**Clinical question.**

"In infants and children with hypotensive septic shock (P), does the use of corticosteroids in addition to standard care (I) when compared with standard care without the use of corticosteroids (C), improve patient outcome (e.g., hemodynamics or survival) (O)?"

**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 topic

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? Neither Mark Coulthard nor Arno Zaritsky has a conflict of interest.

**Search strategy (including electronic databases searched).**

PubMed
Medline
Embase
Cochrane Library
AHA EndNote Library (24 March 2008)

• **State inclusion and exclusion criteria**

**PubMed Search (Lars Erikkson, Herston Medical Library)**

- septic shock AND corticosteroids AND((randomized controlled trial[Publication Type] OR (random*[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) OR systematic[ab])

85 hits

**Medline Ovid Search (Lars Erikkson)**

1. exp Shock, Septic/ 15094
2. exp Adrenal Cortex Hormones/ 285562
3. 1 and 2 1132
4. child*.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 1492519
5. 4 and 3 73
6. 5 73
7. limit 6 to english language 48
8. limit 7 to "therapy (sensitivity)" 44
9. limit 7 to systematic reviews 4
10. 8 or 9 44
11. limit 10 to comment 3
12. limit 10 to editorial 2
13. limit 10 to case reports 7
14. 11 or 13 or 12 10
15. 10 not 14 34
16. from 15 keep 1-34 34

**PubMed Search August 2009 (Lars Erikkson, Herston Medical Library)**

1. steroids.mp. or exp Steroids/ 637235
2. exp Adrenal Cortex Hormones/ or Adrenal Cortex Hormone*.mp. 293877
3. Glucocorticoid. or Glucocorticoid*.mp. 66582
4. Corticosteroid*.mp. 58124
5. 4 or 1 or 3 or 2 716751
6. exp Sepsis/ 72560
7. exp Shock, Septic/ 15461
8. Toxic Shock.mp. 3265
9. Endotoxic Shock.mp. 1702
10. Systemic Inflammatory Response Syndrome.mp. or exp Systemic Inflammatory Response Syndrome/ 75332
11  warm shock.mp.  9
12  Septic?emia.mp.  13531
13  Septic?emic shock.mp.  101
14  exp Shock/ or shock.mp.  134722
15  6 and 14  19322
17  11 or 16 or 8 or 7 or 13 or 9 or 15 or 10  77280
18  17 and 5  3373

(((systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update$ or summary).ti. or review.pt.)) or (meta analysis.pt. or meta analysis/ or “0266-4623”.is.) or (reviewed systematically or systematically reviewed).tw. or (1469-493X or 1366-5278 or 1530-440X).is.) not ((animals/ not humans/) or letter.pt.)  54351

((randomized controlled trial or controlled clinical trial).pt. or (((double blind$ or placebo or random$) not (non random$ or nonrandom$ or unrandom$)).ti. or (random$ adj (enrol$ or assign$)).tw.) and clinical trial.pt.)) not (animals/ not humans/)  349392
21  19 or 20  402867
22  21 and 18  153

Cochrane Library
Search terms = septic AND steroids

Results
2 systematic reviews – irrelevant
46 controlled trials – all imported

AHA EndNote Library (24 March 2008) – search septic AND steroid → 10 hits all imported

Final EndNote Library = 259 references

* Number of articles/sources meeting criteria for further review:
10 (Marik is background material only)
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Evidence Supporting Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Annane 2002, 288; B&amp;E Sprung 2008, 358; E</td>
</tr>
<tr>
<td>Fair</td>
<td>Bollaert 1998, 645; E Briegel 1999, 723; E Oppert 2005, 2457; E Russell 2009, 811; B</td>
</tr>
<tr>
<td>Poor</td>
<td>Oppert 2000, 1747; E</td>
</tr>
</tbody>
</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint – shock reversal  

**Italics** = Animal studies

#### Evidence Neutral to Clinical Question

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</thead>
<tbody>
<tr>
<td>Good</td>
<td>Sprung 2008, 358; B</td>
</tr>
<tr>
<td>Fair</td>
<td>Bollaert 1998, 645; B Yildiz 2002, 251; B Oppert 2005, 2457; B</td>
</tr>
<tr>
<td>Poor</td>
<td>Oppert 2000, 1747; B</td>
</tr>
</tbody>
</table>

**Level of evidence**

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

#### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Evidence Opposing Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Markovitz 2005, 270; B</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
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<tr>
<td>Poor</td>
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</tbody>
</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint – shock reversal  

**Italics** = Animal studies
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The only data available in children is a retrospective study (Markovitz, 2005, 270), a study in the developing world (Slusher, 1996, 579) and a small RCT (Valoor, 2009, 121).

The retrospective study (Markovitz, 2005, 270) queried the Child Health Corporation of America's hospital discharge database for children with a discharge diagnosis of severe sepsis, who also received mechanical ventilation and evaluated the association between the use of corticosteroids and outcome. A total of 6,693 patients were identified from 27 participating hospitals. Age, haematologic-oncology diagnosis and steroid use were independent predictors of mortality in multivariate analysis. It was concluded that steroids were given to the more severely ill children and that steroid use was associated with increased mortality. Because of the limitations of this database, it is uncertain if the use of steroids was directly related to the occurrence of septic shock. For example, some children may have received steroids secondary to their underlying diagnosis rather than as therapy for septic shock.

The study (Slusher, 1996, 579) in the developing world (Kenya & Nigeria) was an extension of the finding that dexamethasone administered prior to antibiotics reduced hearing loss in children with *H. influenzae* meningitis. This well-designed and completed study hypothesized that administering dexamethasone at the time of antibiotics would improve outcome in children with sepsis. A total of 72 children were enrolled and the authors found no difference in survival to discharge (placebo 89%, dexamethasone 83%). None of these children received intubation, mechanical ventilation or vasoactive drugs.

In a pilot study in India (Valoor, 2009, 121), 38 children with septic shock unresponsive to fluid therapy were randomized without blinding to receive IV hydrocortisone (5 mg/kg/day in 4 divided doses) until shock reversal. The authors suggested that malnutrition present in nearly half of their patients may alter the response to steroids. The median time to shock reversal in the steroid group was 49.5 hrs versus 70 hrs in the placebo group (not statistically significant) and there was a tendency to use less vasoactive drugs in the steroid group.

Acknowledgements: Thanks to Lars Erikkson at the Herston Medical Library, Brisbane, Australia for assistance with the search strategies.
## Citation List

<table>
<thead>
<tr>
<th>Citation Marker</th>
<th>Full Citation</th>
</tr>
</thead>
</table>

### Comments
- **Annane, 2002**
  - Hydrocortisone/fludrocortisone – short corticotropin stimulation test
  - Internal validity:
    - Randomised – computer generated, stratified location, blocks 4
    - Allocation concealment – yes
    - Follow-up – only 1 patient lost
    - Analysis – intention to treat
    - Blinded – yes
    - Both groups treated similarly – when/ where does the Etomidate story unfold? Groups were similar at start of trial – yes
  - Results
    - Corticotropin Responders – no effect of stress dose steroids
    - Corticotropin Non-responders NNT = 7 (save one life at 28 days)
    - All patients NNT = 8
    - Etomidate – excluded pts who received etomidate during 6 hrs prior to randomisation (amended June 1997)
    - Interim analysis –O'Brien & Fleming stopping boundary
  - Evidence: Supportive (B=survival; E= shock reversall)
  - Quality: Good
  - LOE: 5

- **Bollaert, 1998**
  - Adult patients
Septic shock & vasopressors
Corticotropin stimulation test (Short Synacthen test) (excluded if absolute cortisol deficient – but none were)
Primary end point – shock reversal
Secondary end point – 28 day all cause mortality
Powered to detect 30% difference in rate shock reversal
Trial stopped early because of dramatic differences, but “stopping rule” was not stated

Internal validity:-
Randomised – by pharmacist not explicitly stated
Allocation concealment – by pharmacist not explicitly stated
Follow-up – probably complete
Analysis – one patient died before randomization, one given incorrect medication
Blinded – yes
Both groups treated similarly – yes
Groups were similar at start of trial – yes

Results:-
Shock reversal 7 days 15/22 (68%)- steroids versus 4/19 (21%) - placebo
Crude 28-day mortality was 32% (steroids) versus 61% (placebo)

Evidence: Supportive E = shock reversal; Neutral B= survival (28 day all cause mortality)
Fair (trial stopped early i.e. when they found what they wanted)
LOE: 5

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
</table>

Institut für Anaesthesiologie, Klinikum Grosshadern, Ludwig-Maximilians-Universität München, Munich, Germany.

Comments
Primary end point – shock reversal (end of vasopressor support)
Secondary end point – haemodynamics & MODS development
N = 40
Interim analysis after 24 patients – no adverse hydrocortisone effects

Internal validity:-
Randomised – permuted block design
Allocation concealment – not stated
Follow-up – telephone,? how many
Analysis – not stated
Blinded – double blind placebo
Both groups treated similarly – probably
Groups were similar at start of trial – yes (Table 1)

Results
Mortality Hydrocortisone 4/20; placebo 6/20 (Type II error)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
</table>
Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University, Philadelphia, PA, USA. paul.marik@jefferson.edu  
Comments  
Consensus statement expert panel  
Delphi method  
Meta-analysis random effects model (Cochrane software)  
Internal validity:-  
Randomised –  
Allocation concealment –  
Follow-up –  
Analysis –  
Blinded –  
Both groups treated similarly –  
Groups were similar at start of trial –  
Evidence: Not part of the evidence evaluation – background material |
Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J.  
Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, USA.  
Comments  
Retrospective cohort study  
Patients identified Children's Health Corporation of America database  
Primary endpoint – mortality  
Secondary endpoint – hospital LOS  
Internal validity:- |
### Results

More likely to die if received steroids although trend to lower mortality if centre routinely used steroids?

Not supportive

**Evidence:** Opposing – B= survival of event  
**Quality:** Poor  
**LOE:** 4

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**Oppert, 2000**  

Plasma cortisol levels before and during "low-dose" hydrocortisone therapy and their relationship to hemodynamic improvement in patients with septic shock.

Oppert M, Reinicke A, Gräf KJ, Barckow D, Frei U, Eckardt KU.  
Department of Nephrology and Medical Intensive Care, Berlin, Germany.

**Comments**

- Adults septic shock  
- Prospective observational study n = 20  
- Low dose steroid  
- Short Corticotropin stimulation test – used to split patients into two groups – appropriate/inadequate response to corticotropin  
- Table 4 "rapid versus no rapid haemodynamic" improvement  

**Internal validity:**

- Randomised – prospective observational study  
- Allocation concealment – not applicable  
- Follow-up – complete  
- Analysis –  
- Blinded –  
- Only one group – all patients received low dose hydrocortisone  
- Groups were similar at start of trial –

**Evidence:** Supportive – E= shock reversal; Neutral – B= survival of event;  
**Quality:** Fair  
**LOE:** 5

---

**Oppert, 2005**  

Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock.

Department of Nephrology and Medical Intensive Care, Charite Universitätsmedizin Berlin, Humboldt University, Berlin, Germany.

**Comments**

- Prospective randomised 153 septic shock pts
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
<th>Evidence</th>
<th>Quality</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short corticotropin stimulation test</strong>&lt;br&gt;Hydrocortisone or placebo&lt;br&gt;Primary endpoint – shock reversal&lt;br&gt;Secondary endpoint – cytokine production following ex vivo LPS stimulation&lt;br&gt;Etomidate in 7 pts</td>
<td>Internal validity:-&lt;br&gt;Randomised – pharmacy&lt;br&gt;Allocation concealment – opaque envelopes&lt;br&gt;Follow-up – 7 patients lost&lt;br&gt;Analysis – intention to treat&lt;br&gt;Blinded – yes&lt;br&gt;Both groups treated similarly – yes&lt;br&gt;Groups were similar at start of trial – yes</td>
<td>Results – shock reversal sooner in the steroid treated group</td>
<td>Evidence: Supportive – E= shock reversal; Neutral – B= survival of event</td>
<td>Quality: Fair</td>
<td>LOE: 5</td>
</tr>
</tbody>
</table>
with sepsis.


University of Texas Southwestern Medical Center, Dallas, USA.

Comments
72 African children with severe sepsis
treatment with dexamethasone

Internal validity:-
Randomised – precise method not stated, block randomisation blocks 8
Allocation concealment – not stated
Follow-up – not stated but seems complete
Analysis – not stated
Blinded – yes
Both groups treated similarly – yes
Groups were similar at start of trial – yes
Part financial support from Roche

Evidence: Neutral – C= survival to hospital discharge (Is there a Type II error?)
Quality: Fair
LOE: 1

Sprung, 2008

Hydrocortisone therapy for patients with septic shock.

Hadassah Hebrew University Medical Center, Jerusalem, Israel 91120. sprung@cc.huji.ac.il

Comments
CORTICUS low dose hydrocortisone included non responders to corticotropin test
Multicentre, randomised, double-blind placebo-controlled study 52 ICU's
Patients > 18yrs septic shock; exclusions
Computer randomisation, stratified centre, blocks 4
Power analysis; interim analysis O'Brien Fleming stopping method

Internal validity:-
Randomised – yes
Allocation concealment – yes
Follow-up – only 1 withdrew consent
Analysis – intention to treat
Blinded – yes
Both groups treated similarly – Etomidate in 51/251 Hydrocortisone & 45/248 placebo
Groups were similar at start of trial – yes

Results
Mortality (primary end point) – no significant difference
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
<th>Authors</th>
<th>Institution</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Valoor, 2009 | 2009 | Pediatr Crit Care Med. | Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. | Valoor HT, Singhi S, Jayashree M. | Department of Pediatrics Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. | Pilot study in North India; n = 38  
Shock reversal (inotrope use)  
Internal validity:-  
Randomised – computer generated random number table  
Allocation concealment – sealed envelopes  
Follow-up –  
Analysis –  
Blinded –  
Both groups treated similarly –  
Groups were similar at start of trial –  
Results  
No benefit – trend earlier shock reversal HOC group (49.5 hrs vs 70 hrs)  
Evidence: good quality study, not supportive/neutral, Type II error  
Evidence: Neutral – E= shock reversal  
Quality: Fair  
LOE: 5 |
| Yildiz, 2002 | 2002 | Crit Care. | Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. | Yildiz O, Doganay M, Aygen B, Güven M, Keleștimur F, Tutuû A. | Department of Infectious Diseases, School of Medicine, Erciyes University, Kayseri, Turkey.  
yildizorhan@hotmail.com | N = 40; steroid = prednisolone  
Primary end point 28 day all cause mortality  
Secondary adverse events  
Short Corticotropin stimulation test  
Internal validity:-  
Randomised – computer generated randomisation procedure  
Allocation concealment – method not stated  
Follow-up – in hospital complete  
Analysis – presume intention to treat  
Blinded – yes |
<table>
<thead>
<tr>
<th>Both groups treated similarly – yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups were similar at start of trial – yes (Table 2)</td>
</tr>
<tr>
<td>Results</td>
</tr>
<tr>
<td>Mortality – steroid 8/20; standard 12/20 (Type II error)</td>
</tr>
</tbody>
</table>

Evidence: Neutral – B= survival of event
Quality: Fair
LOE: 5
Reference List


Journal Article


United States


United States
