

High-Dose Intravenous Vitamin C and Thiamine as Adjunct Therapy for Septic Shock in the Pediatric ICU: A Case Report

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Abstract

Pediatric sepsis and septic shock continue to be a life-threatening medical condition worldwide. Over the past decades, there has been a focus on the early identification and treatment of sepsis primarily with bundled and goal directed therapy. Despite these advances, morbidity and mortality have remained high, prompting investigation into novel therapies. High-dose vitamin C, thiamine and hydrocortisone (triple therapy) have been studied to be beneficial in the adult population with septic shock. However, there is a lack of evidence supporting this triple therapy in pediatric patients. This patient case presents an adult patient by age with a weight similar to that of an eleven-year-old boy in septic shock. After four days of receiving triple therapy, the vasopressor was weaned off and septic shock resolved. Based on our outcomes, this case report warrants the need for future studies investigating the use of high-dose vitamin C, thiamine and hydrocortisone as therapeutic options for sepsis or septic shock in the vulnerable pediatric population.

Keywords: Ascorbic acid; High-dose Vitamin C; Pediatric; Sepsis; Septic shock;

Introduction

Pediatric sepsis continues to be a global healthcare burden and a leading cause of death in children [1-2]. The landmark study (SPROUT) was an international study which demonstrated a prevalence of 8.2% in children less than 18 years of age with severe sepsis, similar to that in the critically ill adult population. The SPROUT study also concluded an overall hospital mortality of 25% associated with severe sepsis in developed countries [3].

Sepsis has been redefined in 2017 as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" [4]. This life-threatening state elicits an inflammatory response that can lead to circulatory and metabolic abnormalities, such as septic shock [4, 5]. The Surviving Sepsis Campaign (SSC) has established guidelines for the management of sepsis in adult and pediatric populations. Otherwise known as the "1-hour bundle", this mainstay therapy seeks to resuscitate and properly manage sepsis or septic shock [2, 6]. This bundle includes antibiotic(s)

to treat infection, fluid resuscitation for hemodynamic instability, and vasopressors for refractory hypotension. However, over the last few years there has been an interest investigating novel therapeutic approaches to effectively treat sepsis and septic shock, most notably the use of ascorbic acid (vitamin C) [7, 8, 9].

Although a small retrospective study, Marik et al. demonstrated a mortality benefit with the use of high dose vitamin C, thiamine and hydrocortisone (triple therapy) for the treatment of severe sepsis and septic shock in the adult population [7].

Vitamin C is a water-soluble antioxidant and an enzyme cofactor for various biosynthetic pathways [10]. The key roles for vitamin C in sepsis include the following: (1) in a hypoxic state endothelial cells are damaged by reactive oxygen species and vitamin C acts as an antioxidant to protect the cells, thus maintaining endothelial integrity; (2) in sepsis or septic shock catecholamine and vasopressin production are diminished and vitamin C acts as a cofactor in their biosynthetic pathway; lastly (3) vitamin C is concentrated in the leukocytes, thus improving immune function by supporting lymphocytic proliferation, chemotaxis, and assisting with bacterial killing [8, 10, 11].

Thiamine is an essential vitamin and enzyme cofactor involved in various metabolic pathways [12]. Marik and colleagues included thiamine in their study due to its role in vitamin C metabolism [7]. Vitamin C is a precursor to oxalate which can accumulate in the kidney at high doses, thus increasing the risk for nephrolithiasis [7, 13, 14]. Thiamine is a co-enzyme involved in the pathway of preventing oxalate formation [7]. Furthermore, it has been proven that critically ill patients present with remarkably low levels of vitamin C and thiamine [8].

Majority of studies involving the use of vitamin C for sepsis focus on adult patients [7, 8, 9]. Limited evidence exists to support the use of vitamin C, thiamine and hydrocortisone for septic shock in the pediatric population nor weight-based dosing for children with sepsis. In this case report, we present an adult patient by age with a weight of 36 kilograms (kg) in septic shock treated with high-dose vitamin C, thiamine and hydrocortisone.

Patient Information

Patient SR is a 23-year-old male with chromosome 13q deletion (46, XY, del (13) (q22q34) born with imperforate anus, severe cognitive and motor delays, and congenital anomalies including scoliosis leading to respiratory insufficiency requiring nighttime ventilatory support of bi-level positive airway pressure (BiPAP). His past medical history consisted of epilepsy, chronic otitis media, and dysphagia. The patient's surgical history included colostomy, mucus fistula creation, and gastrostomy. He was admitted to the pediatric intensive care unit (PICU) with

overwhelming sepsis secondary to colitis, urinary tract infection, and tracheitis that led to acute respiratory failure, multi-organ failure, and septic shock requiring vasopressor support.

This patient was typically admitted to the PICU due to his pediatric-like weight of 36 kg and having pediatric subspecialists consulting in his care. According to the Centers for Disease Control (CDC) growth chart, this patient's weight represents the 50th percentile weight of an average eleven year old boy, therefore warranting care in a pediatric unit [Figure 1].

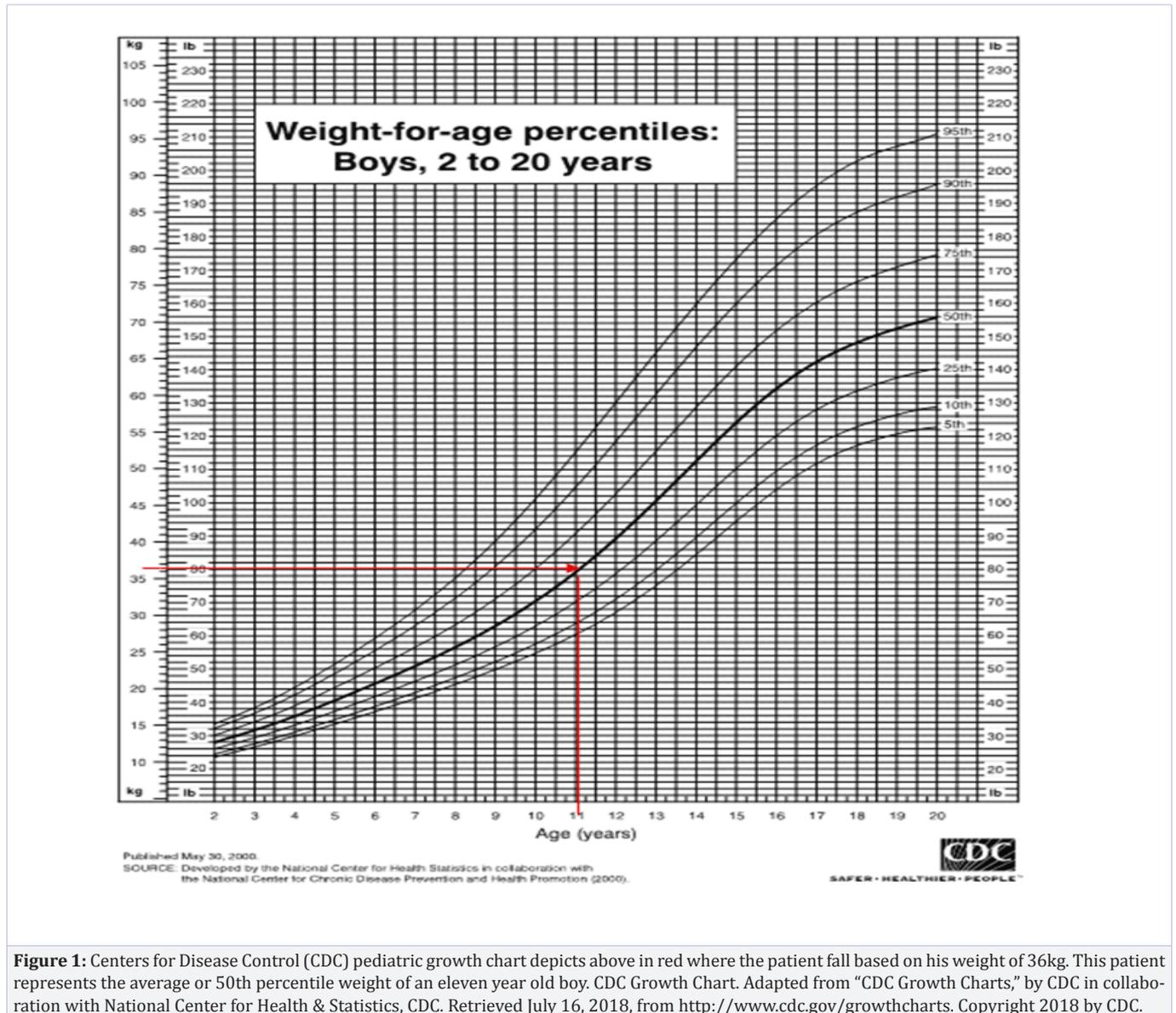


Figure 1: Centers for Disease Control (CDC) pediatric growth chart depicts above in red where the patient fall based on his weight of 36kg. This patient represents the average or 50th percentile weight of an eleven year old boy. CDC Growth Chart. Adapted from "CDC Growth Charts," by CDC in collaboration with National Center for Health & Statistics, CDC. Retrieved July 16, 2018, from <http://www.cdc.gov/growthcharts>. Copyright 2018 by CDC.

Clinical Findings

This patient presented to the PICU with fever, hypoxia, and decreased level of consciousness. On physical exam, he was noted to be in moderate distress, conscious but weak, non-verbal, tachycardic heart sounds, rales on lung auscultation, distended abdomen with well-healed abdominal scars, a colostomy bag on the right side of the abdomen with liquid stools, inflamed and bulging mucus fistula on the left side of the abdomen, dependent scrotal edema, and limb deformities including syndactyly of 2nd and 3rd digits of the left hand. On day 19 of hospitalization, his clinical status declined. His heart rate trended around 130 bpm, blood pressure declined to 75/30 mmHg with SpO₂ at 91%. He was febrile to 100.4°F with a white blood cell count of 17,200/mm³. In addition, the patient's PaO₂/FiO₂ was > 100 with ventilatory support, platelets were 37 x 10³/mm³, bilirubin < 1.2 mg/dL, Glasgow Coma Score was 9, creatinine was 0.7 mg/dL and the patient was on dopamine at a rate of > 5 mcg/kg/min.

Diagnostic Assessment

He was diagnosed with presumed sepsis and treated empirically with vancomycin, meropenem, and aztreonam due to previous history of pseudomonal infections. He developed acute respiratory failure secondary to pneumonia requiring intubation.

His illness quickly progressed to septic shock, requiring dopamine and sedation with dexmedetomidine. His mucus fistula developed purulent drainage. His feeds were discontinued due to intestinal ileus and he received total parental nutrition with added vitamins and minerals. The lower respiratory sputum and mucus fistula cultures grew multidrug-resistant *Pseudomonas aeruginosa* sensitive to aztreonam, ceftazidime, meropenem, and piperacillin/tazobactam. The mucus fistula culture also grew rare colonies of vancomycin resistant enterococcus faecium (VRE) sensitive to linezolid. Despite the treatments provided he remained in septic shock.

At hospital day 26, he was still receiving dopamine infusion at 9 mcg/kg/minute titrated up to 10 mcg/kg/minute by day 27. In addition, he was also receiving an inotrope infusion of milrinone to improve cardiac output. On day 26, vitamin C, hydrocortisone and thiamine (triple therapy) as modeled in previous studies were initiated [7, 8, 9]. [Figure 2]

Within 48 hours after the initiation of triple therapy the mean arterial pressure increased to the 80s, thus allowing the infusion rate of the vasopressor, dopamine, to be decreased by approximately 50 percent [Figure 3]. Subsequently at hour 96, the dopamine and milrinone were weaned off and remained off for the remainder of his hospitalization. His septic shock resolved and he completed treatment for his sepsis.

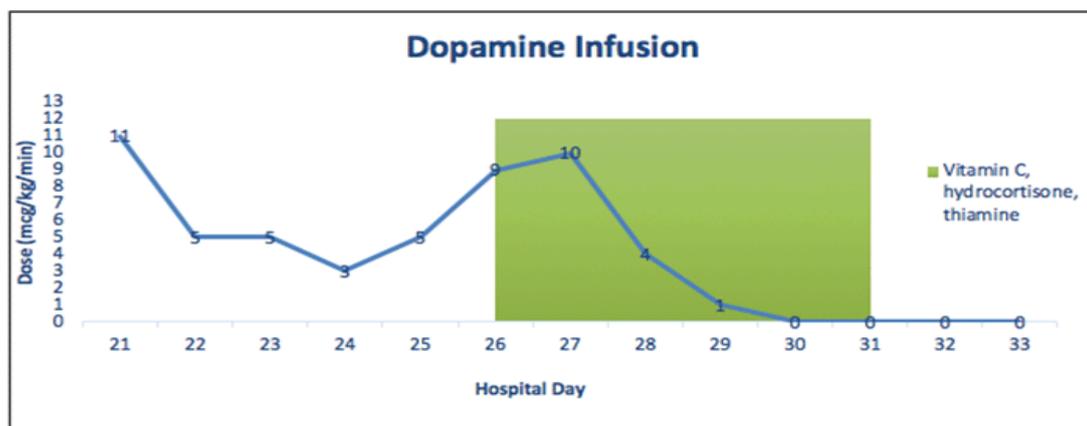


Figure 2: Dopamine Infusion Timeline

The Graph above illustrates the weaning of dopamine following the administrations of vitamin C, hydrocortisone and thiamine -area highlighted.

Therapeutic Intervention

The patient was given intravenous vitamin C 1,500mg (41 mg/kg/dose) every six hours, hydrocortisone 50mg (1.4 mg/kg/dose) every six hours, and thiamine 200mg (5.5 mg/kg/dose) every 12 hours for five days. The dopamine was being infused

at a peak of 11 mcg/kg/minute starting at hospital day 21 and tapered to 9 mcg/kg/minute at day one of high-dose vitamin C therapy. The dopamine was weaned to maintain mean arterial pressure (MAP) of >60mmHg [Figure 3].

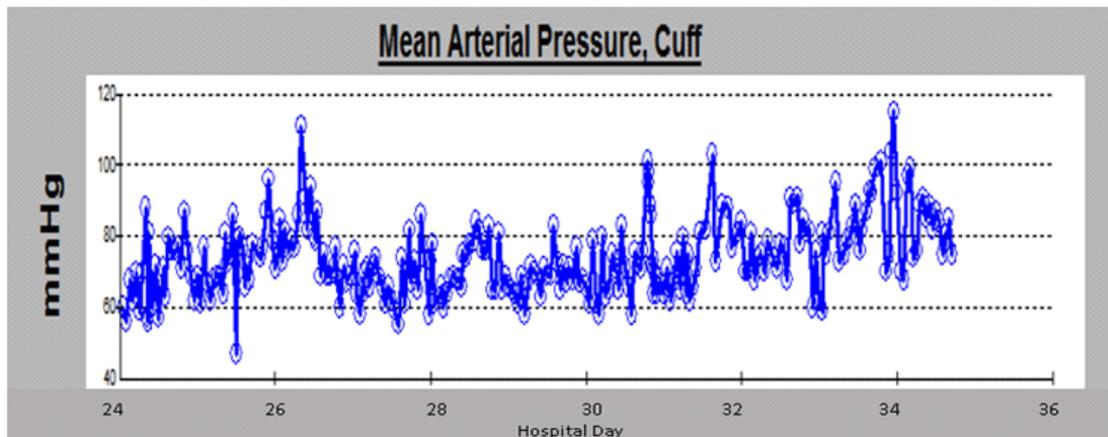


Figure 3: Mean Arterial Pressure (MAP) Graph

This graph illustrates the mean arterial pressures pre and post vitamin C, hydrocortisone and thiamine infusions. The MAP of >60 was achieved.

Follow up and outcomes

On the fourth day of high dose vitamin C, hydrocortisone and thiamine the vasopressor was weaned off and septic shock resolved. There were no adverse side effects and no further requirement for vasopressor medication(s). The patient was discharged home after completing an appropriate antibiotic regimen.

Discussion

Pediatric sepsis is a life-threatening medical condition commonly treated in pediatric intensive care units (PICUs). It is estimated that that over one-third of children who die in tertiary care PICUs within the United States have severe sepsis [3]. Recent reports of a rising prevalence of pediatric sepsis reflect an expanding vulnerable population, with chronic comorbidities, increasing rates of multidrug-resistant organisms and a surge in sepsis surveillance [3]. Over the past decades, there has been a focus on the early identification and treatment of sepsis primarily with bundled and goal-directed therapy [6]. Despite these advances, morbidity and mortality have remained high, prompting investigation into novel therapies.

This case illustrates the use of combination weight-based intravenous vitamin C, hydrocortisone and thiamine (triple therapy) in a presumed pediatric patient who presented with septic shock. The clinical result of our case is supported by extensive experimental and clinical studies which have demonstrated the safety and potential benefits of these agents in non-surgical critically ill patients [7]. In addition, high-dose vitamin C has been considered as an effective and safe adjunct therapy in surgical critically ill patients with septic shock [9].

In the pediatric considerations of the Surviving Sepsis Campaign guidelines (SSCG) 2012, timely hydrocortisone was strongly recommended (grade 1A evidence) for children with fluid-refractory catecholamine-resistant septic shock and

suspected or proven adrenal insufficiency [2]. In one randomized controlled trial, thiamine was reviewed and shown to statistically significantly lower lactate levels at 24 hours and decrease mortality, in the subgroup of thiamine deficient patients [12]. Vitamin C has been studied widely and is known to contribute to immune defense, play a role in mediating inflammation and in the synthesis of cortisol, catecholamines, and vasopressin [10, 11]. This is significant in our case as the addition of triple therapy, including high-dose vitamin C, resulted in weaning and discontinuation of vasopressors. Although studies exist for hydrocortisone alone, high-dose vitamin C and thiamine have not been trialed in pediatrics.

A small retrospective study in the adult population (Marik et al.) showed a significant reduction in hospital mortality in the treatment group compared to the control group, 8.5% vs. 40.4%, respectively [7]. Conducting a similar study with prospective randomized design may be beneficial to confirm these findings in the adult population [15]. Of high importance, is to utilize our findings to spur a prospective, randomized trial in the pediatric population, where sepsis is reported to be on the rise [3]. This will provide validation of the outcomes and provide better insight into the use of these therapeutic options in sepsis and septic shock.

Furthermore, few large clinical trials have addressed the management of critically ill children with severe sepsis and no literature has been published in the use of triple therapy in the pediatric population. Consequently, debate remains about the optimal approach to both basic and adjunct therapies. For example, vasoactive strategies and the use of triple therapy would benefit from further evaluation in rigorous pediatric trials. The low frequency of pediatric sepsis necessitates broad, ideally international, collaboration across many sites to achieve adequate study size to evaluate this adjunct combination [3]. Although the Marik et al. study supports triple therapy in adults with severe sepsis and septic shock, investigation is lacking

in the pediatric population [7]. Due to the outcome of our case report, we felt compelled to report this novel use of triple therapy in our PICU patient, and stimulate future investigation as a prospective, randomized, controlled designed study in the pediatric population.

Informed Consent

Consent has been obtained from the patient's legal guardian and medical decision maker.

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