

A Survey of Stated Physician Practices and Beliefs on the Use of Steroids in Pediatric Fluid and/or Vasoactive Infusion-Dependent Shock*

Kusum Menon, MD, MSc, FRCPC¹; James D. McNally, MD, PhD, FRCPC¹;
Karen Choong, MB, MSc, FRCPC²; Roxanne E. Ward, BA³; Margaret L. Lawson, MD, MSc, FRCPC¹;
Tim Ramsay, MSc, PhD⁴; Hector R. Wong, MD⁵

Objective: Limited evidence exists on the use of corticosteroids in pediatric shock. We sought to determine physicians' practices and beliefs with regard to the management of pediatric shock.

Design: Cross-sectional, Internet-based survey.

Setting: Canada.

Subjects: Physicians identified as practicing pediatric intensive care in any of 15 academic centers.

Measurements and Main Results: Seventy of 97 physicians (72.2%) responded. Physicians stated that they were more likely to prescribe steroids for septic shock than for shock following cardiac surgery (odds ratio, 1.9 [95% CI, 0.9–4.3]) or trauma (odds ratio, 11.46 [95% CI, 2.5–51.2]), and 91.4% (64/70) would administer steroids to patients who had received 60 cc/kg of fluid and two or more vasoactive medications. Thirty-five percent of respondents (25/70) reported that they rarely or never conducted adrenal axis testing before giving steroids to patients in shock. Eighty-seven percent of respondents (61/70)

stated that the role of steroids in the treatment of fluid and/or vasoactive drug-dependent shock needed to be clarified and that 84.3% would be willing to randomize patients into a trial of steroid efficacy who were fluid resuscitated and on one high-dose vasoactive medication. However, 74.3% stated that they would start open-label steroids in patients who required two high-dose vasoactive medications.

Conclusions: This survey provides information on the stated beliefs and practices of pediatric critical care physicians with regard to the use of steroids in fluid and/or vasoactive drug-dependent shock. Clinicians feel that the role of steroids in shock still requires clarification and that they would be willing to randomize patients into a trial. This survey may be useful as an initial framework for the development of a future trial on the use of steroids in pediatric shock. (*Pediatr Crit Care Med* 2013; 14:462–466)

Key Words: adrenal insufficiency; pediatric critical care; pediatric intensive care; septic shock; shock; steroids

*See also p. 541.

¹Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada.

²Department of Pediatrics, McMaster University, Ottawa, ON, Canada.

³Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada.

⁴Department of Epidemiology and Community Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada.

⁵Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH.

This work was performed at the Children's Hospital of Eastern Ontario.

Dr. McNally is an academic pediatric intensivist paid to provide clinical service and engage in scholarly activity, including research. Dr. Choong received grant support from CIHR. Dr. Ward receives payment for writing and reviewing the manuscript/preparation: Children's Hospital of Eastern Ontario Research Institute—paid salary for role as Critical Care Clinical Research Manager. Dr. Wong receives grant support from NIH and payment for lectures from SCCM. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: menon@cheo.on.ca

Copyright © 2013 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies

DOI: 10.1097/PCC.0b013e31828a7287

Approximately 2,000 children per year in Canada develop clinical signs of shock requiring life-saving treatments in emergency departments and ICUs. The initial aim of shock management is to improve end-organ perfusion through IV fluid resuscitation followed by vasoactive medications. When shock states persist despite significant fluid and/or vasoactive infusions, steroids have been suggested as adjunctive therapy (1). The scientific rationale for steroids in refractory shock is compelling and has been widely debated in both the adult and pediatric literature for over 40 years. Recent large adult-based randomized controlled trials have provided conflicting answers with some suggesting more harm than benefit (2, 3). No sufficiently powered trials have evaluated steroids in the treatment of pediatric shock.

Developing evidence-based guidelines for pediatric shock management has proven difficult given the conflicting adult evidence and the absence of pediatric trials. A large retrospective

study of patients with sepsis and the subsequent 2009 update of the American College of Critical Care Medicine guidelines both maintain equipoise on the question of adjunctive steroid therapy for pediatric sepsis (1, 4). The guidelines further demonstrate a significant knowledge gap by recommending a hydrocortisone dose ranging from 1 to 50 mg/kg/d for children with septic shock. Consequently, clinicians providing care to these children are left to make individual judgments at the bedside, potentially resulting in significant practice variation and polarized opinions on the subject (5–7).

An understanding of current physician practices and beliefs is essential prior to future interventional trials of steroids in pediatric shock. To date, three studies have assessed the practice of pediatric intensive care physicians in the management of patients with shock or adrenal insufficiency (5–7). All three demonstrated variability in physician practices and beliefs but had significant limitations including proxy reporting by medical directors (5), a differing/alternative focus (6), or a single-center design (7) preventing broad-based conclusions. Due to limited current evidence on physician practices with regard to the use of steroids in shock, it is difficult to determine whether consensus or equipoise exists on the management of pediatric shock patients. We therefore performed a survey study of pediatric critical care physicians in Canada to determine their current practices and beliefs with regard to use of corticosteroids in the management of shock and their willingness to participate in a future trial on the subject.

METHODS

Sampling Frame

All currently practicing attending pediatric intensivists at the 15 academic health science centers in Canada were identified as the population of interest. We identified potential respondents by contacting one pediatric intensivist at each of the study sites who was asked to provide the names and e-mail addresses of all the physicians currently practicing pediatric critical care in their ICU.

Questionnaire Development

Development of this self-administered questionnaire was according to recently published recommendations for survey methodology (8). First, we generated relevant items for the questionnaire through literature reviews and in-depth interviews with experts in the field including members of the Canadian Critical Care Trials Group. The generated items were then grouped into domains which primarily included practice patterns and beliefs around the use of corticosteroids in pediatric fluid and/or vasoactive infusion-dependent shock. A question on the effect of etomidate usage on the subsequent use of steroids for shock was not included as a previous study in the Canadian pediatric intensive care population showed that none of the 369 critically ill children had received etomidate prior to PICU admission (9).

Questionnaire Testing

The questionnaire was sent to five individuals with methodological and/or content expertise in the field who would not be respondents for the final version and included pediatric

intensivists, a pediatric intensive care fellow (an intensivist from Brazil), a pediatric endocrinologist, and an experienced pediatric critical care research coordinator with training in epidemiology. Individual questions were extensively revised based on feedback from this group. The questionnaire was then sent to five adult intensivists who were asked to examine the flow, salience, acceptability, and administrative ease of the questionnaire after which further revisions to the content and order of the survey were made.

Questionnaire Administration

We administered the survey (see Appendix 1) between February and March 2012 in English using web-based software (Fluid-Surveys; <http://www.fluidsurveys.com>) and did not provide any incentives for completion of the survey. Each potential participant received an e-mail invitation to complete the survey. Two weeks later, a reminder e-mail was sent to those who had not completed the survey. A third and final e-mail was sent to potential participants who had not responded 2 weeks after the second reminder. The electronically generated database was then downloaded into SPSS version 19, which was then verified by both the research coordinator and principal investigator for accuracy.

Statistical Analysis

We summarized survey responses using proportions and modes for categorical data, medians for continuous data with interquartile ranges (IQR), and odds ratios (OR) with 95% CIs for comparisons between proportions. For descriptive analyses, we used the actual number of respondents for the denominator. We collapsed categories, where appropriate to summarize responses in a meaningful manner. We included data from incomplete questionnaires. Accordingly, the denominators for certain analyses vary.

RESULTS

Demographics

Ninety-nine pediatric intensive care physicians were eligible for the survey and 97 received the survey (two were accidentally omitted). The overall response rate was 72.2% (70/97), and the response rates among centers ranged from 53.9% to 100%. The completion rate of the returned surveys was 97.4%. The number of years of clinical practice by physicians in the participating units was evenly distributed in 5-year blocks from less than 5 years to greater than 20 years (18.6%, 21.4%, 20.0%, 18.6%, and 21.4%). The number of PICU beds ranged from 5–10 to over 20 beds with the most common response being 11–20 beds (42.9%). The number of admissions per year ranged from less than 200 (2.9%) to greater than 2,000 (4.3%) with the majority of units reporting between 600 and 1,000 (44.3%). The median number of practicing intensivists per center was 6 (IQR, 4–10).

Definition of Shock and Burden of Problem

Respondents were provided with clinical scenarios and asked to identify all cases that they would define as fluid and/or

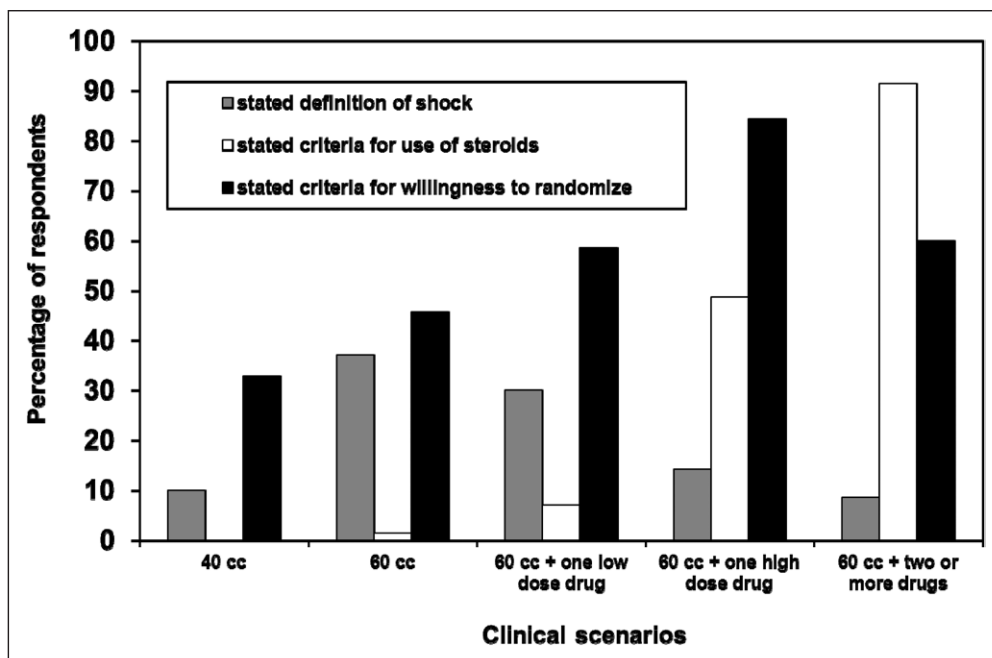


Figure 1. The reported use of corticosteroids in shock. *Gray bars* = stated definition of shock; *white bars* = stated criteria for use of steroids; *black bars* = stated criteria for willingness to randomize.

vasoactive drug-dependent shock (**Fig. 1**). Hypotension despite 60 cc/kg of fluid was the most common definition chosen (37.1%, 26/70) followed by hypotension despite 60 cc/kg of fluid and one low-dose vasoactive infusion (30.0%, 21/70).

Respondents were asked to provide an estimate of the overall prevalence of patients with moderate-to-severe shock treated at their center (defined in this instance as hypotension despite 60 cc/kg of fluid and at least one vasoactive medication). The majority of centers reported either less than 50 or 50–100 admissions for shock per year (mode of the estimates in 7/15 and 6/15 centers, respectively) and only one center estimated over 200 annual admissions. Ninety-one percent of respondents' estimates (64/70) of the number of shock patients were the same or within one category of the mode from their institution.

Practice Patterns for Steroid Administration in Shock

Physicians stated that they were more likely to prescribe steroids for septic shock than for shock following cardiac surgery (OR, 1.9 [95% CI, 0.9–4.3]) or trauma (OR, 11.4 [95% CI, 2.5–51.2]). However, the majority of clinicians surveyed (74.2%, 52/70) admitted to using steroids in patients with fluid and/or vasoactive drug-dependent shock secondary to diagnoses other than sepsis.

When asked about their threshold for using steroids in patients with shock, 92.9% (65/70) stated they would not administer steroids for a patient who had received 60 cc/kg of fluid and was only on one low-dose vasoactive medication, but 91.4% (64/70) stated that would administer steroids to patients who had received 60 cc/kg of fluid and were on two or more vasoactive medications (Fig. 1).

Eighty percent of respondents (56/70) reported using exclusively hydrocortisone as their steroid of choice for fluid/

vasopressor-dependent shock with the remaining respondents stating that they would use only methylprednisolone (8.6%, 6/70), methylprednisolone or hydrocortisone (7.1%, 5/70), only dexamethasone (2.9%, 2/70), or methylprednisolone, hydrocortisone, or dexamethasone (1.4%, 1/70). No respondents reported using fludrocortisone. The majority of respondents (81.4%, 57/70) reported using doses of hydrocortisone within a narrow range from 1 mg/kg/dose (47.1%, 33/70) to 100 mg/m²/d (14.3%, 15/70) to 5 mg/kg/d (12.9%, 9/70). Just over 1% of clinicians surveyed stated that they would use only 50 mg/m²/d of hydrocortisone.

Remaining responses included 4–5 mg/kg load followed by 1 mg/kg q6h (2.9%), 10 mg/kg/dose (1.4%), and one reference to guideline dosing.

Respondents were asked to identify all criteria that they would use to discontinue steroid therapy. Forty-seven percent of responding practitioners (33/70) chose resolution of shock alone, 20% (20/70) chose discontinuation of all vasoactive infusions alone, and 10% (7/70) chose both criteria. Seventeen percent of respondents (12/70) simply identified a time limit as their criteria for discontinuation of steroid therapy. Only three respondents linked their stated duration of therapy to the results of the patient's adrenal axis testing.

Adrenal Function Testing

Thirty-six percent of respondents (25/70) reported that they rarely or never conducted adrenal axis testing before giving steroids to patients in shock, whereas 37.1% of respondents (26/70) stated that they often or always conducted such testing prior to starting steroids. The most frequent type of adrenal axis testing reported as being performed was a random cortisol level (61.4%) with 50.0% reporting conducting low-dose (0.5–1.0 µg) adrenocorticotrophic hormone (ACTH) testing (respondents were asked to select all applicable answers).

Stated Beliefs on a Controlled Trial of Steroids

Eighty-seven percent of respondents (61/70) stated that the role of steroids in the treatment of fluid and/or vasoactive drug-dependent shock needed to be clarified. Forty-six percent stated that they would be willing to randomize patients in early shock (patients who have received 60 cc/kg of fluid but no vasoactive medications) and 84.3% of them in late shock (received 60 cc/kg of fluid and at least one high-dose vasoactive medication) (Fig. 1). With regard to their colleagues' practice, 44.3% of respondents felt that most or all of their

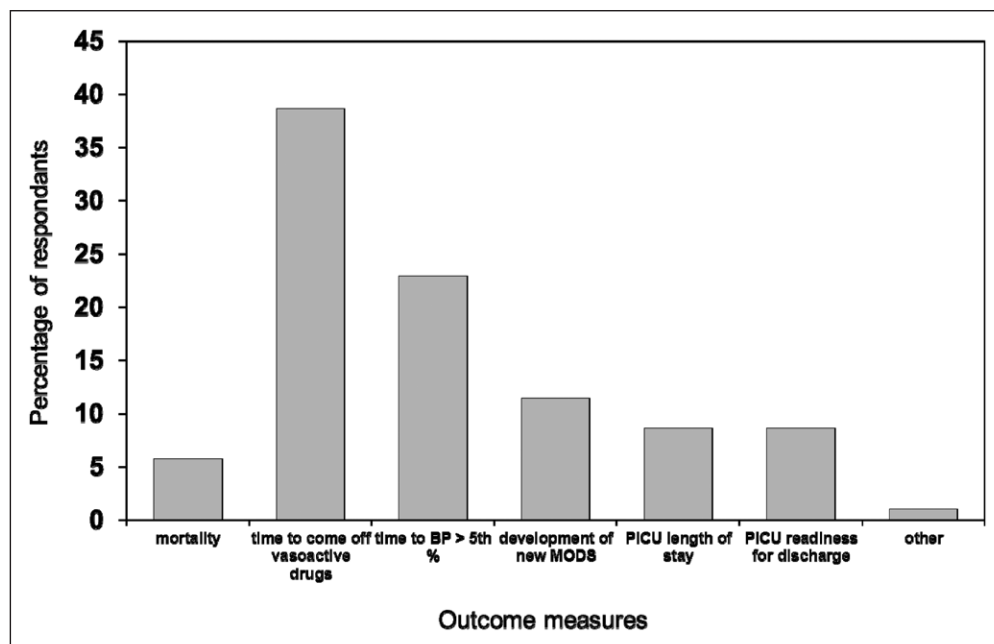


Figure 2. Clinically significant and feasible outcome measures for a trial on steroids in shock. MODS = multiple organ dysfunction syndrome.

colleagues would be willing to randomize patients into a trial of steroid versus placebo in early pediatric shock and 61.4% of their colleagues would be willing to randomize patients in late shock.

The majority of physicians (74.3%) stated that they would not start open-label steroids on a patient who had been randomized into a trial of steroids versus placebo and who had received greater than or equal to 60 cc/kg of fluid and was on one high-dose vasoactive drug, but 74.3% would start open-label steroids on a patient who had received greater than or equal to 60 cc/kg of fluid and was on two or more vasoactive drugs.

The single most clinically significant and feasible primary outcome measure chosen by respondents for a future trial was the time to discontinuation of all vasoactive drugs (38.6%, 27/70) with time to hemodynamic stability (BP > 5th percentile for age) being the second most common (22.9%, 16/70). The choices for the single most clinically significant and feasible primary outcome measure for a future trial on the use of steroids for persistent shock are shown in **Figure 2**.

DISCUSSION

Our survey provides an assessment of pediatric intensivists' beliefs regarding the role of steroids in the management of children with fluid and/or vasoactive infusion-dependent shock. Interestingly we found that thresholds for defining, treating, and randomizing patients with fluid and/or vasoactive infusion-dependent shock differed. The most common definition of shock chosen was hypotension despite 60 cc/kg of fluid; the most common point at which clinicians would start steroids for shock was hypotension following fluid and two vasoactive medications, and the stage of shock at which clinicians were

most willing to randomize patients was if patients were hypotensive following fluid and one high-dose vasoactive medication.

Physician practice regarding the administration of steroids by shock etiology was also explored. Physicians reported administering steroids more commonly in septic shock patients than in the trauma or postoperative cardiac surgery population. This is noteworthy given that the pediatric critical care literature on adrenal insufficiency is inconclusive as to whether sepsis itself increases a patient's risk for adrenal dysfunction (9, 10) but suggests that trauma (9) and cardiac surgery (11, 12) patients are at

risk for adrenal insufficiency. The reasons for this discrepancy are unclear but may simply reflect the preponderance of studies focusing on pediatric septic shock (13–16). There was also a significant discrepancy in the endpoints chosen by respondents for discontinuation of steroids, which will need to be carefully considered in the design of a future trial.

Multiple studies have shown that random cortisol levels alone may be inadequate for the detection of adrenal dysfunction (9, 16–18). Despite this literature, the majority of those surveyed who reported conducting adrenal axis testing (64.8%) stated that they performed random cortisol levels. This may be related to difficulties conducting an ACTH stimulation test in an acute situation or the lack of clear evidence that ACTH stimulation testing is useful in the face of conflicting studies on the association of the results of adrenal testing with clinically important outcomes (9, 18).

The variation in the reported dose of hydrocortisone that clinicians would use for fluid and/or vasoactive drug-dependent shock is consistent with the variability in the published literature. The four most recent randomized controlled trials (2, 3, 13, 14) used four different dosing regimens, and the 2007 American College of Critical Care Medicine guidelines for the management of pediatric and neonatal shock (1) recommend anywhere from 1–2 to 50 mg/kg/d of hydrocortisone for the treatment of resistant septic shock.

Finally, our survey explored physicians' perceptions of potential enrollment criteria for a trial on the role of steroids in pediatric shock given the varied inclusion criteria use for previous randomized controlled trials (2, 3, 14). The majority of respondents stated that they would be willing to enroll patients who were still hypotensive despite 60 cc/kg of fluid and one high-dose vasoactive medication, and only 24.3% of participants stated that they would start open-label steroids

on patients who met the above criteria. However, almost 75% of participants would start open-label steroids if their patient deteriorated and required two high-dose vasoactive medications. This suggests that a future trial would likely have to enroll patients at an earlier stage of shock to maximize compliance. Deterioration of patients following recruitment at an earlier stage of shock could also be a secondary outcome measure of steroid efficacy.

Two thirds of respondents stated that they would choose either time to discontinuation of all vasoactive drugs or time to hemodynamic stability as the most clinically significant and feasible primary outcomes measures. These outcome measures are consistent with pediatric studies that have demonstrated significant associations between adrenal insufficiency and time on inotropes (16), increased fluid and vasopressor requirements (9), and earlier reversal of shock (14). Pediatric studies on adrenal insufficiency in critical illness have been unable to demonstrate an association between adrenal insufficiency and mortality (9, 14, 19, 20) due to their small sample sizes and the low overall mortality rate in pediatric ICUs (21). This is reflected in our survey in which only 5.7% of respondents identified mortality as the most clinically significant and feasible outcome measure.

Strengths of this study are that it is a national survey that included all 15 level 3 pediatric ICUs in Canada and addresses physician beliefs regarding a future randomized controlled trial on the use of steroids in pediatric shock. A limitation of this study is that it reflects stated rather than actual physician practices, and future observational studies on actual steroid usage patterns may add valuable extra information. In addition, our results may not be generalizable outside of Canada due to the inclusion of only Canadian sites.

This survey provides information on the stated beliefs and practices of pediatric critical care physicians with regard to the use of steroids in fluid and/or vasoactive drug-dependent shock. Furthermore, our data suggest that the majority of physicians surveyed would be willing to randomize patients into a trial. This survey provides information that could serve as a basis for the development of inclusion criteria and primary outcome measures for a future trial on the use of steroids in pediatric shock.

REFERENCES

- Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666–688
- Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
- Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
- Markovitz BP, Goodman DM, Watson RS, et al: 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
- Hildebrandt T, Mansour M, Al Samsam R: The use of steroids in children with septicemia: Review of the literature and assessment of current practice in PICUs in the UK. *Paediatr Anaesth* 2005; 15:358–365
- Menon K, Lawson M: Identification of adrenal insufficiency in pediatric critical illness. *Pediatr Crit Care Med* 2007; 8:276–278
- Benken ST, Hutson TK, Gardiner RL, et al: A single-center review of prescribing trends and outcomes of corticosteroid replacement therapy in critically ill children with septic shock. *Open Crit Care Med J* 2010; 3:51–56
- Burns KE, Duffett M, Kho ME, et al; ACCADEMY Group: A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008; 179:245–252
- Menon K, Ward RE, Lawson ML, et al; Canadian Critical Care Trials Group: A prospective multicenter study of adrenal function in critically ill children. *Am J Respir Crit Care Med* 2010; 182:246–251
- Briegel J, Jochum M, Gippner-Steppert C, et al: Immunomodulation in septic shock: Hydrocortisone differentially regulates cytokine responses. *J Am Soc Nephrol* 2001; 12(Suppl 17):S70–S74
- Ando M, Park IS, Wada N, et al: Steroid supplementation: A legitimate pharmacotherapy after neonatal open heart surgery. *Ann Thorac Surg* 2005; 80:1672–1678
- Wald EL, Preze E, Eickhoff JC, et al: The effect of cardiopulmonary bypass on the hypothalamic-pituitary-adrenal axis in children. *Pediatr Crit Care Med* 2011; 12:190–196
- Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732
- Valoor HT, Singhi S, Jayashree M: Low-dose hydrocortisone in pediatric septic shock: An exploratory study in a third world setting. *Pediatr Crit Care Med* 2009; 10:121–125
- Bouachour G, Tiro P, Gouello JP, et al: Adrenocortical function during septic shock. *Intensive Care Med* 1995; 21:57–62
- Hatherill M, Tibby SM, Hilliard T, et al: Adrenal insufficiency in septic shock. *Arch Dis Child* 1999; 80:51–55
- Briegel J, Schelling G, Haller M, et al: A comparison of the adrenocortical response during septic shock and after complete recovery. *Intensive Care Med* 1996; 22:894–899
- Zimmerman JJ, Donaldson A, Barker RM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Real-time free cortisol quantification among critically ill children. *Pediatr Crit Care Med* 2011; 12:525–531
- Min M, Tin U, Aye M, et al: Hydrocortisone in the management of dengue shock syndrome. *Southeast Asian J Trop Med Public Health* 1975; 6:573–579
- Sumarmo, Talogo W, Asrin A, et al: Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics* 1982; 69:45–49
- Pollack MM, Patel KM, Ruttimann UE: PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; 24:743–752