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

**Worksheet author(s)**
Steve Schexnayder

**Date Submitted for review:** 1/13/10 (re-revision)

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**Clinical question.**

"In infants and children with hypotensive septic shock (P), does the use of etomidate as an induction agent to facilitate intubation (I) compared with a standard technique without etomidate (C) improve patient outcome (hemodynamics, survival) (O)?"

PEDS 047-A

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

**State if this is a proposed new topic or revision of existing worksheet:** NEW

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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. The reviewer is a pediatric intensivist in a large pediatric referral center. I have no conflicts of interests related to this drug, other than intellectual conflicts associated with my occasional clinical use of etomidate to facilitate intubation.

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

**Pubmed**

1. Shock, septic 21230
2. Etomidate 1923
3. Shock, septic AND etomidate 36
4. Limit “shock, septic” AND “etomidate” to “all child” 4

**Cochrane Central Register of Controlled Trials**

1. Shock, septic 276
2. Etomidate 236
3. Shock, septic AND etomidate 36
4. Limit “shock, septic” AND “etomidate” to “all child” 1

**Cochrane Central Register of Systematic Reviews**

1. Shock, septic 0
2. Etomidate 0
3. Shock, septic AND etomidate 0
4. Limit “shock, septic” AND “etomidate” to “all child”

**Embase**

'sepic shock'/exp AND 'etomidate'/exp AND ((newborn)/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim) OR (pediatric OR paediatric) AND ('etomidate'/exp OR 'etomidate') AND shock 17

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**State inclusion and exclusion criteria**

Exclusion: adult and neonatal (at time of birth) unless recent RCTs (since 2005 COSTaR); studies not in peer-reviewed journals (i.e. abstracts only);

studies that did not address the question; case reports; review articles

Inclusion: pediatric studies that are relevant to question after review of each reference identified in search; a few selected adult studies are including that were very applicable to the question

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

45 from initial review. On review of these 45, ten met criteria for additional review. These include four LOE 4 and six LOE 5 studies (three adult studies; one pediatric study using the index drug but not in this population).
## Summary of evidence

### Evidence Supporting Clinical Question

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<td>Zuckerbraun 2006 E</td>
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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*italics* = Animal studies
### Evidence Neutral to Clinical question

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Schenarts, 2001 E
Vinclair 2008 E

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Guldner, 2003 E

### Evidence Opposing Clinical Question

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den Brinker 2005 C
den Brinker, 2008 E
Sprung 2008 C
Cuthbertson 2009 C

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Mohammad 2006 E

### Level of evidence

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

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

No pediatric studies address this question posed for this specific clinical scenario. Several studies report the use of etomidate to facilitate endotracheal intubation in children (one prospective [Zuckerbraun 2006, p.602 LOE 4], two retrospective [Sokolove 2001, p. 18, LOE 4, Guldner 2003; p.134 LOE 5]). Many other studies address the pediatric use of etomidate in procedural sedation, but are not applicable to this setting of critically ill child. Because there is substantial risk for mortality when intubating children with hypotensive septic shock, etomidate has been considered an attractive choice because of its minimal effect on hemodynamics. In the face of hypotensive septic shock associated meningitis with increased intracranial pressure, etomidate is even more attractive because of its beneficial effect on intracranial pressure while preserving hemodynamics.

Etomidate specifically inhibits the conversion of 11-deoxycortisol to cortisol by directly inhibiting the 11β hydroxylase (CYP11B1) enzyme. It also inhibits the conversion of cholesterol to pregnenolone (though CYP11A inhibition) as well as the conversion of 11-deoxycorticosterone to corticosterone and subsequently corticosterone to aldosterone (both through CYP11B2 inhibition). Adrenal insufficiency in the face of fluid-refractory septic shock is well recognized, although a precise strategy for diagnosing this condition is unknown. Adult guidelines suggest clinical suspicion, rather than ACTH stimulation testing, is most appropriate in this setting. Pediatric specific guidelines for diagnosing and treating this condition are lacking.

Etomidate has been associated with increased mortality when used as a continuous infusion for sedation in adults, presumably through its action on adrenal function. In healthy adults, adrenal suppression generally resolves within 24 hours of a single dose of etomidate (Schenarts 2001 p. 1 LOE 5) but is known to last longer in critically ill adults (Vinclair 2008 p. 714, LOE 5). Adrenal suppression has been documented in both healthy and critically ill children, specifically in the setting of meningococcemia (den Brinker, 2008, p.163, LOE 4).

Previous adult studies have shown improved survival when both corticosteroids and mineralocorticoids are provided during septic shock. More recent adult data suggests there may be a negative effect of etomidate on survival in the setting of septic shock even when replacement hydrocortisone is provided (Sprung, 2008, p. 111 LOE 5; Cuthbertson BH, 2009, p. XXX, LOE 5). The mechanism for the differences in these findings are unclear.

**Acknowledgements:**
none

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**Citation List**

The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock.

Comment: In this a-priori sub-study of the CORTICUS trial (Sprung, 2008, p. 111), etomidate given within 72 hours resulted in diminished corticotropin response as well as significantly higher mortality in both univariate and multivariate analyses. Administration of hydrocortisone did not change the mortality of those patients who received etomidate. LOE 5, good quality as it relates to this question.

Adrenal insufficiency in meningococcal sepsis: bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality.

Comment: This pediatric study demonstrates the importance of adrenal insufficiency in a population of very sick children (meningococcemia). While the study was not designed to evaluate the effect of etomidate, there was significant adrenal suppression in children who received etomidate. LOE 4, quality good.

One single dose of etomidate negatively influences adrenocortical performance for at least 24h in children with meningococcal sepsis.

Comment: This retrospective analysis in critically ill children with meningococcal sepsis found marked adrenal suppression after etomidate for at least 24 hours. Particularly concerning is that 7/23 patients intubated with etomidate died vs. 1/8 who was intubated without etomidate. LOE 4, quality good.
Etomidate for rapid-sequence intubation in young children: hemodynamic effects and adverse events.

Comment: In this retrospective review of a five year experience did not specific address the population of children with septic shock. None of the patients had septic shock as their primary reason for intubation. LOE 5, quality poor as related to this question.

The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate.

Comment: While this adult retrospective study is LOE 5 and poor quality in relation to this question, it nevertheless is important information in that it documents the adrenal insufficiency associated with etomidate in the setting of sepsis.

Adrenocortical dysfunction following etomidate induction in emergency department patients.

Comment: In this small RCT in adults, adrenal dysfunction resolved within 12 hours of single doses of etomidate when used for rapid sequence intubation. LOE 5 (adult population, not specifically sepsis) quality good.

The safety of etomidate for emergency rapid sequence intubation of pediatric patients.

Comment: This retrospective review of pediatric patients who received etomidate for RSI concluded there was no evidence of “clinically important adrenal suppression” which was defined as a recognized need for exogenous corticosteroid replacement. The number of patients with sepsis is unknown, but based on the data provided, represented a maximum of 5% of those reviewed. Approximately 5% of patients had decreases in systolic blood pressure to below on standard deviation of normal. LOE4, quality poor in assessing this question.

Hydrocortisone therapy for patients with septic shock.

Comment: In a post hoc analysis of this RCT of adults with septic shock, death rates were higher in both hydrocortisone and control groups (for patients that received etomidate (45% in etomidate with hydrocortisone vs. 31.5% for no etomidate with hydrocortisone and 40% in etomidate with placebo vs. 29.6% no etomidate with placebo).LOE 5, quality good.

Duration of adrenal inhibition following a single dose of etomidate in critically ill patients.

Comment: This prospective adult study assessed the duration of adrenal insufficiency after the administration of etomidate in critically ill patients without septic shock, and found that the duration of adrenal suppression is longer than in healthy patients. LOE 5, quality good.

Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department.

Comment: Only 2 patients had shock as their primary indication for intubation, although 15 did have a diagnosis of shock. Eight patients were in hypotensive shock at the time of intubation. An additional 15 patients were in compensated shock at the time of intubation. Blood pressure was maintained better in this small subgroup than in patients without shock. Eight patients received corticosteroids for shock in the series, but were all were already in shock at the time of intubation. LOE 4, quality fair.