

# Corticosteroid Use in the Intensive Care Unit

## At What Cost?

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**Hypothesis:** Corticosteroid use has a significant effect on morbidity and mortality in the intensive care unit (ICU).

**Design:** Case-control study.

**Setting:** Burn-trauma ICU in a level 1 trauma center.

**Patients:** All patients who received corticosteroids while in the ICU from January 1, 2002, to December 31, 2003 (n=100), matched by age and Injury Severity Score with a control group (n=100).

**Interventions:** None.

**Main Outcome Measures:** We considered the following 7 outcomes: pneumonia, bloodstream infection, urinary tract infection, other infections, ICU length of stay (LOS), ventilator LOS, and mortality.

**Results:** Cases and controls had similar APACHE II (Acute Physiology and Chronic Health Evaluation II) scores and medical history. In univariate analysis, the cor-

ticosteroid group had a significant increase in pneumonia (26% vs 12%;  $P<.01$ ), bloodstream infection (19% vs 7%;  $P<.01$ ), and urinary tract infection (17% vs 8%;  $P<.05$ ). In multivariate models, corticosteroid use was associated with an increased rate of pneumonia (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.21-5.75) and bloodstream infection (OR, 3.25; 95% CI, 1.26-8.37). There was a trend toward increased urinary tract infection (OR, 2.31; 95% CI, 0.94-5.69), other infections (OR, 2.57; 95% CI, 0.87-7.67), and mortality (OR, 1.89; 95% CI, 0.81-4.40). Patients in the ICU who received corticosteroids had a longer ICU LOS by 7 days ( $P<.01$ ) and longer ventilator LOS by 5 days ( $P<.01$ ).

**Conclusions:** Corticosteroid use is associated with increased rate of infection, increased ICU and ventilator LOS, and a trend toward increased mortality. Caution must be taken to carefully consider the indications, risks, and benefits of corticosteroids when deciding on their use.

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**C**ORTICOSTEROIDS ARE USED in the intensive care unit (ICU) for a variety of indications, including sepsis, airway edema, and spinal cord injury. Enthusiasm for the use of corticosteroids has waxed and waned

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during the past several decades. Corticosteroids were initially used for treatment of sepsis in the 1950s and 1960s. In 1976, Schumer<sup>1</sup> reported an impressive reduction in mortality in patients with septic shock treated with methylprednisolone or dexamethasone, which led to increased use of corticosteroids for sepsis throughout the

1970s and 1980s. Two large, multicenter trials,<sup>2,3</sup> published in 1987, led to a decline in the use of corticosteroids. The Veterans Administration Systemic Sepsis Cooperative Study Group<sup>2</sup> found no difference in 14-day mortality or complications, and Bone et al<sup>3</sup> found a higher mortality rate in the cohort who had received corticosteroids. The trend toward increased mortality was again shown

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by Cronin et al<sup>4</sup> with a meta-analysis in 1995. In 2002, Annane et al<sup>5</sup> published results of a prospective study that showed a significant reduction in the risk of death in patients with sepsis who received cor-

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**Table 1. Descriptive Statistics**

Variable	Mean (SD)		t Test*	P Value
	Steroid Group (n = 100)	Control Group (n = 100)		
ISS	22.0 (11.9)	21.6 (10.8)	-0.23	.82
Age, y	44.7 (19.0)	45.3 (19.7)	0.22	.83
APACHE II score	12.9 (6.5)	12.6 (6.6)	-0.38	.70
GCS score	11.2 (4.8)	11.0 (4.9)	-0.29	.77

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale; ISS, Injury Severity Score.

\*Two-tailed t test.

**Table 2. Descriptive Statistics**

Variable	% of Patients		$\chi^2$ Statistic	P Value
	Steroid Group (n = 100)	Control Group (n = 100)		
Pulmonary disease	5	5	0	>.99
Hypertension	16	14	0.16	.69
Diabetes	8	6	0.31	.58
Other medical conditions	21	19	0.13	.72

ticosteroids, with no difference in adverse events. The current trend favors the use of corticosteroids, especially in the setting of sepsis and relative adrenal insufficiency. The increasing use of corticosteroids by practitioners for treatment of sepsis has led to an increasing level of comfort with the use of corticosteroids for other indications in the critically ill. This study was designed to evaluate the morbidity and mortality related to corticosteroid use in the trauma ICU.

## METHODS

### SETTING

The study was approved by the institutional review board at Eastern Virginia Medical School, Norfolk. Sentara Norfolk General Hospital is a level I trauma center, with 16 burn trauma and neurointensive care unit beds. Approximately 1600 trauma consultations are performed annually, with 400 trauma admissions to the ICU. Protocols in the ICU include intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dL (4.4-6.1 mmol/L), oral care with Listerine (listerfluor fluoride dental rinse; Pfizer Inc, New York, NY), 30° elevation of the head of the bed, use of silver-impregnated Foley catheters, small-bowel feeding tubes with early enteral nutrition, and mandatory line changes with a new site every 10 days in an effort to prevent infections. All protocols were successfully implemented and followed for all patients included in this study.

### DATA COLLECTION

The trauma database for the years 2002 to 2003 was queried for all patients admitted to the ICU by the trauma service. The

computerized pharmacy orders were then queried for each patient for the use of methylprednisolone, hydrocortisone, dexamethasone, and prednisone. This process identified 100 patients who had received corticosteroids while in the trauma ICU. Each corticosteroid recipient was then matched using patients from the same period derived from the initial trauma database query by age ( $\pm 5$  years) and Injury Severity Score ( $\pm 5$ ) to a control group of 100 patients. We then conducted a medical chart review to collect data, including ICU length of stay (LOS), ventilator LOS, Glasgow Coma Scale score at the time of admission to the ICU, medical history, infectious complications, and mortality. The infectious complications included pneumonia, urinary tract infection (UTI), bloodstream infection (BSI), and other infections (ie, wound infections, intra-abdominal infections, and *Clostridium difficile* colitis). In the corticosteroid cohort, we collected the hospital day that corticosteroid therapy was started, the type of corticosteroid given, the length of corticosteroid therapy, and the indication for the corticosteroid therapy. An APACHE II (Acute Physiology and Chronic Health Evaluation II) severity score was calculated for each patient on the basis of measurements within the first 24 hours of admission.

## DEFINITIONS

Pneumonia was defined by a positive bronchoalveolar lavage finding with more than 100 000 organisms or evidence in the medical chart of the nonintubated patient of elevated white blood cell count, fevers, and x-ray findings suggestive of pneumonia. The bronchoalveolar lavage in our ICU is generally performed without bronchoscopy. Urinary tract infection was defined as a yield of greater than 100 000 organisms on a quantitative culture. Bloodstream infection was defined as 2 or more positive cultures or a positive culture in the setting of an invasive line and fever. Other infection was defined by positive culture of *C difficile* colitis, a computed tomographic scan demonstrating an intra-abdominal abscess, or evidence of wound infection as noted in the medical chart. Relevant medical history was classified as pulmonary disease, hypertension, diabetes mellitus, and other medical conditions, including coronary artery disease, and was obtained from the patient history. Mortality was defined as in-hospital mortality.

## OUTCOMES

We measured 7 outcomes, including pneumonia, UTI, BSI, other infection, ICU LOS, ventilator LOS, and mortality.

## STATISTICAL ANALYSIS

We used the Statistical Analysis System software (SAS Institute Inc, Cary, NC) to assess the links between corticosteroid use and each of the 7 outcomes with univariate analysis. We also conducted multivariate regression analysis (logistic regression and ordinary least squares) controlling for age, APACHE II score, and medical history.

## RESULTS

There was no significant difference between the 2 groups for Glasgow Coma Scale score, APACHE II score (**Table 1**), and medical history (**Table 2**). On average, the corticosteroids were first given on hospital day 5, with 43% given on day 1 and 60% given by day 2. The average length of corticosteroid course was 6.6 days, with a range of 1 to 31 days. Thirty patients received cortico-

steroids for 1 day and 57 patients for longer than 2 days. The indications for corticosteroid therapy on retrospective medical chart review were as depicted in the following tabulation:

Indication	No. of Patients
Spinal cord injury	30
Septic shock	6
Adrenal insufficiency	23
Optic neuritis	10
Stridor/airway edema	19
Closed head injury	1
Corticosteroid use at home	3
Unknown	8

Our ophthalmologists, in consultation for orbital fractures, routinely give corticosteroids for treatment of traumatic optic neuritis. The otolaryngologists typically prescribe corticosteroids for treatment of stridor or airway edema perioperatively after fixation of facial fractures. In addition, corticosteroids were given to patients who developed stridor on extubation by the trauma service.

In univariate analysis, the corticosteroid group had significantly increased rates of pneumonia, BSI, and UTI (**Table 3**). In multivariate models, corticosteroid use was significantly associated with increased rates of pneumonia and BSI, with a trend toward increased UTI, other infection, and mortality (**Table 4**). Previous lung disease was also associated with an increased risk of pneumonia. Advanced age and elevated APACHE II scores were associated with an increased mortality.

The average (range) ICU LOS for patients receiving corticosteroids was 17.6 days (1-113 days) compared with 10.2 days (1-48 days) for the control group. Seven patients in the corticosteroid group had an ICU LOS longer than 50 days. Outcomes among these 7 patients included pneumonia in 2, BSI in 3, UTI in 3, and other infection in 1. The average ICU LOS for the remaining 93 patients in the corticosteroid group was 13.9 days. The average (range) ventilator LOS for the corticosteroid group was 9.9 days (0-68 days) compared with 4.9 days (0-32 days) in the control group. Controlling for confounders using ordinary least squares logistic regression, ICU patients who received corticosteroids had a longer ICU LOS by 7 days ( $P < .01$ ) and a longer ventilator LOS by 5 days ( $P < .01$ ) (**Table 5**).

## COMMENT

Corticosteroids are well known for their broad-ranging immunosuppressive effects,<sup>6</sup> which may place the patient at increased risk for infectious complications. In addition, trauma is known to cause an immediate release of inflammatory mediators, which frequently induces a systemic inflammatory response and results in severe depression of the immune system.<sup>7</sup> Certainly the combination of these 2 factors places the patient at an increased risk for severe infections.

Our study found a significantly increased risk of infection in patients who received corticosteroids. A similar relationship had previously been noted by DeMaria et al,<sup>8</sup> who found a significant increase in the incidence

**Table 3. Frequencies of Poor Outcomes by Univariate Analysis**

Variable	% of Patients		$\chi^2$ Statistic	P Value
	Steroid Group (n = 100)	Control Group (n = 100)		
Pneumonia	26	12	6.37	.01
BSI	19	7	6.37	.01
UTI	17	8	3.70	.05
Other infection	12	5	3.15	.07
Mortality	20	13	1.78	.18

Abbreviations: BSI, bloodstream infection; UTI, urinary tract infection.

and severity of infections in patients with central nervous system trauma who had received corticosteroids. Gerndt et al<sup>9</sup> also noted a 2.6-fold increase in the risk of pneumonia in patients with spinal cord injury who had received corticosteroids, consistent with our data. Meta-analysis of corticosteroid treatment for sepsis<sup>4</sup> did not find an increase in secondary infection rates in patients treated with corticosteroids, but did find a trend toward increased mortality due to secondary infection in the corticosteroid-treated group. Our group had a similar trend toward increased mortality.

The ICU and ventilator LOS were prolonged in the corticosteroid group, which was likely secondary to the increased infection rate in this cohort. The ICU LOS was 4 days greater in the corticosteroid group when patients with LOS longer than 50 days were excluded from the analysis. There were 9 infections in the 7 patients with LOS longer than 50 days. Steroid use was previously noted by Gerndt et al<sup>9</sup> to be associated with prolonged ICU and ventilator LOS among patients receiving corticosteroids for treatment of spinal cord injuries.

Most of the corticosteroids were given early in the hospital course, with 60% given by hospital day 2. The infection rate did not appear to be related to the length of corticosteroid course or to the type of corticosteroid given. Most of the corticosteroids were given before the development of infection, except in the 6 patients with septic shock.

The indication for corticosteroid use in our population was varied. The use of corticosteroids for spinal cord injury within the first 8 hours of injury is considered standard of care. Bracken et al<sup>10</sup> in 1990 demonstrated improved neurologic recovery when methylprednisolone was given within the first 8 hours after injury. The current use of corticosteroids for treatment of septic shock associated with adrenal insufficiency is supported by the data from Annane et al,<sup>5</sup> who showed an improved mortality with no increase in adverse events. In 2003, Annane et al<sup>11</sup> concluded that corticosteroids for treatment of sepsis reduced ICU mortality and increased the proportion of shock reversal by day 7. Caution must be taken in the population with sepsis to restrict the use of corticosteroids to those with adrenal insufficiency.

Steroids are commonly given for airway edema and stridor, although this use is not supported by prospective trials. Markovitz and Randolph<sup>12</sup> reviewed 3 studies

**Table 4. Odds of Poor Outcome, Controlling for Confounders, by Logistic Regression**

Variable	OR (95% CI)				
	Pneumonia	BSI	UTI	Other Infection	Mortality
Steroid use	2.64 (1.21-5.76)*	3.25 (1.26-8.38)*	2.32 (0.95-5.68)	2.58 (0.87-7.67)†	1.89 (0.82-4.40)
APACHE II score	1.07 (1.00-1.13)*	1.04 (0.97-1.11)	1.04 (0.97-1.11)	1.03 (0.95-1.11)	1.16 (1.08-1.25)*
Age	1.00 (0.98-1.03)	1.00 (0.98-1.04)	0.99 (0.97-1.02)	0.98 (0.95-1.00)	1.04 (1.01-1.07)*
Pulmonary disease	4.16 (1.00-17.26)*	2.64 (0.56-12.41)	0.76 (0.09-6.62)	1.34 (0.15-12.32)	0.24 (0.02-2.93)
Diabetes	2.02 (0.55-7.47)	1.10 (0.25-4.82)	0	0	0.20 (0.02-1.90)
Hypertension	0.71 (0.23-2.16)	0.75 (0.22-2.55)	1.51 (0.43-5.22)	0	0.83 (0.25-2.74)
Other medical conditions	1.13 (0.41-3.08)	2.40 (0.82-7.08)	0.81 (0.23-7.81)	0	0.33 (0.10-1.11)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

\* $P < .05$ .

† $P < .10$ .

**Table 5. Chance of Longer LOS, Controlling for Confounders, Expressed as Slope of Regression Line**

Variable	ICU LOS	Ventilator LOS
Steroid use	7.35*	5.05*
APACHE II score	0.29†	0.32‡
Age	0.04	0.06
Pulmonary disease	2.06	-0.49
Diabetes	-6.49	-4.98†*
Hypertension	3.64	-0.92
Other Infection	3.41	-1.41

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; LOS, length of stay.

\* $P < .05$ .

† $P < .10$ .

‡ $P < .01$ .

in adults with a total of 1047 patients and found no difference in the rate of reintubation or postextubation stridor. A meta-analysis of 4 trials of corticosteroid therapy in adult patients<sup>13</sup> looked at the rates of stridor and reintubation and found so few events that the results were uninformative. There is clearly a need for a large, multicenter prospective trial to study the benefit of corticosteroids in adults for airway edema and stridor before the use is accepted.

Twenty-three of our patients received corticosteroids for treatment of relative adrenal insufficiency documented by a low random cortisol level in the setting of stress, but with no evidence of sepsis. Many of these patients were not hemodynamically unstable. This is not an area that has been well studied in the literature, and there does not seem to be a basis for corticosteroid therapy in this population unless they are unresponsive to adequate resuscitation and pressors. Certainly the role of relative adrenal insufficiency in the critically ill trauma patient deserves further study before recommendations on treatment can be made.

Ten patients received corticosteroid therapy for traumatic optic neuritis, which is not well supported in the ophthalmology literature. The International Optic Nerve Trauma Study<sup>14</sup> showed no visual improvement for corticosteroid therapy or optic canal decompressive sur-

gery. In 3 cases, the patient received corticosteroids at home. In 8 cases, we were unable to find the indication for corticosteroids in the medical chart review.

Thirty-nine of the 100 patients in our study received corticosteroids for an indication supported by the literature. The remaining 61 should not have received corticosteroids based on a strict interpretation of the current literature. Certainly the risk of infection outweighs the potential benefit in these cases. In addition, the impact of prolonged ICU and ventilator LOS is not without cost. The average cost of 1 day in our ICU is \$1456.84, with an average cost per ventilator day of \$313. Steroids added 7 ICU days at a cost of \$10 197.88 and 5 ventilator days with a cost of \$1565. This results in an average overall cost excess for the 61 patients of \$717 535.68.

Although our data clearly show an increased risk of infection and increased ICU and ventilator LOS with corticosteroids, there are weaknesses in the construct of this investigation. The study was performed retrospectively, using medical chart review to acquire the data, with the inherent problems associated with this type of study. In addition, our sample size was small, with a low power for statistical analysis. There are certainly many possible confounders in a critically ill patient, which are difficult to account for in our analysis. We were able to match our corticosteroid and control groups on the basis of age and Injury Severity Score, but it is hard to know retrospectively how well matched the 2 groups were. Despite the problems inherent to a study of this nature, we believe that corticosteroid use adds a significant risk for morbidity and mortality in the ICU and should be used with caution.

In conclusion, corticosteroid use is associated with an increased rate of infection, increased ICU and ventilator LOS, and a trend toward increased mortality. Caution must be taken to carefully consider the indications, risks, and benefits of corticosteroids when deciding on their use.

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**Author Contributions:** Dr R. C. Britt had full access to all data in the study and takes responsibility for the data and the accuracy of the data analysis.

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## Invited Critique

**M**achiavelli once said, "Anyone wishing to see what is to be must consider what has been."<sup>1</sup> For nearly 40 years, enthusiasm for steroid use in the intensive care unit (ICU) has been like a pendulum, cyclically swinging toward and then away from their use. Currently, enthusiasm for steroid use appears to be on an upswing. Despite decades of conflicting data, steroids are once again being advocated for the treatment of sepsis. In addition, with a greater appreciation for the prevalence of "relative" adrenal insufficiency in the ICU, the use of steroids appears to be increasing. A historical review of the subject would lead one to proceed down this path with caution.

Britt and associates at Eastern Virginia Medical School have clearly articulated the results of a well-designed case-control study examining the complications associated with steroid use in the ICU. Their findings of significantly increased rates of pneumonia, bloodstream infections, urinary tract infections, ventilator days, and ICU length of stay serve as a warning to those who advocate increased steroid use. It is also noteworthy that these results may have been even more significant, had their institution not already implemented a series of protocols designed to limit infections.

If one considers the indications for the use of steroids in the ICU, the benefits may not outweigh the risks. Use of steroids to treat traumatic optic neuritis is not well supported in the literature. Likewise, steroids may not alter reintubation rates in those with airway edema. The literature does not provide guidance for steroid use in "relative" adrenal insufficiency. Steroid use in sepsis remains controversial, and in the treatment of spinal cord injury, steroids have recently been de-emphasized. Given the paucity of documented benefit, the infectious risks of steroids need to be carefully considered before initiation of therapy.

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