WORKSHEET for Evidence-Based Review of Science for First Aid

Worksheet author(s)  Date Submitted for review:  12/3/2008

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Clinical question.
Does the administration of a second dose of injectable epinephrine improve outcome from a severe allergic reaction?

P – Persons with severe allergic reactions who have been administered injectable epinephrine/adrenaline
“severe allergic reactions” includes anaphylaxis, for which there is controversy regarding an exact definition, particularly on the grounds of clinical findings

I – “administration of a second dose of injectable epinephrine/adrenaline”

C – administration of only a single dose of injectable epinephrine/adrenaline

O – difference in clinical status
  Mortality or morbidity
  Positive or negative

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

Search strategy (including electronic databases searched).

Search Term Generation

MeSH Logic and Searches by PICO format

Question

“Does the administration of a second dose of injectable epinephrine improve outcome from a severe allergic reaction?”

Patients

Persons with severe allergic reactions who have been administered injectable epinephrine/adrenaline

Key search terms as patient descriptors:
  Severe allergic reactions
  Anaphylaxis

Medline search terms:

Anaphylaxis
  Mapped in MeSH subordinate to Hypersensitivity with no further subheadings

Items 1 - 5 of 5

✓ 1: Anaphylaxis

An acute hypersensitivity reaction due to exposure to a previously encountered ANTIGEN. The reaction may include rapidly progressing URTICARIA, respiratory distress, vascular collapse, systemic SHOCK, and death.
### Passive Cutaneous Anaphylaxis

An evanescent cutaneous reaction occurring when antibody is injected into a local area on the skin and antigen is subsequently injected intravenously along with a dye. The dye makes the rapidly occurring capillary dilatation and increased vascular permeability readily visible by leakage into the reaction site. PCA is a sensitive reaction for detecting very small quantities of antibodies and is also a method for studying the mechanisms of immediate hypersensitivity.

Year introduced: 1967 (1965)

### prostaglandin-generating factor of anaphylaxis

Oligopeptide released from human lung parenchymal tissue during anaphylaxis

Date introduced: September 14, 1982

### Receptors, Leukotriene

Cell-surface receptors that bind leukotrienes with high affinity and trigger intracellular changes influencing the behavior of cells. The leukotriene receptor subtypes have been tentatively named according to their affinities for the endogenous leukotrienes LTB4; LTC4; LTD4; and LTE4.

Year introduced: 1994

### SRS-A

A group of leukotrienes; (LTC4; LTD4; and LTE4) that is the major mediator of bronchoconstriction; hypersensitivity; and other allergic reactions. Earlier studies described a "slow-reacting substance of ANAPHYLAXIS" released from lung by cobra venom or after anaphylactic shock. The relationship between SRS-A leukotrienes was established by UV which showed the presence of the conjugated triene. (From Merck Index, 11th ed)

Year introduced: 1973 (1967)

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**Allergic Reaction**

Mapped in MeSH database to **Hypersensitivity**

Entry Terms (i.e. terms that would lead back to Hypersensitivity, hence, no point in creating separate searches under any of these terms other than as text searches: Author note.):

- Hypersensitivities
- Allergy
- Allergies
- Allergic Reaction
- Allergic Reactions
- Reaction, Allergic
- Reactions, Allergic

### Hypersensitivity

MeSH Tree for **Hypersensitivity**

Note below Anaphylaxis as subheading of **Hypersensitivity, Immediate** with no subheadings
Thus, for performing searches, **anaphylaxis**, was chosen as being the “cleanest” term for a severe allergic reaction not to include the other terms that be included by using the term ”allergic reaction” which would default to **hypersensitivity**, and, hence, include the rest of the subordinate terms.

**Interventions**

“administration of a **second dose** of **injectable epinephrine**”

Key search words for intervention:

Epinephrine (Adrenaline)

Second dose (to include Multiple dose)

Injectable

FASAB focus for first level interventions, per discussions suggests focus on self-administered epinephrine in the out-of-hospital setting

**Thus, the following refinements used to seek more directly applicable information**

Epi Pen, Epipen, Epi-pen
Anapen
Auto-injector, auto injector, autoinjector

Adrenaline and Epinephrine to be used as the fall-back terms since they are the active pharmacologic agent and the exercise is to attempt to locate evidence in regards to the use of the pharmacologic agent, not limited to via the above devices.
Epinephrine

= MeSH heading

Entry Terms (As above, any of the following terms will be searched under Epinephrine – as a brief note, the British system has historically been more allied to adrenaline, based, largely, on the more precise nomenclature in terms of the origins of the substance: Author Note):

- 4-(1-Hydroxy-2-(methylamino)ethyl)-1,2-benzenediol
- Adrenaline
- Epifrin
- Epitrate
- Adrenaline Bitartrate
- Epinephrine Hydrogen Tartrate
- Epinephrine Bitartrate
- Lyophrin
- Micronefrin
- Micronephrine
- Racepinephrine
- Racemic Epinephrine
- Epinephrine, Racemic
- Vaponefrin
- Adrenaline Hydrochloride
- Hydrochloride, Adrenaline
- Medihaler-Epi

MeSH trees including Epinephrine

All MeSH Categories
  Chemicals and Drugs Category
    Organic Chemicals
      Alcohols
        Amino Alcohols
          Ethanolamines

All MeSH Categories
  Chemicals and Drugs Category
Adrenaline

MeSH heading search produced links to “Epinephrine”

- **Epinephrine**
  - s.
- **3-(3,4-dihydroxyphenyl)-N-methylserine [Substance Name]**
  - RN given refers to (DL)-Tyr isomer
  - Date introduced: February 25, 1987
- **NAD(P)H-adrenaline oxidase [Substance Name]**
  - forms adrenochrome
  - Date introduced: December 19, 1984
- **3,4-diisovaleryl adrenaline [Substance Name]**
  - precursor of adrenaline in iris-ciliary body
  - Date introduced: October 16, 1984
5: **adrenaline-N-methyltransferase [Substance Name]**
   Date introduced: January 1, 1980

6: **adrenaline sulfate [Substance Name]**
   Date introduced: January 1, 1979

7: **dipivefrin [Substance Name]**
   used in treatment of both primary and open angle glaucoma; RN given refers to (−)-isomer
   Date introduced: January 1, 1977

3 through 6 map to epinephrine.

Thus, “epinephrine” more relevant as MeSH term, but “adrenaline” still useful as a text word search term, particularly to seek British-influenced articles.

**Search Histories**

**Cochrane via OVID**

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PubMed

SH – PubMed – Hypersensitivity and anaphylaxis AND epi or adrenaline – general terms

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SH – PubMed – Eliminations on above general searches

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#52 Search ((("second dose") AND (#41)) NOT (#48)) NOT (#51)

#50 Search ((("second dose") AND (#41)) NOT (#48)

#49 Search (((bronchiolitis) OR (#46)) OR (#45)) NOT (#44)

#48 Search ((bronchiolitis OR (#46)) OR (#45)

#47 Search bronchiolitis

#46 Search bronchitis

#45 Search asthma

#44 Search ("second dose") AND (#41)

#43 Search "second dose"

#41 Search epinephrine

#40 Search adrenaline

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#22 Search allergic reaction

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18 Search "Hypersensitivity/drug therapy"[Mesh] 38049
17 Search "Hypersensitivity"[Mesh] 228796

SH – PubMed - Hypersenitivity and Epi as MeSH terms and comparisons to results above

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SH – PubMed – Final Summary

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<tr>
<td>#2</td>
<td>Search ((epinephrine) OR (adrenaline)) AND (((auto injector) OR (autoinjector) OR (auto-injector)) OR ((epipen) OR (epi-pen)) OR (epi pen))</td>
<td>98</td>
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</tbody>
</table>
**JSTOR**

Basic Search

| #1 | ((epinephrine) AND (anaphylaxis)) AND (year:[1996 TO 2008]) | 111 |

Majority of returns were only “Front Matter” or “Back Matter” = Tables of contents for journals.

**Web of Knowledge**

| #5 | 1,362 | #4 AND #1  
|  | Timespan=All Years |
| #4 | 70,463 | #3 OR #2  
|  | Timespan=All Years |
| #3 | 18,578 | Topic=(adrenaline)  
|  | Timespan=All Years |
| #2 | 63,000 | Topic=(epinephrine)  
|  | Timespan=All Years |
| #1 | 21,767 | Topic=(anaphylaxis)  
|  | Timespan=All Years |

Searches specifically seeking older references to origins of use of Epinephrine/Adrenaline for treatment of anaphylaxis

**Science Direct Database**

*This search was undertaken in response to initial review by FASAB work group to, in the absence of actual comparative trials or other prospective evaluations, to seek more detailed background information from older studies that may have addressed the question of the value and safety of repeating epinephrine.*

*PubMed, including “Old PubMed” only indexes articles at the most to the early 1950s. Several articles reviewed from the above searches had referred to articles published earlier than 1950.*

*By a simple chance maneuver access to several older resources came about. In the Science Direct journal access system from Elsevier, each reference has a link for “related articles.” Using this link from one article led to relevant articles as far back as the 1890s, when anaphylaxis was first being described and, independently, a biologically active extract of the adrenal gland was being initially described.*

“Related articles” search to

And limited to “Journals only” and “1969 and before” > 355 articles
   These 355 titles were reviewed with selection of 11 particularly relevant articles
   These 11 articles were reviewed, leading to 10 more articles through direct or second-order
   reference links through performing the same “related articles” search on each of the 11:

Based on a search of references in several of the articles above, several additional articles were retrieved

**Google Scholar**

Search string – “Adrenalin Anaphylaxis” - Limited to 1910-1920
   124 results
   3 additional sources beyond some found through other searches

**Comparison**

– a single dose of injectable epinephrine/adrenaline

No direct trials found.

**Outcome**

– difference in clinical status
  mortality or morbidity
  Positive or negative

No direct studies looking at the clinical question of difference in outcome between one and two IM or SC doses of epinephrine in anaphylaxis or severe allergic reaction. One retrospective observational series reported on the “need” for more than one dose of epinephrine and one patient survey reported the use of a second dose of epinephrine, but no specific criteria were cited or proposed for deciding whether a second dose was necessary or for judging the utility and/or safety of a second dose.

### State inclusion and exclusion criteria

**Included -**
- Human
- All ages
- International as catalogued in Medline

**Attempted to limit to -**
- Clinical trials – none found directly addressing the PICO question
- Randomized Controlled Trials – none found directly addressing the PICO question

**Exclusions -**
- After initial review of a refined PubMed results with over 1000 articles, articles prior to 1996 in the PubMed and WoS searches were excluded, though some older articles are included which were in the reference set of an initially selected article.
- Other exclusions are built into the search structures listed above.
Following review with the FASAB working group – decision to expand search to older articles to seek fundamental logic and development of the therapeutic recommendations for multiple dose epinephrine

* Number of articles/sources meeting criteria for further review:
Ultimately narrowed the field to 202 articles for abstract review (based on limiting a 1965-forward MedLine search to 1996 forward following a “titles only” review of results back to 1965. (On initial review of the older set, it did not appear to contain articles that seeming likely to add to the question, particularly, no clinical trials or RCTs were found there.) Following review of these abstracts 49 articles were reviewed in detail.

Only one Cochrane review addressed an allied topic and that was simply the framework for a review yet to be executed.

Addendum: Based on review with FASAB working group and commentaries regarding seeking older literature to look for foundations of concept

Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>Varies</th>
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Outcomes – Please define outcomes for this question, place them after letters below and use letters to identify studies which evaluate this outcome

A = Improved speed of resolution of signs and symptoms of anaphylaxis
B = Arrest of progression of signs and symptoms of anaphylaxis
C = 
D = 
E = *Italics = Animal studies*

* Only “studies” found were retrospective observational epidemiologic studies documenting the use of multiple doses in different, uncontrolled settings. Uncontrolled in the sense of not having a standardized definition of symptoms and signs for which the initial and subsequent doses were administered.

### Evidence Neutral to Clinical question

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Outcomes

A = Improved speed of resolution of signs and symptoms of anaphylaxis
C = 
E =
B = Arrest of progression of signs and symptoms of anaphylaxis  

- Only “studies” found were retrospective observational epidemiologic studies documenting the use of multiple doses in different settings with no standardized criteria for the decision to administer either the initial or subsequent doses of epinephrine.

**Evidence Opposing Clinical Question**

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**Outcomes**

A = Improved speed of resolution of signs and symptoms of anaphylaxis
B = Arrest of progression of signs and symptoms of anaphylaxis
C = E =
D = *Italics = Animal studies*

* Only “studies” found were retrospective observational epidemiologic studies documenting the use of multiple doses without any standardized criteria for deciding on a second dose, nor for defining outcome.
This literature review revealed no published controlled trials evaluating the relative benefit of more than one dose of injectable epinephrine in either the non medical or medical settings of severe allergic reactions.

This literature review revealed several small retrospective series of chart reviews or survey studies revealing that, in a not insignificant number of cases either the person experiencing an allergic reaction or a responsible party felt that more than one dose of epinephrine was required to treat the reaction.

This literature review revealed several case reports of adverse reactions to epinephrine, though none specifically cited the reaction being associated with a second dose of epinephrine. Almost all of the case reports involved additional factors that either attributed to or accounted for the adverse reaction such as pre-existing patient conditions, wrong dose(1:1000 injected intravenously, for example)

Historical literature demonstrated the progression from realizing that either dried suprarenal gland or, ultimately, extract from suprarenal glands had a vasoconstrictive and hypertension generating effect. These discoveries were occurring at the same time as the nature of anaphylaxis was being elucidated. As these studies were using a physiologic substance it was often applied in a graded response to the clinical condition of either the human patient or experimental animal, leading to apparent acceptance of administering more epinephrine titrating to clinical improvement.

Acknowledgements: Elizabeth Fitzpayne, Librarian
Boston Medical Library Branch
Massachusetts Medical Society
For her assistance in retrieving a number of articles

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### Citation List

Articles from [Science Direct](https://www.sciencedirect.com) Relevance search to Chaudhuri2008, noted above

<table>
<thead>
<tr>
<th>Article Title</th>
<th>Source</th>
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<tbody>
<tr>
<td>Anaphylaxis.</td>
<td><em>The Lancet, Volume 176, Issue 4547, 22 October 1910, Pages 1224-1225</em></td>
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</table>
| THE TREATMENT OF ANAPHYLACTIC SHOCK. | *The Lancet, Volume 180, Issue 4643, 24 August 1912, Page 557*  
John R. O'Brien, H. M. Wilson |
| OBSERVATIONS ON THE TREATMENT OF ANAPHYLAXIS. | *The Lancet, Volume 187, Issue 4841, 10 June 1916, Pages 1171-1172*  
Albert "S. Leyton, Helen G. Leyton |
| THE PHENOMENA OF ANAPHYLAXIS. | *The Lancet, Volume 189, Issue 4873, 20 January 1917, Pages 105-109* |
| THE PHENOMENA OF ANAPHYLAXIS. | *The Lancet, Volume 189, Issue 4873, 20 January 1917, Pages 124* |
Crofton -

THE PHENOMENA OF ANAPHYLAXIS.
The Lancet, Volume 189, Issue 4875, 3 February 1917, Pages 198-199
W. W. C. Topley, A. S. Leyton

PROPHYLAXIS AND ANAPHYLAXIS
The Lancet, Volume 224, Issue 5798, 13 October 1934, Pages 817-818

Adrenal cortex extract in canine anaphylactic shock: Dragstedt, C. A., Mills, M. A., and Mead, F.
B.: J. Exper. Therap.9: 359, 1937
Journal of Allergy, Volume 9, Issue 1, November 1937, Page 95

43: 69, 1942
Journal of Allergy, Volume 13, Issue 6, September 1942, Pages 632-633

The effect of stress factors on asthma induced in guinea pigs by aerosolized antigens
Journal of Allergy, Volume 24, Issue 4, July 1953, Pages 302-308
Samuel M. Feinberg, Saul Malkiel, Floyd C. McIntire

THE ROLE OF EPINEPHRINE AND THE EFFECT OF AMINE OXIDASE INHIBITOR
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Journal of Allergy 1954;25:104-11
Rebhun J, Feinberg SM.

Additional articles retrieved from reviews of references to above articles and from submitting these
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availability of older articles (either through Countway Library historical collection search engine
or individual relevant journals not covered in Science Direct)

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Swann AW. Urticaria Treated With Epinephrin. The American Journal of the Medical Sciences
1913;145:373-7.
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26. Sicherer SH, Simons FER, Section on Allergy and Immunology (American Academy of Pediatrics). Self-injectable epinephrine for first-aid management of
34. Topley WWC. The Phenomena of Anaphylaxis. The Lancet 1917;189:276-.