Journal Club Summary

**Etomidate in Sepsis**
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Jack Gervais, MD and Jeffrey Holmes, MD

**BACKGROUND:**
There is robust evidence that the use of a single bolus of etomidate for induction in rapid-sequence-intubation (RSI) can result in a measurable decrease in serum cortisol and a blunted response in ACTH response testing. There are also some retrospective data suggesting that the use of etomidate may increase hospital length of stay (LOS) and decrease survival. However, there is little prospective randomized data to determine if this is a clinically relevant phenomenon, and there is ongoing debate if etomidate is an appropriate agent for RSI induction in potentially septic patients.

**DISCUSSION:**
There has been ongoing debate about the safety of the use of etomidate in septic patients, centered on concern for impaired adrenal function. The fire was fueled following a 2007 analysis of the CORTICUS study, which determined that the use of etomidate was related to increased mortality. However, these conclusions are limited by the retrospective nature of the data and lack of randomization. There have been ongoing efforts to determine, in a prospective fashion, if etomidate does indeed contribute to adrenal insufficiency and/or outcomes.

The first article discussed (Hildreth et. al. J Trauma. 2008) aims to determine if there is a measurable degree of adrenal suppression following single bolus administration of etomidate. This study demonstrated that there is a measurable and statistically significant degree of adrenal suppression (as measured by serum cortisol levels and 4 and 6 hour ACTH stimulation testing) in patients receiving etomidate compared to those receiving midazolam as an induction agent for RSI. This study also suggested that there is higher mortality, longer ICU and hospital LOS, and longer ventilator time in the etomidate group, though these were not the primary outcomes. This study was performed on trauma patients, so the applicability to patients with suspected sepsis may be limited.

The second article reviewed examines the association between etomidate and mortality in a prospective, nonrandomized manner. This study did not show a significant association between etomidate use and mortality. There was a non-significant trend towards longer hospital length of stay. This study was limited by its nonrandomized nature, small sample sizes, and lack of standardized dosing.

The final article is a follow up to the above study, in which the same authors performed a randomized-controlled trial comparing etomidate and midazolam, with a primary outcome measure of hospital LOS. They also analyzed mortality as a secondary
outcome. There was a nonsignificant trend towards decreased hospital LOS and towards increased mortality in the etomidate group. While this study was well designed, it was limited primarily by a low number of patients. It was not powered to evaluate mortality differences, which is probably a more clinically relevant outcome than LOS. It was further limited because enrollment was based on suspected sepsis, though the results were not different in a pre-planned subgroup analysis of those patients with confirmed sepsis. However, this is the best study to date to compare etomidate to an alternative agent in a randomized controlled fashion.

We also briefly discussed, though did not perform a details review, of a recent study comparing etomidate and ketamine and the effect on adrenal function as well as illness severity (SOFA score) and mortality - (Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial controlled trial. Jabre, Combes et al. The Lancet. July 2009). Only 16% of patients had a final diagnosis of sepsis, while most were trauma patients. While there was a significant difference in adrenal function studies favoring the ketamine group, there was no significant different in illness severity scoring or mortality.

SUMMARY:
At this time, there appears to be little doubt the etomidate leads to a measurable decrease in adrenal function, based on several studies that show decreased baseline cortisol levels and impaired adrenal stimulation testing. However, there is insufficient data to determine if this has a clinically meaningful effect on patient outcomes. While there is retrospective data to suggest increased mortality and prolonged hospital stay, there are no prospective, randomized, controlled studies proving a significant association between single bolus etomidate use and adverse outcomes. More data from larger studies will be necessary to definitively answer this question. Until then, the use of etomidate in patients with suspected sepsis appears to be acceptable. However, alternative agents, such as ketamine, which also has a favorable hemodynamic profile in septic patients, would be a very reasonable alternative.