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

**Worksheet author(s)**

| Jesús López-Herce | DateSubmitted for review: 28-03-2009 |

**Clinical question.**

In infants and children with hemorrhagic shock following trauma (P), does the use of graded volume resuscitation (I) as opposed to standard care (C), improve outcome (hemodynamics, survival) (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:** 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).**

Initial search for: "hemorrhagic shock" AND "trauma" AND (infant" OR "children") AND ("resuscitation" OR “volume resuscitation") AND ("outcome" OR "ROSC" OR "survival")

Initial search shock" AND “hemorrhagic” and “wounds and injuries”. Other search “fluid therapy”/“hypotension”/“mortality”/“therapy” and “shock”/“therapy” and “shock” and “traumatic”/“therapy”

Search in: PubMed, EMBASE, AHA EndNote library, Trypdatabase, Cochrane Library

**PUBMED:**

Shock hemorrhagic and wounds and injuries: 1913 articles
Shock and fluid therapy and hypotension and mortality: 112 articles
Shock/*therapy and shock, traumatic/*therapy: 1556 articles
Fluid therapy and hypotension/mortality/*therapy: 9 articles
Hemorrhagic shock and trauma: 2766
Cochrane: 3 articles

**EMBASE:**

('fluid'/exp OR 'fluid') AND hemorrhage AND (′shock'/exp OR ′shock′) AND [1990-2009]/py: 2668 articles
(′shock′/exp OR ′shock′) AND hemorrhage AND wounds AND injury AND [1990-2009]/py: 141 articles
(′shock′/exp OR ′shock′) AND hemorrhage AND injury AND [1990-2009]/py: 5042 articles
(′shock′/exp OR ′shock′) AND trauma AND (′therapy′/exp OR ′therapy′) AND [1990-2009]/py: 13047 articles

AHA EndNote library: No additional articles. Searched on hemorrhagic shock, fluid therapy, trauma, children

Trypdatabase: No additional articles. Searched on hemorrhagic shock, fluid therapy, traumatic shock

**State inclusion and exclusion criteria**

**Inclusion criteria:**

- Condition: hemorrhagic shock following trauma
- Treatment: volume and time to fluid resuscitation

**Exclusion criteria**

- Hypovolemic non hemorrhagic shock
- Septic shock
- Cardiogenic shock
- Other treatments (hypothermia, norepinephrine, vasopressin, hemoglobin-based carrier)

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

- Articles in children: 0
- Articles in adults with hemorrhagic shock following trauma: 9
- Articles in animals with hemorrhagic shock: 19
## Summary of evidence

### Evidence Supporting Clinical Question

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<tr>
<th>Good</th>
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<td>Nascimento 2006 E</td>
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<td>Wade 2003 C</td>
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| Poor                  | Hambly 1996 C   |

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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

*Italics = Animal studies*
### Evidence Neutral to Clinical Question

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

### Evidence Opposing Clinical Question

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A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint  
B = Survival of event  D = Intact neurological survival  Italics = Animal studies
A significant percentage of patients who die after trauma do so in the first hours after the accident due to hemorrhagic shock. The treatment of shock is therefore one of the measures that could potentially save more lives in patients suffering severe trauma. Despite this, there are very few clinical trials that have studied the treatment of hemorrhagic shock in adults (Bikell 1994, Dunham 1991, Dutton 2002, Mattox 1991, Wade 2003) and none in children.

Up to now, the early treatment of hemorrhagic shock has been based on control of the hemorrhage and volume expansion with fluids. The aim of early treatment is to maintain an adequate perfusion and oxygenation of the tissues without increasing bleeding. Many studies have been performed in experimental animals (Chiara 2003, Cryer 2005, Kentner 2005, Soucy D 1999, Talving 2006), and some in adults (Bickell 1994, Hambly 1996, Kwan 2003, Mattox 1991, Wade 2003) investigating which is the most suitable type of fluid, the time to start treatment, and the volume of fluid to be administered initially.

For many years, aggressive initial volume expansion with fluids, usually crystalloids, was recommended to achieve a normal blood pressure. However, in animal studies (Burris 1999, Lu YQ 2007, Mapstone 2003, Ozturk 2007) and in one in adults with chest trauma (Bickell 1994), it was found that this treatment could worsen the prognosis, increasing bleeding by raising the blood pressure and diluting clotting factors in the blood.

Studies in animals that have compared different types of fluids (crystalloids, artificial and natural colloids, and hypertonic and hypertonic hyperoncotic solutions) have found contradictory results (in general, there has been no significant difference in the vital prognosis, although some studies have found that the administration of smaller volumes of hyperoncotic hypertonic solutions maintains the hemodynamic parameters equally or better than crystalloids, and improves certain parameters of tissue oxygenation, inflammation, and coagulation.

Several studies in animals have compared the early administration of fluids with delayed administration. There have been variable results. In animals with very severe hemorrhagic shock, the early administration of fluids improves the prognosis with respect to delayed administration (Bruscagin 2002, Burris 1999, Lee 2007, Lu 2007, Mapstone 2003, Soucy 1999). However, in animals (Abu-Hatum 2003, Bourguignon 1998) and patients (Bickell 1994, Dutton 2002, Hambly 1996, Sampalis 1997) with non-severe hemorrhage, early and aggressive administration does not improve the prognosis and can even worsen it.

Most of the studies that have considered the volume of fluids to be administered in the treatment of trauma-related hemorrhagic shock have compared different types of fluids (crystalloids versus colloids or hypertonic solutions), and it is therefore difficult to analyze the individual effect of fluid volume. In the majority of studies, it has been shown that the administration of large volumes of fluids does not improve the prognosis, except in cases of severe hemorrhagic shock with massive bleeding, and that this fluid regimen can lead to interstitial edema with poorer tissue perfusion, cerebral edema in the event of associated head injury, and dilution of the coagulation factors with an increased risk of bleeding.

In addition, many of the studies performed have mainly analyzed the effect of treatment on mortality and have excluded as ineffective those measures that do not achieve significant changes in mortality (Bikell 1994, Dunham 1991, Dutton 2002, Mattox 1991, Wade 2003). However, it must be taken into account that mortality in the trauma patient depends only partially on the severity of the hemorrhage. The type of lesion, previous diseases, focal organ damage, and the onset of multiorgan failure are very important prognostic factors. It is therefore essential that studies should evaluate the efficacy of treatments of hemorrhagic shock by analyzing their effects on hemodynamic parameters, perfusion, and cerebral and tissue oxygenation, and on the onset of multiorgan failure.

New strategies for the early treatment of trauma-related hemorrhagic shock have recently been proposed. These include hypothermia, artificial hemoglobin transporters (hemoglobin-based carriers), and vasoconstrictor drugs such as norepinephrine and vasopressin.
Although some experimental studies in animals have found that these measures can improve tissue perfusion, there is still no evidence of their utility in humans (Cavus 2009).

At the present time, there are no studies in infants and children with trauma-related hemorrhagic shock that compare the time of fluid resuscitation or the volume of fluid. Nor is there evidence from studies in adults on which to establish a recommendation.

The early treatment of children with hemorrhagic shock secondary to trauma should include control of the origin of bleeding and fluid therapy with the minimum volume of fluids necessary to maintain adequate tissue perfusion.

**Acknowledgements**: To Antonio Rodriguez Nuñez for revising the manuscript

**Citation List**


LOE 5. Good. This study in rats with uncontrolled hemorrhagic shock compared 11 group treatments (different type and volume of liquids). There were no different in the survival between groups. High volume of fluids increases blood loss.


LOE 5. Good. This was the first prospective study compared immediate versus delayed fluid resuscitation in 598 adults with penetrating torso injuries. The recommendations of delayed resuscitation are based in this study. The limitations of this study were the method of randomization and that 8% of patients with delayed resuscitation was treated with fluids. Survival was significantly higher in delayed resuscitation 70% versus 62% (p= 0.04). The incidence of complications was also lower in delayed fluid resuscitation group (p = 0.08).


LOE 5. Good. In this study the early fluid resuscitation increases intracranial pressure in animals with hemorrhagic shock and head injury. This study supports delayed fluid administration in hemorrhagic shock and head injury. However the number of animals in each group was low.


LOE 5. Good. In this study in dogs fluids resuscitation with normal or hypertonic fluids produce more hemodynamic and metabolic benefits than non resuscitation.


LOE 5. Good. This study compared non resuscitation with Ringer solution, hetastarch an hypertonic saline in 86 rats with uncontrolled hemorrhage. Fluid administration produce higher survival than non fluid administration.


LOE 5. Good. This study shows the positive effects of alternative treatments in combination with graded volume. The combination of low dose of hypertonic saline plus vasopressin produces better hemodynamic and oxygenation cerebral parameters than aggressive fluid resuscitation in pigs with uncontrolled hemorrhagic shock. Higher survival was achieved with hypertonic saline plus vasopressin although it was not statistically significant because the number of animals in each group was low.


LOE 5. Good. This study showed that small volume of hypertonic hyperoncotic fluid produces better hemodynamic than normal saline in hemorrhagic shock in pigs.

LOE 5. Good. This study in rats with hemorrhagic shock showed that organ perfusion and microvascularization do not return to normal situation with fluid treatment although hemodynamic parameters (blood pressure and cardiac output) are normal.


LOE 5. Good. This was a randomized study in hypovolemic trauma adult patients compared rapid versus conventional fluids infusion. Rapid infusion showed better perfusion and coagulopathy parameters and less needing of blood transfusions. There are no differences in mortality. The main limitation of the study is the low number of patients studied (36 patients). Moreover, 8 patients who died in the first 8 hours were not analyzed.


LOE 5. Good. This was a randomized study in 110 adult patients with hemorrhagic shock to compare fluid therapy resuscitation to achieve low or normal BP. There were no differences in the mortality and duration of active hemorrhage between groups.


LOE 5. Good. In this study in rats with hemorrhagic shock hyperoncotic (HES) and hypertonic-hyperoncotic (HyperHES) fluids achieved higher capillary perfusion perfusion than normal saline. Non differences were found between HES and HyperHES fluids.


LOE 5. Good. In this study low volume, moderate volume and normal volume fluids resuscitation were compared in an infant animal model of traumatic hemorrhagic shock. Normal volume of fluids produces better hemodynamic parameters and metabolic parameters than limited resuscitation volume.


LOE 5. Good. High volume resuscitation volume achieved higher survival than no fluids or low volume resuscitation fluids in uncontrolled hemorrhage rats without bleeding increase.

Hambly PR, Dutton RP Excess mortality associated with the use of a rapid infusion system at a level 1 trauma center. Resuscitation. 1996;31:127-33

LOE 5. Poor. This was a retrospective study that compared mortality with use of rapid infusion system with expected mortality derived to a registry and historical controls. Although mortality with rapid infusion system was higher the poor methodology does not permit to establish a conclusion.


LOE 5. Good. This study compare hypertonic-hyperoncotic solution with Ringer’s solution in uncontrolled hemorrhagic shock in rats. There were no significant differences in hemodynamic parameters and survival between the two treatments.


LOE 5. Good. In this Cochrane revision six clinical randomized studies in adults comparing volume and duration of fluid administration were analyzed. The articles were very different in methodology and results and no conclusion can be establish.


LOE 5. Good. In this study in rats volume-controlled hemorrhagic shock delayed fluid resuscitation produce higher inflammatory response. There were no differences in hemodynamic parameters.

LOE 5. Good. In this study in rats with severe hemorrhagic shock and active bleeding fluid resuscitation produces higher survival rate than non resuscitation. Moderate fluid administration avoid excessive hemodilution and coagulopathy without hemodynamic differences in relation with high volume administration.


LOE 5. Good. This is a bibliographic revision of randomized animal studies about fluid treatment of uncontrolled hemorrhage. The conclusion is that some fluids are better than no fluids. However excessive fluids could be bad. However “excessive” is not defined.


LOE 5. Good. In this multicenter randomized study on 422 adult patients hypertonic hyperoncotic fluid versus crystalloid in prehospital treatment were compared. Although high blood pressure and fewer complications were found with hypertonic hyperoncotic fluid no difference in mortality was found.


LOE 5. Good. This study compares general and renal hemodynamic response to different fluids treatment of hemorrhagic shock in dogs. There were no differences in renal hemodynamics between normal saline, hypertonic and hypertonic-hyperoncotic fluids.


LOE 5. Good. In this complicated study in rats with uncontrolled hemorrhage shock different injuries and treatment were compared. Animals treated with fluids had higher survivals that non resuscitated. Non differences were found between normal saline, Ringer's Lactate and hypertonic fluid.


LOE 5. Fair. This was an observational study compared intravenous fluid replacement versus no fluid. Although fluid replacement was associated with an increase in mortality the clinical characteristic between two groups were very different and did not permit to establish a conclusion.


LOE 5. Good. In this study in rats with severe hemorrhagic shock fluid resuscitation with isotonic saline produces higher survival rate than non resuscitation. Moderate volume expansion infused at a rapid rate achieved higher survival and less additional hemorrhage than higher volume


LOE 5. Good. In this study in pigs with hemorrhagic shock secondary to severe hepatic injury, no hemodynamic, survival and rebleeding differences were observed between early and delayed hypertonic saline dextran administration.


LOE 5. Poor. This was a randomized study including 1309 adult patients comparing prehospital fluids administration versus non fluids administration. No differences in mortality and complications between the groups was observed. However there were many protocol violations in both groups.


LOE 5. Fair. This was a revision compared hypertonic saline dextran versus normal saline in adults with hypotensive penetrating injuries. There were no global differences in mortality, although in patients who required surgery hypertonic saline dextran treated patients had higher survival.

Watters JM, Tieu BH, Differding JA, Muller PJ, Schreiber MA. A single bolus of 3% hypertonic saline with 6% dextran provides optimal initial resuscitation after uncontrolled hemorrhagic shock. J Trauma. 2006;61:75-81

LOE 5. Good. In this study in pigs with liver injury hyperoncotic and hypertonic hyperoncotic fluids produce higher increase in arterial pressure and saturation than normal saline.