A history of adjunctive glucocorticoid treatment for pediatric sepsis: Moving beyond steroid pulp fiction toward evidence-based medicine

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Objectives: **To review the history of clinical use of corticosteroids with particular reference to adjunctive therapy for severe pediatric sepsis and, in this context, to provide an overview of what is known, what is not known, and what research questions are particularly relevant at this time.**

Data Source: **Literature review using PubMed, cross-referenced article citations, and the Internet.**

Conclusions: **The history of corticosteroid use in clinical medicine has been colorful, noisy, and always controversial. Therapeutic corticosteroid indications that initially seemed rational have frequently been refuted on closer, rigorous clinical trial inspection. Although it may be prudent to provide stress-dose steroids to children with septic shock who are clinically at risk for adrenal insufficiency (chronic or recent steroid use, purpura fulminans, etomidate or ketoconazole administration, hypothalamic, pituitary, adrenal disease), the safety and efficacy of stress-dose steroids as general adjunctive therapy for pediatric septic shock have not been established. Glucocorticoid administration does add potential risk to critically ill children. In particular, although adjunctive corticosteroids may hasten resolution of unstable hemodynamics in septic shock, this may occur at the metabolic cost of hyperglycemia. Clinical practice that fosters innovative therapy (off-label use) over research probably represents bad medical and social policy. Accordingly, pediatric critical care researchers have a responsibility to generate pediatric-specific evidence-based medicine for adjunctive corticosteroid therapy for severe sepsis in children. (Pediatr Crit Care Med 2007; 8:530–539)**

KEY WORDS: Thomas Addison; corticosteroids; cortisol; hydrocortisone; sepsis; septic shock; children; pediatric critical care medicine; corticotropin; bacterial meningitis; history of medicine

Novels written for the mass market, intended to be "a good read,"—often exciting, titillating, thrilling. Historically they have been very popular but critically sneered at as being of subliterary quality. The earliest ones were the dime novels of the nineteenth century, printed on newsprint (hence "pulp" fiction) and sold for ten cents. Westerns, stories of adventure, even the Horatio Alger novels, all were forms of pulp fiction.—R Harris, *A Glossary of Literary Terms*, 1997

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Birth of Endocrinology

Although the adrenal glands were first described by Eustachio in 1563 (1), most discussions regarding the medical use of steroids begin with a discussion of Thomas Addison (Fig. 1), who graduated as a medical doctor from the University of Edinburgh in 1815 (2). That same year, Addison moved to London to work in the Lock Hospital. There, under the tutelage of Thomas Bateman, Addison became interested in diseases of the skin; eventually this interest would lead him to describe the alterations in skin pigmentation that are characteristic of Addison's disease. In 1817, Addison enrolled as a physician student at Guy's Hospital in London, and by 1819 he was elected to the Royal College of Physicians. During the next 2 decades, Addison had the good fortune to work with Dr. Richard Bright and Dr. Thomas Hodgkin (3), both lecturers at Guy's Hospital on the subject of practical medicine. Addison subsequently collaborated with Bright to write a textbook of medicine titled *Elements of the Practice of Medicine*, published in 1839. In 1855, Addison published a monumental endocrinology monograph titled *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules* (4). This work represented Addison's initiation into the formal study of endocrinology (5). Although Addison's work involving adrenal failure was criticized locally, a colleague in Paris, Armand Trousseau, also recognized clinical adrenal failure and provided the eponym, Addison's disease (6).

In conjunction with Dr. Richard Bright, Addison took note of people dying with damage to their suprarenal capsules (adrenal glands). He first reported his observations in a lecture delivered in 1849 titled "Anemia—disease of the supra renal capsules." In 1866, E. H. Greenhow published a case series of adrenal failure associated with death. His survey included essentially all cases collected throughout Europe. In conjunction with his Croonian Lectures delivered to the Pathologic Society, Greenhow published a book titled *Addison's Disease* in 1875, essentially a compilation of the clinical experience with Addison's disease to that date (7). Addison's early work identified the constellation of clinical signs and symptoms associated with adrenal dam-

Figure 1. Thomas Addison. Figure accessed on January 10, 2007, at http://www.iqb.es/historiamedicina/personas/addison.htm. Printed with permission.

age and promoted his recognition as the "father" of the field of endocrinology.

Early Adrenal Physiology/Biochemistry

Numerous experiments in the early 1900s demonstrated the key role of the adrenal glands in maintaining normal hemodynamics. Some cases of clinical shock were found to be associated with hemorrhage of the adrenal gland, as reported in 1934 (8). Based on these observations, some types of shock were actually attributed to so-called adrenal exhaustion (9, 10). Subsequent experiments confirmed the importance of the adrenal cortex. Investigators at the University of Buffalo (11) and Princeton (12) were the first to prepare extracts of adrenal cortex and subsequently use these preparations to relieve adrenal insufficiency symptoms in both adrenalectomized animals and patients with Addison's disease. Swingle et al. (13) reported that preparations of adrenal cortex extract were effective in treating shock in terms of restoring circulating blood volume, relieving hemoconcentration, increasing blood pressure, and restoring kidney function, including increased excretion of both potassium and ammonia and retention of both sodium and chloride. Later studies, like those of Hinshaw et al. (14–16) using similar animal models, demonstrated that corticosteroid replacement in conjunction with antibiotics resulted in improved survival in adrenalectomized dogs challenged with lethal doses of bacteria. In 1932 Harvey Cushing (17) described the multiple clinical manifestations associated with basophilic adenomas of the pituitary gland. A description of hypothalamus-pituitary-adrenal function and glucocorticoid secretion was recorded by Selye (18) in 1936, when he noted adrenal hypertrophy, gastric ulceration, and thymolymphatic dysplasia as the classic triad of the stress response.

Steroid Hormone Characterization

Also during the 1930s, numerous adrenal steroid compounds were being isolated and structures identified in the laboratories of Thadeus Reichstein, Edward Calvin Kendall, and Phillip Showalter Hench (19). These pioneer physiology chemists were awarded the Nobel Prize for Physiology in Medicine in 1950 for their combined work related to steroid hormone characterization of the adrenal cortex, which ultimately culminated in the isolation and identification of cortisone as a novel compound in 1935 (20). Initial synthesis of compound E (cortisone) was achieved in the laboratories of the Mayo Foundation and Merck and Company when a practical method was achieved to introduce a hydroxyl moiety to carbon 17 of the steroid framework (21). By 1948, sufficient quantities of cortisone were isolated in Kendall's and Sarrett's laboratories to be used in small clinical investigations. During the next 2 decades the various steroidogenic enzymes were isolated, characterized, and subsequently cloned.

Initial Steroid Clinical Trials

In September 1948, Hench et al. (22) administered the first injections of cortisone acetate to patients with rheumatoid arthritis and rheumatic fever, demonstrating clinically the anti-inflammatory/immunosuppressive properties of cortisone. In 1952, corticosteroids were shown to reduce granulocyte adherence to vascular epithelium after an inflammatory stimulus using the classic ear chamber model (23). By November 1950, cortisone was available to physicians throughout the United States through drug supply houses, and translational research permitted the first treatment of congenital adrenal hyperplasia orchestrated by both Crigler and Wilkins (24) and Bartter et al. (25) with cortisone.

Infection-Associated Adrenal Apoplexy

Probably the first link between adrenal pathology and critical care medicine occurred in 1911 with a report in *The Lancet* by Rupert Waterhouse (26), who was a pathologist and assistant physician at the Royal United Hospital in Bath, England. In this article Waterhouse described clinical purpura fulminans and its association with acute hemorrhagic necrosis of the adrenal glands (suprarenal apoplexy). During the following several years, a Copenhagen pediatrician, Carl Friderichsen (27), published his observations on nearly 30 similar clinical cases, calling the syndrome *nebennier-enapoplexie bei kleinen Kindern* (adrenal apoplexy in small children). In 1934, Bamatter (28) coined the term *Waterhouse-Friderichsen syndrome* in honor of the first two describers. Writing again in 1955, Friderichsen (29) reported on an additional 250 cases. He noted the association with meningotoxemia. He also indicated that before 1938, all detailed cases had been fatal, but with the advent of sulfonamides and penicillin, case reports of survival were now beginning to appear in the literature (29).

Cortisone Treatment of Clinical Shock

During the early 1950s, with frequent clinical and necropsy evidence for adrenal insufficiency associated with meningococcemia, children with evidence of circulatory collapse in shock were being routinely treated with cortisone. Based primarily on results of impressive animal experiments (described previously), corticosteroids were routinely used for adjunctive treatment of sepsis in the 1950s and 1960s (30). The first clinical evidence suggesting the use of therapeutic corticosteroids for severe generalized infections was published by Hahn et al. (31) in 1951. A summary of a trial that enrolled 82 pediatric and adult subjects with severe infection was published by Jahn et al. (32) in 1954. More than half of the subjects were children, infected primarily with *Haemophilus influenzae* and *Neisseria meningitidis*. Overall mortality was ~33%, but the investigators noted, "There is no question that the administration of ACTH or cortisone in sufficient amounts to patients with severe infections will result in rapid and striking clinical improvement." Multiple small clinical investigations examining corticosteroids in this clinical setting were conducted between 1950 and 1971, but good clinical trial design was absent (33). More than a decade passed before the first prospective, randomized, placebo-con-

trolled trial of hydrocortisone in sepsis was conducted, by Bennett et al (34).

Steroids for Sepsis—Burgeoning Strict Critical Care Clinical Research Design

Primarily base on the study by Schumer (35), high-dose glucocorticoids became accepted therapy for septic shock in the late 1970s and early 1980s, although an earlier study that enrolled both children and adults demonstrated no benefits of hydrocortisone in patients with severe sepsis (36). This era might be described as the industrial dosing revolution of corticosteroids as adjunctive treatment of severe sepsis. Dose of glucocorticoid, typically methylprednisolone, was high, generally 30 mg/kg, and duration of dosing short, typically ≤1 day. During this time, rigorous clinical trial design emerged in critical care medicine. Results of three such trials, all published in the *New England Journal of Medicine*, ascertained that high-dose, short-duration methylprednisolone did not decrease sepsis mortality and might be associated with serious adverse side effects, such as gastrointestinal hemorrhage (37–39). Reviews of the clinical trials using high-dose corticosteroids, administered as a single dose during the initial hours of septic shock, concluded that this approach likely conferred no beneficial effect on mortality (40–42). An additional important conclusion of the meta-analyses of these early steroid sepsis trials was the need for methodologically rigorous experimental design in future studies (40–42).

Steroids as Adjunctive Treatment for Bacterial Meningitis

Enthusiasm for the use of adjunctive steroids for sepsis was heightened during the late 1980s when reports began to appear extolling the benefits of dexamethasone therapy for bacterial meningitis. An initial report summarizing two clinical investigations that enrolled a total of 200 infants by Lebel et al. (43) indicated that children with meningitis who received dexamethasone became afebrile earlier and in addition were less likely to acquire moderate or severe neurosensory hearing loss. These clinical effects were correlated with faster normalization of cerebral spinal fluid glucose and faster decrease in cerebral spinal fluid lactate and protein levels. A subsequent study by Odio et al. (44) that enrolled 101 infants with culture-proven bacterial meningitis confirmed the beneficial effect of dexamethasone in this setting. Twelve hours following enrollment, those children treated with dexamethasone demonstrated decreased cerebral spinal fluid tumor necrosis factor and platelet-activating factor, whereas those children receiving placebo actually demonstrated increases in cerebral spinal fluid inflammatory markers. Again, reduction in neurosensory hearing loss, as assessed at 15 months following enrollment, was apparent in the dexamethasone-treated children. In their discussion, the authors emphasized the importance of administering the dexamethasone before initiation of antibiotics. Other clinical trials subsequently reported a beneficial effect of dexamethasone in both adult and pediatric meningitis (45–47). Beneficial affects were confirmed for not only the most common bacterial pathogen, namely *H. influenzae*, but also for *Streptococcus pneumoniae* and *N. meningitidis*. A subsequent meta-analysis of 11 studies examining dexamethasone therapy for childhood bacterial meningitis from 1988 to 1996 concluded that adjunctive dexamethasone therapy was clearly beneficial in terms of reducing sensory neural hearing loss secondary to *H. influenzae* B meningitis, and if dexamethasone was initiated with or before antibiotic therapies, a suggested benefit for pneumococcal meningitis was also apparent (48). Dexamethasone treatment led to more rapid resolution of initial fever but was associated with a greater incidence of secondary fevers as well as gastrointestinal bleeding. Similarly, a Cochrane review that included 18 studies enrolling 1,853 subjects concluded that overall adjunctive corticosteroids were associated with a lower case fatality rate as well as lower incidence of sensory neural hearing loss and long-term neurologic sequelae (49). In this review, adverse events were not noted to be significantly increased with the use of corticosteroids. The 27th Edition of the Red Book (2006 Report of the Committee of Infectious Diseases, American Academy of Pediatrics) (50) states that dexamethasone may be beneficial for infants and children with *H. influenzae* meningitis in terms of reducing the risk of neurologic sequelae, specifically neurologic hearing loss, if given before or concurrent with the first dose of antibiotics. The Committee noted that there is likely no benefit if dexamethasone is given >1 hr following the antibiotic. Regarding pneumococcal meningitis, there was no consensus for the use of adjunctive corticosteroids. Here the committee explained that insufficient data are available demonstrating a clear benefit in children. If used, corticosteroids should be administered before or concurrent with the first dose of antibiotic. No recommendations were provided for cases of meningococcal meningitis.

Invocation of Relativity in the Adrenal Response to Stress: Pediatric Data

Sepsis and associated systemic inflammatory response represent a common cause of acute so-called relative adrenal insufficiency and dysfunctional adrenal reserve in adults (51–60) as well as children (61–65). In adults with severe sepsis, Annane et al. (58) reported that nonsurvivors demonstrated higher basal plasma cortisol concentrations compared with survivors and also exhibited diminished cortisol response to corticotropin. A study of Brazilian children with severe sepsis by Pizarro et al. (65) seemed to indicate similar findings, with the highest mortality (53%) noted in a group of 15 children with random total baseline cortisol >20 μg/dL but incremental increase in cortisol following corticotropin <9 μg/.

However, for pediatric patients with meningococcemia (n = 96), significantly lower cortisol levels were identified by Riordan et al. (61) in those patients who died (median 38.5, range 16–74) compared with those who survived (median 45.3, range 16–186 μg/dL, $p < .05$), although absolute adrenal failure (serum cortisol <5 μg/dL) was not noted. Two of three children with levels <18 μg/dL and hypotension died. No association of cortisol levels with meningococcal severity scores or shock status could be ascertained, but lower cortisol levels and higher adrenocorticotropic hormone levels were characteristic of those who died. In a similar smaller study of children with meningococcemia (n = 33) conducted by Hatherill et al. (62), no statistical relationship could be claimed regarding cortisol levels and outcome, although survivors demonstrated numerically higher basal and corticotropin-stimulated minus basal (Δ) cortisol levels compared with nonsurvivors. Children exhibiting a Δ cortisol <7.2 μg/dL had significantly higher Pediatric Risk of Mortality scores and required more vasoactive-inotropic support compared with

children who had a more robust Δ cortisol response. In another study of pediatric meningococcal disease, by van Woensel et al. (66), relatively lower levels of cortisol and higher levels of adrenocorticotropic hormone were associated with a more severe disease course. Accordingly, serum cortisol levels of 45.7 ± 5.1, 36.9 ± 1.5, and 22.5 ± 3.0 μg/dL were recorded for children with meningococcal meningitis, meningococcal sepsis, and fulminant meningococcal sepsis, respectively. In this study, levels of interleukin (IL)-6, IL-8, and IL-10 also correlated with disease severity. Yet another study of severe pediatric meningococcal disease (n = 62) by de Kleijn et al. (67) confirmed that low serum cortisol and high adrenocorticotropic hormone levels were associated with poor outcome as median serum cortisol levels of 41.7 (range 26.5–77.4), 35.9 (range 10.6–89.3), and 23.5 (range 11.5–37.8) μg/dL were recorded for children with sepsis survival, septic shock survival, and septic shock nonsurvival, respectively. More recently, an investigation by Öneb-li-Mungan et al. (68) examining generic pediatric sepsis (n = 102) also found a relationship between lower serum cortisol levels and more severe disease. In this study, serum cortisol levels of 29.4 ± 1.5 (range 7–46), 30.8 ± 0.8 (range 20–45), and 10.4 ± 1.5 (range 2–19) μg/dL were characteristic of nonseptic control children, children with sepsis (mortality 26%), and children with septic shock (mortality 71%), respectively. Serum cortisol levels in survivors and nonsurvivors were 33.9 ± 0.9 and 19.7 ± 1.8 μg/dL, respectively ($p < .01$). Most recently, Sarthi et al. (69) assessed 30 children with septic shock for adequacy of adrenal function using low-dose (1 μg) corticotropin stimulation. Thirty percent demonstrated cosyntropin-stimulated minus basal cortisol (Δ) concentrations <9 μg/dL. These children with inadequate adrenal reserve exhibited a higher incidence of catecholamine refractory shock but no difference in mortality compared with children with adequate adrenal reserve based on this low-dose corticotropin stimulation test.

Semantics Turn Out to Be Very Important

Comparisons of studies correlating adrenal status with outcome are hampered by lack of consensus regarding what constitutes a sufficient vs. insufficient adrenal response to intense stress, such as severe sepsis (55, 60, 70). Moreover, Hamrahian et al. (71) pointed out that quantification of total vs. free cortisol will generate different answers particularly in patients with hypoalbuminemia. Recently, Annane et al. (72) used the gold standard overnight metyrapone stimulation test to assess the diagnostic value of the standard (high-dose) corticotropin stimulation test in relation to defining the prevalence of sepsis-associated relative adrenal insufficiency. Baseline serum cortisol ≤10 μg/dL, corticotropin-stimulated minus basal (Δ) cortisol <9 μg/dL, and (derived) free cortisol <2 μg/dL were found to be associated with positive likelihood ratios of ∞, 8.46, and 9.50, respectively. As defined by metyrapone testing, the best predictors of adrenal insufficiency were baseline cortisol <10 μg/dL or Δ cortisol <9 μg/dL, whereas the best predictors of normal adrenal response were baseline cortisol ≥44 μg/dL or Δ cortisol ≥16.8 μg/dL.

Even in the presence of elevated plasma cortisol concentration, relative local cortisol insufficiency may occur at sites of inflammation (corticosteroid resistance syndrome) secondary to 1) depletion of corticosteroid-binding globulin; 2) activation of 11-β-hydroxysteroid dehydrogenase (type 2); 3) depression of glucocorticoid receptors; 4) diminution of receptor affinity for cortisol; and 5) elevation of antiglucocorticoid compounds or receptors (73).

Stress-Dose Cortisol Replacement for Severe Sepsis

In an effort to therapeutically address the concept of relative adrenal insufficiency and/or inadequate adrenal reserve, more recent interventional investigations have examined provision of low or so-called stress-dosing of cortisol as adjunctive therapy for septic shock and severe sepsis, with the knowledge that cortisol can restore the vascular responsiveness to catecholamines in adults with septic (74) and hemorrhagic shock (75). An overview summary of seven such studies generally confirms the benefit of stress-dose cortisol in hastening hemodynamic stability in the setting of adult septic shock (76–82).

In a double-blind, crossover investigation involving 40 adults with septic shock conducted by Keh and Sprung (79), hydrocortisone treatment was associated with an increase in mean arterial pressure and systemic vascular resistance and a decrease in heart rate, cardiac index, and norepinephrine requirement. Shock reversal in the cortisol-treated group was faster than in the placebo group. Cortisol treatment (but not placebo) was associated with a reduction of plasma nitrite/nitrate (following 3 days of cortisol treatment, serum nitrite/nitrate concentrations decreased by ~32%, $p = .009$), which was correlated with a reduction in need for vasopressor support. Biomarkers of proinflammation (IL-6, IL-8), endothelial activation (soluble E-selectin), neutrophil activation (CD11b, CD64 expression), and anti-inflammation (soluble tumor necrosis factor receptors, IL-10) were all attenuated during cortisol administration. However, blood monocyte human leukocyte antigen-DR expression was only minimally depressed (no immune paralysis). Measures of *in vitro* phagocytosis and IL-12 were increased. Rebound hemodynamic and immunologic effects were appreciated with withdrawal of hydrocortisone on day 3, prompting the investigators to suggest weaning of steroid dosing for patients with severe sepsis, as opposed to abrupt withdrawal. In this important clinical biological plausibility study of stress cortisol for septic shock, baseline serum total cortisol levels ranged from 30 to 40 μg/dL and increased approximately five-fold above this baseline during cortisol administration.

With reference to children, endogenous cortisol secretion increases approximately four-fold in the setting of meningococcal disease (66–68, 83). Accordingly, to mimic the body's stress response, a dose of hydrocortisone equivalent to four times the normal cortisol secretion has been recommended (61, 84).

A landmark trial of adjunctive low-dose hydrocortisone plus fludrocortisone for adults (n = 299) with septic shock was conducted in France by Annane (85) and rekindled interest in endocrinology and metabolism within the field of critical care medicine. This investigation demonstrated faster resolution of septic shock and organ dysfunction in general for subjects receiving replacement steroids. Moreover, a significant decrease in mortality (~20%, relative) was reported for subjects demonstrating a Δ cortisol <9 μg/dL at enrollment. Unfortunately, this trial was tainted with subsequent knowledge that a significant number of subjects had been intubated with etomidate (70), which is known to inhibit 11-β-hydroxylase, a rate-limiting enzyme in the synthesis of cortisol (86, 87). With

this discussion came recommendations to discontinue the use of etomidate in the intensive care unit (88) or alternatively provide hydrocortisone replacement if etomidate is used (89).

With this suggestion that stress-dose cortisol might be beneficial for adults with septic shock (85), a larger international trial, CORTICUS, was designed (90). As with the previous investigation, the primary outcome measure was all-cause 28-day mortality in subjects who exhibited a corticotropin stimulated minus baseline serum cortisol increment of <9 μg/dL. This investigation was slated to enroll 800 adults with sepsis from 2002 to 2005 at 52 European performance sites, but the trial was halted for futility following enrollment of 500 subjects (91). Cortisol (no fludrocortisone in this study) or placebo was prescribed at 50 mg intravenously every 6 hrs for 5 days followed by a rapid wean. Although hastened resolution of shock occurred in the group receiving corticosteroids (3.1 vs. 5.7 days), no benefit in terms of reduced mortality was noted either for the total cohort or for subjects with Δ cortisol <9 μg/dL (~50% of the total population). Nosocomial infection, new sepsis, new septic shock, and measures of hyperglycemia were significantly more prevalent in the hydrocortisone-treated group. Principal investigator for the CORTICUS trial, Charles Sprung, surmised that routine adjunctive hydrocortisone for adult septic shock cannot be recommended and that corticotropin adrenal stimulation testing cannot be recommended to guide hydrocortisone therapy. Adjunctive hydrocortisone may have a role for adult septic shock that persists for >1 hr despite aggressive fluid and vasoactive-inotropic resuscitation.

A meta-analysis of 505 septic adults included in steroid replacement trials before the CORTICUS investigation similarly reported that low-dose corticosteroids can reduce vasoactive-inotropic infusion requirements and hasten the reversal of shock (92). Other meta-analyses, examining several trials of adjunctive glucocorticoid therapy for adults with sepsis, all conducted before the CORTICUS investigation, concluded that 1) short-course, high-dose glucocorticoid therapy decreases survival and hence is not recommended for severe sepsis; 2) a 5- to 7-day course of low-dose cortisol with rapid weaning improves survival and hastens shock reversal for adults with vasoactive-inotropic infusion dependent septic shock; and 3) in the absence of vasoactive-inotropic infusion requirement, corticosteroids should not be used to treat sepsis (79, 92–96) (Fig. 2). If patients from the CORTICUS trial are included in one such meta-analysis (94), there is no benefit of adjunctive steroids in reducing septic shock mortality (G Benard, Sepsis Controversies, Society of Critical Care Medicine 2007 Annual Scientific Symposium).

Insufficient Pediatric Data

Clinical trials examining adjunctive corticosteroid therapy for pediatric sepsis are meager. A randomized, double-blind trial of adjunctive cortisol for dengue shock syndrome (n = 98 total, 48 of whom received cortisol) by Min et al. (97) reported a case fatality rate of 19% in the steroid group and 44% in the placebo group (illness severity, age, and gender matched). Later, a prospective observational trial of nine children with dengue shock treated with high-dose methylprednisolone (nine of nine) and mannitol (six of nine) conducted by Futrakul et al. (98) reported improved hemodynamics in seven patients. However, a subsequent study by Sumarmo et al. (99) yielded opposite conclusions. Mortality, duration of shock, and volume of fluid resuscitation were virtually identical in the two illness severity-, age-, and gender-matched groups of children with dengue shock (n = 97 total), treated with cortisol (n = 47, 50 mg/kg once) or placebo (n = 50). Similarly, Tassniyom et al. (100) conducted a randomized, controlled trial of a single dose of methylprednisolone (30 mg/kg) vs. placebo among 63 children with dengue shock. Baseline characteristics between the two groups were very similar. Mortality was 12.5% in the methylprednisolone group and 12.9% in the placebo group. In addition, no differences in organ dysfunction between groups could be ascertained. From a study of African children with sepsis, Slusher et al. (101) concluded that moderate-dose dexamethasone (0.05 mg/kg every 8 hrs for 2 days, with the initial dose delivered before antibiotics) did not improve sur-

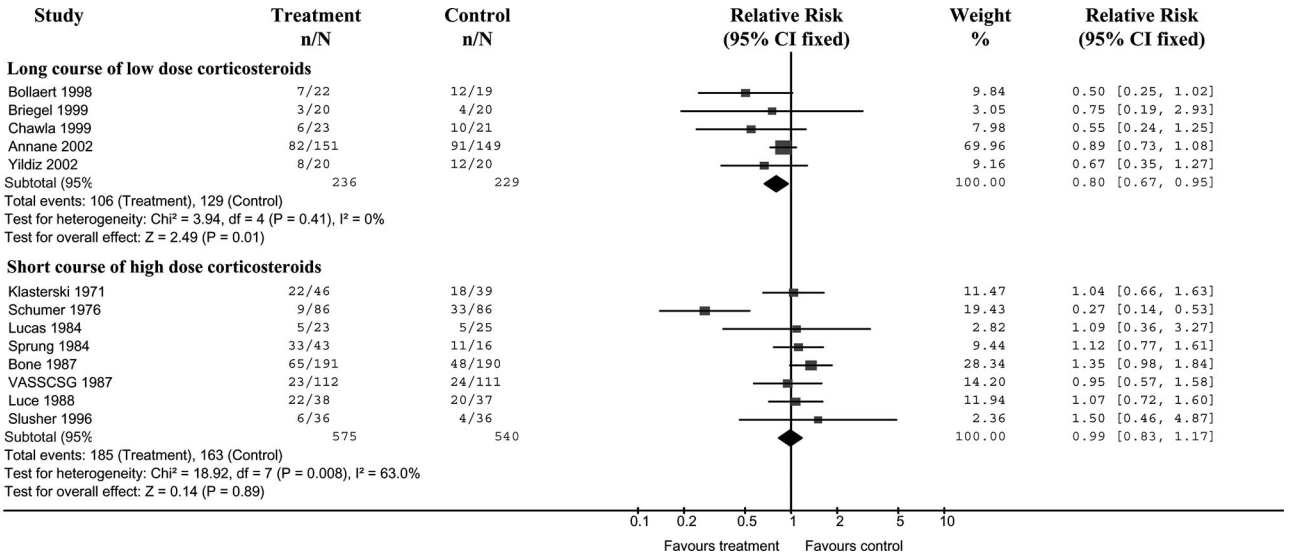

Figure 2. Relative risk of all-cause 28-day mortality in septic shock patients treated with low-dose or high-dose corticosteroids. Marker size is proportional to the percentage weight of the study. *Horizontal lines*, 95% confidence interval (*CI*); *diamonds*, pooled analysis; *horizontal diamond width*, 95% CI. Adapted with permission from Keh and Sprung (79).

Table 1. Steroid use and mortality for pediatric severe sepsis

Received Concurrent Steroids?	Mortality		Crude OR (95% CI)	Total
	Died (%)	Lived (%)		
Neonates				
Yes	427 (29)	1,050 (71)	2.29 (1.94, 2.71)	1,477
No	289 (15)	1,627 (85)		1,916
Totals	716 (21)	2,677 (79)		3,393
Nonneonates				
Yes	521 (30)	1,209 (70)	1.60 (1.37, 1.88)	1,730
No	333 (21)	1,237 (79)		1,570
Totals	854 (26)	2,446 (74)		3,300

OR, odds ratio; CI, confidence interval.

vival to discharge, time to hemodynamic stability, hospital length of stay, or duration of fever.

One retrospective cohort study by Markovitz et al. (102) using the Pediatric Health Information System database examined factors associated with outcome in children with severe sepsis as operationally defined by a combination of infection plus need for a vasoactive-inotropic infusion and mechanical ventilation. Among the 6,693 children meeting this definition of severe sepsis, 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) (Table 1). Similarly, children who received steroids required longer duration of vasoactive-inotropic infusion and mechanical ventilation support and required a significantly longer pediatric intensive care unit length of stay and hospital length of stay. A crucial liability of this investigation related to lack of illness severity data. However, an important conclusion from this epidemiologic study using the Pediatric Health Information System administrative database was that no evidence exists indicating that steroids are associated with improved outcome in critically ill children with sepsis. Although steroids may have been given preferentially to more severely ill children, their use was associated with increased mortality. The authors emphasized that clinicians should maintain equipoise on the question of adjunctive steroid therapy for pediatric sepsis pending prospective randomized clinical trials. Preliminary single-institution data suggest that even controlling for illness severity, adjunctive corticosteroids administered to children with sepsis syndrome do not improve outcomes (mortality, mechanical ventilator days, vasoactive-inotropic infusion days) or reduce resource utilization (pediatric intensive care unit days, hospital days, hospital costs) (103).

Other adult investigations have concluded that results of corticotropin stimulation testing does not predict hemodynamic improvement with adjunctive corticosteroids for patients with vasoactive-inotropic-dependent septic shock (104); that administration of adjunctive corticosteroids to critically ill patients based on arbitrary baseline or incremental serum cortisol concentrations does not improve survival (105); and that corticosteroid use in the intensive care unit is associated with increased rate of infection, increased days of mechanical ventilation, increased intensive care unit length of stay, and a trend toward increased mortality (106).

Evidence-Based Medicine Means Doing the Experiment

Although it seems prudent to provide stress-dose steroids to children with septic shock clinically at risk for stress adrenal insufficiency (chronic steroid use, recent steroid use, purpura fulminans, etomidate or ketoconazole administration, hypothalamic, pituitary, adrenal disease) as suggested by the Task Force for Hemodynamic Support of Pediatric and Neonatal Sepsis, American College of Critical Care Medicine (65), safety and efficacy of stress-dose steroids as general adjunctive therapy for pediatric septic shock have not been established. Provision of stress-dose cortisol may be beneficial or even life-saving in children with an insufficient adrenal response to severe stress, such as sepsis. However, pediatric evidence-based data for this indication currently do not exist.

Glucocorticoid administration does add potential risk to critically ill children, including antianabolic effects, attenuated immunity, depressed wound healing, calcium mobilization, impaired insulin action and associated hyperglycemia, and perhaps alterations in brain development (107). Although adjunctive corticosteroids for severe sepsis may hasten resolution of unstable hemodynamics (76–82), this may occur at the metabolic risk of hyperglycemia (Fig. 3). Augmentation of gluconeogenesis and anti-insulin effects of cortisol are of particular concern, given adult data indicating the significant risk of nosocomial sepsis, multiple organ dysfunction syndrome, and death associated with hyperglycemia (108, 109). Risk of hyperglycemia and associated increased mortality secondary to the gluconeogenic effects of cortisol deserve close scrutiny in children as well (110–112).

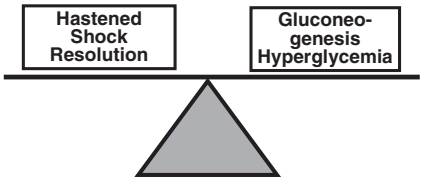

Figure 3. Adjunctive corticosteroids for severe sepsis: a question of balance.

Steroid treatment for disease states can be associated with worse outcomes: Early, prolonged dexamethasone prescribed to decrease the incidence and severity of bronchopulmonary dysplasia may increase the incidence of cerebral palsy (113). Methylprednisolone prescribed in the setting of traumatic brain injury actually increased mortality and morbidity (114). Methylprednisolone prescribed to reduce the incidence and severity of acute respiratory distress syndrome fibroproliferative disease was associated with significantly increased 60- and 180-day mortality for patients who were enrolled ≥14 days after the onset of acute respiratory distress syndrome (115). Although methylprednisolone increased the number of ventilator-free and vasopressor-free days during the first 28 days following enrollment, it was also associated with a higher rate of neuromuscular weakness.

Existing clinical guidelines for hemodynamic support of pediatric and neonatal patients in septic shock are clear to point out, "Studies are required to determine whether American College of Critical Care Medicine guidelines for hemodynamic support of pediatric and neonatal septic shock will be implemented and associated with improved outcome" (65). Although it is highly desirable to develop

evidence-based guidelines for use of adjunctive corticosteroids for pediatric severe sepsis, three significant barriers impair design and implementation of clinical trials to support or refute this notion.

The first barrier includes existing, widely variable, but emphatic practices regarding use of adjunctive corticosteroids for severe sepsis in children. Surveys conducted in the United Kingdom (116), Canada (117), and the United States (118) have confirmed that significant controversy and no consensus exist regarding the method for assessing adequacy of the adrenal stress response and regarding treatment of apparent adrenal insufficiency (indication, drug, dose, duration).

The second barrier is lack of an appropriate, consensus-determined, clinically meaningful primary outcome measure for pediatric sepsis interventional trials. Because of a significantly lower mortality in children with severe sepsis (approximately 15% to 20%), conduct of a sepsis interventional trial with reduction of mortality as the primary end point is unrealistic, as thousands of patients would be required for both arms of an investigation for an expected 20% relative treatment effect (119). At first, consideration of hastened resolution of septic shock might seem an appropriate surrogate clinical outcome measure for corticosteroid interventional trials. Many pediatric intensivists reflexively initiate stress-dose cortisol in the setting of volume and vasoactive-inotropic infusion recalcitrant septic shock (116). Compromised endothelial integrity, systemic vasoplegia, impaired cardiac contractility, and mitochondrial/cytopathic dysoxia all contribute to hemodynamic instability in sepsis, and stress-dose cortisol would logically be expected to modulate multiple biochemical pathways associated with each of these processes (70). Adult patients with sepsis demonstrate a clearly different dose-response curve to norepinephrine compared with control patients without sepsis, and a significant improvement in the dose-response relationship among adults with sepsis is seen following administration of hydrocortisone (74). Such fundamental observations have been ascertained by personal testimony but not data for critically ill children.

Hastened resolution of septic shock has repeatedly been shown to be associated with improved outcomes (65, 76–81, 120–122). However, hastened resolution of septic shock may not be an appropriate outcome measure for clinical trials of sepsis, as faster resolution of shock does not necessarily correlate with reduced mortality (102, 123, 124).

The third barrier is substantial lack of clinical equipoise regarding the benefit and safety of adjunctive corticosteroid for pediatric severe sepsis. Several relevant comments are appropriate at this juncture: Usual care, not linked to strong evidence is ephemeral and very subject to secular change. Drugs migrate into pediatric use from adult experience, often with meager evidence of safety and efficacy. However, in the absence of a well-defined clinical practice (wide variation that is largely unexplained), it is reasonable to randomize (in a clinical trial) two well-founded yet competing beneficial treatment strategies (with or without corticosteroid) that lie within the boundaries of competent or good care.

What Next Along the Yellow Brick Road?

Several aspects of the current use of stress-dose corticosteroids for pediatric severe sepsis are unsatisfactory: Safety and efficacy are unproven; wide practice variability exists; risks of adverse events in children, such as hyperglycemia, myopathy/neuropathy, and nosocomial infections, are unknown; and there is potential for increased risk of mortality.

Anecdotes is not the plural of evidence. Off-label use of corticosteroids could be argued to represent bad clinical practice: Dosing regimens are typically extrapolated and variable among practitioners, every patient is an experiment (without institutional review board review or endorsement) with n = 1 and power = 0, and no data accrual occurs regarding safety and efficacy. Innovative therapy has the potential to evolve into standard care with risk for therapeutic misconception based on limited knowledge or misconstrued information. Unfortunately, uncontrolled use of stress-dose corticosteroids has crept into the pediatric intensive care unit and now frequently represents standard or conventional care. This standard is unproven, embedded, variable, ephemeral, and subject to secular change. It has been noted that rules that foster innovative therapy (off-label use) over research represent bad social policy (Fost N: Emergency Research in Children. Ethical, Regulatory and Clinical Challenges in Children. Best Pharmaceuticals for Children Act. Bethesda, MD, 2006).

History reveals a long and colorful tale of the use of steroids in clinical medicine authored by bedside physicians and Nobel laureates alike. The road to Oz, as the metaphor for evidence-based medicine regarding use of adjunctive steroids for pediatric sepsis, may be arduous, even treacherous, but it is time for pediatric intensivists to attend to the significant task of generating pediatric evidence-based medicine in this area: 1) Establish by data and then consensus what constitutes an inadequate adrenal response to severe stress and how this is best quantified; and 2) identify the true benefit/risk ratio associated with corticosteroid administration in critically ill children, by assessing both short- and long-term morbidities. International multicenter pediatric critical care research networks (e.g., Australia and New Zealand Intensive Care Society Study Group, Canadian Critical Care Trials Group, Collaborative Pediatric Critical Care Research Network [CPCCRN], European Society of Pediatric and Neonatal Intensive Care [ESPNIC], Indian Pediatric Intensive Care Group, International Group on Mechanical Ventilation, Pediatric Acute Lung Injury and Sepsis Investigators [PALISI], UK Pediatric Intensive Care Society Study Group, WFPICCS [World Federation of Pediatric Intensive and Critical Care Societies] (Sepsis Initiative) are now a reality. We can do this.

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