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

Worksheet author(s)
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Clinical question.
In adult cardiac arrest due to anaphylaxis (P), does any modification of treatment (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, 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 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).
PubMed/MEDLINE (no date limits): "Heart Arrest" or "Cardiopulmonary Resuscitation" as MeSh AND "Anaphylaxis" as MeSH OR "Anaphylaxis" as textword
   Above string filtered separately for RCTs and sytematic reviews.
       All results read in full.
       Hand review of references from articles

Cochrane: same as initial PubMed search string

Ovid/MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1950 to Present): exploded term “Anaphylaxis” AND (exploded term “Heart Arrest” OR exploded term “Cardiopulmonary Resuscitation”)
   Above string with and without case reports excluded
   All results hand searched for relevance (excluding items not discussing treatment, etc)
   Citing references examined using similar methodology

Ovid/EMBASE searched using same string as MEDLINE

AHA EndNote search: “cardiac arrest” AND “anaphylaxis” as keywords

Forward search of selected references double checked using Google Scholar

Search of current, in-process, and recruitment-phase trials at www.clinicaltrials.gov and www.controlledtrials.com using search term “Anaphylaxis”. State inclusion and exclusion criteria

Single case reports simply describing current treatment strategies were excluded, as were reviews of the general treatment of anaphylaxis and allergic reactions if they offered no new information or useful references. Also excluded were references greater than twenty years old (unless they described a novel intervention), single reports of adverse side effects of specific medications, dental practice guidelines, and unrelated basic science or animal studies. Otherwise, all results of the searches described above were evaluated for content relevant to the question. Case series or reports challenging current protocols or describing novel approaches were reviewed.

Number of articles/sources meeting criteria for further review:
Twenty-five articles met criteria for further review. Of these, 3 were LOE 1 (RCT or systematic review), 2 was LOE 2 (case-control/convenience sample), 17 were LOE 4 (case reports), and 3 were LOE 5 (different population or nonhuman model).
## Summary of evidence

### Evidence Supporting Clinical Question

| Good | | | | | |
|------|---|---|---|---|
| Fair | | | Brown, 2004 |
| Poor | | | Heytman, 2004 |
| Bautista, 2002 |
| Heytman, 2004 |
| Nicolas, 1984 |
| Pumphrey, 2000 |
| Pumphrey, 2003 |
| Sampson, 2006 |
| Schumer, 2008 |
| Thomas, 2005 |
| | | Brown, 2005 |
| | | Kill, 2004 |
| Momeni, 2007 |
| Rocq, 2007 |
| Soar, 2005 |
| B = Return of spontaneous circulation |
| C = Survival to hospital discharge |
| E = Other endpoint |
| Italics = Animal studies |

### Evidence Neutral to Clinical question

| Good | | | | | |
|------|---|---|---|---|
| Fair | Sheikh, 2007 |
| Sheikh, 2008 |
| Ranft 2004 |
| Simons & Gu, 2001 |
| | Lieberman, 2005 |
| McLean-Tooke, 2003 |
| Soar, 2008 |
| Winberry, 2002 |
| | Galli, 2005 |
| B = Return of spontaneous circulation |
| C = Survival to hospital discharge |
| E = Other endpoint |
| Italics = Animal studies |
### Evidence Opposing Clinical Question

<table>
<thead>
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<th>Level of evidence</th>
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- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

*Italics = Animal studies*
A search of the existing literature revealed no controlled human studies addressing this clinical question in a scientifically rigorous fashion, likely due to the inherent logistical and ethical challenges associated with studying an unpredictable entity with a time-honored treatment standard. Most authors cite the historic efficacy of epinephrine as the first-line treatment of anaphylactic shock, with or without cardiac arrest. The known physiologic effects of epinephrine are also cited as justification for its use. Although some authors caution against overdose of bolus epinephrine [Pumphrey, 2000] or titration of intravenous infusions by inexperienced personnel [Sheikh, 2008; Soar, 2008], most agree that in the setting of profound shock or cardiac arrest, the benefits of giving epinephrine early outweigh the risks.

An area of interest for further research is the use of alpha-agonists or vasopressin either in addition to or instead of epinephrine [Brown, 2005; Heytman, 2004; Sampson, 2006]. Multiple case reports and small case series have described the efficacy of vasopressin in anaphylactic shock refractory to epinephrine [Kill, 2004; Schummer, 2008]. Also, multiple sources emphasize aggressive fluid resuscitation [Anonymous, 2000; Brown, 2005; Brown, 2004; Soar, 2005; Soar, 2008], again primarily based on an interpretation of the relevant pathophysiology.

The 2000 International Guidelines for CPR and ECC state that “No data is available on how cardiac arrest procedures should be modified... [but that] Reasonable recommendations can be based on experience with nonfatal cases.” Since the publication of these guidelines, no new research of a sufficiently high quality has emerged to justify modifying current guidelines.

Acknowledgements:
Laurie Morrison

Citation List

- **RANDOMIZED/BLINDED CANINE MODEL – LOE 5 fair**

- **SYSTEMATIC REVIEW – LOE 4 poor (not based on RCTs)**
- Excerpt
  - “Although there are no RCTs, adrenaline is the logical treatment, and there is consistent anecdotal evidence supporting its use to ease breathing and circulation problems associated with anaphylaxis.”

- **RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED CROSSOVER TRIAL – LOE 4 fair**
- Excerpt
  - “A prospective human study of an epinephrine protocol, providing good evidence for the efficacy and tolerability of a continuous intravenous infusion of epinephrine combined with volume resuscitation. It
also reports the universal occurrence of relative bradycardia when hypotension occurs in the setting of sting anaphylaxis.”

- EDITORIAL INTRODUCTION TO TOPIC-FOCUSED ISSUE – LOE 5 poor
- Excerpt: “...there is no international consensus on the classification and nomenclature of anaphylaxis.”

- CASE STUDIES AND REVIEW – LOE 4 fair
- *Describes intra-op anaphylaxis and cardiac arrest not responsive to epinephrine, but improved after an α-agonist. They cite some suspected downsides to β-agonists in cardiac arrest.*
- Excerpts:
  - “This series of two cases is notable for the fact that excellent care including aggressive volume resuscitation and high-dose infusions of adrenaline was not successful, whereas the addition of metaraminol produced immediate responses in both cases.”
  - “We believe that early administration of an α-agonist (e.g. metaraminol or equivalent) when patients are unresponsive or show limited response to epinephrine, will... hopefully translate into improved outcomes following intra-operative anaphylaxis.”
  - “There are no clinical trial data providing evidence for treatment of acute anaphylaxis. The recommendations are based on clinical observations, interpretation of pathophysiology and animal models.”

- CASE REPORTS – LOE 4 poor

- CONSENSUS GUIDELINE – LOE 4 poor
- *Cites ERC guidelines regarding anaphylaxis with cardiac arrest.*

- SYSTEMATIC REVIEW – LOE 4 poor (not based on RCTs)
- Introduction:
  - Adrenaline (epinephrine) is the recommended first line treatment for patients with anaphylaxis. This review discusses the safety and efficacy of adrenaline in the treatment of anaphylaxis in the light of currently available evidence. A pragmatic approach to use of adrenaline auto-injectors is suggested.
- Summary points
  - Anaphylaxis is a severe life threatening reaction that can affect all age groups
  - The severity of previous reactions does not predict the severity of subsequent reactions
  - Intramuscular adrenaline is the first line treatment for anaphylaxis, with intravenous adrenaline reserved for unresponsive anaphylaxis or circulatory collapse
  - Early use of adrenaline in anaphylaxis is associated with improved outcomes
Any patient with a systemic allergic reaction should be considered for an adrenaline auto-injector, depending on risk of further reactions.

There is a clear need to improve education of both patient and physician on the use of and indications for adrenaline auto-injectors.

**Other points**

- “[The effects of inhaled adrenaline] have only been shown in healthy volunteers and have, as yet, not been confirmed in patients during anaphylaxis.”
- “Evidence [from a case report] suggests that a poor outcome from anaphylaxis is associated with late administration of adrenaline.”

**Mink SN, Simons FER.** Constant infusion of epinephrine, but not bolus treatment, improves haemodynamic recovery in anaphylactic shock in dogs. Clin Exper Allergy. 2004; 34(11):1776-1783

- **RANDOMIZED CONTROLLED CROSSOVER CANINE STUDY** – LOE 5 fair
- **Along with a previous experiment by the same group, this randomized, controlled, crossover canine study provides insights into the optimal route for administration of epinephrine in anaphylactic shock.**


- **CASE REPORT – LOE 4 poor**


- **CASE REPORT – LOE 4 fair**
- **Anaphylaxis patient with PA catheter monitoring throughout; suggests need for fluid bolus with epinephrine.**
- **No relevant citing references**


- **RETROSPECTIVE CASE REVIEW – LOE 4 fair**
- **The author, a pathologist, reports retrospectively on 38 anaphylactic shock deaths for which the perimortem postural history of the patient was available.**
- **Excerpts**
  - “A possible mechanism suggests itself to explain this striking pattern of sudden deaths after a change to a more upright posture.... If this hypothesis is correct, once the vena cava is empty, epinephrine—no matter where or how it is given—could not circulate and so could not reverse the shock; nor could external cardiac massage reestablish the circulation if there is no blood in the vena cava.”
  - “The events during the nonfatal wasp sting reaction reported here suggest that those with epinephrine should be instructed to remain supine rather than sit up to use their autoinjectors if they feel faint.”

**Pumphrey RSH.** Lessons for management of anaphylaxis from a study of fatal reactions. Clinical and Experimental Allergy. 2000; 30(8):1144-50

- **RETROSPECTIVE CASE REVIEW – LOE 4 fair**


- **SYSTEMATIC REVIEW – LOE 1 fair (methods not reported)**
- **No citing references**
- CASE REPORT – LOE 4 poor
- Terlipressin given after and/or with large doses of epinephrine, precluding isolation of specific effects.
- No citing references

- CONSENSUS GUIDELINE – LOE 4 fair
- Excerpt
  - “Potent vasopressors, such as noradrenaline, vasopressin, or metaraminol, might be required to overcome vasodilatation if epinephrine and fluid resuscitation have failed to maintain a systolic blood pressure of greater than 90 mm Hg. Recent case reports and animal studies have demonstrated that vasopressin is useful when treating hemorrhagic and septic shock. The effect of vasopressin on systemic anaphylaxis has not been investigated, except in clinical case reports.”

- CASE SERIES AND REVIEW – LOE 4 fair
- Excerpts
  - “When little or no evidence is available, recommendations based on clinical experience and physiological rationale should be considered. Our cases demonstrate clearly that vasopressin may help if circulatory function deteriorates quickly despite adequate standard treatment.”
  - “A significant issue faced by clinicians is how to proceed if epinephrine and fluid resuscitation are unsuccessful, or excessive use of these interventions is not suitable. In case of profound hypotension, a decision needs to be made promptly. The available evidence, although largely anecdotal, is compelling and favors an empirical addition of a potent vasoconstrictor bolus to resuscitate patients with severe anaphylaxis. Drugs successfully used have included norepinephrine, the α1-agonists methoxamine, and metaraminol, and the pituitary hormone vasopressin. Our cases clearly demonstrate the immediate positive effect of vasopressin in restoring normal hemodynamic function.”
  - “Standard treatment of anaphylactic shock, including discontinuation of the causative agent, administration of epinephrine, and infusion of IV fluids, did not stabilize cardiocirculatory function, and adding arginine vasopressors resulted in prompt hemodynamic stabilization.”
  - “Our cases demonstrate clearly that vasopressin may help if circulatory function deteriorates quickly despite adequate standard treatment.”

- SYSTEMATIC REVIEW – LOE 1 fair (Not based on RCTs)
- Updated and unchanged in 2009.
- Excerpts
  - The evidence base in support of the use of adrenaline is unclear [and] the use of adrenaline in anaphylaxis appears to be based largely on extrapolation from first principles, expert opinion, tradition, ...and on evidence from fatality series in which most individuals dying from anaphylaxis had not received prompt adrenaline treatment.
• Distinction between anaphylactic reactions and an anaphylactoid reaction is no longer recommended as the clinical picture and emergency treatment of anaphylaxis are similar regardless of the pathophysiologic mechanism.

• Based on the current evidence, we believe that the benefit of using appropriate doses of intramuscular adrenaline is likely to far exceed the risk.

• There have been no prospective human studies performed during the management of anaphylaxis to evaluate ...adrenaline given intramuscularly or to assess... adverse effects. Case reports and large mortality reviews indicate that side effects involving the myocardium can be serious, usually in the setting of inappropriate dosing. However, there is now increased awareness that the heart itself may be a target organ in anaphylaxis and that electrocardiographic changes suggesting ischaemia, myocardial failure, and dysrhythmias can occur even if adrenaline has not been given

• ...Adrenaline is not contraindicated in individuals with underlying ischaemic heart disease as the decrease in filling pressure due to anaphylaxis is likely to result in further coronary ischaemia.

• ... if a severe reaction develops and adrenaline is administered at the generally recommended initial doses for anaphylaxis, which are lower than the doses recommended for resuscitation, it might not adequately counteract the effects of vasodilation and distributive-hypovolaemic shock on its own, even when given as an intravenous infusion.

• It is difficult, particularly in retrospect, to dissect potential adverse effects of adrenaline from the known effects of anaphylaxis. Because of potential harm from the use of intravenous adrenaline in inexperienced hands, guidelines generally recommend that the intravenous route is reserved for cases that do not respond to initial treatment with intramuscular adrenaline and where cardiovascular collapse and cardiac arrest is considered imminent. A controlled infusion is safer than bolus administration. It should be given in a resuscitation area that has electrocardiography and physiological monitoring by medical and nursing staff who are trained in its use.

• I repeated their search strategy of [http://clinicaltrials.gov](http://clinicaltrials.gov) and found the following trial, not yet recruiting: Intravenous Heparin as an Adjunct for the Treatment of Anaphylactic Reactions in an Emergency Department, which is “based on promising experimental results in a porcine model.” No references were available. A search of [http://www.controlledtrials.com](http://www.controlledtrials.com) yielded no results.


• SYSTEMATIC REVIEW – LOE 1 fair (not a review of RCTs)

• Excerpt

  o “Antihistamines are a second line treatment for an anaphylactic reaction. The evidence to support their use is weak, but there are logical reasons for them.... Used alone, they are unlikely to be life-saving in a true anaphylactic reaction.”


• CASE CONTROL, CONVENIENCE SAMPLE – LOE 2 poor

• Excerpt

  o “The scientific basis for the recommended doses [in children] is weak. The recommended doses are based on what is considered to be safe and practical to draw up and inject in an emergency.”


• PROSPECTIVE RANDOMIZED BLINDED PLACEBO CONTROLLED 6-WAY CROSSOVER STUDY – LOE 2 fair
Excerpts
- The best site for IM injection is the anterolateral aspect of the middle third of the thigh.
- The subcutaneous or inhaled routes for adrenaline are not recommended for the treatment of an anaphylactic reaction because they are less effective than the IM route.

- SYSTEMATIC REVIEW – LOE 4 poor
- Excerpts
  - Wide variations in aetiology, severity and organ involvement preclude standardised treatment recommendations. The lack of clinical trials necessitates guidelines based on consensus opinion.
  - There are case reports that vasopressin may benefit severely hypotensive patients. Case reports also suggest that, when relative or severe bradycardia is present, there may be a role for atropine.
  - All of the following are unreferenced and apparently consensus-based/expert opinion.
    - In addition to the ALS drugs, consider the following therapies.
      - Rapid fluid resuscitation: Near-fatal anaphylaxis produces profound vasodilation and a relative hypovolaemia. Massive volume replacement is essential. Use at least two large-bore cannulae with pressure bags to give large volumes (as much as 4–8 L IV fluid may be necessary in the immediate resuscitation period).
      - Antihistamines: Give an antihistamine IV if antihistamine has not already been given before the arrest. (Reference cites basic science studies of histamine’s role in anaphylaxis.)
      - Steroids: Steroids given during a cardiac arrest will have little immediate effect but, if ROSC is restored, they may be effective in the post-resuscitation period.
      - Prolonged CPR: Patients with anaphylaxis are often young, with healthy hearts and cardiovascular systems. Effective CPR may maintain sufficient oxygen delivery until the catastrophic effects of the anaphylactic reaction resolve.

- CONSENSUS GUIDELINE – LOE 4 poor
- Excerpts (unreferenced)
  - The intramuscular route for adrenaline is the route of choice for most healthcare providers. There is a much greater risk of causing harmful side effects by inappropriate dosage or misdiagnosis of anaphylaxis when using IV adrenaline. Many healthcare providers will have given IV adrenaline as part of resuscitating a patient in cardiac arrest. This alone is insufficient experience to use IV adrenaline for the treatment of an anaphylactic reaction.
  - The intramuscular route for adrenaline is not recommended after cardiac arrest has occurred.
  - Large volumes of fluid may leak from the patient’s circulation during an anaphylactic reaction. There will also be vasodilation. If there is intravenous access, infuse intravenous fluids immediately. Give a rapid IV fluid challenge... and monitor the response; give further doses as necessary. There is no evidence to support the use of colloids over crystalloids in this setting. Consider colloid infusion as a cause in a patient receiving a colloid at the time of onset of an anaphylactic reaction and stop the infusion..... Do not delay the administration of IM adrenaline attempting intra-osseous access.
  - There is little evidence on which to base the optimum dose of hydrocortisone in anaphylaxis.
Some patients develop severe bradycardia after an anaphylactic reaction. Consider IV atropine to treat this.


- SHORT CUT REVIEW (focused literature review [their terminology]) – LOE 4 fair
- Excerpt
  - “Glucagon can be useful to treat an anaphylactic reaction in a patient taking a beta-blocker.”


- REVIEW – LOE 4 poor