**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).

**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 topic

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

None.

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

### PubMed

Etomidate AND Sepsis OR septic shock OR intubation OR intubation (Limit to pediatrics)

Detail below:


### EMBASE

Etomidate AND Endotracheal intubation OR Sepsis OR septic shock (Limit to pediatrics)

Detail below:

1. exp *SEPSIS/ (12586)
2. sepsis.mp. (49204)
3. 1 or 2 (49204)
4. exp Septic Shock/ (11527)
5. 4 or septic shock.mp. (13379)
6. 3 or 5 (57714)
7. exp ENDOTRACHEAL INTUBATION/ (14145)
8. intubation.mp. (28123)
9. 7 or 8 (28123)
10. exp *ETOMIDATE/ (888)
11. etomidate.mp. (3356)
12. 10 or 11 (3356)
13. 12 and (9 and 6) (25)
14. limit 13 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (4)

Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from key articles, and the AHA EndNote Master Library were also reviewed.

**State inclusion and exclusion criteria**

The following studies were excluded: Etomidate use in healthy children for procedural sedation or facilitation of intubation.

*Will include good adult studies – RCTs, meta-analysis to flush out paper*

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

25 studies were included in the formal review – others are included only for background.
### Summary of evidence

#### Evidence Supporting Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
E1 = Hemodynamics  
E2 = Adrenal function  
E3 = Incidence of MODS  
E4 = Length of stay  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
### Evidence Neutral to Clinical question

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### Evidence Opposing Clinical Question

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Introduction

A key component of any resuscitation is management of the airway. Rapid sequence intubation (RSI) has become the standard of method to facilitate tracheal intubation in the emergency setting. To perform a RSI, an intravenous induction agent is injected to induce unconsciousness followed by a rapidly acting neuromuscular blocking agent. An ideal induction agent would be rapidly acting, permit ideal intubation conditions and have minimal side effects. Commonly used induction agents include thiopental, propofol, ketamine, benzodiazepines and opioids. All have their strengths and weaknesses and it is becoming clear that one dose of one drug will not be ideal for all patients.

Pharmacology

Etomidate is an induction agent that was introduced into European clinical practice in 1972 (Bergen and Smith 1997 pgs 221-230). It is an imidazole derivative, chemically distinct from other induction agents and acts through inhibition of the reticular activating system through γ-aminobutyric acid (GABA) receptor agonism. Similar to other imidazole agents such as clonidine and dexmedetomidine, it also acts on α2β-adrenoreceptors which may explain its stable hemodynamic profile (Paris et al. 2003 pgs 889-895). A single dose of etomidate (0.2-0.4 mg/kg) results in hypnosis in 1 arm-brain circulation (approximately 5-15 seconds) with return of consciousness in 5-14 minutes. It has been also given successfully PR at a dose of 6.5 mg/kg (Linton and Thorington 1983 pgs 309-310). Etomidate is primarily metabolized in the liver; however, its short duration of effect is due to redistribution of the drug to inactive tissues. Therefore, duration of action is not affected by hepatic function. It has no analgesic properties and can burn on injection.

In addition to its rapid onset, etomidate has a number of properties which make it a tempting RSI induction agent. An induction dose of etomidate reduces intraocular pressure for approximately 5 minutes. It also reduces intracranial pressure (ICP) but, unlike barbiturates or propofol, does not cause a decrease in mean arterial pressure (MAP) maintaining cerebral perfusion pressure (CPP) (Bergen and Smith 1997 pgs 221-230). In children undergoing cardiac catheterization for ASD device closure or radiofrequency ablation, an induction dose of etomidate results in minimal changes to most hemodynamic parameters (Sarkar et al. 2005 pgs 645-650). Transient hypoventilation and apnea has been reported with etomidate use, but of short duration (20 seconds). Myoclonus is a frequently reported side effect of etomidate use (up to 65% of exposures). It is likely related to inhibition of cortical suppression of extra-pyramidal activity and can be treated with benzodiazepines. While etomidate raises the threshold for generalized seizures, it can lower the threshold for focal seizure activity.

Etomidate and the Adrenal Gland

The most concerning side effect of etomidate usage is its effect on corticosteroid production. Etomidate acts on several pathways in a dose-dependent manner but its dominant effect is to inhibit 11β-hydroxylase which converts 11-deoxy cortisol (11-DOC) to cortisol and deoxycorticosterone to corticosterone. It also blocks adrenal response to adrenocorticotrophic hormone (ACTH) (Wagner et al. 1984 pgs 1415-1421). This effect came to light in the early 1980s when etomidate was used for long-term sedation of mechanically ventilated trauma patients. It was noted that a large increase in mortality (28% vs. 47%) was associated with duration of mechanical ventilation and sedation with etomidate (Ledingham and Watt 1983 pgs 1270). All patients receiving etomidate had sub-normal serum cortisol levels at some point in their ICU stay and the mortality effect reversed when patients were switched back to benzodiazepines for long term sedation.

Etomidate is no longer recommended for long term sedation. However, a single bolus of etomidate has been shown to affect adrenal function for up to 48 hours (Absalom et al. 1999 pgs 861-867; Schenarts et al. 2001 pgs 1-7; Mohammad et al. 2006 pgs R105; Cotton et al. 2008 pgs 62-67; Vinclair et al. 2008 pgs 714-719). Studies on adrenal function in the critically ill are complicated by a lack of an accepted definition. However, etomidate exposure has been associated with a low response to a corticosyntropin-stimulation test (CST) (Malerba et al. 2005 pgs 388-392; de Jong et al. 2007 pgs R61; Kim et al. 2008 pgs 988-991). Interestingly, this effect has been used to treat the acute phase of Cushing’s disease in both adults and children (Greening et al. 2005 pgs 140-143; Dabbagh et al. 2009 pgs 238-239).

Etomidate and Sepsis

Choosing an appropriate induction agent in pediatric patients with septic shock can be difficult. These patients have diminished hemodynamic reserve and may not tolerate the decrease in myocardial contractility and systemic vascular resistance associated with most induction agents. Given etomidate’s hemodynamic profile, it would seem like an ideal agent for intubation of these patients. In an animal septic heart model, the effect on cardiac function of 5% commonly used induction agents was compared. Etomidate administration resulted in a less pronounced drop in cardiac work compared to other agents (propofol, midazolam, methohexitnone) though not when compared to ketamine (Zausig et al. 2009 pgs R144).
However, etomidate’s effect on cortisol synthesis has caused concern. A recent prospective study in children with septic shock demonstrated an association of diminished response to a CST and mortality (Casartelli et al. 2007 pgs 1609-1613). Several large adult studies suggest that many septic patients have absolute or relative adrenal insufficiency and may benefit from steroid supplementation (Annane et al. 2002 pgs 862-871) though a mortality benefit was not demonstrated in the recent CORTICUS trial (Sprung et al. 2008 pgs 111-124).

Etomidate in pediatrics

There have been several studies looking at using etomidate as an induction agent in children. Zuckerbraun used etomidate for RSI in a single-center ED in 77 patients (Zuckerbraun et al. 2006 pgs 602-609). 15 of these patients had a primary diagnosis of “shock” though only 2 patients had shock recorded as a primary reason for intubation. There were eight patients in hypotensive shock at the time of intubation; there was no statistically significant drop in BP (only 2.5%) following etomidate compared to patients not in septic shock. This was also true for all patients in shock (compensated or hypotensive). 8 patients received steroids for adrenal insufficiency during their course in hospital and all had cortisol levels measured but some were up to 9 days post-etomidate.

The use of etomidate was retrospectively reviewed in 100 consecutive patients having an RSI in the ED (Sokolove et al. 2000 pgs 18-21). It is unclear from the study if there were any patients with sepsis though if there were, they were in the minority (<5%). The mean change in BP was 1% and only 4 patients developed hypotension post-etomidate (none had sepsis). Guldner and colleagues retrospectively reviewed 105 patients who received etomidate for RSI in pediatric ED and noted a small mean increase in SBP though there were no septic patients in the study (Guldner et al. 2003 pgs 134-139).

Den Brinker (den Brinker et al. 2005 pgs 5110-5117) studied 60 children with purpura fulminans and divided them into shock non-survivors, shock survivors and sepsis survivors. 88% of the non-survivors were intubated with etomidate. Regression analysis demonstrated that intubation with etomidate was significantly predictive for adrenal dysfunction. A retrospective study by the same authors in 60 children with purpura fulminans found 23 that had been intubated with etomidate (den Brinker et al. 2008 pgs 163-168). Etomidate use was associated with adrenal dysfunction (cortisol levels and cortisol/ACTH ratios) for 24 hours post-intubation. Even after 24 hours, cortisol/11-DOC levels remained significantly lower in children exposed to etomidate. 8 children died in the cohort, 7 had received etomidate. There was no significant difference in vasopressor or PRISM score between children intubated with etomidate and those intubated with other medications.

Etomidate in adults

Etomidate use in the adult trauma patient has been associated with an increased risk of acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS) longer length of stay and a low response to a CST (Cotton et al. 2008 pgs 62-67; Hildreth et al. 2008 pgs 573-579; Warner et al. 2009 pgs 45-50).

A number of adult studies have looked at the use of etomidate in intubation of septic shock. Some studies have suggested that etomidate exposure has little effect on mortality or adrenal function (Riche et al. 2007 pgs 1761-1766; Tekwani et al. 2009 pgs 11-14) but these may be underpowered. A retrospective analysis of a single-center database revealed no difference in steroid administration or outcome associated with induction agent chosen (Ray and McKeown 2007 pgs R56).

A recent randomized controlled trial compared etomidate to ketamine for intubation of critically ill adults (with a combined sepsis/trauma subgroup defined a priori) and demonstrated more adrenal insufficiency in the etomidate group but no change in mortality or organ function scores (Jabre et al. 2009 pgs). A retrospective study of 477 patients with severe sepsis who had undergone an ACTH-stimulation test prior to admission demonstrated an association of etomidate usage with hospital mortality in univariate analysis but not multivariate analysis (Lipiner-Friedman et al. 2007 pgs 1012-1018). Annane randomized 300 adult patients with septic shock to steroid supplementation or placebo (Annane et al. 2002 pgs 862-871). The exclusion criteria were amended 21 months into the study to include etomidate exposure as it was noted that 94% of patients who received etomidate were non-responders to a CST. Etomidate-exposed patients in the treatment group did have a significantly higher survival rate than those in the placebo arm.

The largest study to date examining adrenal function and steroid replacement in septic shock is the CORTICUS study (Sprung et al. 2008 pgs 111-124). This was a multicenter double-blind placebo-controlled trial in which 251 adults were randomized to receive IV hydrocortisone for 5 days followed by a tapering protocol and 248 patients received placebo. There was no difference in mortality between the two groups, regardless of response to an ACTH-stimulation test. 51 of 251 patients in the study group (20.3%) and 45 of 248 (18.1%) in the placebo group received etomidate before study entry. A statistically higher number of patients who received etomidate did not respond to a CST (58/96; 60.4%) vs. those that did not receive etomidate (175/403; 43.4%). Although the study was not designed to examine etomidate’s effect on mortality, a sub-study analysis demonstrated an increased risk of death in patients who received etomidate, regardless if they received steroid supplementation or not (Cuthbertson et al. 2009 pgs). This suggests that even if etomidate is used for patients with sepsis, simply giving steroid replacement subsequently may not counteract the effect.

35 critically ill adults (not septic) were randomized to receive etomidate or thiopental as part of a general anaesthetic. Baseline cortisol levels and an ACTH-stimulation test at 24 hours post-GA were performed. Most anesthetics were for surgical procedures, 7 were for intubation (5 in etomdiate group). No significant difference in cortisol levels was noted there were 15 (88%) of the etomidate and 5 (29%) of the control group patients that had relative adrenal insufficiency 24 hours post-GA.

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Adrenal function
Adults


A placebo-controlled randomized study evaluating the use of hydrocortisone/fludrocortisone replacement in adult patients with septic shock on 28 day mortality. 300 adult patients were enrolled after undergoing a CST. 229 were non-responders. 21 months into the trial, patients receiving etomidate were excluded as 94% were non-responders. Mortality rate in non-responders who received etomidate was 54.8% in treatment group and 75.7% in group that received placebo (significant) - perhaps steroid supplmentation can counteract the deleterious effects of etomidate. Overall mortality - 53.0% in steroid group, 63% in control.

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Fair (non-randomized controls for etomidate)
Outcome: Mortality, vasopressor weaning
Adults


An excellent pharmacological/historical review of etomidate.

Not included in literature review.

A prospective observational study in which 22 children (median age 10 months) with septic shock had a CST performed on their first morning in the PICU (two centres). 10 patients (45%) had less than a 250 nmol/L increase in serum cortisol (non-responders). 60% (6/10) died vs. only 1 responder (1/12 8.3%). Baseline cortisol level was higher in nonsurvivors. PRISM scores were significantly higher in the non-responder group. Univariate analysis showed that baseline cortisol > 690 and non-response to CST were associated with death. This was borne out after regression analysis to control for gender and PRISM score.

Not for inclusion - background.


A retrospective study looking at adult trauma patients that had received an ACTH-stimulation test (done for septic shock, SIRS requiring vasopressors, unexplained hypotension despite resuscitation) during their ICU stay. These were matched with historical controls. Patients with absolute adrenal insufficiency were excluded. 198 patients met criteria - 137 had complete data and were included in final analysis. 83/137 (60.6%) were nonresponders and had longer ICU LOS and ventilator days and a trend to a higher injury severity score. 87 patients received etomidate, most (78) occurred 48+ hours prior to CST testing. Etomidate exposure was a significant risk factor for adrenal insufficiency (interestingly, septic shock is not).

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Fair
Outcome: Adrenal function
Adults


An a priori sub-study of the CORTICUS trial to determine if etomidate bolus was associated with an increase in CST non-responders and an increase in mortality. Of the 499 patients in the CORTICUS study, 96 received etomidate. The number of non-responders was higher in etomidate-exposed patients (61% vs. 45%). Univariate analysis demonstrated an increased risk of mortality (OR 1.70) and this bore out in one of the 2 models they used to adjust for treatment group, response to CST, baseline cortisol level and SAPS score. Hydrocortisone administration resulted in no change in mortality. No difference in time to resolution of shock was noted. As a sub-study, the power needs to be questioned

Evidence: Opposing
Level of Evidence: 5 (adult study)
Quality of Evidence: Fair (controls not randomized b/w etomidate or not)
Outcomes: Mortality, adrenal function
Adult study
Further analysis of the CORTICUS data, entered into the table but not COS statement as CORTICUS already there.

2nd case report - not included.


A retrospective cohort study in 405 critically ill adults who received an ACTH-stimulation test in their ICU. The test was performed on patients with suspected dysfunction (prolonged, fluid-refractory hypotension). Low responders were more likely to be septic, have higher SOFA/SAPS scores and higher mortality (27% vs 14%). Patients who received steroids showed a trend to increased mortality in low-responders vs. high-responders (26% vs. 16%; p 0.054). Of the septic patients, low-responders were sicker (ventilation, higher FiO2, tachycardia, vasopressors, oliguria, higher Cr and BUN, acidemic, thrombocytopenia, hypoglycemia, eosinophilopenia). Etomidate use was associated with a low response in univariate but not multivariate analyses.

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Adrenal function
Adults.


This is a retrospective study conducted over two study periods (Oct 1997-99 and Oct 2001-2004) in a university-affiliated PICU. 69 patients with purpura fulminans (58/69 had positive culture for N. meningitidis) were enrolled, all those who had received steroid therapy prior to admission were excluded (9 patients). On admission, 31 patients were ventilated, 23 intubated with etomidate (mean dose 0.29 mg/kg - higher dose associated with mortality). Levels of ACTH, 11-DOC, cortisol, lactate and IL-6 were drawn at time 0 (admission), 12h and 24h. Children intubated prior to admission had significantly higher disease severity though these were not different between those intubated etomidate and those not (measured IL-6, lactate, vasopressor score, PRISM). There was a trend to lower admission glucose in the etomidate group. Cortisol levels were significantly lower and ACTH and 11-DOC levels were significantly higher in the etomidate group. Dosage of etomidate or time from intubation to admission related to cortisol, ACTH, 11-DOC or ratios on admission suggesting no dose-dependent effect. ACTH level on admission was significantly related (by ANCOVA) to intubation with etomidate and disease severity, age and gender were not. Within 24 hours, cortisol/ACTH ratios were comparable between the two groups though cortisol/11-DOC remained low in the etomidate group. 7/8 children who died received etomidate. In total, 1/8 (12.5%) who did not receive etomidate died vs. 7/23 (30%) who did. 7 children received steroids for suspected adrenal insufficiency, 6 of them had received etomidate. It is not clear if any of the children who died received steroids.

Evidence: Opposing
Level of Evidence: 3
Quality of Evidence: Fair
Outcome: Adrenal function, mortality
Children.

This is a prospective observational pediatric study of patients with clinical meningococcal sepsis (purpura fulminans). 69 children were enrolled (50 + BC for N.meningitidis) of which 31 were intubated prior to admission to PICU. All children received fluid and 51/69 were on inotropes on admission. 23/31 were intubated with a single dose of etomidate, the remainder were given various combinations of opioids, midazolam, propofol and ketamine. Measurements of both free and bound cortisol, ACTH, IL-6, 17-hydroxypregesterone, 11-deoxycortisol, CBG, albumin and aldosterone levels were obtained. Children were divided into 3 groups - nonsurvivors (8), shock survivors (43) and sepsis survivors (9). Non-survivors were more often intubated with etomidate but also had higher severity of illness scores (IL-6, lactate, PRISM, SOFA, lower CRP, and lower glucose). Non-survivors had decreased cortisol levels, increased ACTH levels and lower cortisol:ACTH ratios. In multivariate analysis, cortisol:ACTH levels were significantly related to IL-6 levels and etomidate exposure. There was no difference in cortisol:ACTH levels or IL-6 levels in those intubated without etomidate (small numbers) and those not intubated. Multiple regression analysis found only etomidate exposure was predictive for cortisol:11-DOC levels.

In summary, total cortisol levels correlated with free cortisol levels (different than in adults, possibly due to FFP replacement in the study population), the most severely ill children had signs of adrenal insufficiency on PICU admission (high ACTH/low cortisol) and with increasing disease severity, there was decreasing 11B-hydroxylase function with no change in 21-OH activity. Interestingly, etomidate reduced 11B-hydroxylase activity independently of disease severity. Exposure to etomidate seemed to have a severe impact on adrenal function, though a direct correlation with mortality can't be made.

Evidence: Opposing
Level: 4
Quality: Good
Outcome: Laboratory adrenal function
Children


A case report of using etomidate infusion to control cortisol levels in a patient with Cushing's disease (ACTH-dependent). Hydrocortisone was titrated to maintain cortisol levels in normal ranges prior to adrenalectomy could be performed.


This is a retrospective chart review examining charts of patients less than 10 years of age intubated in a single-center ED using etomidate as part of an RSI. 105 children were identified, mean age of 3 (+/-2.9 years). Indications for intubation: trauma (57%), nontraumatic respiratory distress (20%), nontraumatic altered mental status (13%), miscellaneous (10%). The number of patients with sepsis is not indicated. Median dose was 0.32 mg/kg. A small percentage of patients received morphine (3%) or midazolam as well (7%). 45% of patients intubated on first attempt. Only 52 patients had BP documented both pre and post-intubation though there was no discernable difference in the patients that had vitals measured and those that didn't. Both SBP and DBP increased (4 and 7mmHg respectively) from pre-procedure to within 10 minutes of etomidate (including span of intubation?). 4 patients had immediate adverse events (1 transient desaturation, 3 emesis).
There was no myoclonus or seizures in the ED (4 patients with previously known seizure disorders had a seizure during their hospital stay). 38 received steroids (mostly for ventilator weans). 1 patient received steroids for sepsis and no patients had documented or suspected adrenal insufficiency. 3 patients died, all had catastrophic TBI.

Evidence: Neutral
Level of Evidence: 5 (no septic patients identified)
Quality of Evidence: Poor
Outcome: Hemodynamics
Children


Adult trauma patients were randomized (non-blinded) to etomidate vs. fentanyl/midazolam for RSI in the ED. Cortisol levels were measured pre-intubation and 4-6 hours post and an ACTH-stimulation was performed. 30 patients were enrolled. Etomidate exposure was associated with significant decreases in post-intubation cortisol, response to CST and increases in hospital LOS, ICU LOS and ventilator days. There was a trend to more intravenous crystalloid requirements with a significant increase in prbc/FFP requirements. All fluid orders were under the direction of the attending physician and not protocolized. 2 patients died, both in the etomidate group.

Evidence: Opposing
Level of Evidence: 5 (adult trauma)
Quality of Evidence: Good
Outcome: Adrenal function, LOS
Adult trauma study


A prospective randomized controlled single blinded study in which 655 adult patients requiring emergency intubation (pre-hospital) were randomized to receive either etomidate or ketamine for induction. 469 patients were analyzed (others excluded mostly for discharged from ICU within 3 days or died on transport). A priori, a combined subgroup of trauma and sepsis was defined. Baseline characteristics were similar in both groups. There were 104 (22%) trauma patients and 76 sepsis (16%) patients. There was no difference in maximum SOFA score, intubation conditions/complications, mortality, catecholamine usage, ventilator free days, or ICU LOS b/w the two groups. 232 patients had adrenal function measured, baseline cortisol, 30 and 60 min CST were all lower in the etomidate group. 81% of etomidate patients were defined as non-responders vs. 42% of ketamine group though there was no difference in mortality b/w responders and nonresponders. There was also no difference in the combined trauma/sepsis subgroup in SOFA score or mortality.

Evidence: Neutral (mortality), Opposed (adrenal function)
Level of Evidence: 5
Quality of Evidence: Good
Outcome: Mortality, adrenal function, incidence of MODS
Adults

A retrospective study looking at adults with septic shock intubated by RSI who had a ACTH-stimulation test within 24 hours of intubation. Patients previously on corticosteroids/ketoconazole were excluded. 65 patients were analyzed in the study of which 25 received etomidate and 40 received midazolam (0.07 mg/kg mean dose). Overall hospital mortality was 45% (36% in etomidate group and 50% in midaz, NS). Relative adrenal insufficiency was significantly higher in etomidate group (84 vs. 48%) There was no effect on choice of induction agent on mortality. Use of etomidate was the only variable significantly affecting incidence of relative adrenal insufficiency.

Evidence: Neutral (mortality); Opposing (adrenal)
Level of evidence: 5 (adults)
Quality of evidence: Fair
Outcome: Mortality, adrenal function
Adults


A retrospective analysis performed on trauma patients in the ICU after a large increase in mortality was noted (22-29% vs. 44%) over one year. Detailed analysis revealed that there was only major change - the use of etomidate for sedation and analgesia (in combination with opiates). The authors hypothesize this is secondary to adrenal suppression.

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Mortality
Adults


A small cohort of healthy children received rectal etomidate for induction of general anaesthesia at a dose of up to 6.5 mg/kg. Hypnosis occured with 5 minutes and was associated with minimal cardiopulmonary side effects.

Not included in literature review.


A retrospective analysis of data from the CORTICUS study plus databases of previously published studies. All patients that received an ACTH-stimulation test within 24 hours from the onset of sepsis and who met the criteria for severe sepsis or septic shock were included. 477 patients were evaluated - 237 (50%) had received at least one dose of etomidate prior to inclusion into the study. In patients who did not receive etomidate (240 patients), cortisol levels did not vary between survivors and nonsurvivors but the maximum change was much lower. In etomidate treated patients, nonsurvivors had lower cortisol levels and lower maximum change.
values though the differences were small. In univariate analysis, etomidate was associated with an increased risk of death (not in multivariate analysis), especially in patients that did not receive steroids. Overall, cortisol levels alone do not predict outcome though the change following ACTH does.

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Mortality, adrenal function
Adults


A prospective cohort study in which 62 intubated adult patients (>24 hours) had a CST performed 24 hours post intubation 21 had severe sepsis (33.9%). 28 patients received only etomidate for intubation, others received a combination of fentanyl/midazolam, propofol, ketamine or thiopental. 27 patients were non-responders (43.5%), 8 of these patients had low basal cortisol levels. Univariate analysis - nonresponder group had more men, higher disease severity, lower MAP, lower CrCl. Nonresponders were more likely to receive etomidate for intubation (19/27 - 70% - meaning 30% of non-responders did not receive it) which bore out on multivariate analysis (OR 12.21). 33% of nonresponders and 11% of responders received steroids. 70% of nonresponders and 31% responders died (significant). Non-responders had more organ dysfunction, higher pressor needs and higher mortality rates. Are we using etomidate in sicker patients?

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Adrenal function
Adults


A retrospective study of 152 adults with septic shock who had an ACTH-stimulation test. 38 (25%) received etomidate prior to the test with no baseline differences b/w the patients that got etomidate and those that did not. Relative adrenal insufficiency occurred in 20/38 (76%) of etomidate-exposed patients vs. 58/114 (51%) of naive patients (significant). There was no significant difference in hospital mortality.

Evidence: Neutral (mortality); Opposing (adrenal function)
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Adrenal function, mortality
Adults


An animal study (mice) studying the effect of etomidate, thiopental and dexmedetomidine on wild-type and alpha2a-receptor knockout mice. Etomidate acts as an alpha2-agonist in mice which may explain its stable hemodynamic profile in humans.
Not included in literature review.


A retrospective database single-center study of adults admitted with septic shock. A previously developed protocol required steroid replacement (without cortisol levels or ACTH-stim tests) on all catecholamine-resistant patients or those requiring high dose NE (.28 mcg/kg/min). Complete information was available on 159 patients - 74 received etomidate. Overall hospital mortality was 65%; 69% in patients who received etomidate though they had higher APACHE scores compared to other groups (though not significant). 87 patients received hydrocortisone for hypotension and there was no association b/w induction agent and requirement for steroids (though this was a clinical requirement, no CSTs were performed). There was no difference in mortality in etomidate patients who received steroids vs. those who did not. Patients who received etomidate required fewer vasopressor infusions at induction and less cardiovascular intervention (ie ephedrine boluses) compared to other agents (especially propofol/midazolam) although not significant.

Evidence: Supportive (good hemodynamics, no increase in mortality)
Level of evidence: 5 (adults)
Quality of evidence: Poor (no controls)
Outcomes: Mortality, hemodynamics

Adults


A prospective observational adult study in which 118 adult patients with intra-abdominal sepsis requiring surgical intervention had an ACTH-stimulation test within 24 hours of onset of septic shock. A subgroup of patients received etomidate for induction during their surgical intervention and was analyzed retrospectively. Baseline cortisol was higher in non-survivors (higher cortisol levels predicted mortality) with no relation of response to ACTH-stim test to mortality. 69/118 (58%) received etomidate for induction of anesthesia and there was no difference in baseline cortisol, cortisol response or mortality b/w the two groups.

Evidence: Neutral
Level of Evidence: 5 (adults)
Quality of Evidence: Fair (no randomized controls)
Outcome: Adrenal function, mortality

Adults


In this prospective study, 12 children (mean age 9.2 +/- 4.8 years) were sedated with intermittent morphine and midazolam in the cath lab and arterial and venous catheterization was performed. All patients were breathing spontaneously (5 had SVT ablation, 7 had ASD device closure). After baseline measurements were obtained, all received 0.3 mg/kg of etomidate. One patient required PPV secondary to hypoventilation, all others continued to breathe spontaneously. There was no significant difference in any hemodynamic variable before and after etomidate administration (including RAP, PAWP, PAP, BP, SaO2, SvO2, HR, pH, CO2, Qp:Qs, PVR, SVR). Adrenal function was not measured.

Evidence: Supportive
Level of Evidence: 5 (not septic)
Quality of Evidence: Poor (no controls)
Outcome: Hemodynamics
Children


A randomized, non-blinded single center study - adult patients were randomized to have a RSI using etomidate vs. midazolam. 31 patients were enrolled. 70% of etomidate patients had abnormal ACTH-stim tests at 4 hours post-dose, almost all patients had normal tests at 12 and 24 hours. Baseline cortisol levels were lower in the etomidate group. Cortisol levels were always in normal ranges though were generally lower in the etomidate group. It is not reported if any patients had sepsis. There was no difference in outcome (LOS, ventilator-free days).

Evidence: Neutral (LOS), Opposing (adrenal function)
Level of Evidence: 5 (adults, unclear number of septic patients)
Quality of Evidence: Good
Outcome: ACTH-stimulation test, LOS
Adults


This is a retrospective review of 100 consecutive patients presenting to one of two pediatric tertiary EDs and intubated with etomidate. Patients over the age of 10 or those that received multiple doses of etomidate were excluded. Mean age was 4.4 +/- 3.0 years. Trauma was the most common diagnosis (72%; of note, one of the two sites had a protocol in which etomidate was only used for trauma patients; followed by status (13%), pulmonary disease (10%) and other (5%). No septic patients were identified in the other category though at least one patient was hypotensive at the time of intubation (range of SBP 50-170). 9% of patients received a benzodiazepine with etomidate (mean dose 0.37 mg/kg). 84% of patients had BP measurements (pre-intubation and lowest within 20 minutes of intubation) with a mean decrease of 1 mmHg. 4 patients had significant hypotension (SBP < 1SD for age), 3 trauma patients (one TBI, one bleeding pelvic #, one car-ped) and a patient with myasthenia gravis.
14 patients (14%) received steroids during their admission for airway edema, SCI, meningitis, myasthenia gravis, asthma or organ donation. No patients received steroids for suspected adrenal insufficiency. No laboratory evalulation of adrenal function was reported.

Evidence: Neutral
Level of Evidence: 4 (unclear if there are septic patients)
Quality of Evidence: Poor
Hemodynamic response
Children

This is a large multi-center randomized double-blind study in which adult patients with septic shock were randomized to treatment with hydrocortisone or placebo. 499 patients entered the study. 51/251 (20.3%) of patients in the treatment group and 45/248 (18.1%) in the treatment group received etomidate prior to study entry and 22/251 (8.8%) and 20/248 (8.1%) respectively received it afterward. 58/96 patients who had received etomidate (60.4%) had no response to corticotropin compared to 175/403 (43.4%) who did not receive it (p=0.004). Median time b/w last dose of etomidate and enrollment was 14 hours (range 1-67 hours). It is difficult to say whether etomidate was reserved for the sickest patients. Overall, there was no difference in 28-day mortality b/w the treatment vs. placebo group, regardless of response to ACTH. Numerous post hoc analyses were performed and revealed an increase in mortality at 28 days among patients who had received etomidate, regardless if they had received steroids. Patients in the steroid group had a shorter time to reversal of shock, especially in those who had a response to ACTH though the steroid group also had an increased risk of superinfection.

As compared to the Annane study (JAMA), the patients were healthier (32% placebo mortality vs. 61%), no fludrocortisone was given, a longer window for enrollment was used (72h vs. 8h), and steroid were tapered.

Evidence: Opposing
Level of Evidence: 5 (adults)
Quality of Evidence: Fair (randomized trial but etomidate not studied therapy)
Outcome: 28-day mortality
Adults


A prospective nonrandomized observational cohort single centre study examining ED intubation of septic adults. Primary outcome was in-hospital mortality. 106 patients met study criteria - 74 patients received etomidate with 32 patients receiving other agents (22 BDZ, 3 ketamine, 1 propofol, 1 ketamine/BDZ, 5 none). Patients were otherwise similar (50% of etomidate pts received steroids vs. 69% of etomidate-naive patients; NS) and no difference in in-hospital mortality or LOS was noted (trend to shorter hospital LOS in etomidate-naive patients). Adrenal function was not measured. Small study, likely underpowered.

Evidence: Neutral
Level of Evidence: 5
Quality of Evidence: Poor
Outcome: Mortality, LOS
Adults


An adult prospective observational study of patients requiring endotracheal intubation either prehospital or in the ED using etomidate. Patients with septic shock were excluded. 80% of patients had adrenal inhibition at 12 hours, 9% at 48 hours and 7% at 72 hours. At 24 hours, patients with adrenal insufficiency required higher vasopressor doses. No change in LOS or ventilator-free days was noted.

Not included, no septic patients.

An early study attempting to clarify the mechanism of previously recognized low cortisol levels and high mortality in patients receiving etomidate by continuous infusion. Etomidate was demonstrated to inhibit several enzymes responsible for the conversion of cholesterol to cortisol and reduce adrenal sensitivity to ACTH.

Not included in literature analysis.


This is a retrospective adult study examining data from a previous prospective study (hypertonic saline vs. LR in hypotensive blunt trauma patients). There were 209 patients in the initial trial of which 107 had a RSI (35 received etomidate). The groups were otherwise similar in mode of injury, trauma scores, scene time and initial presentation to ED. The etomidate patients had a higher risk of ARDS and MODS, even after correcting for type of resuscitation fluid, APACHE, massive transfusion and trauma score (OR 3.86 for ARDS OR 3.69 for MODS).

Evidence: Opposing
Level of Evidence: 5
Quality of Evidence: Fair
Outcome: ARDS or MODS
Hypotensive blunt trauma patients, Adults


An ex vivo animal study on a septic rat heart preparation in which a randomly assigned induction agent was administered (propofol, midazolam, S-Ketamine, methohexitone or etomidate). Etomidate was the only agent that had no negative chronotropic effect. All agents except midaz and ketamine reduced cardiac contractility in a dose-dependent manner. Ketamine and midazolam increased contractility, ketamine also had a positive lusitropic effect. Cardiac work reduced by all agents (ketamine the best, propofol the worst, etomidate -17%). The authors conclude that etomidate is safe at lower concentrations but markedly reduces cardiac work at higher concentrations (similar to what might be seen with a bolus or long term continuous infusion).

Evidence: Opposing
Level of Evidence: 5 (animal study)
Quality of Evidence: Good
Outcome: Hemodynamics
Animal study


A prospective single-center study examining the use of etomidate for RSI in ED in patients under 21 years of age. Of 101 patients who underwent RSI, 77 received etomidate. The mean age of patients was 8.2 +/- 6.2 years and 15 of them had a primary diagnosis of "shock". The mean dose of etomidate was 0.31 mg/kg. 48 of the 77 patients in which data was available were intubated on first attempt though "successful intubation conditions" were achieved in 68/69 patients. 10 patients had oropharyngeal secretions/blood/emesis complicating intubation. No myoclonus or pain on administration was reported. Changes in hemodynamics
were measured by maximum increase/decrease percentage compared to baseline. The mean maximum decrease was 10% though 12 patients had a drop in SBP more than 20% from baseline and 7 met PALS criteria for hypotension. 5/7 required no intervention, 2/7 did (one with hemorrhagic shock, one with septic shock). A subgroup of patients in decompensated shock (n=8) had only a 2.5% drop in SBP compared to those not in decompensated shock. When combined with the 15 patients in compensated shock and compared with patients not in shock, there were no differences. The etiology of the shock was not reported. 3 patients had a seizure in the ICU, all 3 had reasons to be prone to seizures (seizure disorder, hypocalcemia, TBI).

29/77 patients received steroids, 8 for presumed adrenal insufficiency. All had random cortisol levels drawn at some point during their admission, 7/8 had low baseline levels. 6/7 were drawn after etomidate administration but with a large range (up to 9 days post-etomidate) making association difficult. No stimulation tests were performed. 3/77 patients died, two had low cortisol levels and received steroids (both were trauma patients).

Evidence: Supportive
Level of Evidence: 4 (case series)
Quality of Evidence: Poor
Outcome: Hemodynamics, absolute adrenal insufficiency
Children