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

**Worksheet author(s)**

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**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 (eg, hemodynamics or survival) (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?  Therapy**

State if this is a proposed new topic or revision of existing worksheet: New Topic

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**Conflict of interest specific to this question**

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

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

<table>
<thead>
<tr>
<th>Search strategy</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related articles search on Sprung CL et al. Hydrocortisone therapy for patients with septic shock. NEJM 2008; 358:111-24.</td>
<td>103 citations</td>
</tr>
<tr>
<td>Cochrane Library: searched on “corticosteroids AND septic shock”</td>
<td>11 citations, none new</td>
</tr>
<tr>
<td>Cochrane Library: searched using MeSH terms above</td>
<td>16 citations, none new</td>
</tr>
<tr>
<td>Dialog search was done of Science Citation Index on Anname D JAMA 2002; 288:862 (less expensive search):</td>
<td>861 citations</td>
</tr>
<tr>
<td>EMBASE search was run on 1974-2009 portion of the database. Search was limited to “children” and “clinical trials”</td>
<td>27 citations</td>
</tr>
<tr>
<td>In late February 2009 I saw the relevant study by Valoor HT et al. I did a “related articles” search of PubMed using that paper and found 3 additional relevant papers that the above search strategy did not identify.</td>
<td></td>
</tr>
</tbody>
</table>

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**State inclusion and exclusion criteria**

Specifically tried to limit the review of potentially relevant papers to “Clinical Trials.” I did not restrict search to children except for the EMBASE search since there is little pediatric data and I wanted to know if there were any pediatric studies that I missed using my other search strategies. Recent reviews were read to identify any citations that I missed with my search, but are not included unless of high quality (eg, Cochrane systematic review)

Case series, animal studies, neonates were excluded. I also excluded older studies using high-dose steroids since initial case series suggesting a benefit were subsequently dismissed after large RCTs showed harm from high dose steroid therapy.

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

124 citations that were possibly relevant were reviewed in more detail by reviewing abstracts and when needed the papers. From these, 10 clinical trials were included in the final detailed review. In addition, a selection of additional studies and reports are included since they provide important background information that will help the reader better understand the potential importance and areas of controversy surrounding the diagnosis of adrenal insufficiency and the use of stress dose steroids, as well as the important adverse effects of etomidate in this population.

Of note, recommendations on the diagnosis and management of corticosteroid insufficiency in adult critically ill patients (not limited to sepsis) was published in 2008 (Marik PE, et al. Crit Care Med 2008; 36:1937-1949). Although this study was mostly focused on adults, the recommended terminology is adopted in this review, which is somewhat different from the previous terminology used to describe absolute and relative adrenal insufficiency associated with critical illness.
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annane 2002, BE</td>
<td>Briegel 1999, E</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Russell 2009, B*</td>
<td>Oppert 2000, E</td>
<td></td>
</tr>
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<td></td>
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<td>Oppert 2005, E</td>
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</tbody>
</table>

*Survival greater in patients treated with vasopressin and stress-dose hydrocortisone, but tended to be worse in those who received stress-dose hydrocortisone and study norepinephrine

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = SHOCK RESOLUTION  
Italic = Animal studies

#### Evidence Neutral to Clinical question

<table>
<thead>
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<th>Level of evidence</th>
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<td>Yildiz 2002, E</td>
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<tr>
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<td>Russell 2009, E</td>
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<td></td>
<td>Briegel 1999, B</td>
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<td>Oppert 2000, B</td>
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<td></td>
<td>Oppert 2005, B</td>
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</tbody>
</table>

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = SHOCK RESOLUTION  
Italic = Animal studies
Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
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<th>Markovitz 2005, B</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</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 = SHOCK RESOLUTION

*Italicics = Animal studies*

The purpose of this evidence evaluation is to determine if the use of corticosteroids improves clinical outcome compared with “standard care” in children with hypotensive septic shock. As reviewed by Dr. Zimmerman,(Zimmerman, 2007, 530) corticosteroids have been used in adults and children with septic shock for more than 50 years, yet the answer to this question remains uncertain. This is partly because of the wide range of steroid doses and regimens that were used and controversy over how adrenal insufficiency is clinically defined. Furthermore, the natural history of sepsis has evolved over the years from a high incidence of rapidly progressive septic shock developing in previously healthy children due to H. influenza, S. pneumonia and N. meningitidis. In developed countries, sepsis now more often develops as a complication of an underlying medical condition or following multiple trauma or major surgery.

In the late 1970’s and early 80’s there was a good bit of enthusiasm for high-dose (e.g., 30 mg/kg of methylprednisolone) short term (typically one day) treatment of septic shock based on the publication by Schumer et al.(Schumer, 1976, 333) that consisted of 2 parts: a 172 patient prospective randomized controlled trial (RCT) and a 328 patient retrospective study evaluating methylprednisolone or dexamethasone versus no steroid therapy. Subsequent large RCT’s and meta-analyses concluded that high-dose, short courses of potent corticosteroids were not only ineffective, but there was a suggestion of harm.(Cronin, 1995, 1430; Lefering, 1995, 1294)

Over the last 15-20 years there has been a resurgence of interest in the use of stress-dose corticosteroids in critically ill patients with septic shock secondary to a number of studies showing that sepsis can induce relative adrenal insufficiency. Relative or absolute adrenal insufficiency is important since a low baseline cortisol concentration or an inadequate cortisol response to ACTH-stimulation is associated with fluid refractory, vasopressor-dependent septic shock and with increased mortality, at least in some studies.(De Kleijn, 2002, 330; den Brinker, 2005, 5110; Pizarro, 2005, 855; Sarthi, 2007, 23; Zimmerman, 2007, 530) Some of these studies in children included measurement of endogenous ACTH concentrations in addition to measurement of cortisol concentration; a high ACTH:cortisol ratio was associated with more severe shock and increased mortality, suggesting that the hypothalamic and pituitary response was adequate, but the patients had an impaired ability to synthesize cortisol.(den Brinker, 2005, 5110; Pizarro, 2005, 855) As summarized in the recent consensus statement on critical-illness related corticosteroid insufficiency (the new term recommended to describe this entity, abbreviated CIRCI), a failure to increase endogenous cortisol concentration by at least 9 mcg/dL following a standard (250 μg) ACTH stimulation test was associated with nonsurvival.(Marik, 2008, 1937; Zimmerman, 2007, 530)

Unfortunately, defining relative or acquired adrenal insufficiency based on the total cortisol concentration is also controversial since this concentration can be misleading. In normal individuals, more than 90% of cortisol is bound to cortisol binding globulin, and to a lesser extent, to albumin.(Marik, 2008, 1937) Cortisol binding globulin has high affinity but can be saturated when the endogenous cortisol concentration is increased. This explains the increased percentage of free cortisol seen in septic shock patients compared with patients with sepsis (without shock) and normal controls.(Ho, 2006, 105) Since hypoproteinemia is common in critically ill patients, the total cortisol concentration may be low, but the free cortisol concentration may be elevated as recently reported.(Hamrahian, 2004, 1629; Ho, 2006, 105)
Another area of controversy is the use of 250 mcg of cosyntropin (ACTH) to test the ability of the adrenal gland to increase cortisol production since in neonates and young children, this will result in a very high ACTH concentration and may produce an "adequate response (ie, >9 mcg/dl of cortisol) even in patients who have diminished synthetic capability and poor response to endogenous ACTH. Therefore, some other authors suggest that a 1 mcg dose of ACTH provides better discrimination of patients who may have diminished responsiveness to endogenous ACTH(Langer, 2006, 448; Sarthi, 2007, 23).

A 2008 publication summarized the results of an extensive literature review on how best to diagnose and treat critical illness related corticosteroid insufficiency (CIRCI) and concluded that despite the theoretic advantage of measuring free cortisol, measuring the total concentration is still recommended.(Marik, 2008, 111) The current consensus is that CIRCI is best diagnosed by a delta cortisol of <9 μg/dL (248 nmol/L) after 250 mcg of cosyntropin, or a random total cortisol concentration <10 μg/dL (276 nmol/L). The consensus group could not recommend measuring free cortisol concentrations since the optimal free concentration is not known and the test is not readily available. Indeed, the free concentration measurement may not be standardized since a much higher free concentration was reported by Hamrahian et al(Hamrahian, 2004, 1629) compared with Ho et al.(Ho, 2006, 105)

The consensus group on CIRCI also performed a meta-analysis of six randomized controlled trials, which typically used 200 – 300 mg/day of hydrocortisone in adults with septic shock,(Annane, 2002, 862; Bollaert, 1998, 645; Briegel, 1999, 723; Chawla, 1999, 33A; Oppert, 2005, 2457; Sprung, 2008, 111); the results from this meta-analysis are summarized in the figures below. Note that one of the included studies(Chawla, 1999, 33A) was only published as an abstract, so it is not included in the evidence evaluation table in this worksheet. The following figure shows the effects of hydrocortisone on shock reversal. “Responders” or “non-responders” in this figure refers to their cosyntropin response.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1 Responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollaert</td>
<td>12/18</td>
<td>2/14</td>
<td>1.10 0.90 1.39</td>
<td>6.81</td>
<td>1.01 0.60 1.70</td>
</tr>
<tr>
<td>Annane</td>
<td>14/18</td>
<td>15/18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppert</td>
<td>6/6</td>
<td>6/9</td>
<td>2.00 1.69 2.37</td>
<td>33.23</td>
<td>1.15 1.59</td>
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<tr>
<td>Sprung</td>
<td>95/118</td>
<td>6/136</td>
<td></td>
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<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>170</td>
<td>290</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total events: 129 (Treatment), 103 (Control)</td>
<td>Test for heterogeneity: χ² = 4.03, df = 3 (P = 0.26), P = 25.6%</td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 3.94 (P = 0.0001)</td>
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<tr>
<td>O2 Non-responders</td>
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<td></td>
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<tr>
<td>Bollaert</td>
<td>5/4</td>
<td>2/9</td>
<td>0.59 0.39 0.86</td>
<td>15.59</td>
<td>1.47 1.04 2.07</td>
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<tr>
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<td>12/12</td>
<td>5/115</td>
<td>3.48 1.70 6.80</td>
<td>27.95</td>
<td>1.26 1.02 1.55</td>
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<tr>
<td>Oppert</td>
<td>66/126</td>
<td>59/108</td>
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<tr>
<td>Sprung</td>
<td>255</td>
<td>245</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>140</td>
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<tr>
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<td>Test for overall effect: Z = 3.72 (P = 0.0002)</td>
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<tr>
<td>O3 Both</td>
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<tr>
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<td>12/20</td>
<td>5.30 4.04 6.90</td>
<td>4.15</td>
<td>1.62 1.02 2.85</td>
</tr>
<tr>
<td>Chawla</td>
<td>16/23</td>
<td>9/21</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td>Total events: 33 (Treatment), 21 (Control)</td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 2.39 (P = 0.02)</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>476</td>
<td>476</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 314 (Treatment), 228 (Control)</td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 5.85 (P = 0.00001)</td>
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</table>

Figure 2. Meta-analysis of treatment with moderate-dose hydrocortisone on shock reversal at day 7 in patients with septic shock grouped by response to adrenocorticotropic hormone. RR, relative risk; 95% CI, 95% confidence interval.

In addition to the studies included in the above meta-analysis, a sub-analysis of the large double-blind RCT examining the effect of vasopressin versus norepinephrine in septic shock(Russell, 2008, 877) provides additional data on the hemodynamic and 28-day mortality outcome effects of stress-dose hydrocortisone in adults with vasopressor-dependent septic shock.(Russell, 2009, 811) This analysis included 799 adults with fluid-refractory, norepinephrine dependent septic shock; 293 received corticosteroids and norepinephrine (NE) study drug, 296 received corticosteroids and vasopressin study drug and 190 did not receive any corticosteroids during the 28-day study period. The groups were well matched at baseline and the dose and timing of corticosteroid use was left to the discretion of the care team and was
similar between groups. There was no increase in the rate of weaning off NE comparing patients who received steroids versus those without steroids. The 28-day mortality was the primary endpoint: 131 (44.7%) of the NE+steroid study drug patients died versus 106 (35.9%) of the Vasopressin+steroid group, p=0.03 (ARR = 8.8%, NNT = 12 (95% CI 6 – 111). Conversely, in patients who did not receive corticosteroids, 19/89 (21.3%) of NE study drug patients vs. 34/101 (33.7%) of the vasopressin study group patients died, p=0.06, which suggests that vasopressin+NE alone was harmful, but vasopressin+NE plus stress-dose hydrocortisone was beneficial. The 90-day mortality was also significantly lower in the steroid+vasopressin group compared with the steroid+NE group. After adjustment for age, gender, APACHE II and severity of shock stratification, the mortality benefit was still significant (p=.02). There was a trend towards less organ dysfunction, such as days alive and free from shock (p=0.09) and there were more days free from ventilation (p=0.03) in the steroid+vasopressin group. Overall, any organ failure was less likely in the steroid+vasopressin group (p=0.02).

In a planned subgroup analysis of these patients, vasopressin concentrations were measured during therapy. Compared with patients who received vasopressin without corticosteroids, the vasopressin concentration increased by a mean of 33% more at 6 hrs and 67% more by 24 hrs if the patient also received corticosteroids (p=0.06 and p=0.025, respectively). Over 24 hours, there was no change in vasopressin concentrations from very low baseline levels in the steroid+NE group (see figure). The rate of complications were similar between groups, but there were significantly more cardiac arrests in NE+steroid group (2.4% v. 0.3%).

The relationship between steroid use and mortality in the same six RCT’s included in the figure showing the effect of steroid use on shock resolution is seen in the following figure taken from the consensus statement on critical illness related corticosteroid insufficiency. (Marik, 2008, 1937) As seen in this figure, the combined analysis of these studies do not show an overall survival benefit from moderate-dose hydrocortisone, but subgroup analysis of the Annane study that randomized 300 patients to stress-dose hydrocortisone plus fludrocortisone showed a 30% decrease in 28-day all cause mortality in those patients who had a <9 μg/dl increase in cortisol concentration in response to ACTH stimulation (hazard ratio, 0.67; 95% CI 0.47 – 0.95, p=0.02). (Annane, 2002, 862)
It is important to note, however, that this trial was inadvertently affected by a significant number of subjects who were intubated with etomidate. Etomidate inhibits 11β-hydroxylase, the rate-limiting enzyme in cortisol synthesis. In a letter to the editor, Dr. Annane noted that 72 patients received etomidate within 12 hours of study enrollment; 68 of these patients were nonresponders to ACTH stimulation. Overall, 77 patients received etomidate and 94% were nonresponders to ACTH stimulation. He also compared the resuscitation required in patients on the day following etomidate to 177 etomidate-free patients. Patients who received etomidate required more fluid loading (2484±2156[SD] vs. 1925±1366 ml, p=0.049) and a greater amount of vasopressors (p<0.001) to maintain cardiovascular homeostasis. Finally, a comparison of etomidate-treated patients who received hydrocortisone with etomidate-treated placebo patients showed that the combination of hydrocortisone (50 mg every 6 h) and fludrocortisone (50 µg daily) for 7 days significantly reduced 28-day mortality in these etomidate-treated patients (76% vs. 55%, p=0.03).

Because of the potential effect of etomidate use on adrenal gland function, the recent large randomized trial of corticosteroids in septic shock (CORTICUS Trial) specifically assessed the effect of etomidate on the patient’s response to hydrocortisone versus placebo. This prospective, randomized, double-blind trial with 499 patients was performed at 52 centers from 3/02 to 11/05. Patients were admitted to the ICU with evidence of SIRS and onset of shock within the previous 72 hours (defined by BPsys <90 mm Hg despite adequate fluid replacement or a need for vasopressor support for at least 1 hour). Patients were randomized to receive 50 mg of hydrocortisone q6h X 5 days, which was then tapered over 6 days or placebo. They also performed an ACTH stimulation test (250 mcg) and measured cortisol levels at 60 mins to determine if the patient was a responder or non-responder. All cortisol levels were measured in a central lab. Inadequate ACTH response was defined by a < 9 mcg/dL (248 nmol/L) increase in cortisol concentration.

Reversal of shock was defined as BPsys >90 for at least 24 h without vasopressor support. Superinfection was defined as a new infection occurring 48 hours or more after initiation of study drug. Patients were excluded if death was imminent, there was underlying disease with poor prognosis, or the patient was on immunosuppression or treatment with long-term corticosteroids within the past 6 months or short-term corticosteroids in the past 4 weeks.

The main endpoint was 28-day mortality in ACTH non-responders. They estimated the need for a sample size of 800 patients to achieve an 80% power to detect an absolute decrease in mortality of 10% from an expected death rate of 50% in ACTH non-responders. Of 499 patients, 233 (46.7%) did not have an adequate response to ACTH (125 in corticosteroid [CS] group and 108 in the placebo [P] group) consistent with other reports of a high rate of CIRCI in patients with septic shock. Etomidate was used in 51/251 CS patients and 45/248 P pts (20.3 v. 18.1%) before enrollment and in 22 and 20 patients, respectively, after enrollment. Of note, 58/96 (60.4%) patients who received etomidate were non-responders compared with 175/403 without etomidate (43.4%, P=0.004). Median time from etomidate to enrollment was 14 hours (range 1 to 67 hrs).

Groups were well matched for severity of illness, underlying conditions, and baseline cortisol concentration. Indeed, it is interesting that the baseline cortisol level in non-responders who received hydrocortisone (HC) was 30±20 mcg/dl vs 29±19 mcg/dl in the placebo (P) group; in ACTH responders the baseline concentrations were 27±19 in the HC group vs. 29±21 in the P group. Non-responders increased cortisol level by 3±4 mcg/dl vs ~17±8 mcg/dl in responders. Norepinephrine was used in ~90% of patients; vasopressin was only used in 5 patients total. Dopamine was used on only about 10% of patients. There was no difference in overall 28-day survival (34.3% vs. 31.5% comparing CS vs. P; p = 0.51), or when comparing ACTH non-responders: 39.2% vs 36.1%, CS vs P, p = 0.69) or ACTH responders (28.8% vs
28.7% CS v P, p=1.0). Post-hoc analysis showed a trend towards a beneficial survival effect in the HC group for those patients who were hypotensive within 30 hours after study entry (44.9% vs. 56.1% mortality). Of note, the likelihood of death was significantly increased at 28 days in patients who received etomidate prior to randomization in both groups (23/51 in HC 45.1% and 18/45 40% in the P group) compared with patients not receiving etomidate (63/200 31.5% in HC and 60/203 29.6% in P group; p=0.03).

The proportion of patients with shock reversal was similar 76% vs. 70.4% in the CS vs P ACTH non-responder groups and 84.7% vs 76.5% comparing CS vs P in the ACTH responder groups. The time interval until shock reversal was significantly shorter among patients receiving HC for all patients (p<0.0001) and for both those who responded to ACTH (p<0.0001) and those who did not respond to ACTH (P=0.06). See Kaplan-Meier figure below. The overall median time to shock reversal was 3.3 days (95% CI 2.9 to 3.9) in the HC group vs 5.8 days (5.2 to 6.9) in placebo patients. In ACTH responders who received hydrocortisone it was 2.8 days (2.1 to 3.3) vs. 5.8 days (5.2 to 6.9) in placebo-treated patients; in ACTH non-responders who received hydrocortisone it was 3.9 days (3.0 to 5.2) vs 6.0 days (4.9 to 9.0). Non-response to ACTH was associated with an overall increased mortality risk: 38% vs. 29%, consistent with other studies as noted previously.

With respect to adverse events, the likelihood of superinfections increased in the CS group (OR: 1.37 (1.05 to 1.79), as did the incidence of hyperglycemia and hypernatremia. Superinfections occurred in 33% of the CS patients vs 26% of the P group, and 85% of CS patients had hyperglycemia vs 72% in the P group (hyperglycemia was defined as >150 mg/dl from day 1 to 7). Hypernatremia (Na>150 meq/L on any day from 1 to 7) occurred in 29% vs. 18% for CS vs. P patients.

In comparing the CORTICUS trial to the Annane JAMA study(Annane, 2002, 862) the following observations may be pertinent:

- Annane study patients were more ill, as documented by a higher SAPS II score at baseline and their entry requirement was BPsys <90 mmHg for more than 1 hr despite fluid and vasopressor therapy. Mortality was 61% in the placebo group vs. 31.5% in the CORTICUS study; however, in the CORTICUS trial, patients whose BP <90 mmHg for more than one hour had a mortality of 56.1% (the number meeting that criteria was not reported). Furthermore, the absolute mortality reduction from the use of hydrocortisone in these hypotensive high-risk patients was 11.2%,

which was similar to the Annane study.

- The 2002 Annane study only allowed enrollment within 8 hrs of meeting entry criteria vs. 72 hrs in the CORTICUS study.
- Fludrocortisone was used in the Annane study, but it is likely that 200 mg/day of hydrocortisone provides adequate mineralocorticoid activity.
- The Annane study stopped treatment abruptly at 7 days instead of 11 day total therapy in the CORTICUS study that included a 6-day taper.
- Etomidate was used in 24% of Annane study patients and 26% of CORTICUS study patients.

The CORTICUS trial authors concluded that hydrocortisone cannot be recommended as general therapy for septic shock in patients who are vasopressor-responsive, and corticotropin testing cannot be recommended to determine which patients should receive hydrocortisone. Hydrocortisone may have a role in patients treated early after the onset of septic shock who remain hypotensive despite the administration of high-dose vasopressors.

There is little pediatric data from randomized trials regarding the effect of corticosteroids on septic shock resolution and survival. A study by Slusher et al(Slusher, 1996, 579) was based on prior observations that pretreatment with
dexamethasone (Dex) before antibiotics in children with H. influenza meningitis improved outcome and reduced cytokine production. They wanted to test if giving corticosteroids prior to antibiotics in children with sepsis would be beneficial. If effective, early Dex use could easily be adopted along with antibiotics and thus had the potential to improve outcome in 3rd world countries. This was a randomized, double blind, prospective trial of moderate dose (0.2 mg/kg) dexamethasone in children with sepsis. The trial was conducted in 2 missionary hospitals; one in Kenya and one in Nigeria. Children had to meet criteria for sepsis syndrome or shock with evidence of infection and judged to be moderately to severely ill. Dex was given 5 to 10 min before ceftriaxone and continued every 8 hours for 2 days (6 doses).

They enrolled 72 children from 1 month to 16 years of age between 9/91 and 10/92. Groups were similar at baseline. About 40% of the children were malnourished. Of note, as commented on in the recent Valoor trial reviewed below,(Valoor, 2009, 121) malnutrition may alter corticosteroid responsiveness. Children were ill prior to treatment for 1 to 14 days with a median of 4 days in the Dex group and 3 days in the placebo group. There was no difference in survival: 83% of Dex and 89% of placebo patients survived to discharge. A wide variety of pathogens were identified with no differences between groups. Malaria was identified in 3 children and was not thought to contribute to their illness. Hemodynamic stability at 48 h was achieved in 33% of Dex and 49% of placebo group children. The median length of hospitalization was 11 days in both groups.

No consistent treatment protocol was used and the Dex treatment course was short. Many of the children had diarrhea and were malnourished so they may have needed aggressive fluid resuscitation rather than steroids. None of these children were intubated or on vasoactive drugs—they only provided fluids, antibiotics and oxygen. This limits the generalization of these results.

In the only other clinical trial in children (LOE 2), Valoor et al(Valoor, 2009, 121) conducted an exploratory study in a third world country (from a PICU in Chandigarh, India) using a randomized, but not blinded trial design in 38 children from 2 months – 12 years of age with septic shock that was unresponsive to fluid alone and who required vasoactive drug support. They defined septic shock as PALS-defined hypotension or 3 of the following clinical signs: decreased pulse volume, capillary refill time ≥3 seconds, tachycardia and low urine output. Fluid unresponsiveness was defined by persistence of shock signs after 20 ml/kg X3 boluses in 30 minutes. They excluded patients with underlying lymphoid/hematologic malignancies, nephrotic syndrome, HIV, cystic fibrosis, diabetes mellitus, or if the child was on immunosuppression or glucocorticoid therapy in the last week.

Children were enrolled within 30 mins from the time fluid-refractory shock was recognized. IV hydrocortisone (5 mg/kg/day) was given in 4 divided doses until signs of shock were reversed, and then they were treated with half the dose for a total of 7 days. (Note that the dose was stopped and not weaned, so some children could have deteriorated from induced adrenal insufficiency in chronically malnourished children.) Fluid therapy was guided by achieving a goal CVP of 10-12 cm H2O. Hemodynamic stability was defined by BPsys≥5th percentile for age with any 2 of the following: pulse rate normal for age, UOP >1 ml/kg/hr and capillary refill <3 seconds “without further need for fluids and inotropes” (this was the primary endpoint—and it was not clear if this meant they had to be off inotropes).

The time to shock reversal was a median of 49.5 (95% CI, 26 – 144) hours for the cortisol group compared with 70 (12-269) hrs in the placebo (P) group, p=0.65. 12/19 survived in the cortisol group compared with 13/19 in controls. GI hemorrhage occurred in 1 cortisol patient and 0 controls. Of note, 9 hydrocortisone-treated children (47.3%) and 8 controls were malnourished (weight for age <80% of expected). No patient received etomidate. There was not even a trend towards a difference in HR, BPsys, or BPdia in the first 12 hours in children receiving steroids. Of note, there were 4 deaths in each group within 24 h of admission suggesting that some of the patients were moribund on enrollment. There was a trend towards a lower inotrope score in cortisol compared with P patients (20 [15-60] vs 50 [20-80], p=0.15).

In their discussion, they note that malnourished children without acute illness often have hypercortisolemia, but the effects of cortisol are blunted due to glucocorticoid resistance secondary to down-regulation of glucocorticoid receptors, expression of an inactive form of the receptor or due to repression of phosphorylation of the hormone/receptor complex.(Manary, 2006, 550) Since malnutrition was common in this and the Slusher study, it could affect their response to exogenous corticosteroids. Furthermore, there was often a delay between illness onset and presentation to the referring hospital, so these children were stressed for some time prior to study enrollment. The study by Sarthi et al(Sarthi, 2007, 23) from India supports the conclusion that malnourished children may have a different stress dose response since the median baseline cortisol concentration in 30 children with fluid-refractory septic shock was 71 μg/dl (95% CI 48.7 – 166.4), higher than reported in many other studies.
The relatively low mortality rate in children with sepsis (estimated at 10.3% by Watson et al(Watson, 2003, 695)) makes powering a pediatric study using mortality as the outcome virtually impossible. Even using the observed mortality of 24% in 6,693 children with septic shock in the PHIS database(Markovitz, 2005, 270) would require about 1,600 children in each arm of the study to observe a ~16% relative decrease in mortality (ie, from 24% to 20%) with an 80% power. Septic shock was defined in the analysis of this discharge database by the need for vasoactive drug support and mechanical ventilation in children with ICD-9 diagnostic codes consistent with an infection. Based on these power calculations, it is very unlikely that a randomized controlled trial could ever be done to definitively answer the question posed for this evidence evaluation and instead surrogate markers, such as shock resolution, likely will need to be used to design a clinical trial.

In addition, if the desire is to give sufficient hydrocortisone to achieve cortisol concentrations seen in children with septic shock who had a good outcome, the dose required to achieve these concentrations is not clear. The commonly used adult dose is 100 mg/M²; thus, for a 5 kg infant (~0.3 M²), this is about 6 mg/kg/day. In a 27.7 kg child (~1 M²), the dose is nearly 4 mg/kg/day, whereas the dose in a 70 kg (1.73 M²) person is about 2.4 mg/kg/day. Thus, it seems that basing the dose on body surface area may be preferred but the data are lacking.

As previously reviewed, several studies suggest that hydrocortisone therapy helps septic patients resolve their shock (ie, vasopressor dependence) with CIRCI, but that hydrocortisone therapy is not helpful in those with an adequate endogenous cortisol response. Based on the usual criteria for study entry, this means that the latter group of patients has a need for vasopressor support despite having an adequate endogenous hypothalamic-pituitary-adrenal response. Thus, these normal endogenous stress cortisol responders may actually identify a group of patients who are physiologically more ill than those whose cortisol response is relatively inadequate because they have CIRCI. If exogenous corticosteroids are given to the group with high basal concentrations and a normal cortisol response, the higher concentrations of cortisol achieved may produce unwanted immunosuppression and explain the higher rate of superinfections observed in patients who received hydrocortisone in the recent CORTICUS trial.(Sprung, 2008, 111)
Relative adrenal insufficiency occurs fairly frequently in children and adults with septic shock. (De Kleijn, 2002, 330; den Brinker, 2005, 5110; Pizarro, 2005, 855; Sarthi, 2007, 23) Unfortunately, there is a lack of high quality data to make a strong recommendation on the best method to define “critical illness-related adrenal insufficiency.” (Marik, 2008, 1937) In the absence of any better data for children, the consensus definition developed by an international panel should be used: “Critical illness-related corticosteroid insufficiency is caused by adrenal insufficiency together with tissue corticosteroid resistance and is characterized by an exaggerated and protracted proinflammatory response. Critical illness-related corticosteroid insufficiency (CIRCI) should be suspected in hypotensive patients who have responded poorly to fluids and vasopressor agents, particularly in the setting of sepsis. At this time, the diagnosis of tissue corticosteroid resistance remains problematic. Adrenal insufficiency in critically ill patients is best made by a delta total serum cortisol of < 9 microg/dL after adrenocorticotrophic hormone (250 microg) administration or a random total cortisol of < 10 microg/dL.” There is insufficient data to recommend using an ACTH-stimulation test to determine which patients should receive stress-dose hydrocortisone. Furthermore, there is insufficient data to recommend using a standard dose (250 μg) versus lower dose (e.g., 1 μg) ACTH-stimulation test to identify children with CIRCI. Similarly, there is also insufficient data to recommend for or against the measurement of free rather than total cortisol to identify absolute or relative adrenal insufficiency.

The recently published guidelines for hemodynamic support of infants and children with septic shock recommend using stress-dose hydrocortisone for children with known adrenal insufficiency or hypothalamic-pituitary suppression as may follow the recent use of steroids. (Brierley, 2009, 666) These international guidelines recommend using stress-dose hydrocortisone in children with a baseline cortisol concentration <10 μg/dl or an ACTH-stimulated peak cortisol concentration < 18 μg/dl as well as in children with catecholamine-refractory shock. Based on data from the large CORTICUS trial showing an increased risk for superinfections in patients treated with corticosteroids, (Sprung, 2008, 111) children with low-risk of death from sepsis should not receive stress dose steroids. Since these sepsis guidelines were published, (Brierley, 2009, 666) there was one more trial suggesting that hydrocortisone therapy may be useful in a subgroup of septic shock patients. The post-hoc analysis of the VASST trial (Russell, 2009, 811; Russell, 2008, 877) suggests that stress-dose hydrocortisone in patients receiving vasopressin for septic shock is associated with a significant improvement in outcome compared with the use of norepinephrine plus hydrocortisone (without vasopressin).

The optimal dose of stress-dose hydrocortisone to use in children is not known. The recent pediatric sepsis guidelines recommend doses from 2 to 50 mg/kg/day with little evidence to support a specific dose. (Brierley, 2009, 666) In adults, doses from 200 to 330 mg/day are typically used, either in divided doses or commonly as a 100 mg bolus and then an infusion of 10 mg/hr (i.e., 330 mg on day one, then 240 mg on subsequent days). The duration of treatment is also unclear, with the recent CORTICUS trial suggesting that a 2-week treatment course in adults may produce a degree of immune paralysis leading to an increased risk of secondary infections. (Sprung, 2008, 111)

Another source of confusion is converting stress-dose hydrocortisone from surface area to weight-based dosing. For example, 100 mg/M² is about 6 mg/kg in a 5 kg infant, ~4 mg/kg in a 28 kg child and ~2.4 mg/kg in a 70 kg adolescent. The treatment duration is also uncertain as is the need to wean the dose to prevent rebound adrenal crisis.

There is clear documentation that etomidate potently inhibits 11ß-hydroxylase, the rate limiting enzyme in cortisol biosynthesis. There is strong circumstantial evidence documenting relative adrenal insufficiency for 24 hours or more in critically ill adults and children who received etomidate for sedation during endotracheal intubation. (den Brinker, 2007; den Brinker, 2005, 5110; Vinclair, 2008, 714), which extends to trauma patients as well as septic patients. (Cotton, 2008, 62; Kim, 2008, 988) Furthermore, there is evidence linking etomidate use with a higher risk of mortality. (Annane, 2005, 325; Annane, 2002, 862; Sprung, 2008, 111) These and other studies in children (Pizarro, 2005, 855) led to the recommendation to avoid the use of etomidate in patients with septic shock. (Annane, 2005, 325; Bloomfield, 2006, 161) At the least, it seems appropriate to give stress-dose hydrocortisone to critically ill patients who received etomidate.

Acknowledgements:
Citation List


No Abstract. This is a letter to the editor.


This is an editorial on a paper by Malerba in Intensive Care Medicine. He reviews the data from other studies showing the adverse effects of etomidate.


This is a letter to the editor where the authors answer questions about their 2002 JAMA study. In the letter, Dr. Annane notes that 72 patients received etomidate within 12 hours of study entry and 68 were non-responders to ACTH stimulation.


LOE 1 study in adults and LOE 5 for children with very good study design.

Subsequent analysis revealed that a substantial minority of these patients had received etomidate. This was a late (severe) septic shock requiring more than 1 hour of refractory hypotension for study enrollment. Patients were sicker in this trial then in any subsequent trial since they had to have at least 1 hour of persistent systolic hypotension (BPsys <90 mmHg)


See related research article by Mohammed et al., [http://ccforum.com/content/10/4/R105](http://ccforum.com/content/10/4/R105). This is an editorial on this paper showing a much higher rate (50% higher likelihood) for adrenal insufficiency in septic patients who received etomidate.


Showed that epinephrine increased cardiac output and SVR in the dose used, but also increased lactate concentration.


LOE 1 for adults, LOE 5 for children. Fair study design and relatively small sample size.


This is an LOE 1 study in adults with fair study design. It is LOE 5 for children.

The fair study design designation is given because it is a relatively small study group and they selected only those patients who had hyperdynamic septic shock as documented by measurement of cardiac index. All patients required vasopressor support and could not be on dobutamine or dopexaine (ie, an inotropic agent). This requirement for a hyperdynamic vasodilated state limits the generalizability of their results to all patients with septic shock. The results are strong that hydrocortisone improves shock resolution. The infusion rate of hydrocortisone used in this study is somewhat high: at 0.18 mg/kg/hr, a 70 kg adult
would receive 302 mg in a day. Most other studies use 10 mg/hr, which will deliver 240 mg/day after the loading dose.
No funding sponsorship.


This is a consensus guideline for the hemodynamic management of septic shock in children. As noted in the title, the process of creating these guidelines began in 2007, which were not published until 2009. They used a modified Delphi method with consensus reached on included recommendations. There is no indication regarding the strength of the recommendation in this paper.


Cannot judge the methodologic quality since this was only presented as an abstract and was never published in a peer-reviewed journal. It is surprising that 2 authors included this study in a meta-analysis of the use of steroids in septic shock.


This study is cited because it illustrates the association of etomidate use with failure to show an adequate response to ACTH stimulation. The study is limited by its retrospective nature and probable selection bias to perform testing in trauma patients who were not responding adequately to resuscitation. Thus, the high rate of adrenal insufficiency is not surprising. They attempted to control for risk factors known to be associated with AI and still found that etomidate exposure significantly added to the risk of AI. This was not an outcome study.


Good quality systematic review and meta-analysis of the clinical data up until 1995 on the use of steroids for patients with septic shock. This is one of several meta-analyses at this time suggesting that high-dose short course corticosteroids were harmful.


This is a well done prognosis study showing an association between low cortisol concentrations and mortality in children with meningococcemia. In addition, they observed high ACTH concentrations with low cortisol concentrations resulting in large differences in the cortisol:ACTH ratio between survivors and nonsurvivors in children who died suggesting that this population had an adequate hypothalamic-pituitary response but were relatively unresponsive to endogenous ACTH stimulation. The cortisol:ACTH ratio was inversely related to disease severity (PRISM score). The IL-6 concentrations were markedly increased in the septic shock nonsurvivors. Other studies suggest that IL-6 stimulates ACTH production. Increased TNF, which would be expected with high IL-6 has been described to interfere with cortisol production. In this study there was a good correlation between the IL-6 concentration and ACTH concentration.
No funding support.

This retrospective study clearly shows that a single bolus of etomidate effects adrenal function for at least 24 h. Although not clearly stated in the paper, the study population appears to be the same as that included in their 2005 trial—they appear to have re-analyzed some of the data and perhaps blood samples. There are nice graphs showing the changes in the ratio of ACTH to cortisol and 11-beta hydroxylase to cortisol over time consistent with a transient block of cortisol biosynthesis.

It is important to note that this trial was performed in children with meningococcus—therefore, it is not clear if the findings will be entirely similar in other septic shock populations. Also, just over 50% of the children were intubated; most of these received etomidate (74%).

This study clearly shows a potentially significant adverse effect from a single dose of etomidate. It is interesting that the glucose concentration on admission was significantly lower in the patients who received etomidate, suggesting that there was a reduced steroid effect.

No funding support


This study's findings are similar to those reported by De Kleijn et al. The study population had meningococcal sepsis or septic shock. Like other studies, they found a lower cortisol concentration in those children who died. They did not find an advantage of measuring free cortisol concentrations to help determine outcome, although it should be noted that free concentrations were calculated and not directly measured, however other studies show that the calculated concentrations are highly correlated with directly measured concentrations. In addition, the IL-6 concentrations were markedly increased in nonsurvivors.

Note that this same population was re-analyzed in their 2007 paper.
No funding support.


This study was not specific for patients with septic shock. Instead, they recruited patients with medical or surgical illnesses who had an APACHE III score of at least 15. They dichotomized patients into those with albumin <2.5 g/dL and those with a concentration equal to or higher than 2.5 g/dL. Only 11/36 with low albumin had sepsis. The patients with hypoalbuminemia were studied at a mean of 21.2 +/- 16.2 days of hospitalization. Those with higher albumin concentrations were studied at a mean of 6.4 +/- 5.6 days. The baseline cortisol concentrations were largely in the normal range, suggesting that this study population is quite different than described in studies of patients with acute septic shock. It is concerning to me that the percentage of total cortisol that was free was reportedly a mean of 42.2% in the 14 patients with an ACTH-stimulated cortisol response <18.5 mcg/dl and a mean of 26.3% in those with a higher peak cortisol concentration. Other studies report a free fraction in critical illness around 21% and in less ill patients around 15%. This suggests that their assay for free cortisol concentration may have been flawed.

They note that cortisol binding globulin has high affinity but low capacity; in normals the binding capacity is exceeded at around 25 mcg/dL, so that higher total concentrations will increase the free concentration. When this occurs, it appears that albumin binding becomes important, making the albumin concentration potentially important in determining how much cortisol in a total measurement is free cortisol.

Supported in part by a grant (M01RR000080) to the Clinical Research Center of Case Western Reserve University from the National Center for Research Resources.


This study enrolled patients with septic shock or sepsis. Importantly, the findings vary from those reported by Hamrahian et al in the NEJM. The study populations are markedly different. In addition, the free cortisol fraction was much lower in this trial than reported by Hamrahian. In this trial the free cortisol
was 21.1% of total concentration in patients with septic shock versus 7% of total in patients with sepsis and only 3.7% of total concentration in the controls. They documented that CBG was decreased by a mean of 48% in septic shock patients and 35% in sepsis patients compared with controls, confirming other observations of a fall in CBG with sepsis. Finally, they showed that the absolute increase in free concentration in response to ACTH was similar in all 3 groups, but not reflected by a change in total concentration in the septic shock patients, who had a high concentration at baseline. In Hamrahan's study the free fraction was 40% or more of total, which seems unlikely. These patients had a higher baseline concentration than Hamrahan's study. They note that 10 mg/hr of hydrocortisone produces total cortisol concentrations of ~3100 nmol/L (~112 mcg/dl). One would anticipate that the free concentration will be very high in this situation.

It is interesting to note that their ACTH non-responders had higher baseline concentrations than the responders, which differs from Annane's 2002 trial. No patient in this trial received etomidate, which may be an important difference between the study populations.


Miscellaneous


Miscellaneous


Clinical Trial

Journal Article

This was a post-hoc study using the VASST study group to evaluate the effects of steroids.


Article


This was one of the first trials examining the role of steroids in patients with septic shock. This retrospective study suggested a significant benefit from steroid therapy, but subsequent studies failed to show any benefit from high dose methylprednisolone or dexamethasone and indeed suggested increased mortality.

This trial does not contribute to answering the hypothesis regarding stress dose hydrocortisone.


This was an LOE 1, poor quality trial that is not applicable to the question of using stress-dose hydrocortisone. This was a mixed group of children who were often malnourished and had delayed presentation. None of the children were on mechanical ventilation, no consistent treatment protocol was used, many of the children had diarrhoea, suggesting that aggressive fluid resuscitation was likely needed. No patient was on vasoactive drug support--all treated with antibiotics, oxygen and IV fluids alone.

This study does not really help answer the question.


LOE 1 (for adults) high quality multicenter RCT study

Study was supportive for shock resolution but neutral for any survival benefit with a trend towards higher rate of new infections in those patients who received hydrocortisone.

This study showed faster shock resolution in patients who received hydrocortisone and those who responded to ACTH (both with p<0.001, but somewhat surprisingly shock resolution was not statistically related to hydrocortisone therapy in patients who failed to respond to ACTH stimulation (p=0.06).

Supported by a contract (QLK2-CT-2000-00589) from the European Commission, the European Society of Intensive Care Medicine, the European Critical Care Research Network, the International Sepsis Forum, and the Gorham Foundation. Roche Diagnostics provided the Elecsys cortisol immunoassay.


LOE 2, moderate quality study

There was a high incidence of malnutrition in this study group as well as delayed presentation, making it difficult to apply the results to developed countries. Malnutrition increases endogenous cortisol concentrations, but is associated with glucocorticoid resistance. There was no measurement of the
patient's cortisol concentrations or their response to ACTH stimulation. Furthermore, there were 4
deaths in each group within 24 h of admission, suggesting some of these children were fairly moribund
by the time they reached the PICU. No patient received etomidate.


This is a prognosis study with prospective data collection in a cohort of patients.
Grenoble France; no funding support.

36. Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The Epidemiology of Severe Sepsis in Children in

[ISRCTN36253388]. *Critical Care.* 2002;6(3):251

See related Commentary: [http://ccforum.com/content/6/3/190](http://ccforum.com/content/6/3/190)
LOE 5 (adult); but LOE 1 for adults since it was a blinded RCT

The small number of patients (20 per group) increases the likelihood of missing significant differences between

  groups. For example, there were twice as many patients with gram + sepsis in the steroid group versus

  control group and almost twice as many gram negative sepsis in the steroid group, but this difference

  was not significant. More patients (16) in the control group had an underlying condition versus the

  steroid group.

They used low-dose replacement therapy: 5 mg in AM and 2.5 mg at 1800.

This was a mixed bag of patients in terms of severity, including patients with sepsis, severe sepsis and septic

  shock.

38. Zimmerman JJ. A history of adjunctive glucocorticoid treatment for pediatric sepsis: moving beyond

This is an excellent review of the history of the discovery of hydrocortisone and its subsequent use in children

  with shock. He also reviews the diagnosis of adrenal insufficiency. Based on his detailed review of the

  literature, he strongly recommends the need to conduct an appropriately designed clinical trial to

  evaluate the role of stress dose corticosteroid therapy.