WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

Dr Jane Foster
Dr Jasmeet Soar

Date Submitted for review:
Updated following webinar 17 August 09
Also updated search 19 September 2009
CoSTR agreed by ALS TF

Clinical question.

In adult patients with ROSC after cardiac arrest (prehospital [OHCA], in-hospital [IHCA]) (P), does the use intravenous fluids (I) compared with not using fluids (or standard resuscitation) (C), improve outcomes (eg. survival of event, survival to hospital discharge, intact neurological survival) (O).

Question modified during process to (does not make a difference to WS):

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) who have cardiovascular dysfunction (P), does the use of intravenous fluids (I) as opposed to standard care (or other intravenous fluids) (C), improve outcome (O) (eg. survival)

Is this question addressing an intervention/therapy, prognosis or diagnosis? INTERVENTION
State if this is a proposed new topic or revision of existing worksheet: **NEW**

Conflict of interest specific to this question

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

Search strategy (including electronic databases searched).

Search strategies were tailored to the databases searched, allowing for variation in MeSH terms and updated based on WSE/E3 feedback.

1) Medline (19 September 2009):
Infusions, intravenous OR blood transfusion OR plasma substitutes OR colloids
AND
Cardiopulmonary resuscitation OR heart arrest (exploded) OR ventricular fibrillation OR return of circulation OR ("post-cardiac arrest syndrome" OR "cardiac arrest syndrome"

141 Results

2) Embase (19 September 2009):
Plasma substitute (exploded) OR Hartmann solution OR ringer solution OR hypertonic solution OR fluid resuscitation (exploded) OR goal directed
AND
Heart arrest (exploded) OR cardiopulmonary arrest (exploded) OR asystole (exploded) OR heart ventricle fibrillation OR return of circulation

149 Results

3) AHA Endnote Library :
Cardiopulmonary resuscitation OR ventricular fibrillation
AND

Infusions, intravenous

4) Cochrane systemic reviews and central register of controlled trials (19 September 2009)
Cardiopulmonary resuscitation OR heart arrest OR return of circulation
AND
Infusions, intravenous OR hematological agents OR goal directed

164 Results

5) Google Scholar (19 September 2009)
Fluid
AND
Cardiopulmonary arrest OR ventricular fibrillation
AND
(at least one of) Colloid OR blood OR saline OR goal directed

1650 results

The reference lists of relevant papers identified were also hand-searched for additional sources, and abstracts from relevant resuscitation conferences were also searched.

Include studies looking at adults ≥18 years in human studies

Include animal model studies

Include studies with fluids administered to induce hypothermia

Exclude single cases, but include case series

Exclude papers that focus on trauma-related resuscitation

Exclude papers focusing on fluid administration during CPR (the subject of worksheet ALS-16A by same authors)

- Number of articles/sources meeting criteria for further review: 14

Summary of evidence

Evidence Supporting Clinical Question

Good					
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

Evidence Neutral to Clinical question

Good					**Gaieski et al, 2009 CD** **Nordmark et al, 2009 E** **Sunde et al, 2007 CD** ***Kaakinen et al, 2006 E***
Fair					**Jacobshagen, 2009 E** **Kim et al, 2007 CE** **Kliegel et al, 2007 CDE** **Kliegel et al, 2005 CDE** **Virkkunen et al, 2004 CE** ***Krieter et al, 2002E*** ***Bertsch et al, 2001E*** ***Leonov et al, 1992E***
Poor					**Kim et al 2005 E** **Bernard et al, 2003 C**
	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					
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*

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

The role of fluids given during CPR are covered in ALS 016A by the same authors

This WS looks at role of fluids after ROSC in patients with cardiovascular dysfunction
We have assumed all patients have cardiovascular dysfunction to a varying degree after ROSC (See Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002; 40: 2110-6.).

The studies included in this WS can be divided into 3 groups:

1. Fluid infusion for haemodilution
2. Fluid infusion for induction of therapeutic hypothermia after ROSC (TH)
3. Hypertonic fluid infusion
4. Fluid infusion as part of goal-directed therapy to improve haemodynamic status as part of a post resuscitation care bundle/package of care.

All the studies assessed have been graded LOE 5 and neutral as they do not directly answer the question as they do not specifically look at the impact of fluids alone or do not have a control group that enables the effect of the fluid infusion to be assessed.

1. One animal study [Leonov, 1992, 45-53] used fluids to induce haemodilution with 50ml/kg of dextran 40 in 0.9% NaCl, while removing 35ml/kg of blood via cardiopulmonary bypass. This group was also maintained at higher mean arterial pressures than the control group with a noradrenaline infusion. Global cerebral blood flow was 51-60% of baseline in the control versus 85-100% of baseline the intervention group ($p = <0.01$). Oxygen delivery was the same in both groups due to a lower arterial oxygen content with haemodilution. This study is of fair quality, with a control group but no clear randomization method.
Fluid therapy was combined with hypertension. This study does not show a clear benefit or harm from fluid infusion.

2. Incorporation of TH into ALS guidelines for post-ROSC care has lead to a growing number of studies using the rapid infusion of cold intravenous fluids to induce TH.
7 human studies [Bernard, 2003, 9-13, Jacobshagen, 2009, Kim, 2005, 715-9, Kim, 2007, 3064-70, Kliegel, 2005, 347-51, Kliegel, 2007, 46-53, Virkkunen, 2004, 299-302] infused intravenous fluid after ROSC to induce TH. Of these, 5 did not have a control group without fluids. One study [Bernard, 2003, 9-13] used retrospective controls in which it is not clear whether these controls received fluid or not. None of the 6 papers report serious adverse effects directly related to the use of fluid. [Kliegel, 2005, 347-51] reported 2 patients with radiological evidence of pulmonary oedema, but they did not feel that these patients were compromised and so continued intravenous infusions. [Kim, 2005, 715-9] used echocardiography to compare ejection fraction before and after fluid infusion and found that values were not significantly different. Even a patient with a calculated ejection fraction of 9% did not have changes in oxygenation or pulmonary artery pressure estimates following fluid infusion of 2L over 30 minutes.
These studies provide evidence that comatose and ventilated patients with myocardial dysfunction tolerate fluid infusion, but do not show a benefit in terms of survival from fluid use.

One recent retrospective study [Jacobshagen 2009, epub] studied the effect of fluids after ROSC to induce therapeutic hypothermia, on oxygenation. Resuscitation from cardiac arrest is associated with a deterioration in PaO2/FiO2 ratio. The infusion of a large volumes of cold fluid caused deterioration in the PaO2/FiO2 ratio that was not statistically significant.

3. Three animal studies [Bertsch, 2001, 153-6, Kaakinen, 2006, 183-90, Krieter, 2002, 1031-6] study the use of hypertonic fluid after ROSC. None of the 3 studies had a control group that did not receive fluid. All three studies found that hypertonic fluid was of benefit compared with 0.9% NaCl. [Kaakinen, 2006, 183-90] studied hypothermic cardiac arrest, and found that hypertonic saline increased 7 day survival ($p = 0.9$), encouraged faster neurological recovery ($p = 0.03$), lowered intracranial pressure ($p = 0.028$), higher cerebral perfusion pressure ($p = 0.049$) and less ischaemia on histopathology scoring ($p = 0.01$). [Krieter, 2002, 1031-6, table of contents] found that levels of both protein s-100 and Troponin I were lower in the hypertonic group, equating to less neurological and cardiac damage. [Bertsch, 2001, 153-6] also found lower levels of Troponin I in the hypertonic group.
These studies suggest that hypertonic fluid may provide neurological and cardiac protection, but human studies are required and there are no studies comparing with no fluid.

4. Several papers have discussed the post-cardiac arrest syndrome, drawing similarities between it and severe sepsis. This leads to the hypothesis that fluid use could be key area of post-resuscitation care, as with severe sepsis. As yet, there is insufficient evidence to define the optimal CVP post-cardiac arrest [Neumar, 2008, 2452-83]. Two studies [Gaieski, 2009, 418-24, Sunde, 2007, 29-39] were identified that looked at the inclusion of fluid as part of post-cardiac arrest early goal directed therapy. Both used ice cold normal saline to induce hypothermia and further intravenous fluid to maintain CVP >8, combined with other components of a care bundle. Neither study had a control group that did not receive fluids, and are therefore level 5 evidence. Gaeski et al showed an improvement in survival to discharge versus a historical control group with the use of early goal-directed therapy that was not

statistically significant (p=0.16). Sunde et al found an improved survival with favourable outcome, with 56% compared to 26% in the control group (p=<0.001). However, this was a historical control group without true control of other variables and with the introduction of a care bundle and is therefore multifactorial and not attributable to fluid alone.

In summary, there is insufficient evidence to recommend the routine use or omission of fluid post-ROSC following cardiac arrest. In the studies included, rapid fluid infusion has shown harm in only a small number of patients.

Questions that require further study:

Larger studies to assess optimal dosing of fluids after ROSC from cardiac arrest
Effects of fluids after ROSC from cardiac arrest on cardiovascular function

Acknowledgements:

Citation List

Citation Marker	Full Citation*
[Bernard, 2003, 9-13]	**Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation. 2003;56(1):9-13.** ***Hypothermia.*** ***LOE 5. Poor. Neutral*** ***Historical controls.*** ***N = 22.*** ***30ml/kg 4℃ lactated Ringers over 30 mins.*** ***It is unclear whether the control group received fluids. Little information regarding control group.*** ***Outcomes:*** ***No adverse effects. No pul oedema.*** ***Survival to discharge = 8/14 VF arrest patients, 2/8 other rhythms.***
[Bertsch, 2001, 153-6]	**Bertsch T, Denz C, Janke C, Weiss M, Fassbender K, Luiz T, et al. Hypertonic-hyperoncotic solutions decrease cardiac troponin I concentrations in peripheral blood in a porcine ischemia-reperfusion model. Exp Toxicol Pathol. 2001;53(2-3):153-6.** ***LOE 5.*** ***Animal. Control group, non-randomised*** ***Outcome = troponin*** ***10 animals, 5 hypertonic, 5 normal saline*** ***Significantly lower troponin in hypertonic group, thus may be cardioprotective***
Jacobshagen, 2009, epub	Jacobshagen C, Pax A, Unsöld BW, Seidler T, Schmidt-Schweda S, Hasenfuss G, Maier LS. Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation. 2009 Aug 10. [Epub ahead of print] ***LOE5 Neutral, fair*** ***Looks at effects of IV fluids to cool patient on respiratory function – the FiO2/PaO2 ratio is bad to start with and only gets slightly worse with a large cold fluid bolus. No control group to show safety.***

[Gaieski, 2009, 418-24]	**Gaieski DF, Band RA, Abella BS, Neumar RW, Fuchs BD, Kolansky DM, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2009;80(4):418-24.** ***Goal-directed therapy including intravenous fluid to maintain CVP >8 and 2L 4℃ saline to induce therapeutic hypothermia.*** ***Human study. Good quality. Retrospective control group. No group that did not receive fluids, therefore level 5.*** ***N=20 in patient group following protocol for goal-directed therapy.*** ***Improved survival of 50% compared with 22% in historic control patient (p = 0.16, therefore not statistically significant)***
[Kaakinen, 2006, 183-90]	**Kaakinen T, Alaoja H, Heikkinen J, Dahlbacka S, Laurila P, Kiviluoma K, et al. Hypertonic saline dextran improves outcome after hypothermic circulatory arrest: a study in a surviving porcine model. Ann Thorac Surg. 2006;81(1):183-90.** ***Hypertonic fluid administration.*** ***LOE 5. Good. Neutral.*** ***Animal study, RCT. No group that did not receive fluid.*** ***N=24. Hypothermic arrest.*** ***4ml/kg hypertonic saline dextran (7.5%/6%) or 0.9% saline given immediately post-ROSC and 4 hours post initiation of reperfusion AND both groups received Ringer acetate.*** ***No group that did not receive fluid.*** ***Outcomes:*** ***7 day survival HSD = 75% (9/12), 0.9% saline = 66.7% (8/12) [p = >0.9]*** ***Neurological behaviour HSD group faster recovery, higher behavioral scores day 2 (p = 0.03)*** ***Lower haematocrit in HSD group*** ***Haemodynamic variables – cardiac index (p = 0.11), MAP (p = 0.52) – First administration HSD increased MAP at 60 (p = 0.002) and 90 (p = 0.007), vascular resistance (p = 0.6), CVP (p = 0.65)*** ***Neurological factors – intracranial pressure lower in HSD (p = 0.028), cerebral perfusion pressure higher with HSD (borderline significance p = 0.059), brain lactate levels lower with HSD (p = 0.049), lactate-pyruvate ratio lower HSD (3 hours p = 0.049, 4 hours p = 0.027), brain ischaemia histopathologic score lower with HSD (including early deaths mean 7.0 vs 10.0, p = 0.01, excluding early deaths mean 7.0 vs 9.6 p = 0.049)***
[Kim, 2007, 3064-70]	**Kim F, Olsufka M, Longstreth WT, Jr., Maynard C, Carlbom D, Deem S, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation. 2007;115(24):3064-70.** ***Hypothermia.*** ***LOE 5. RCT. Fair. Neutral*** ***N= 125 + 65 that met inclusion criteria but were not enrolled.*** ***Randomisation list concealed, but clinicians not blinded to treatment. Groups otherwise treated equally.*** ***Most patients received fluid, whether cooled or not. 2L 4℃ 0.9% NaCl in test group. Of the 63 included in the cooling group, 8 received no fluid pre-hospital and 6 <500ml. It is not clear how much fluid the control group patients received.*** ***Outcomes:*** ***Survival: VF group improved survival to discharge than PEA with cold fluids pre-hospital compared to control group, worse survival with cold fluids in PEA group.*** ***Fluid use not assoc with adverse consequences.***
[Kliegel, 2007, 46-53]	**Kliegel A. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation. 2007;73:46-53.**

	Hypothermia ***LOE 5. Fair. Neutral.*** ***N = 20*** ***30 ml/kg Crystalloid (NaCl or Ringer's lactate) 4℃ over 30 minutes. Commenced at 93 (+/- 62) minutes.*** ***Stopped if temperature <33℃ or if evidence of pulmonary oedema.*** ***Cold fluids repeated every 6 hours in order to maintain hypothermia, given at 10ml/kg, for up to 24 hours. Only one patient had a second fluid bolus, given at ROSC + 10 hours.*** ***Outcomes:*** ***No complications secondary to fluid. No clinical signs pulmonary oedema. Haemodynamic variables no relevant changes.*** ***Survival = 8/20 to hospital discharge.*** ***7/20 had favourable neurological outcome.***
[Kim, 2005, 715-9]	**Kim F, Olsufka M, Carlbom D, Deem S, Longstreth WT, Jr., Hanrahan M, et al. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. Circulation. 2005;112(5):715-9.** ***Hypothermia*** ***LOE 5. Poor. Neutral.*** ***N = 17, 285 cardiac arrests during this period.*** ***All patients that met criteria given 2L of 4℃ NaCl over 20-30 minutes.*** ***Outcomes:*** ***Echocardiology confirmation that ejection fraction was reduced in all patients post-arrest, but this did not change significantly with fluid administration. No evidence of fluid overload in any patients.*** ***Cardiac haemodynamics did not worsen.***
[Kliegel, 2005, 347-51]	**Kliegel A, Losert H, Sterz F, Kliegel M, Holzer M, Uray T, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. Resuscitation. 2005;64(3):347-51.** ***Hypothermia.*** ***LOE 5. Fair.*** ***All patients included that met the inclusion criteria. N = 26 (note 167 cardiac arrests in this time period)*** ***2L 4℃ Ringers lactate infused. Mean time of infusion = ROSC + 38 minutes (+/- 29)*** ***No patients included that did not receive fluids.*** ***Outcomes*** ***2 patients had radiographical signs of pul oedema. None required discontinuation of the infusion as no acute cardiac decompensation.*** ***No clinically relevant changes in haemodynamic variables or Hb pre and post fluid administration.*** ***Survival to discharge = 54%*** ***Neurological outcome = 50%*** ***?selected patient group. It seems unlikely that all that met criteria were included. Not justified.***
[Krieter, 2002, 1031-6, table of contents]	**Krieter H, Denz C, Janke C, Bertsch T, Luiz T, Ellinger K, et al. Hypertonic-hyperoncotic solutions reduce the release of cardiac troponin I and s-100 after successful cardiopulmonary resuscitation in pigs. Anesth Analg. 2002;95(4):1031-6, table of contents.** ***LOE 5. Fair. Neutral*** ***Animal study.***

	N = 16 ***0.9 % NaCl 125ml 12.5ml/min or 125ml 7.2% NaCl with 10% hydroxyethyl starch 200000/0.5 at 12.5 ml/min.*** ***No group that did not receive fluid.*** ***Haemodynamic variables – no significant difference between groups.*** ***Haemoglobin level – lower in hypertonic group.*** ***Protein s-100 (brain tissue injury/disruption of blood brain barrier). Levels significantly reduced in hypertonic group.*** ***TnI (cardiac damage). Levels significantly reduced in hypertonic group.***
[Leonov, 1992, 45-53]	**Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. Stroke. 1992;23(1):45-53.** ***Haemodilution with hypertension*** ***LOE 5. Fair. Neutral.*** ***Animal study.*** ***N = 10.*** ***Cardiopulmonary bypass post-arrest. Noradrenaline used to maintain mean arterial blood pressure of 100 mm Hg in group one and 140/130/120/110 reducing by hour in group 2. Group 1 had bypass blood of 15ml/kg re-introduced so haematocrit was >35%. Group 2 had 50ml/kg IV dextran 40 in 0.9% NaCl in while 35ml/kg blood was removed simultaneously, thus had a haematocrit of 20-25% until blood was re-infused after 2 hours.*** ***Outcomes:*** ***Neurological – cerebral blood flow 1-4 hours post-arrest 21-60% in group 1 compared to 85-100% group 2 (p = <0.01), arterial oxygenation decreased with haemodilution global cerebral oxygen uptake measured for 3 dogs in each group. O2 delivery found to be similar in both groups.***
[Neumar, 2008, 2452-83]	**Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation. 2008;118(23):2452-83.**
[Nordmark, 2009]	**Nordmark J, Johansson J, Sandberg D, Granstam SO, Huzevka T, Covaciu L, et al. Assessment of intravascular volume by transthoracic echocardiography during therapeutic hypothermia and rewarming in cardiac arrest survivors. Resuscitation. 2009.** *Hypothermia. Good. Neutral.* *LOE 5* *Human study* *N=24* *No control group that did not receive fluids.* *30 ml/kg 4C N saline for hypothermia.* *Serial echocardiogram, CVP, central venous saturation (jugular) & lactate used to look at haemodynamic effects.* *Found that study group generally intravascularly deplete post-ROSC, therefore fluids may be beneficial. No group without fluid for comparison.* *No harmful effects of fluid use during cooling or re-warming.*

Sunde et al, 2007	Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73(1):29-39. *Care bundle.* *LOE 5* *1-3 L of ice cold 0.9% normal saline to induce hypothermia.Then volume, diuretics or pressors "as indicated" to keep parameters MAP >65-70, CVP 8-12.* *Control group did not receive fluids to initiate therapeutic hypothermia, but received fluids as part of "standard post-ROSC care". Control group were retrospective controls. Fluid balance in control group +2300 +/- 1211, in intervention group +3455+/-1594 (p=0.001)* *Improved survival to hospital discharge and favourable neurological outcome, but as fluids part of care bundle it is difficult to separate the impact of fluid within that.*
[Virkkunen, 2004, 299-302]	**Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation. 2004;62(3):299-302.** ***Hypothermia. Fair. Neutral*** ***LOE 5.*** ***N = 13*** ***Ringer's acetate, ice-cold, 30ml/kg at 100ml/min, commenced 27 minutes (+/- 12) post-ROSC. Stopped prior to target volume if temperature of 33℃ reached or adverse haemodynamic events. No group that did not receive fluids.*** ***Outcomes:*** ***Haemodynamic variables – BP and heart rate = stable.*** ***Survival outcomes/utstein score - 4 survived to hospital discharge, 8 < 10 days post-cardiac arrest.***