Adjunctive corticosteroid therapy in pediatric severe sepsis: Observations from the RESOLVE study*

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Objective: To assess whether corticosteroids, used as adjunctive therapy for pediatric severe sepsis, is associated with improved outcomes.

Design: Retrospective cohort study examining the clinical database derived from the RESOLVE (REsolving severe Sepsis and Organ dysfunction in children: a global perspective, F1K-MC-EVBP) trial of activated protein C for pediatric severe sepsis.

Setting: A total of 104 pediatric centers in 18 countries from which data were originally gathered.

Subjects: Children with severe sepsis (n = 477), requiring both vasoactive-inotropic infusions and mechanical ventilation. Within this cohort, 193 children received corticosteroids during their septic episode and 284 did not.

Interventions: None.

Measurements and Main Results: Baseline summary characteristics demonstrated that children receiving or not receiving corticosteroids had similar demographics and disease severity as indicated by age, gender, mean Pediatric Risk of Mortality scores, and mean number of organ dysfunctions. Use of adjunctive corticosteroids increased during the F1K-MC-EVBP trial. Indications for corticosteroid prescription were therapeutic (89%, mostly shock) and prophylactic (13%). All cause 28-day mortality among children receiving and not receiving corticosteroids was 15.1% and 18.2%, respectively, p = .30. There was no difference in mean vasoactive-inotropic infusion days between the corticosteroid and no corticosteroid groups, 4.5 days vs. 4.3 days, respectively, p = .59. Similarly there was no difference in mean ventilator days between the corticosteroid and no corticosteroid groups, 8.3 days vs. 7.7 days, respectively, p = .38.

Conclusions: Children with severe sepsis who received adjunctive corticosteroid therapy exhibited similar illness severity compared with those who did not. No definitive improvement in outcomes can be attributable to adjunctive corticosteroid therapy in the largest pediatric sepsis trial conducted to date. (Pediatr Crit Care Med 2011; 12:2–8)

Key Words: corticosteroids; sepsis; septic shock; severe sepsis; outcomes; mechanical ventilation; vasoactive-inotropic drugs; mortality; Pediatric Risk of Mortality III; activated protein C; organ dysfunction

Although multiple guidelines suggest consideration of adjunctive stress-dose hydrocortisone for pediatric vasoactive-inotropic refractory septic shock, no high-quality evidence currently exists supporting either the safety or efficacy for this approach (1). A previous retrospective, cohort investigation (2) utilizing the Pediatric Health Information System administrative database (n = 6693) suggested that adjunctive corticosteroid therapy utilized for pediatric severe sepsis was associated with a variety of worse outcomes, but this investigation was limited by lack of illness severity data for the study population. The largest adult trial examining the potential utility of stress-dose hydrocortisone for septic shock, CORTICUS, concluded that although provision of stress-dose hydrocortisone may hasten resolution of septic shock among those whose shock resolves, this intervention did not reduce mortality and may be associated with a higher risk of hyperglycemia, hypernatremia, and hospital-acquired infections (3).

Although no definitive benefit for activated protein C (Xigris; Eli Lilly and Company, Indianapolis, IN) as adjunctive treatment of severe pediatric sepsis was demonstrated in the F1K-MC-EVBP, RESOLVE (REsolving severe Sepsis and Organ dysfunction in children: a global perspective) trial (NCT00049764), a rich database was generated permitting examination of other aspects of pediatric sepsis pathophysiology and therapy (4). Accordingly, we hypothesized that within the RESOLVE data set, we would find no evidence supporting the notion that adjunctive corticosteroids improve outcomes for children with severe sepsis.

MATERIALS AND METHODS

No patient identifiers were required for the purposes of the current investigation. Collection of the original data were approved by each Institutional Review Board participating in the RESOLVE trial.

RESOLVE was a prospective, randomized, double-blinded, placebo-controlled trial (November 2002–April 2005) designed to examine the potential efficacy of activated protein C (Xigris) as adjunctive therapy for pediatric severe sepsis. It was the largest pediatric sepsis trial conducted to date, involving 104 major pediatric centers in 18 countries (4). Inclusion criteria for the clinical investigation included: age, 0–17 yrs; suspected or proven infection; systemic inflammation (modified systemic inflammatory response syndrome criteria); and sepsis-induced cardiovascular and pulmonary organ dysfunctions. That is, all subjects enrolled...
required mechanical ventilation for sepsis-associated pulmonary failure and vasoactive-inotropic infusion(s) to support hemodynamics. “Standard care,” including use of corticosteroids, occurred at the discretion of the primary physician and was not controlled by trial protocol. For the RESOLVE trial, the primary endpoint was a reduction in composite time to complete organ failure resolution (CTCOFR) that scored three organ systems, namely, cardiovascular, pulmonary, and renal. Resolution was defined as the last day the subject required vasoactive-inotropic infusions, invasive mechanical ventilation, and renal replacement therapy. Definitions for organ dysfunctions have been previously published (5). Cardiovascular, respiratory, neurologic, hematologic, renal, and hepatic organ dysfunctions were recorded. Although data regarding skin necrosis and amputations were collected, these complications were not counted as a defined organ dysfunction. Scoring for Pediatric Risk of Mortality III score (6) and Pediatric Overall Performance Category (POPC) score (7, 8) was conducted according to published methodologies.

The F1K-MC-EVBP database was queried for predictor variables (age, gender, admission Pediatric Risk of Mortality III score, baseline POPC score, and number of organ dysfunctions at entry) and outcomes (mortality, days of mechanical ventilation, days of vasoactive-inotropic infusion, CTCOFR, change in POPC score, pediatric intensive care unit [PICU] length of stay and hospital length of stay), comparing children who received (n = 193) or did not receive (n = 284) corticosteroids during the first 6 days post study entry.

**Statistical Methods**

Only subjects who received any study medication and were <18 yrs old in the F1K-MC-EVBP study were included in this analysis. No imputation was conducted for missing data. All statistical analyses were performed, using SAS Version 9.1 (SAS Institute, Cary, NC), and significance tests were performed at a two-sided α level of 0.05.

Data for binary variables were summarized, using percentages, and comparisons across groups were performed, using Pearson’s chi-square test. Continuous and multinomial variables were summarized, using mean and SD values. A Student’s t test, assuming equal variance, was used to examine the difference between two groups for all continuous and multinomial variables.

**RESULTS**

Use of corticosteroids increased during the course of the F1K-MC-EVBP trial. In Figure 1A, the cumulative proportion of patients treated with steroids over time (as measured by the number of enrolled patients) and the cumulative average CTCOFR score are plotted. In Figure 1B, the cumulative proportion of patients treated with steroids over time and cumulative mortality rate are plotted. After initial variability due to low numbers of patients, cumulative steroid use rose from ~30% of patients to ~40%, whereas the cumulative average organ dysfunction score and cumulative mortality rate remained generally stable at ~10 days and ~18%, respectively.

Overall, 40.5% (193 of 477) of subjects were administered corticosteroids during the first 6 days after study entry. Corticosteroids prescribed included hydrocortisone (53%), dexamethasone (29%), methylprednisolone (14%), and prednisolone (4%). Mean and median days of the first corticosteroid dose post enrollment were 2.7 days and 1.0 days, whereas mean and median duration of corticosteroid dosing were 4.3 days and 3.0 days, respectively. Recorded indications for corticosteroid prescription were therapeutic and prophylactic: The vast majority of subjects who received
corticosteroids, 178 (92%) of 193 patients, received corticosteroids for therapeutic indications. On the other hand, 26 (13%) received steroids for prophylactic indications. Eleven (5.6%) of 193 patients received steroids for both therapeutic and prophylactic indications.

Sensitivity analyses suggested that there was little effect on the significance of the association between steroid use and 28-day mortality. If patients who received steroids for ≤2 days were removed from the analysis, the p for the association between steroids use and 28-day mortality was .31. This analysis was based on 155 patients in the steroid group and 284 patients in the nonsteroid group. Additionally, if patients who received only dexamethasone were removed from the analysis, the p for the association between steroid use and 28-day mortality was .45. This latter analysis was based on 170 patients in the steroid group and 284 patients in the nonsteroid group.

No decrease in mortality attributable to adjunctive corticosteroids was apparent per Pearson chi-square test. CTCoFR and change in POPC scores were not different between groups. Resource utilization, including duration of vasoactive-inotropic infusions and mechanical ventilation, as well as PICU length of stay also were not significantly different between groups. Although hospital length of stay was statistically shorter among subjects who did not receive corticosteroids, in view of multiple comparisons in a retrospective data analysis, this difference was not necessarily considered relevant. We performed a multivariate analysis and found that three baseline biomarkers of severity were independent predictors of 28-day mortality: interleukin (IL)-8, IL-6, and protein C. After adjusting for these markers, the p for the association between 28-day mortality and usage of steroids between baseline and day 6 was .81.

Activated protein C was administered to 46.6% of the group receiving corticosteroids and to 52.8% of the group not receiving corticosteroids (p = .1848). To assess the possible association between outcomes and treatment with Xigris and/or low-dose corticosteroids and steroids, multivariate logistic regression models were constructed, using standard stepwise procedures. In the case where the response variable was CTCoFR, the significant covariates in the model were baseline IL-8, baseline IL-6, and baseline Pediatric Risk of Mortality score. When covariate terms were added to this model for Xigris, steroids, and the Xigris by steroids interaction, all three of these treatment terms exhibited p between .75 and .85. Similarly, significant covariate terms in a stepwise model with 28-day all-cause mortality as the response variables were baseline IL-8, baseline IL-6, and baseline protein C, and when Xigris, steroids, and the Xigris by steroids interactions were added to this model, the p values for the three treatment terms were between .35 and .75. Accordingly, accounting for treatment with Xigris had no effect on the stated results with regard to the lack of association between administration of low-dose steroids and outcomes.

**DISCUSSION**

Nearly 100 yrs ago, the first descriptions (9) of fulminant sepsis associated with apoplexy of the suprarenal glands were reported. For patients with purpura fulminans, abnormalities of the hypothalamic-pituitary-adrenal axis, or history of acute or chronic administration of steroids as an aspect of some immunosuppression regimen, the decision to provide adjunctive corticosteroids in the setting of septic shock seems obvious and reasonable. However, the risk/benefit of adjunctive corticosteroids for the usual care of patients with septic shock remains controversial (10).

This debate is reflected in the primary text and appendix of the 2008 International Guidelines for Management of Severe Sepsis, Surviving Sepsis Campaign (11). Using a modified Delphi process, and Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Criteria, a 55-member expert committee concluded: that intravenous hydrocortisone for septic shock, when the current adrenocorticotropic hormone stimulation test (assess that serum cortisol is not recommended to be considered for adult (and pediatric) septic shock when hypotension responds poorly to adequate fluid resuscitation and vasoressors (2C); that the current adrenocorticotropic hormone stimulation test that assesses total serum cortisol is not recommended to identify the subset of adults with septic shock who might benefit from hydrocortisone (2B); that hydrocortisone is preferred over dexamethasone (2B); that hyperglycemia is associated with increased risk of morbidity and mortality among critically ill children (16–20).

Recently, the largest adult trial to date examining the potential benefit of stress-dose corticosteroids for septic shock, CORTICUS, concluded that such pharmacologic intervention provided no benefit in terms of reducing mortality (3). This result was consistent whether or not a subject demonstrated a priori evidence of inadequate adrenal reserve per adrenal stimulation testing (i.e., corticotropin-stimulated minus baseline total serum cortisol <9 µg/dL). As expected, based on several previous clinical trials (3, 21–24), subjects who received hydrocortisone and resolved their shock, exhibited faster resolution of shock (withdrawal of vasoactive-inotropic support) compared with subjects who did not receive hydrocortisone. However, hospital-acquired infections, sepsis, and septic shock, as well as hyperglycemia and hypernatremia, were more prevalent among subjects who received hydrocortisone (3).

Only a few clinical trials have addressed the question of adjunctive corticosteroid therapy for pediatric sepsis. Min
et al (25), in a randomized, double-blinded trial investigating the potential benefit of 3 days of adjunctive hydrocortisone for Dengue shock syndrome (n = 98), reported a case fatality rate of 19% in the steroid group and 44% in the placebo group, p = .005. A subsequent study (n = 97) by Sumarmo et al (26), examining a single 50-mg/kg dose of hydrocortisone, however, claimed no benefit, pointing out that shock resolved in 91 of 97 children within 6 hrs of study entry, regardless of placebo/steroid assignment. Of the six children who died, three each received hydrocortisone or placebo. Conflicting conclusions have also been reported for adjunctive methylprednisolone for pediatric Dengue shock. A Cochrane systematic review (27) on this subject concluded no benefit from adjunctive corticosteroids for pediatric Dengue shock, summarizing four trials that enrolled a total of 284 subjects. Summary relative risk for mortality was 0.68 (95% confidence interval, 0.42–1.11). Likewise, no corticosteroid benefit was apparent in terms of need for erythrocyte transfusion, development of seizures, or occurrence of pulmonary hemorrhage. The authors concluded that “there is insufficient evidence to justify the use of corticosteroids in managing Dengue shock syndrome. As corticosteroids can potentially do harm, clinicians should not use them unless they are participating in a randomized controlled trial comparing corticosteroids with placebo.” Slusher et al (28) similarly concluded that moderate-dose dexamethasone, administered to African children with sepsis with the initial dose delivered before antibiotics, did not improve survival to discharge, time to hemodynamic stability, hospital length of stay, or duration of fever.

With a gradual decrease in pediatric sepsis mortality attributable to continuous quality improvement of general pediatric critical care (29–31), enrollment of adequate number of subjects for appropriate power in contemporary trials of severe sepsis has become problematic, if not limiting. Importance of identifying clinically meaningful outcome measures other than mortality for pediatric critical care medicine interventional studies has been emphasized repeatedly (32–35). Alteration in the pediatric logistic organ dysfunction score (36–38) was used in a small clinical investigation (39) that examined the potential utility of intensive plasma exchange among children with thrombocytopenia-associated multiple organ failure. However, there is ongoing debate regarding pediatric logistic organ dysfunction’s noncontinuous scale, and lack of calibration and external validity (35, 40, 41). It has been astutely pointed out that “The early morbidity of sepsis is reflected in deranged organ function and the need for intensive care unit supportive care; however, this morbidity is not experienced primarily by the patient but rather by the patient’s family and loved ones. After the acute illness resolves, the patient may still require a lengthy hospital stay and subsequent rehabilitation, with the attendant physical, emotional, and financial burdens; long-term morbidity is reflected in reduced health-related quality of life” (42). In a related discussion, it was noted that “It is the inclusion of measures of morbidity in survivors rather than during intensive care that promises to reduce sample size in clinical trials. There has to be a way to make fundamental randomized controlled trials more feasible in pediatric intensive care. Combining significant morbidity with mortality is one way in which it could be achieved” (32). Treatment of sepsis syndrome should be aimed at improving both the duration and quality of survival. In reality, the only real outcomes clinically relevant to critical care are severity of illness-adjusted mortality, residual morbidity, and cost (43). Expanding this notion, clinically meaningful outcome measures need to be patient-centered and might include symptoms, quality of life, duration of life, quality of dying, cost of medical care, and effect of health care on loved ones. It has been suggested that improving quality of life represents the ultimate goal of health care (44). Assessing quality of life after an episode of pediatric sepsis represents a clinically meaningful end point that is just beginning to be explored (45). A previous investigation reported by Markovitz et al (2), utilizing the Pediatric Health Information System database, examined factors associated with outcomes among children (n = 6693) with severe sepsis, operationally defined as a combination of infection plus need for a vasoactive-inotropic infusion and mechanical ventilation. Mortality was 30% for children who received steroids, compared with 18% for those who did not (crude odds ratio, 1.9) (95% confidence interval, 1.7, 2.2). Children who received steroids also required longer duration of vasoactive-inotropic infusions and mechanical ventilation support and required a significantly longer PICU length of stay and hospital length of stay. Investigators of this study concluded that, although steroids may have been preferentially administered to more severely ill children, steroid use was associated with increased mortality. Unfortunately, no quantitative information related to illness severity was available from the administrative database that supported the study.

Baseline characteristics, including illness severity for children enrolled in the RESOLVE trial, were similar among those who received adjunctive corticosteroids and those who did not (Table 1). In addition, most corticosteroid use in the RESOLVE trial was classified as therapeutic intervention for septic shock. It should be noted that children with hematopoietic stem cell transplantation or persistent severe thrombocytopenia (surrogate markers for immunosuppression) were excluded from enrollment in the RESOLVE investigation (4).

Although corticosteroid intervention for adult septic patients has typically been associated with faster resolution of septic shock (3, 21–24, 46–49), no obvious hemodynamic benefit of concurrent steroid administration was ob-

<table>
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<tr>
<th>Table 1. Comparison of baseline characteristics among children in the RESOLVE trial who received or did not receive adjunctive corticosteroid therapy</th>
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<tbody>
<tr>
<td>Received Adjunctive Corticosteroids (n = 193)</td>
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<tr>
<td>Mean ± SD or %</td>
</tr>
<tr>
<td>Age, yrs</td>
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<tr>
<td>Male sex, %</td>
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<tr>
<td>PRISM III, 12-hr score</td>
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<tr>
<td>Organ dysfunctions, n</td>
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<tr>
<td>Baseline POPC score</td>
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CI, confidence interval; PRISM III, Pediatric Risk of Mortality score, version III; POPC, Pediatric Overall Performance Category score.
served for septic children based on the present study or that of Markovitz et al (2). Stress-dose hydrocortisone also shortened the duration of mechanical ventilation as per post hoc analysis of Annane’s initial randomized controlled trial (50) assessing adjunctive steroids for adult severe sepsis. Again, however, the current investigation and that of Markovitz et al (2) failed to confirm this important benefit in children.

Limitations of the present investigation should be acknowledged: This retrospective investigation of the RESOLVE database was not a randomized comparison of placebo vs. corticosteroids as adjunctive therapy for pediatric severe sepsis. Accordingly, there was no protocol for administration and dosing of corticosteroids. Because these decisions were left to the discretion of medical attendants, it is likely that patients received variable doses of steroids on different days. This fact complicates any analysis of RESOLVE steroid dosing or the interpretation of such an analysis. Degree of overlap of vasoactive-inotropic infusion, mechanical ventilation, and interval of steroid dosing in relation to the sepsis event are also not provided. However, all subjects entered in the RESOLVE trial required both vasoactive-inotropic infusions and mechanical ventilation (4). In addition, no data concerning corticosteroid-dosing decisions based on adrenal stimulation testing were available. However, even this seemingly logical practice, at least as it is currently conducted, has recently come under critique (3). Children in the RESOLVE trial received corticosteroids for a mean and median of 4.3 days and 3.0 days, respectively, initiated at a median of 1 day post enrollment. Average duration of mechanical ventilation in the corticosteroid-treated group was 8.3 days. Accordingly, we believe the data are not significantly contaminated with short-duration steroid dosing prescribed for post extubation stridor.

For children with severe sepsis (at least two organ dysfunctions) and similar severity of illness per admission Pediatric Risk of Mortality III scores, those who were treated or not treated with concurrent corticosteroids generally demonstrated similar outcomes in terms of mortality as well as PICU resource utilization as quantified by days of vasoactive-inotropic support, mechanical ventilation, and PICU length of stay. Hospital length of stay was statistically shorter among subjects who did not receive corticosteroids, but the relevance of this isolated finding is unclear. Although the current conclusions are based on retrospective data, combined with the results of the adult prospective, randomized, controlled CORTICUS trial (3), the findings support rationale for equipoise regarding the research question of potential risk/benefit of adjunctive corticosteroids for pediatric sepsis. Although the biochemically and physiologic logic for provision of stress-dose corticosteroids as adjunctive therapy for severe sepsis would seem intuitive, controlled clinical experience has not consistently supported this supposition. Corticosteroid involvement in the complex neurogenic-endocrinologic-inflammatory chemical cross talk that occurs during the sepsis stress response involves more than just modulation of the systemic inflammatory response syndrome (51–54). Faster resolution of hemodynamic instability may not be an appropriate surrogate marker for reduced mortality (3, 55–57). It is likely that attention to variables other than hemodynamics, such as protein catabolism and gluconeogenesis, that are also affected by corticosteroids may deserve closer scrutiny in future interventional trials (58, 59).

**CONCLUSIONS**

Children with severe sepsis enrolled in the RESOLVE trial who received corticosteroids demonstrated similar illness severity compared with those children who did not. Outcomes (mortality, days of vasoactive-inotropic infusion and mechanical ventilation, organ failure resolution, change in POPC score, and PICU and hospital length of stay) were similar in children who did or did not receive corticosteroids as adjunctive therapy in the largest pediatric sepsis clinical trial conducted to date.

**REFERENCES**


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**Table 2. Comparison of various outcome measures among children in the RESOLVE trial who received or did not receive adjunctive corticosteroid therapy**

<table>
<thead>
<tr>
<th>Did Not Receive Adjunctive Corticosteroids (n = 284)</th>
<th>Received Adjunctive Corticosteroids (n = 193)</th>
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<tbody>
<tr>
<td>Mean ± sd or %</td>
<td>Mean ± sd or %</td>
</tr>
<tr>
<td>Mortality, %</td>
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<tr>
<td>MV, days</td>
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<tr>
<td>V-I Support, days</td>
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<td>CTOFPR, days</td>
<td>9.9 ± 4.8</td>
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<tr>
<td>8POPC score</td>
<td>1.3 ± 1.9</td>
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<tr>
<td>PICU LOS, days</td>
<td>12.1 ± 8.0</td>
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<tr>
<td>Hospital LOS, days</td>
<td>18.1 ± 8.9</td>
</tr>
</tbody>
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CI, confidence interval; MV, mechanical ventilation; V-I, vasoactive-inotropic infusion; CTOFPR, composite time to complete organ failure resolution; 8POPC, change in Pediatric Overall Performance Category score; 28 days minus baseline; PICU LOS, pediatric intensive care unit length of stay.


34. Tilby SM: Does PELD measure organ dysfunction... and is organ function a valid surrogate for death? Intensive Care Med 2010; 36:4–7


