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Corticosteroids in Pediatric Septic Shock Are Not Helpful

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“It is said: medicine is the art of healing. Rather, one should say that medicine is the science of healing. The aim of medicine is to arrive at a cure scientifically and not empirically”.

Bernard C. *Pensées: Notes Detachées*”. Bailliere et Fils, 1937.

In the absence of an evidence basis for practice, physicians tell themselves stories. Anecdotes as rationale for behavior are often powerful, but they are not evidence, frequently reflecting no more than recall bias of the natural history of disease. Such therapeutic illusion discourages intellectual honesty and facilitates continued use of inappropriate tests and treatments that may not only increase costs, but also decrease quality of care (1). Such is the current status of adjunctive corticosteroid administration for treatment of pediatric septic shock, initially innovative therapy that has drifted into standard care with therapeutic illusion substituting for lack of quality evidence for this indication.

Multiple adult and a few pediatric investigations ascertain that adjunctive corticosteroids hasten resolution of hemodynamic instability in septic shock (2, 3). Elegant pharmacologic investigations serially examining the dose-response relationship between mean arterial pressure and norepinephrine infusions among adults and children with septic shock, before and after hydrocortisone infusion, provides mechanistic biological plausibility for this clinical observation (4, 5). However, clinicians who prescribe adjunctive corticosteroids because they recall a more rapid reduction in need for vasoactive-inotropic support in children with septic shock, should be aware that this is an unreliable surrogate outcome, because it is not associated improved patient-centered, clinically meaningful outcomes such as survival (6). Two contemporary high-quality interventional trials examining adjunctive corticosteroid therapy for adult septic shock conflict in regards to possible benefit of this intervention in reducing sepsis mortality. The first trial, conducted 1995-1999 within a research network of 19 performance sites in France, enrolled 299 subjects who had undergone corticotropin stimulating testing (7). Among the *a priori* defined corticotropin non-responder group (76.6% of all subjects) mortality was 53% in the hydrocortisone-treated group and 63% in the placebo-treated group (hazard ratio, 0.67% [CI 0.47, 0.95], $p=$

0.02). Debate continues regarding the role of concurrent fludrocortisone administration in the hydrocortisone-treated group, and the possible confounding role of etomidate, an inhibitor of 11 β hydroxylase that catalyzes the rate-limiting step in cortisol synthesis, that was administered to 24% of subjects. Subsequently the Corticosteroid Therapy of Septic Shock (CORTICUS) trial enrolled 499 subjects, 2002-2005, at 52 European intensive care units (8). CORTICUS investigators concluded that 28 day all cause mortality did not differ between the hydrocortisone-treated group (34.3%) and the placebo-treated group (31.5%) ($p = 0.51$). Lack of benefit was postulated to relate to an increased incidence of superinfection and new septic episodes in the hydrocortisone-treated group. No differences in mortality were seen between corticotropin testing subgroups at any time point, prompting the authors to conclude that corticotropin stimulation testing does not reliably identify which patients will benefit from adjunctive hydrocortisone therapy. Multiple descriptive investigations involving tens of thousands of patients ascertain no mortality benefit of adjunctive corticosteroids for adult septic shock.

Quality evidence justifying administration of adjunctive corticosteroid for pediatric septic shock does not exist. Although a few randomized control trials examining adjunctive corticosteroids for pediatric septic shock have been published, these studies enrolled small numbers of subjects, reported inconsistent conclusions, and demonstrated significant methodological flaws. On the other hand, least seven high quality descriptive cohort investigations have reported either harm or no benefit with this intervention for this indication (9-15). For example, follow-up analysis of the investigation data base for RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective) trial permitted an examination of the role of adjunctive corticosteroids on outcomes in pediatric septic shock (10). In this interventional trial designed to examine the potential benefit of adjunctive activated protein C (Xigris) in pediatric sepsis, RESOLVE enrolled 477 children, 193 who received adjunctive corticosteroids (mostly classified as therapeutic intervention for septic shock) and 284 who did not. At enrollment all patients were receiving mechanical ventilation and vasoactive-inotropic support. Age, gender, Pediatric Risk of Mortality (PRISM III) scores, baseline number of dysfunctional organs and baseline Pediatric Overall Performance Category (POPC) scores did not differ between corticosteroid-treated and corticosteroid not-treated groups. Similarly the investigators reported that outcomes including mortality and duration of mechanical ventilation, vasoactive-inotropic support and PICU stay did not differ between the two study groups.

It is perhaps understandable that some pediatric intensivists maintain a paranoid vigilance for Waterhouse- Fredericksen syndrome (that involves purpura fulminans, adrenal hemorrhage, and Addisonian crisis) for any child presenting with shock. In reality, this clinical triad is a very rare event in contemporary pediatric septic shock. Immunizations for common childhood bacterial pathogens including *Neisseria meningitides*, *Hemophilus influenza*, and *Streptococcus pneumoniae* are now widely available. Accordingly the landscape of infection disease in the PICU has completely changed since the introduction of this key public health measure. Moreover, universal screening for 21-hydroxylase deficiency, responsible for 95% of cases of congenital adrenal insufficiency, is now commonplace, at least in developed countries. Documentation of adrenal insufficiency for these children should be identifiable in the medical record as ICD-9-CM 255.41 and ICD-10-CM E27.40.

For some children presenting with or at risk for unstable hemodynamics, there is no disagreement that prescription of stress dose hydrocortisone is indicated (16). Such patients include children with: acute or chronic corticosteroid dosing, hypothalamic-pituitary-adrenal axis disorders, congenital adrenal hyperplasia, multiple endocrinopathies, and treatment with ketoconazole or etomidate.

Often physicians rationalize that it is best to err on the side of treatment, but may unintentionally underestimate the adverse effects of treatment (17). Believing that corticosteroids for sepsis “can’t hurt” discounts the real risk/benefit ratio for this drug class. A single dose of corticosteroids alters mRNA expression for 20-30% of the human genome (18). Corticosteroid side effects such as hyperglycemia, impaired wound healing, diffuse neuromuscular weakness (including the diaphragm), and hospital acquired infection may be particularly relevant for the critically ill child. Exogenous corticosteroids may amplify aspects of the sepsis-induced stress response, increasing the risk of transition to a metabolic distress syndrome associated with host collateral damage manifested as multiple organ dysfunction syndrome (MODS) (19). Corticosteroid activation of atrogenes represents a key antecedent for stress-associated protein catabolism to mobilize amino acids for synthesis of acute phase reactants, expand immune system elements, and augment energy substrate availability (20). However, if protein catabolism is excessive or prolonged, it may manifest as poor wound healing and muscular weakness that may impair mechanical ventilation weaning and early mobilization. Corticosteroid-induced gluconeogenesis and peripheral insulin resistance may result in hyperglycemia, which in turn has been associated with excess mortality and MODS among critically ill children (21). All aspects of adaptive immunity are down regulated in children with sepsis, and corticosteroid administration augments this repression (11, 22). T lymphocyte receptor signaling, T and B lymphocyte functioning, antigen presentation and peroxisome proliferator facilitated receptor- α activation are all adversely affected. For septic children who are already in a state of immune suppression, it makes little sense to administer potent anti-inflammatory agents like corticosteroids, when immune activation may actually be the more appropriate intervention (23). Not surprisingly corticosteroid administration to critically ill children is an important risk-factor for hospital- acquired infection (24).

Multiple examples of practitioners trying to do the right thing, based on biological plausibility, but with absence clinical evidence for effectiveness, have been chronicled: bicarbonate and calcium administration during cardiopulmonary resuscitation, hyperoxia for depressed neonates and critically ill patients in general, activated protein c for severe sepsis, and therapeutic hypothermia for pediatric traumatic brain injury and anoxic-ischemic-reperfusion events were all assumed to be valuable “last ditch” interventions, until they were eventually systematically evaluated, with quality data actually demonstrating harm. Although corticosteroids may aid in winning the battle of unstable sepsis hemodynamics, use of this drug class ultimately may contribute to losing the sepsis war in terms of mortality and long-term morbidity.

For nearly a century pediatricians have debated, frequently with religious fervor, the potential benefits and risks of adjunctive corticosteroids prescribed for pediatric septic shock. With intellectual honesty one must conclude that the cumulative published literature

does not endorse this intervention. If physicians first follow the dictum of “primum non nocere”, children with (severe) sepsis not in shock or children with septic shock stabilized with fluid and vasoactive-inotropic support should not receive empiric corticosteroid therapy. Assuming that the rational pediatric intensivist practices within the frame work of science, it should be pointed out that science requires testing of its ideas to ascertain if predictions and even prejudices are borne out by experiment. Testing of theories is what distinguishes (medical) science from other creative fields (25). As adjunctive corticosteroids may produce either benefit or harm for the child with septic shock, there exists scientific, ethical and health economic imperative to conduct a high quality interventional trial to generate evidence to support or refute this common sepsis therapy. Prescription of corticosteroids for children with septic shock should only occur within a research protocol designed to quantify both the risks as well as benefits of this practice.

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