HHS Public Access

Author manuscript

Pediatr Crit Care Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Pediatr Crit Care Med. 2015 October ; 16(8): 793–795. doi:10.1097/PCC.0000000000000532.

It's About Time . . .

Jerry J. Zimmerman, MD, PhD, FCCM

Faculty, Pediatric Critical Care Medicine, Seattle Children's Hospital, University of Washington, School of Medicine, Room FA.2.300B-3, 4800 Sand Point Way NE, Seattle, WA 98105, Phone: 206-987-3862, Fax: 206-987-3866, Pager: 206-469-6136, jerry.zimmerman@seattlechildrens.org

Keywords

pediatric septic shock; randomized controlled trial; corticosteroids; equipoise; clinically meaningful outcome measures; evidence based medicine

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

The call to action article by Menon and Wong (1) reminds us of our responsibility to pursue evidence basis for best practice, even when it is uncomfortable to wander from the *status quo*. Although training, individual experience, and pathophysiologic rationale are important in defining one's clinical practice, there is really no substitute for well conducted science to define the benefits and risks of a particular intervention.

Most septic shock corticosteroid interventional trials have reported hastened resolution of shock for patients treated with corticosteroids e.g. (2-4). These results are consistent with focused adult (5) and pediatric (6) observational studies that document the benefit of corticosteroids in facilitating weaning of vasoactive-inotropic support. On the other hand current accumulated evidence analyzed by systematic review and meta-analysis reveals lack of benefit in reducing mortality (7-9). Similarly numerous adult descriptive studies have concluded lack of a mortality benefit for this intervention (10-14). Although large, well conducted, randomized controlled trials (RCTs) examining adjunctive corticosteroid for pediatric septic shock are lacking, five descriptive investigations have reported no mortality benefit or increased mortality associated with this intervention (15-19). This paradox has remained one of the most important, unresolved critical care research questions for decades.

Corticosteroids should not be considered a simple replacement for vasoactive-inotropic drugs, the common first-line agents utilized for septic shock. Corticosteroids alter transcription of 20-25% of the genome (20), and accordingly this drug class mediates a multitude of effects beyond hemodynamics. In general the adverse effects of corticosteroids in the pediatric intensive care unit (PICU) are probably under appreciated. In reference to prescription of corticosteroids (for septic shock), the notion that, “it can't hurt”, is not true and needs to be abandoned. Adverse effects of corticosteroids among critically ill patients that could be associated with increased risk of mortality include hyperglycemia secondary to gluconeogenesis (21, 22), ICU-acquired weakness (including the diaphragm) secondary to

lean body catabolism (23), unresolved, reactivated, or hospital acquired infections secondary to immunosuppression (24, 25) and transition to delirium (26). Contemporary sepsis pathophysiology postulates emergence of immunosuppression concurrent with the systemic inflammatory response (27). Septic children exhibit repression of gene programs associated with adaptive immunity, and this state is exaggerated with administration of corticosteroids (28).

Menon and Wong (1) consider a number of important considerations for design of an RCT of adjunctive corticosteroids for recalcitrant pediatric septic shock. Some of these deserve additional discussion:

Community as well as individual equipoise may be the most difficult challenge for such an investigation. However, as the true benefits and risks of corticosteroids in this clinical scenario are not clear, equipoise is justified. Given this conclusion, not only must physicians be willing to enroll septic children into the RCT, but intellectual honesty must trump thoughts of ‘bailout’ study drug administration if a subject’s hemodynamic status deteriorates. If rescue therapy is commonly employed in the RCT design, more children will need to be enrolled and more children will die from sepsis in the quest to establish rigorous evidence for benefit and harm of corticosteroids for this indication (29). To address the legitimate nervousness of the bedside physician, an RCT safety aim should be included, namely, occurrence of mortality or need for ‘rescue’ extracorporeal life support. A closely engaged data safety monitoring board with clear safety and statistical stopping rules will be paramount.

A survey of Canadian pediatric critical care medicine (PCCM) practitioners inquiring what would be the preferred primary outcome for a trial of corticosteroids for pediatric septic shock reported that the majority would choose a hemodynamic outcome—time to cessation of vasoactive-inotropic support or time to hemodynamic stability (30). These outcomes will be import to chronicle, as clinicians prescribe corticosteroids for sepsis-associated hemodynamic instability. However, using these variables as primary outcome measures would be a mistake, as per the disconnect between resolution of septic shock and long term outcomes as discussed above. Adult investigators examining hydrocortisone (2) as well as a non-specific nitric oxide synthase inhibitor (31) as adjunctive therapies for septic shock have discussed that resolution of septic shock is not an appropriate surrogate outcome measure, as this is not associated with durable, clinically meaningful outcomes (32). Composite time to complete organ dysfunction resolution was utilized as the primary outcome measure in the RESOLVE trial of activated protein c for pediatric severe sepsis (33). Regrettably, the relationship with this variable and longer term outcomes is not known. However, a tool for quantification of global pediatric organ dysfunction, Pediatric Logistic Organ Dysfunction (PELOD) (34), is available and has been specifically validated in children with sepsis (35). In addition individual organ-specific measures have now been validated for cardiovascular, pulmonary, renal, and coagulation dysfunctions.

Menon and Wong (1) ascertain that utilizing mortality as a primary outcome measure for an interventional trial in pediatric septic shock is not feasible. However, it has been suggested that combining mortality and significant morbidity would constitute a patient-centered,

clinically meaningful, long term outcome measure (36). The Functional Status Scale was developed as an easy-to-use instrument to measure functional disability in clinical trials (37). Analysis of the RESOLVE data base indicated that in addition to 17% mortality, 34% of surviving subjects exhibited a worsening their Pediatric Overall Performance Category (POPC), and 18% met criteria for poor functional outcome (38). POPC provides a coarse and FSS a more granular quantification of functional status. The ongoing, Life After Pediatric Sepsis Evaluation (LAPSE) observational trial (5R01HD0733625) was specifically designed to analyze health-related quality of life as an outcome measure for pediatric sepsis interventional trials. Accordingly LAPSE will quantify magnitude and duration of health-related quality of life deterioration among survivors of pediatric septic shock during the first year after PICU admission. Significantly impaired functional status and health-related quality of life following pediatric sepsis appear to occur at a much higher frequency than mortality, and if used as primary outcome measures would require much smaller enrollment numbers as compared to using mortality.

Inclusion and exclusion criteria for the trial will need to be thoughtfully derived. Although it would be ideal to employ a readily available biomarker to identify the group of children with septic shock with the greatest benefit and lowest risk for adjunctive corticosteroid administration, this will likely not be possible. One conclusion of the CORTICUS trial was that standard corticotropin stimulation testing measuring baseline and stimulated total cortisol does not serve this function (2). Menon and Wong (1) discuss that low-dose corticotropin stimulation testing and free cortisol measurement for this purpose are not quite ready for prime time. In fact at this juncture we do not really understand the concept of and potential intervention for relative adrenal insufficiency or critical illness related corticosteroid insufficiency, particularly among critically ill children. If results were available in real time for decision making related to trial enrollment, PERSEVERE (PEdiatRiC SEpsis biomarkEr Risk model) might be utilized to identify children at greater risk of sepsis illness severity and risk of death from pediatric septic shock (39).

In recent years, multiple examples of high quality PCCM interventional trials can be cited, and these investigations have been conducted with and without the infrastructure of organized PCCM research networks. Experienced principal and performance site investigators, data coordinating centers, and data safety monitoring boards are available. Physician-scientists and clinician-educators can successfully collaborate in rigorous conduct of investigational protocols. We have the means to undertake a trial of corticosteroid therapy for pediatric septic shock, if we conscientiously decide to do so.

Corticosteroids have drifted into PCCM sepsis clinical practice without solid evidence of safety or efficacy. Best available evidence at this time suggests that this intervention may be beneficial or may be harmful. Accordingly, there is scientific, ethical and health economic imperative to conduct an RCT of adjunctive corticosteroids for pediatric septic shock (40). Menon and Wong have sounded the clarion call (1). It seems clear that as the PCCM community we have a responsibility to thoughtfully design and then participate in a definitive RCT. If conducted appropriately, the science that the trial generates will inform clinical practice regardless of the outcome.

In conclusion, one additional quotation from Claude Bernard: “It is through the experimental method that science is carried forward—not through uncritically accepting the authority of academic or scholastic sources. In the experimental method, observable reality is our only authority. . . ”

Acknowledgments

Copyright form disclosures: Dr. Zimmerman received grant support from the National Institutes of Health (NIH), Seattle Children's Research Institute, and ImmuneXpress; served as a board member for the Society of Critical Care Medicine (Reimbursement to attend board and committee meetings); is employed by Seattle Children's Hospital, Children's University Medical Group, University of Washington; lectured for various institutions (Reimbursement for invited lectures); received royalties from Elsevier Publishing (Co-Editor for textbook, Pediatric Critical Care); and received support for article research from the NIH. His institution received grant support from the NIH, Seattle Children's Research Institute, and ImmuneXpress (Research funding).

References

1. Menon K, Wong HR. Corticosteroids in Pediatric Shock-A Call to Arms. *Pediatr Crit Care Med*. 2015; XX:00–00.
2. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008; 358:111–124. [PubMed: 18184957]
3. Oppert M, Schindler R, Husung C, Offermann K, Graf KJ, Boenisch O, Barckow D, Frei U, Eckardt KU. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med*. 2005; 33:2457–2464. [PubMed: 16276166]
4. Annane D, Seville V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *Jama*. 2002; 288:862–871. [PubMed: 12186604]
5. Annane D, Bellissant E, Seville V, Lesieur O, Mathieu B, Raphael JC, Gajdos P. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. *Br J Clin Pharmacol*. 1998; 46:589–597. [PubMed: 9862249]
6. Hebbat KB, Stockwell JA, Leong T, Fortenberry JD. Incidence of adrenal insufficiency and impact of corticosteroid supplementation in critically ill children with systemic inflammatory syndrome and vasopressor-dependent shock. *Crit Care Med*. 2011; 39:1145–1150. [PubMed: 21336126]
7. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *Jama*. 2009; 301:2362–2375. [PubMed: 19509383]
8. Volbeda M, Wetterslev J, Glud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015; 41:1220–1234. [PubMed: 26100123]
9. Wang C, Sun J, Zheng J, Guo L, Ma H, Zhang Y, Zhang F, Li E. Low-dose hydrocortisone therapy attenuates septic shock in adult patients but does not reduce 28-day mortality: a meta-analysis of randomized controlled trials. *Anesth Analg*. 2014; 118:346–357. [PubMed: 24445635]
10. Beale R, Janes JM, Brunkhorst FM, Dobb G, Levy MM, Martin GS, Ramsay G, Silva E, Sprung CL, Vallet B, Vincent JL, Costigan TM, Leishman AG, Williams MD, Reinhart K. Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry. *Crit Care*. 2010; 14:R102. [PubMed: 20525247]
11. Casserly B, Gerlach H, Phillips GS, Lemeshow S, Marshall JC, Osborn TM, Levy MM. Low-dose steroids in adult septic shock: results of the Surviving Sepsis Campaign. *Intensive Care Med*. 2012; 38:1946–1954. [PubMed: 23064466]
12. Funk D, Doucette S, Pisipati A, Dodek P, Marshall JC, Kumar A, Cooperative Antimicrobial Therapy of Septic Shock Database Research G. Low-dose corticosteroid treatment in septic shock: a propensity-matching study. *Crit Care Med*. 2014; 42:2333–2341. [PubMed: 25072758]

13. Povoia P, Salluh JI, Martinez ML, Guillaumat-Prats R, Gallup D, Al-Khalidi HR, Thompson BT, Ranieri VM, Artigas A. Clinical impact of stress dose steroids in patients with septic shock: insights from the PROWESS-Shock trial. *Crit Care*. 2015; 19:193. [PubMed: 25928214]
14. Kalil AC, Sun J. Low-dose steroids for septic shock and severe sepsis: the use of Bayesian statistics to resolve clinical trial controversies. *Intensive Care Med*. 2011; 37:420–429. [PubMed: 21243334]
15. Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med*. 2005; 6:270–274. [PubMed: 15857523]
16. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med*. 2011; 12:2–8. [PubMed: 20228689]
17. Atkinson SJ, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, Hall M, Freishtat RJ, Sen A, Meyer K, Checchia PA, Shanley TP, Nowak J, Quasney M, Weiss SL, Banschbach S, Beckman E, Howard K, Frank E, Harmon K, Lahni P, Lindsell CJ, Wong HR. Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. *PloS one*. 2014; 9:e112702. [PubMed: 25386653]
18. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, Shanley TP, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Shekhar RS, Gertz S, Dawson E, Howard K, Harmon K, Beckman E, Frank E, Lindsell CJ. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med*. 2015; 191:309–315. [PubMed: 25489881]
19. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, Nadkarni VM, Thomas NJ, Sepsis Prevalence O, Therapies Study I, the Pediatric Acute Lung I, Sepsis Investigators N. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med*. 2015; 191:1147–1157. [PubMed: 25734408]
20. Galon J, Franchimont D, Hiroi N, Frey G, Boettner A, Ehrhart-Bornstein M, O'Shea JJ, Chrousos GP, Bornstein SR. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *Faseb J*. 2002; 16:61–71. [PubMed: 11772937]
21. Yung M, Wilkins B, Norton L, Slater A. Glucose control, organ failure, and mortality in pediatric intensive care. *Pediatr Crit Care Med*. 2008; 9:147–152. [PubMed: 18477927]
22. Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC. Glucose level and risk of mortality in pediatric septic shock. *Pediatr Crit Care Med*. 2005; 6:470–472. [PubMed: 15982437]
23. Lodeserto F, Yende S. Understanding skeletal muscle wasting in critically ill patients. *Crit Care*. 2014; 18:617. [PubMed: 25673028]
24. Costello JM, Graham DA, Morrow DF, Potter-Bynoe G, Sandora TJ, Laussen PC. Risk factors for central line-associated bloodstream infection in a pediatric cardiac intensive care unit. *Pediatr Crit Care Med*. 2009; 10:453–459. [PubMed: 19307818]
25. de Mello MJ, de Albuquerque Mde F, Lacerda HR, Barbosa MT, de Alencar Ximenes RA. Risk factors for healthcare-associated infection in a pediatric intensive care unit. *Pediatr Crit Care Med*. 2010; 11:246–252. [PubMed: 19794325]
26. Schreiber MP, Colantuoni E, Bienvenu OJ, Neufeld KJ, Chen KF, Shanholtz C, Mendez-Tellez PA, Needham DM. Corticosteroids and transition to delirium in patients with acute lung injury. *Crit Care Med*. 2014; 42:1480–1486. [PubMed: 24589640]
27. Hotchkiss RS, Coopersmith CM, McDunn JE, Ferguson TA. The sepsis seesaw: tilting toward immunosuppression. *Nat Med*. 2009; 15:496–497. [PubMed: 19424209]
28. Wong HR, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Weiss SL, Shanley TP, Bigham MT, Banschbach S, Beckman E, Harmon K, Zimmerman JJ. Corticosteroids are associated with repression of adaptive immunity gene programs in pediatric septic shock. *Am J Respir Crit Care Med*. 2014; 189:940–946. [PubMed: 24650276]
29. Holubkov R, Dean JM, Berger J, Anand KJ, Carcillo J, Meert K, Zimmerman J, Newth C, Harrison R, Willson DF, Nicholson C. Is “rescue” therapy ethical in randomized controlled trials? *Pediatr Crit Care Med*. 2009; 10:431–438. [PubMed: 19307815]

30. Menon KMJ, Choong K, Ward RE, Lawson ML, Ramsay T, Wong HR. A survey of stated physician practices and beliefs on the use of steroids in pediatric fluid and/or vasoactive infusion dependent shock. *Pediatr Crit Care Med*. 2013; 14:00–00.
31. Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, Silverman MS, Takala J, Donaldson J, Arneson C, Grove G, Grossman S, Grover R. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med*. 2004; 32:21–30. [PubMed: 14707556]
32. Curley MA, Zimmerman JJ. Alternative outcome measures for pediatric clinical sepsis trials. *Pediatr Crit Care Med*. 2005; 6:S150–156. [PubMed: 15857550]
33. Nadel S, Goldstein B, Williams MD, Dalton H, Peters M, Macias WL, Abd-Allah SA, Levy H, Angle R, Wang D, Sundin DP, Giroir B. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet*. 2007; 369:836–843. [PubMed: 17350452]
34. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F. Groupe Francophone de Reanimation et d'Urgences P. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med*. 2013; 41:1761–1773. [PubMed: 23685639]
35. Leclerc F, Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Martinot A, Gauvin F, Hubert P, Lacroix J. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. *Am J Respir Crit Care Med*. 2005; 171:348–353. [PubMed: 15516535]
36. Pearson GA. Mathematical morbidity in paediatric intensive care. *Lancet*. 2003; 362:180–181. [PubMed: 12885473]
37. Pollack M, Holubkov R, Glass P, Dean JM, et al. The Functional Status Score (FSS): A New Pediatric Outcome Measure. *Pediatrics*. 2009 In Press.
38. Farris RW, Weiss NS, Zimmerman JJ. Functional outcomes in pediatric severe sepsis: further analysis of the researching severe sepsis and organ dysfunction in children: a global perspective trial. *Pediatr Crit Care Med*. 2013; 14:835–842. [PubMed: 24108117]
39. Wong HR, Weiss SL, Giuliano JS Jr, Wainwright MS, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, Hall M, Freishtat RJ, Sen A, Meyer K, Checchia PA, Shanley TP, Nowak J, Quasney M, Chopra A, Fitzgerald JC, Gedeit R, Banschbach S, Beckman E, Lahni P, Hart K, Lindsell CJ. Testing the prognostic accuracy of the updated pediatric sepsis biomarker risk model. *PloS one*. 2014; 9:e86242. [PubMed: 24489704]
40. Venkatesh B, Myburgh J, Finfer S, Webb SA, Cohen J, Bellomo R, McArthur C, Joyce CJ, Rajbhandari D, Glass P, Harward M, investigators AC. The ADRENAL study protocol: adjunctive corticosteroid treatment in critically ill patients with septic shock. *Crit Care Resusc*. 2013; 15:83–88. [PubMed: 23931038]