 Animal references (2 pediatric and 15 adult)
- 4) 2 Cochrane Reviews (Aung review is included under 2)

• State inclusion and exclusion criteria

Excluded: references that were comments, general reviews (but not meta-analyses), opinions, studies where vasopressin was compared to other drugs (except epinephrine), adult case reports (since RCTs available). Excluded studies dealing with post-resuscitation use of vasopressin, adult animal studies, studies addressing physiologic variables (e.g. coronary artery perfusion pressure, end-tidal pCO₂)

Included: randomized controlled trials (RCT), meta-analyses of RCTs, case series, studies using retrospective controls, pediatric case reports (since very little evidence available), pediatric animal studies; included only articles which addressed vasopressin use in cardiac resuscitation and studies that looked at patient outcomes such as hospital admission/discharge, ROSC, survival/mortality, neurologic outcomes.

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

DETAILED REVIEW: 4 pediatric references (including one case report)
13 adult references (including two meta-analyses)
2 pediatric animal references

Summary of evidence

Evidence Supporting Clinical Question

Good				Gil-Anton 2010 ^{ABCD}	Wenzel ^{ABC} 2004 (asystole) (Adult – LOE 1) Voelckel 2002 ^{AE} Lindner 1997 ^B (Adult LOE 1) <i>Biondi-Zoccai^A (meta-anal 33 studies incl 2 adult)</i>
Fair				Mann 2002 ^{ABC}	Grmec 2006 ^{A,B,C} (Adult LOE 3) Lindner 1996 ^{ACD} (Adult LOE 4) Mentzelopoulos ^{ABC} (Adult – LOE 1)
Poor				Matok 2007 ^{ABC}	Guyette 2004 ^{AB} (Adult LOE 2)
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Animal studies(pediatric)

Evidence Neutral to Clinical question

Good					Callaway 2006 ^{ABC} (Adult LOE 1) Gueugniaud 2008 ^{ABCDE} (Adult LOE 1) Lindner 1997 ^{ACD} (Adult LOE 1) Mukoyama 2009 ^{ABCD} (Adult LOE 1) Stiel 2001 ^{ABCD} (Adult LOE 1) Voelckel 2000 ^{AC} Wenzel 2004 ^{ABC} (VF/PEA) (Adult LOE-1) Aung 2005 ^{ABCD} (Adult LOE 1 – meta-analysis) Biondi-Zoccai 2003 ^{AC} (Adult LOE 1 – meta-analysis) Wyer 2006 ^{CD} (Adult LOE 1 – EB Review)
Fair					Grmec 2006 ^D (Adult LOE 3)
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Evidence Opposing Clinical Question

Good		Duncan 2009 ^{ABCD}			
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Gueugniaud E= survival for 1 year

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:Pediatric

There are 3 human pediatric studies^{4, 12, 13} that provide information about the use of vasopressin in cardiac arrest. Mann 2002¹² is a retrospective review of 6 (out of 70) inpatient pediatric cardiac arrests (4 patients - 2 asystolic, 2 ventricular fib/pulseless v tach) in which vasopressin was used as rescue therapy with apparent benefit. Matok 2007¹³ is a retrospective review of 8 pediatric asystolic arrests (7 patients) where terlipressin was used as a rescue medication in refractory arrest. In both of these reviews, confounding variables include high dose epinephrine use in the majority of arrests, presence of complex cardiac disease (cardiac surgery), and the use of magnesium. Duncan 2009⁴ reported a retrospective review of 1293 inpatient pediatric arrests entered in a central registry (NRCPR) over a five year period from multiple institutions in the US. Only 5% of patients received vasopressin and this was correlated with longer arrests and location in a pediatric intensive care unit. In a multivariate analysis, vasopressin was associated with decreased ROSC but no difference in 24 hr or discharge survival. Finally, there is a single case report⁹ (Lienhart 2005) where a combination of standard dose epinephrine and vasopressin was used successfully in a hypothermic (29.4 C) patient with a submersion related cardiac arrest.

Two pediatric model animal studies (piglet) by the same investigator (Voelckel 2000, 2002)^{17,18} demonstrated that (1) in a prospective, randomized trial comparing vasopressin, high dose epinephrine, and combined vasopressin and epinephrine in asphyxial arrest, epinephrine was better than vasopressin for ROSC and vital organ perfusion; and (2) in a similar design, but with lower doses of epinephrine and vasopressin initially, vasopressin resulted in better outcomes in piglets with ventricular fibrillation cardiac arrest. The difference in dosing may have caused this different outcome from that attained in the first study.

Data derived from adult studies suggest that vasopressin is likely not useful in either out of hospital or in-hospital arrest cardiac arrest although could be attempted as rescue therapy. (see below). Thus, data from other patient populations would not support use of vasopressin in pediatric cardiac arrest patients.

Adult

Although there is some evidence in adult studies^{5,7,10,19} that vasopressin may improve outcome in sub-populations of adult cardiac arrest patients, at least four large, prospective, randomized controlled adult cardiac arrest trials^{3,6,15, 16} (three out-of-hospital, one in-hospital) do not demonstrate improvement in cardiac arrest outcomes with vasopressin regardless of initial rhythm. In two other studies^{7,19} benefit of vasopressin was found only in out-of-the hospital patients who had an asystolic arrest, but not in patients who had ventricular fibrillation or pulseless electrical activity. In an earlier randomized controlled trial of only 40 patients in ventricular fibrillation¹⁰, there was no benefit in ROSC or hospital discharge, but only benefit in 24 hour survival. Only a small observational cohort study of 109 out-of-hospital cardiac arrest patients⁵ over three sequential time periods, showed statistically significant benefit of vasopressin over epinephrine as a first line drug in ROSC, 24 hr survival and a trend towards better hospital discharge. Finally, two meta-analyses^{1,2} and one high quality evidence-based analysis using random effects model²⁰ indicate no benefit of vasopressin over epinephrine in the management of adult cardiac arrest, either by itself or in combination with epinephrine. One additional randomized controlled trial¹⁴ of inpatient adult cardiac arrest patients has shown improvement in ROSC and hospital discharge when a combination of high dose (up to 160 IU) vasopressin + epinephrine + methylprednisolone is used. However, the study does not analyze sub-groups by rhythms and it is not clear whether the benefit is from the steroids, the high doses of vasopressin or the fixed combination.

A summary of these studies by initial rhythm is shown below:

	No Improvement	Improvement
Asystole	Callaway 2006 Gueugniaud 2008 Mukoyama 2009 Stiell 2001 * Aung 2005 (meta-analysis including Stiell/Wenzel/Lindner studies) Biondi-Zoccai 2003 (meta-analysis including Stiell/Lindner studies) Wyer 2006 (evidence-based analysis – Stiell/Wenzel/Lindner studies)	Guyette 2004 (ROSC, pulse ED arr) Wenzel 2004 (Hosp Adm, Hosp D/C)

V Fib/PEA	Guyette 2004 Wenzel 2004 Callaway 2006 Gueugniaud 2008 Mukoyama 2009 Stiell 2001* Aung 2005 (meta-analysis including Stiell/Wenzel/Lindner studies) Biondi-Zoccai 2003 (meta-analysis including Stiell/Lindner studies) Wyer 2006 (evidence-based analysis – Stiell/Wenzel/Lindner studies)	Grmec 2006 (ROSC, Hosp D/C) Lindner 1997 (ROSC, 24 hr surv)
<p>Thus, the preponderance of evidence in adult studies is that vasopressin is of no benefit except possibly as a rescue therapy in selected cases, particularly prolonged arrest (Lindner 1996, Lee 2001). None of the studies, however, showed that there were adverse events from the use of vasopressin either by itself or in combination with epinephrine.</p>		
<p>Acknowledgements:</p>		

Citation List

1. Aung, K. and T. Htay, *Vasopressin for cardiac arrest: a systematic review and meta-analysis*. Arch Intern Med, 2005. **165**(1): p. 17-24.

Comments: LOE 5 Ped (LOE 1 Adult) Quality - Good; Direction - Negative

Meta-analysis included 5 RCTs, including the ones by Stiell, Wenzel, Lindner, Lee and Li. The first three satisfied the highest quality as measured by a Jadad score of 5; the latter two were not well described in the literature and only had a Jadad score of 2. The Wenzel study contained 38% of the patients. Tests for heterogeneity showed that 67% of the variation across the studies was due to heterogeneity rather than chance, with most of the heterogeneity secondary to differences in initial rhythm. There was no publication bias noted. Results of the meta-analysis of the pooled data show that there is no benefit of vasopressin over epinephrine with respect to ROSC, death before hospital admission, death within 24 hours, death before hospital discharge or combination of deaths and neurologically impaired survivors. This lack of effect continued in sub-group analysis by rhythm - v.fib, pulseless electrical activity and asystole (confidence intervals included or were at 1.0, indicating no effect). Mention is made of the Callaway study that was in process at the time. This RCT also showed no effect.

2. Biondi-Zoccai, G.G., et al., *Is vasopressin superior to adrenaline or placebo in the management of cardiac arrest? A meta-analysis*. Resuscitation, 2003. **59**(2): p. 221-4.

Comments: LOE 5 Ped (LOE 1 Adult; Animal) Quality - Fair Direction: Positive for animal studies; neutral for adult

This is a meta-analysis of 33 animal studies dealing with vasopressin for cardiopulmonary arrest either compared to placebo or compared to epinephrine. ROSC is primary outcome variable. Tests of heterogeneity were done and found to be negative. The meta-analysis also included two adult studies, one with 40 patients and the other with 200 patients. A much larger study was still pending at the time of the meta-analysis. Outcome variables were ROSC and survival to hospital discharge. Quality of the studies was not assessed. There was no statistical heterogeneity in the study. Confidence limits in pooled data were too wide to determine a true effect.

3. Callaway, C.W., et al., *Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest*. Am J Cardiol, 2006. **98**(10): p. 1316-21.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Good; Direction - Negative (vasopressin does not improve outcome)

Excellent study. Prospective, randomized, placebo-controlled, blinded (with testing of adequacy of blinding), single EMS system study of adult out-of-hospital non-trauma arrest patients treated with vasopressin or saline after initial epinephrine.. Outcomes measured were ROSC of any length, presence of pulse at admission to ED, survival for one day, and 1 yr survival. No neurologic outcomes were measured. Both univariate and multiple logistic regression statistics were applied, the latter to control for known possible confounding variables such as witnessed arrest, bystander CPR, time from dispatch to study drug, etc. . Analysis done by ECG rhythm for primary outcomes and no differences between groups noted. 1 yr survival assesment done by Kaplan-Meier survival curves. No differences between groups were noted in contrast to the authors'; previous retrospective review in same system where improvement with vasopressin was noted in the asystole group.

4. Duncan, J.M., et al., Vasopressin for in-hospital pediatric cardiac arrest: results from the American Heart Association National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med*, 2009. **10**(2): p. 191-5.

Comments: LOE 2 Ped ; Quality - Good; Direction - Opposing

Retrospective review of all pediatric (< 18 yr) inpatients who required CPR and were entered into a national, multi-institutional CPR registry and who had a completed resuscitation record. Variables recorded were based on Utstein standardized guidelines and outcomes were clearly defined as ROSC>20 min, 24 hr survival, hospital discharge, and neurologic outcome as measured by the Pediatric Cerebral Performance Category scale. Comparison groups were those patients who had received vasopressin (64) vs. those who had not (1229). Both univariate and multivariate logistic regression analysis were done to determine characteristics that correlated with vasopressin use. Event survival was significantly and negatively correlated with vasopressin use after multivariate analysis was performed to minimize possible confounding variables (cardiac arrest < 15 min, age, illness category, initial rhythm, trauma, ECMO, epinephrine use, dopamine, use, tc pacing, hospital type, pulse oximeter use and open chest CPR). There was also a negative correlation of vasopressin use and survival of 24 hrs, survival to hospital discharge and favorable neurologic outcome; however, this did not reach statistical significance.

5. Gil-Anton, J., et al., *Pediatric cardiac arrest refractory to advanced life support: is there a role for terlipressin?* *Pediatr Crit Care Med*, 2010. **11**(1): p. 139-41.

Comments: LOE 4 Ped; Quality: Good; Direction: Supportive

Case series of 5 children from 5 mos-12 yr with in-pediatric ICU cardiac arrest each of whom received terlipressin after at least three epinephrine doses, using standard international guidelines for resuscitation. However, three of the patients received high dose epinephrine, not currently recommended as standard therapy. Terlipressin dose ranged from 10-20 mcg/kg. Etiology of cardiac arrest was sepsis in 4 and bilateral pneumothorax with pneumonia/BPD in 1 pt. At the time of arrest, ECG showed bradycardia-asystole in 3 patients, vent. bradycardia in 1, asystole in 1. The design was prospective, IRB approved, involved informed consent for compassionate drug use by family, reporting to hospital director and state pharmacy administration, identified a responsible physician and commitment to report the results. No control group was analyzed. ROSC occurred in 4/5 patients. Two patients died within 24 hours, two were discharged without sequelae and good neuro status (pediatric cerebral performance category=1) which persisted in 8 and 12 months of clinical follow-up. Two of the 3 patients who received high dose epinephrine died; 1 survived.

6. Grmec, S. and S. Mally, *Vasopressin improves outcome in out-of-hospital cardiopulmonary resuscitation of ventricular fibrillation and pulseless ventricular tachycardia: a observational cohort study.* *Crit Care*, 2006. **10**(1): p. R13.

Comments: LOE 5 Ped (LOE 3 Adult); Quality - Fair; Direction - Positive (for vasopressin improving outcomes)

Prospective, observational cohort study of pre-hospital adults with v fib or pulseless v tach as initial rhythm, using historical controls over three time periods. Comparison of epi only (1998-2000, n=51), epi + vasopressin (2000-

2003; n=31) and vasopress ± epi (2003-2004; n=27). Small numbers and although time to CPR (6-7 minutes) is not significantly different, no data is present w.r.t. time of first and subsequent defibrillation attempts or time of first drug administration. Nevertheless, since epi was given every 3 minutes, and time to resuscitation (ROSC) was measured, it appear that first dose of meds was probably given within several minutes after initiation of CPR. Vasopressin treated cohort had better ROSC with hospitalization, better 24 hour survival and a trend toward better hospital discharge. This positive effect of vasopressin may have been related to early initiation of CPR across all groups i.e. vasopressin works best if there is also early initiation of CPR. The sub-group with AMI did better in all outcomes with vasopressin.

7. Gueugniaud, P.Y., et al., Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med*, 2008. **359**(1): p. 21-30.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Good; Direction: Opposes

Large, multicenter, prospective, randomized, control trial of 2956 adult patients with out of hospital cardiac arrest associated with asystole, pulseless electrical activity and ventricular fibrillation. Exclusions were pts < 18 yr, successful defibrillation without use of a vasopressor, traumatic cardiac arrest, pregnancy, documented terminal illness, presence of DNR order and obvious signs of irreversible cardiac arrest. After 3 initial defibrillation attempts (without drugs), 1442 patients were randomized to receive 1 mg epi + 40 IU vasopressin, and 1452 pts were randomized to receive 1 mg epi + saline. If pt did not have ROSC within 3 minutes, the same combinations were given again and if still no ROSC, both groups were given epinephrine and usual care. Excluded from analysis (no consent when arrived at hospital or did not meet inclusion criteria) were 2.1% of total patients without significant difference between groups. Outcomes were clearly defined as survival to hospital admission, ROSC, survival to hospital discharge, good neurologic recovery (defined by standardized CPC score of 1), survival x 1 yr. Large majority of patients were in asystolic arrest (82-83%) in both groups with only 9 % with v fib and 8% pulseless electrical activity. Bystander CPR was about 27% in both groups; Time to EMT with defib capability was about 7 minutes, Advanced Life Support was about 16 minutes, first injection of drugs was about 21 minutes in each group. Of note is that 79% had automated external defibrillation even though initial rhythm was a shockable rhythm only 9% of the time. Only 21% survived to hospital admission and only about 2% survived to hospital discharge (no difference between groups). One wonders whether the relatively long period of time of 21 minutes before receiving the medications as well as the presence of asystole in the majority of patients may have resulted in little response no matter what drugs were used.

8. Guyette, F.X., et al., Vasopressin administered with epinephrine is associated with a return of a pulse in out-of-hospital cardiac arrest. *Resuscitation*, 2004. **63**(3): p. 277-82.

Comment: LOE 5 Ped (LOE 2 Adult); Quality - Poor; Direction - Positive (vasopressin improves outcome for asystole)

Retrospective, small, observational study in a single urban EMS system of all adult out-of-hospital cardiac arrest patients to which a physician (resident) was sent. Traumatic and obstructed airway cardiac arrests were excluded. Vasopressin was administered per judgment of physician and not according to any fixed protocol. Comparison between the group of patients receiving only epinephrine and those receiving epinephrine + vasopressin was done by using univariate and multivariate logistic regressions. Outcomes were: return of a pulse (ROSC) and presence of a pulse at hospital arrival. Results in sub-group analyses suggest statistically significant better outcome with combination of vasopressin+epinephrine rather than with epinephrine alone in the patients with asystole, but not in patients with with vfib or pulseless electrical activity. Weaknesses are: not blinded w.r.t. vasopressin use, physician determined use of vasopressin without written indications,, no further follow-up after admission to the ED including ultimate survival to hospital discharge, no neurologic outcomes, etc.; no clear definition of what return of pulse meant since Utstein definitions were not used (at least by report).

9. Lee, C.C., et al., Cases of aminophylline and vasopressin use after failed prehospital resuscitation of cardiac arrest. *Prehosp Emerg Care*, 2001. **5**(3): p. 304-7.

Comment: Single case report. Of interest, but not generalizable,.

10. Lienhart, H.G., W. John, and V. Wenzel, Cardiopulmonary resuscitation of a near-drowned child with a combination of epinephrine and vasopressin. *Pediatr Crit Care Med*, 2005. **6**(4): p. 486-8.

Comment: Single case report of 1 yr old, hypothermic, submersion victim with initial sinus bradycardia requiring CPR. Received two doses of high dose epinephrine (1 mg) endobronchially, one dose of atropine, and after 14 minutes of advanced cardiac life support a combination of 0.2 mg IV epinephrine and vasopressin 10 IU. Temperature was 29.4 C in the hospital. Patient had severe neurologic compromise. Hypothermic arrest may have preserved neurologic function; combination of vasopressin and epinephrine may or may not have been better than epinephrine alone, or vasopressin could be considered rescue therapy in prolonged arrest when severe acidosis is present, making epinephrine less effective. In this patient, pH was 7.03. Report has no scientific value except to generate hypotheses.

11. Lindner, K.H., et al., *Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation*. Lancet, 1997. **349**(9051): p. 535-7.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Good; Direction - Primarily Oppose/Partially Supportive (vasopressin does not improve ROSC, hosp d/c, neuro outcomes, but does improve 24 hr survival)

Fifteen yr old, (prior to 2005 Guidelines) prospective, randomised, blinded, comparison of vasopressin (40 IU single dose) vs. epinephrine (1 mg single dose) in adult, out-of-hospital cardiac arrest with ventricular fibrillation. Excluded endotracheal epinephrine. Used Utstein reporting guidelines. Used tape recording of events to document time and events. Small study (40 patients). Outcomes defined as hospital admission to the ICU, survival to 24 hr, hospital discharge, neuro outcome. There was no statistically significant difference between groups in ROSC, survival to hospital discharge, neurologic outcome. There was a significant difference in 24 hour survival where vasopressin was better, and a tendency towards improved rate of hospital admission to ICU for the vasopressin group.

12. Lindner, K.H., et al., *Vasopressin administration in refractory cardiac arrest*. Ann Intern Med, 1996. **124**(12): p. 1061-4.

Comments: LOE 5 Ped (LOE 4 Adult); Quality: Poor (Case Series) Direction: Positive

8 adults with ventricular fibrillatory cardiac arrest, in-hospital, where standard advanced cardiac resuscitation using either std. dose epi or escalating doses of epi in addition to defibrillation attempts did not result in ROSC. Vasopressin 40IU units in either one or multiple doses was used as a rescue drug with resultant ROSC. Four of the patients had received high dose epi (5 mg) at least once before vasopressin. Three of the 8 patients were discharged from the hospital with intact neurologic function, and the other five lived between 30 minutes and 82 hr from ROSC.

13. Mann, K., R.A. Berg, and V. Nadkarni, *Beneficial effects of vasopressin in prolonged pediatric cardiac arrest: a case series*. Resuscitation, 2002. **52**(2): p. 149-56.

Comments: LOE 4 Ped; Quality - Fair; Direction - Supportive

Retrospective review of 70 cardiac arrests, identified by standardized Utstein criteria, in a single institution (children's hospital) and detailed review of the 6 where vasopressin was used. Objective outcomes were measured: ROSC >20 min, ROSC >60 min, survival > 24 hr, survival to hospital discharge. These 6 arrests occurred in 4 pediatric ICU patients with 3 of the arrests occurring in the same patient during a <24 hr period. In 4 of the 6 arrests, there was a ROSC for at least > 60 min after vasopressin. In 5 of the 6 arrests, two doses of 0.4 U/kg IV vasopressin were given after at least two doses of epinephrine; in 3 of the 4 patients, high dose epinephrine was given. ROSC occurred in two of these patients only after the second dose of vasopressin. Both patients who survived more than 24 hours, had two doses of high-dose epinephrine, two doses of vasopressin. and had a ventricular arrhythmia (pulseless wide complex tachycardia and ventricular fibrillation). The two patients who died both had asystole. Confounding variables include length of time of arrest, epinephrine doses, use of magnesium (used in the two patients who survived), arrhythmias. These could not be controlled for in a retrospective, small case series.

14. Matok, I., et al., *Beneficial effects of terlipressin in prolonged pediatric cardiopulmonary resuscitation: a case series*. Crit Care Med, 2007. **35**(4): p. 1161-4.

Comment: LOE 4 Ped; Quality - Poor; Direction - Supportive

Retrospective Review of 8 asystolic cardiac arrests in 7 pediatric patients (age 3 days - 6 yr; 4 open-heart surgery pts; 2 pts with diaphr.hernia, 1 septic shock). in which a standard dose of terlipressin was used after standard arrest management including options for high dose epinephrine. Cardiac arrest patients identified by Utstein criteria including patients who required compressions because of bradycardia. Used long-acting analog of arginine vasopressin and not the more standard short acting arginine vasopressin. Confounding the efficacy of terlipressin is the concomitant use of high dose epinephrine in 6 of the arrests and 5 doses of epinephrine in the other two; 6 of the 8 arrests resulted in ROSC for at least some time; 4 patients survived until discharge. No objective measurement of neurologic function was performed.

15. Mentzelopoulos, S.D., et al., *Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest*. Arch Intern Med, 2009. **169**(1): p. 15-24.

Comments: LOE 5 Ped (LOE 1 Adult); Quality – Fair; Direction - Positive (improved outcome in vasopressin + hydrocortisone + epinephrine group)

Single center, prospective, randomized, double blinded, placebo-controlled study of adult inpatients with cardiac arrest. Excluded patients with pts who were resuscitated with up to 2 countershocks). 100 patients randomized. Study group (n=48) received vasopressin 20 IU + epinephrine 1mg + 40 mg methylprednisolone as initial drugs with subsequent receipt of vasopressin 20 IU + epinephrine 1 mg 4 more times as necessary (Total of 100 IU vasopressin max.). Control group (n=52) received epinephrine 1 mg + saline placebo and was repeated as necessary 4 more times. If post-resuscitation shock was present 4 hours post ROSC, the study group patients received stress dose hydrocortisone (300 mg/day) up to 7 days and control group received saline placebo. Outcome variables: 15 min ROSC, survival to hospital discharge, organ failure-free days, improved hemodynamics. Results showed improved outcome in vasopressin+epi+corticosteroid group both for at least 15 minutes ROSC and percent discharged from hospital. This is a good study, but it is not clear whether the outcome was from the combination of vasopress + epi alone or whether the addition of the steroids in the study group both during the resuscitation as well as subsequently made the difference. It would have been optimal if there had been a vasopress + epi group without steroids to make this clearer. Although there were many non-cardiac causes of arrest, this was equally distributed between the group and a post-hoc analysis also demonstrated that this did not play a role in the study patients. There was no sub-group analysis although as a whole the study patients did better. Distribution of asystole/v fib/pulseless electrical activity were the same between study and control group. (about 60% asystole, 15% v-fib/vtach, 25% PEA)

16. Mukoyama, T., et al., *Reduced effectiveness of vasopressin in repeated doses for patients undergoing prolonged cardiopulmonary resuscitation*. Resuscitation, 2009. **80**(7): p. 755-61.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Fair; Direction - Negative (No improvement with vasopressin)

Prospective, randomized controlled trial of adults with out of hospital, cardiogenic arrest comparing vasopressin only (up to 160 IU) vs. epinephrine only (up to 4 mg). Patients randomised at entry to ED and patients with non-cardiogenic arrest (198 of the 534 randomized patients) excluded from the analysis later. Not clear how randomisation was done. No mention of whether staff was blinded to drugs being used. Levels of vasopressin and epinephrine obtained on arrival (p=NS), but no more levels attained afterwards to determine whether dosing of vasopressin or epinephrine had an effect on blood levels. Deviation from standard Resuscitation Guidelines in the control (epinephrine) group in that interval of drug dosing was 5-10 minutes rather than 3-5 min. Outcomes were standard per Utstein reporting criteria and included survival to hospital discharge (primary), ROSC, and 24 hour survival (secondary endpoints). Of note, most patients were asystolic (78,74%) although no difference between asystolic and v-fib group in ROSC; long time before administration of either drug (33, 35 min, p=NS) might have prevented either group from responding with ROSC. No dose-response data; Single center study.

17. Stiell, I.G., et al., *Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial*. *Lancet*, 2001. **358**(9276): p. 105-9.

Comments: LOE 5 Ped (LOE 1 Adult) Quality - Good; Direction: Negative (vasopressin does not improve outcome)

Prospective, triply blinded, randomized controlled trial of adult (≥ 16 yr old) cardiac arrest inpatients (including ED) of variable etiology performed at three different hospitals, comparing use of vasopressin 40 IU vs. epinephrine 1 mg as the initial drug. 324 arrests assessed but 124 excluded including 50 ineligible patients who came in with pre-hospital arrest and 50 who were not entered in study because of stress/urgency (these had same clinical/demographic distribution as study patients).. 200 patients randomized to vasopressin and epinephrine groups. Outcomes: ROSC, survival for one hour, survival to hospital discharge, neuro fx (using MMSE and cerebral performance scale). Excellent randomization, controlled protocol, exclusions before analysis done by independent panel, only IV administration. Overall mean age is higher than in other studies (70 yr vs. 60-65 in other studies), time to intervention is much shorter (6.1 minutes) than for the OOH arrest studies (15-30 min)

18. Voelckel, W.G., et al., *Comparison of epinephrine and vasopressin in a pediatric porcine model of asphyxial cardiac arrest*. *Crit Care Med*, 2000. **28**(12): p. 3777-83.

Comments: LOE 5 Ped (LOE 1 Animal); Quality - Good; Direction - Negative for vasopressin in asphyxial arrest

Prospective, randomized, controlled, lab investigation using a pediatric animal model (piglets). 18 piglets had induced asphyxial arrest and after the 8 minutes of CPR were randomly assigned to one of three groups - vasopressin, epinephrine (hi dose at 200 mcg/kg) or combined vasopressin and epinephrine (45 mcg/kg). investigators were blinded as to drugs given. Strict protocol was followed regarding induction of asphyxia, time before starting CPR (8 min), time of CPR before drug administration (8 min), times of vital organ blood flow measurement and ROSC. ROSC did not include time in its definition, so unclear whether ROSC for a short time, e.g. 1 minutes, was counted as ROSC. Also, not clear how long CPR continued if drugs and defibrillation did not work to ROSC. Nevertheless, it was striking that not only was the best vital organ perfusion (brain, heart, kidneys) achieved with epinephrine alone, but only 1/6 piglets given vasopressin alone had ROSC compared to 6/6 with only epinephrine and 4/6 with combined epinephrine/vasopressin.

19. Voelckel, W.G., et al., *Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation*. *Crit Care Med*, 2002. **30**(5): p. 957-62.

Comments: LOE 5 Ped (LOE 1 Animal); Quality-Good; Direction - Positive for Vasopressin in V fib Pediatric Arrest

Prospective, randomized, blinded to investigators, using a pediatric pig model in v.fib arrest, comparing intratrial injected vasopressin alone, epinephrine alone or a combination of both with outcomes measured as vital organ bloodflow (myocardial, cerebral, renal and adrenal), ROSC. No controls were used. Significant differences in vital organ blood flow for both vasopressin and vasopressin+epinephrine groups vs. epinephrine only. No significant differences between groups in ROSC. This is the opposite of the experiment in which vasopressin, epinephrine and combination were use asphyxial arrest in piglets, where high dose epinephrine alone was better than either vasopressin alone or a combination of epinephrine+vasopressin. However, the protocols for drug dosing were different in that the initial dose of epinephrine used in the asphyxial study was 4.5 x higher, and the vasopressin dose was 2x higher. Although the second dose was the same as the first dose in the asphyxial study, it was given after a longer period of cardiac arrest than in the asphyxial study and this may have impacted the efficacy of epinephrine in spite of the higher dose. Of note is that the coronary artery perfusion pressure was not significantly different after the second dose between the three groups.

20. Wenzel, V., et al., *A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation*. *N Engl J Med*, 2004. **350**(2): p. 105-13.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Good; Direction - Positive (for vasopressin and asystole)

Prospective, well randomized, double-blinded, multicenter study of vasopressin vs epinephrine in 1219 out-of-hospital-adult cardiac arrest patients of unknown etiology. Significantly higher rates of hospital admission, and hospital discharge. In addition, patients who did not have ROSC with either vasopressin or epinephrine did better with additional doses of epinephrine when they were in the vasopressin group than if they were in the epinephrine group. Weaknesses: no standardization of inpatient care so unclear if this might have impacted outcomes, cause of cardiac arrest not verified.

21. Wyer, P.C., et al., Vasopressin or epinephrine for out-of-hospital cardiac arrest. *Ann Emerg Med*, 2006. **48**(1): p. 86-97.

Comments: LOE 5 Ped (LOE 1 Adult); Quality - Good ; Direction: Negative (vasopressin does not improve outcomes)

Although not a formal meta-analysis, this was a high quality evidence-based review of the literature and then, by using a random effects model did supplementary analyses of the pooled data to summarize results and assess for significant differences among subgroups of patients with different arrest rhythms. Quality appraisal were done independently by 2 reviewers with substantial agreement above chance. Heterogeneity was assessed and was substantial when the 2 Asian studies (Lee, Li) were included.