Review Article on Pediatric Critical Care

Metabolic resuscitation in pediatric sepsis: a narrative review

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Abstract: Sepsis, defined as infection with associated organ dysfunction, accounts for most childhood deaths due to infection globally. Evidence for the optimal support of children with septic shock refractory to the initial sepsis management bundle remains minimal. There is an urgent need for more effective interventions. Administration of hydrocortisone in children with septic shock might fasten shock resolution, and has been shown to dampen the systemic host immune response, augment adrenergic effects, and support the stress response. Ascorbic acid (vitamin C) is one of the most powerful naturally occurring antioxidants and has beneficial effects on multiple pathways which are severely deranged during septic shock. A regimen combining hydrocortisone, ascorbic acid, and thiamine termed "metabolic resuscitation" or "HAT therapy" has been tested in large trials in critically ill adults with sepsis with conflicting results. Available information on intravenous ascorbic acid indicates an excellent safety profile even at very high doses both in adults and children. Given the pharmacological properties and beneficial effects shown both in vitro and in animal studies, and its safety profile, ascorbic acid either as a single therapy or as part of HAT treatment represents a promising candidate for future pediatric sepsis treatments. While pediatric age groups may be more susceptible to ascorbic acid deficiency during sepsis, there is a lack of high-quality trial data on HAT therapy in this age group. A single centre retrospective study identified potential for mortality benefit in children with septic shock, and the results from a randomized controlled pilot trial are being awaited. It is imperative for pediatric research on ascorbic acid and HAT in children with sepsis to critically investigate key questions related to pharmacology, dosing, timing, feasibility, safety, effects on short- and long-term outcomes, and generalisability in view of the global burden of sepsis.

Keywords: Ascorbic acid; hydrocortisone; child; septic shock; thiamine

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Background: the quest for new adjunctive sepsis therapies

In 2017, an estimated 3 million neonates, children and adolescents succumbed to sepsis globally, and as many as 25 million suffered from sepsis (1). Sepsis, more recently defined as infection with associated organ dysfunction (2), thus accounts for most childhood deaths due to infection (3,4). Subsequent to the resolution by the United Nations

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World Health Assembly on sepsis (5,6), there is an increased emphasis on stakeholders in child health, research, and policy making to develop better strategies addressing the health and economic burden due to pediatric sepsis (4,7,8). The challenges to achieve improved outcomes for children with sepsis include availability of preventive measures such as vaccinations, obstacles to structured education and implementation of systematic quality improvement programs, but as well an urgent need for more effective interventions once sepsis is manifest (9). Even in well-resourced settings, sepsis accounts for or is contributing to approximately one in four deaths in Pediatric Intensive Care Units (PICUs) (10-12). Beyond the toll on mortality, survivors of pediatric sepsis and multi-organ dysfunction frequently develop long-term sequelae. This impacts on the functional performance and quality of life of survivors, imposing further burden to families (13).

While observational evidence supports the delivery of an initial sepsis treatment bundle in children (14,15), overall outcomes and survival rates for pediatric sepsis have not sufficiently improved over the past decade (16). Importantly, there has been a paucity of high-quality randomized studies on new interventions in pediatric sepsis since the completion of the activated protein C trial (17). In particular, evidence for the optimal support of children with sepsis or septic shock refractory to the initial sepsis bundle remains minimal, which is in striking contrast to the high mortality observed in this group (18). Septic shock in children commonly presents with overwhelming speed, and the majority of deaths occur within the first 48 hours of presentation (19-22). At a global scale, there is thus a need for pragmatic, safe, and economically viable interventions which can be administered rapidly to children unresponsive to initial sepsis management.

The concept of metabolic resuscitation in sepsis

Unlike many other mammalian species, humans are unable to regenerate ascorbic acid. Adult patients with sepsis are often found to have extremely low ascorbic acid levels, as seen otherwise during scurvy (23). Thiamine deficiency is associated with high lactate and an increased risk of death (24). The properties of ascorbic acid and thiamine at cellular level fed the hypothesis that they may be of value as adjunctive therapy in sepsis-related organ dysfunction (24,25). The potential for ascorbic acid and thiamine to work synergistically with hydrocortisone to support the host response during sepsis has led to a treatment protocol using hydrocortisone (50 mg per dose q 6h), ascorbic acid (1.5 g q6h) and thiamine (200 mg q12h) in critically ill adult patients with sepsis (26). This regimen, also termed "*metabolic resuscitation*" or "*HAT therapy*" (hydrocortisone, ascorbic acid, thiamine) has been shown to be effective in restoring serum ascorbic acid levels (27). A single center study from the United States investigated the impact of applying this metabolic resuscitation regimen on mortality in adults with septic shock (28). The before-after study design used propensity matching and compared 47 patients with matched controls who had comparable baseline characteristics. The hospital mortality in the control group was 40.4% (19 of 47), compared to 8.5% (4 of 47) in the treatment group (P<0.001), resulting in an adjusted odds ratio for mortality of 0.13 associated with treatment (95% CI: 0.04 to 0.48, P=0.002). The study observed rapid improvement in several severity measures such as vasopressor requirement, Sequential Organ Failure Assessment (SOFA) scores, and lactate, indicating faster reversal of septic shock. These promising results have led to some ICUs adopting metabolic resuscitation as practice (29). Before reviewing clinical trial data on HAT, we will first discuss the rationale, safety and efficacy data on HAT components.

Hydrocortisone in sepsis

Steroids exert multiple potentially beneficial effects in septic shock, including dampening of the systemic host immune response, augmentation of adrenergic effects, and supporting the stress response (30). At the same time glucocorticoid therapy may be associated with side effects such as hyperglycaemia, hypertension, critical illness neuropathy, and, possibly, increased risk for hospital-acquired infections (31,32). Several large randomized-controlled trials in adult patients treated in ICU with septic shock have consistently demonstrated faster reversal of septic shock using treatment with hydrocortisone for at least 72 hours, and a good safety profile (adverse events associated with hydrocortisoneaffected only 1.1% of the trial participants) (33-35). Despite the effect on blood pressure and shock reversal, controversy in relation to a mortality benefit of hydrocortisone persists. Adult sepsis guidelines currently recommend clinicians to consider intravenous hydrocortisone in patients in septic shock who are not responsive to fluid and moderate- to high-dose vasopressor therapy (31,32,36). While the previous pediatric Surviving Sepsis Campaign (SSC) recommendations

suggested initiating hydrocortisone if a child is at risk of adrenal insufficiency (37), the use of hydrocortisone in fluid refractory shock remains very common in pediatric age groups (38-40). The recent 2020 pediatric SSC guidelines do not recommend the use of hydrocortisone in fluid-and-inotrope-responsive septic shock. They explicitly state that the benefit of hydrocortisone in paediatric septic shock remains to be determined (14). A large randomized-controlled trial in children comparing hydrocortisone in children with septic shock treated with inotropes versus placebo is currently underway (Stress Hydrocortisone In Pediatric Septic Shock; SHIPSS; ClinicalTrials.gov Identifier: NCT03401398).

Thiamine in sepsis

The interest in thiamine (vitamin B1) as an adjunct in sepsis therapy stems from its role as cofactor for vital steps in the energy metabolism, such as pyruvate dehydrogenase-dependent metabolism of pyruvate to produce acetyl-CoA, and other key enzymes. Severe hypovitaminosis can manifest as Beriberi disease with cardiovascular failure, neurological symptoms, and lactic acidosis, which is attributed to failure of oxygen utilization. Thiamine deficiency has been reported in a number of pediatric critical illness states, such as diabetic ketoacidosis (41). Thiamine deficiency is common in adult and pediatric septic patients (42).

Different doses of thiamine treatment have been reported. Thiamine in general has an excellent safety profile, and adverse events are exceedingly rare (43). Wald *et al.* used 4 mg/kg/d (maximum 200 mg/dose, not stating the number of doses per day) for a duration of four days in children with septic shock and did not observe adverse effects (44). Weiss *et al.* retrospectively reviewed children admitted to a single PICU with septic shock who had received intravenous thiamine therapy over a seven-year study period (42). Their study identified 6 patients and the according thiamine dosing ranged from 1 to 5 mg/kg/d (administered q24h or q12h), with a median duration of 9 days (range 8 to 30 days). Again no side effects were observed. Although lactate levels dropped rapidly in the children treated with intravenous thiamine, the decrease of lactate and of markers of organ dysfunction and shock was similar to matched children not treated with thiamine. In other metabolic diseases, even several fold higher doses of thiamine have been used (45).

In adults with sepsis, observational studies indicate potential benefit with intravenous thiamine therapy: a matched retrospective study of 123 patients receiving thiamine observed higher lactate clearance, and lower 28-day mortality (46). A randomized-controlled trial on thiamine, administered at 200 mg intravenously q12h for up to 7 days in 88 adults with septic shock observed a decrease in lactate from baseline to 24 hours, but did not result in different primary or secondary outcomes compared to placebo (24).

Insights into mechanisms of ascorbic acid in sepsis based on pre-clinical studies

Sepsis-associated organ dysfunction and cellular death occur through ischemia as a result of impaired microcirculation during shock, direct pathogen-related local tissue damage, and complex interrelated processes leading to compromised cellular and mitochondrial function (47,48). Ascorbic acid (Vitamin C) is one of the most powerful naturally occurring antioxidants and has effects on multiple pathways that are severely deranged during septic shock (25): This includes the neutralization of reactive oxygen species and the restoration of anti-oxidant molecules, activation of NFkappaB and mitigation of pro-inflammatory cytokines (49). In addition, ascorbic acid can restore Fe++ and Cu++ concentrations, and reduce glucocorticoid receptor oxidation thereby increasing glucocorticoid responsiveness. *In vitro* and animal data suggest that acorbic acid may protect the capillary endothelium from endotoxin-related damage in the lungs and other organs (50). In an ovine model of gram-negative sepsis induced by *Eschericia coli* infusion, a very high dose of intravenous ascorbic acid (0.5 g/kg loading followed by 0.5 g/kg/hr for 6.5 hours) led to improved cardiac output, blood pressure and renal perfusion, reduced fever and lower inotrope requirement, and restored urine output and hyperlactataemia (51). These findings suggest that ascorbic acid is a promising candidate to reverse the pathophysiology and organ dysfunction associated with sepsis warranting human trials (52).

Safety of high-dose ascorbic acid

The available information on intravenous ascorbic acid indicates an excellent safety profile. A systematic review of studies in adult patients reporting on harm related to high dose intravenous ascorbic acid (defined as ≥6,000 mg/d, ≥75 mg/kg/d, or ≥3,000 mg/m^2/d) identified 74 eligible studies on a total of 2,801 participants (53). The median dose of ascorbic acid was 22,500 mg/d (IQR

8.25–63.75 g/d), which equals to 450 mg/kg/d for a 50 kg adult. A total of 2,310 of these patients received ascorbic acid in nine double-blind RCTs. The adverse event rate in patients treated with ascorbic acid was very low (<1 per 100 patients) and was comparable to controls. Adverse events likely related to high dose ascorbic acid included oxalate nephropathy (n=5), hypernatremia (n=5), hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (n=3), glucometer errors (n=2), and kidney stones (n=1). None of the likely ascorbic acid-related side effects was considered life-threatening. These findings indicate that intravenous high dose ascorbic acid therapy has a very good safety profile and adverse events seem not be more harmful compared to placebo in RCTs. A systematic review of the literature on potential harm associated to high dose ascorbic acid treatment in neonatal and pediatric age groups identified twelve studies reporting on a total of 855 patients, of which 194 received high-dose ascorbic acid (54). Four of these studies were double-blind RCTs. The median ascorbic acid dose was 260 mg/kg/day and ranged from 100 to 1,500 mg/kg/day. Similar to the systematic review on adult patients, the safety related to high dose ascorbic acid in children and neonates was very high with no adverse event associated with ascorbic acid reported (55-60).

Clinical studies on ascorbic acid and HAT therapy in adults with sepsis (*Table 1*)

A recent systematic review on metabolic resuscitation identified nine registered RCTs on variations of metabolic resuscitation in adults with septic shock testing the superiority of this approach compared to standard care (25). The CITRIS-ALI multicenter RCT in adults with sepsis and acute lung injury compared ascorbic acid to placebo. The study reported a mortality benefit associated with the intervention, while other outcomes were similar (mortality 46.3% placebo *vs.* 29.8% intervention, P=0.03) (61). In Australia and New Zealand, the open label VITAMINS trial enrolled 216 adults with septic shock. There was no difference in mortality between the intervention and control arm (22.6% *vs.* 20.5%, P=0.69) (62,63). The double blind ORANGES trial randomized 137 patients and observed faster recovery of shock in the intervention arm (64). Of note, the study protocol allowed the use of open-label corticosteroids in the control (placebo) arm. Three further recent trials in critically ill adults with septic shock have been published, all of which did not show a mortality benefit with ascorbic acid. The ACTS

Table 1 Review of studies on high-dose ascorbic acid (Vitamin C) in critically ill patients with sepsis

Study	Design	Patients	Intervention arms	Time to treatment; and hydrocortisone exposure prior to randomization	Main and mortality outcomes
Marik *et al.*, *Chest* 2017 (28)	Propensity adjusted single institution pre-post study	94 adults with sepsis/ septic shock in ICU	Hydrocortisone (50 mg q6h)/Vitamin C (1.5 g q6h)/thiamine (200 mg q 12h) in n=47 *vs.* historical group [n=47, of which n=28 (59.6%) received hydrocortisone]	N/A	Mortality 8.5% treatment *vs.* 40.4% control (adjusted OR 0.13; 0.04 to 0.48; P=0.002)
Wald *et al.*, *Am J Respir Crit Care Med* 2020 (44)	Single centre propensity-matched observational	557 children with septic shock in ICU	Hydrocortisone (50 mg/m2)/Vitamin C (30 mg/kg q6h)/thiamine (4 mg/kg/d) in n=43 *vs.* hydrocortisone in n=181 *vs.* n=333 controls	Median 12 h (IQR 6–19 h) from PICU admission to start of metabolic resuscitation	Mortality 28% control *vs.* 30% hydrocortisone alone *vs.* 9% intervention (adjusted OR 0.3; 0.1 to 0.9; P<0.05)
CITRIS-ALI; Fowler *et al.*, *JAMA* 2019 (61)	Blinded multicentre RCT	167 adults with sepsis and ARDS in ICU	Vitamin C 50 mg/kg q6hrs in n=84, of which n=56 (67%) received hydrocortisone) *vs.* placebo in n=83 [of which n=54 (65%) received hydrocortisone]	N/A	Mortality 46.3% placebo *vs.* 29.8% intervention (difference 16.6%; 2% to 31.1%, P=0.03)

Table 1 (*continued*)

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Study	Design	Patients	Intervention arms	Time to treatment; and hydrocortisone exposure prior to randomization	Main and mortality outcomes
VITAMINS; Fuji *et al. JAMA* 2020 (62,63)	Open label multicentre, international RCT	216 adults with septic shock in ICU	Hydrocortisone (50 mg q6h)/Vitamin C (1.5 g q6h)/thiamine (200 mg q 12h) in n=109 *vs.* hydrocortisone (50 mg/kg q6h) in n=107	Time from meeting eligibility criteria to the first dose median 12.1 hrs (IQR 5.7–19.0) intervention, and 12.9 hrs (4.0–15.0) for control	Mortality 22.6% intervention *vs.* 20.4% control (difference 2.3%; –8.9% to 13.4%; P=0.69)
ORANGES; Iglesias *et al.*, *Chest* 2020 (64)	Single centre double blind, placebo controlled RCT	137 adults with septic shock in ED	Hydrocortisone (50 mg q6h)/Vitamin C (1.5 g q6h)/thiamine (200 mg q12h) in n=68 *vs.* n=67 controls [of which n=28 (41%) received hydrocortisone]	Time between presentation to ED and first dose of study drug mean 9.9±4.5 hours	Time to shock reversal 27±22 hrs intervention *vs.* 53±38 hrs controls, (P<0.001); ICU mortality 9% *vs.* 14% (P=0.37)
ACTS; Moskovitz *et al.*, *JAMA* 2020 (65,66)	Multicentre double blind, placebo controlled RCT	200 adults with septic shock in ICU	Hydrocortisone (50 mg q6h)/Vitamin C (1.5 g q6h)/thiamine (100 mg q6h) in n=101 *vs.* placebo in n=99 [of which n=14 (14.1%) received open-label corticosteroids after enrolment]	Time from vasopressor initiation to first study drug median 14.5 hrs (IQR 8.1–19.1) intervention versus 13.0 hrs (7.5–20.5) placebo	Mortality 34.7% intervention *vs.* 29.3% control (hazard ratio, 1.3; 95% CI: 0.8–2.2; P=0.26)
ATESS; Hwang *et al.*, *Intensive Care Med* 2020 (67)	Multicentre double blind, placebo controlled RCT	111 adults with septic shock in ED	Vitamin C (50 mg/kg max 3 g q12h)/ thiamine (200 mg q12h) in n=53 (of which 58.5% received hydrocortisone) *vs.* placebo in n=58 (of which 50% received hydrocortisone)	time from ED arrival to first study drug administration median 8.4 h (IQR 5.7–14.9) intervention and 9.9 h (IQR 7.4–15.6) placebo	28-d mortality 20.8% intervention *vs.* 15.5% control (P=0.47)
Coloretti *et al.*, *J Crit Care* 2020 (68)	Propensity-matched single centre pre-post study	137 adults with septic shock in ICU	Hydrocortisone (240 mg/d infusion)/Vitamin C (1.5 g q6h)/thiamine (200 mg q12h) in n=56 *vs.* hydrocortisone in n=56	N/A	Length of mechanical ventilation 3d intervention *vs.* 6d controls (P=0.012). Hospital mortality 50.0% intervention *vs.* 60.7% control (P=0.25)
VICTAS; Sevransky *et al.*, *JAMA* 2021 (69)	Multicentre double blind, placebo controlled RCT	501 adults with septic shock planned to be admitted to ICU	Hydrocortisone (50 mg q6h)/Vitamin C (1.5 g q6h)/thiamine (100mg q6h) in n=252 *vs.* placebo in n=249	time between onset of qualifying organ dysfunction and first dose of study drug 15 hours median (IQR 8–22 hours); 33% hydrocortisone treatment pre-randomization	Ventilator- and vasopressor-free days 25 days intervention versus 26 days placebo (P=0.85). 30-d mortality 22% intervention *vs.* 24% control (unadjusted OR 0.900, 95% CI: 0.594–1.363, P=0.619)

trial observed a higher survival free of shock (median difference 1 day, P=0.02) in the 101 patients randomized to HAT compared to placebo, while other primary and secondary outcomes were not different (65,66). The ATESS trial used a slightly higher ascorbic acid dose (50 mg/kg, max. 3g) and compared ascorbic acid and thiamine with placebo in 111 patients, but did not find significant outcome differences (67). A further single center propensity-matched study observed a shorter duration of ventilation in adults with sepsis receiving HAT therapy compared to hydrocortisone alone (68). The VICTAS trial utilized an adaptive design and was terminated after recruitment of 501 participants as funding was withheld by the main founder, despite interim analyses not having reached neither futility nor superiority thresholds (69-71). The authors calculated a 30.7% probability that full extension of the trial to the originally designed 2,000 participants may show efficacy of HAT on the primary outcome of ventilator- and vasopressor-free days.

Importantly, direct comparison of study findings is hampered by differences between the studies in relation to the type of patients enrolled, time to enrolment, intervention (ascorbic acid alone or HAT therapy), dosing of ascorbic acid and thiamine, use of hydrocortisone in the control arm, treatment with hydrocortisone prior to randomization, and blinding.

Pediatric studies on ascorbic acid and HAT resuscitation—the RESPOND PICU study

In critically ill children, decreases in serum ascorbic acid levels have been demonstrated and seem to be related to the degree of oxidative stress (72). Children could be more susceptible to ascorbic acid deficiency during sepsis due to factors such as chronic malnutrition, a high metabolic rate, and complex congenital conditions and comorbidities. Extrapolation of adult HAT trial results on children is therefore challenging, indicating a need for pediatric data. To date, only one study on metabolic resuscitation has been published (*Table 1*). This propensity-matched retrospective single center cohort study on 557 children with septic shock reported good safety of metabolic resuscitation in 43 children with septic shock (44). In adjusted analyses, HAT therapy was associated with decreased 30- and 90-day mortality (P<0.05) compared to hydrocortisone alone, and compared to standard care without hydrocortisone.

A search of trial registries revealed one registered RCT in pediatric age groups on metabolic resuscitation in septic shock (ACTRN12619000829112). The Resuscitation in Paediatric Sepsis Using Metabolic Resuscitation—A Randomized Controlled Pilot Study in the Paediatric Intensive Care Unit (RESPOND PICU) trial led by the Paediatric Study Group of the Australian and New Zealand Intensive Care Society (ANZICS PSG) is recruiting 60 children admitted to PICU with septic shock treated with inotropes for at least two hours (73). This open label pilot study is expected to yield feasibility and safety data on metabolic resuscitation in critically ill children and will report on short- and long-term outcomes.

Implications for future research

In conclusion, the available evidence for high dose ascorbic acid and metabolic resuscitation indicates an excellent safety profile, but does not support a benefit of standard "high dose" vitamin c therapy in adults. Importantly, ascorbic acid is widely available and can be produced and purchased in healthcare settings around the world at relatively low cost. Given the pharmacological properties and beneficial effects shown in both *in vitro* and animal studies on sepsis-related mechanisms detrimental to the host, ascorbic acid either as a single therapy or as part of HAT treatment remains a potential candidate for future pediatric sepsis treatments. However, in the history on sepsis research, the quest for magic bullets or one-size-fits-all approaches has failed too often. Pediatric intensivists and researchers should embrace lessons learnt in adults following the rapid uptake of HAT outside trials: Subsequent to low quality data and possibly augmented by social media, a change of practice in many institutions ensued despite the initial absence of high quality data (74), and despite several high quality RCTs subsequently not demonstrating clear benefit. By consequence, it is imperative for pediatric research to address key questions related to pharmacology, dosing, timing, feasibility, safety, and effects on short- and long-term outcomes of ascorbic acid and HAT in children with sepsis (*Table 2*). In the near future, we may witness the availability of personalized treatment options such as transcriptomics-based identification of sepsis phenotypes which carry the potential to magnify benefit to risk ratios in highly selected populations (39,75,76). Finally, given substantial differences in epidemiology, host phenotype, and ICU resourcing (77), future studies in the field should seek to incorporate global trial sites which have not been

Table 2 Gaps in knowledge and priorities for future research on hydrocortisone, ascorbic acid, and thiamine (HAT) therapy in pediatric sepsis

Research questions	Considerations
Optimal dosing and duration of ascorbic acid therapy	Single dose versus continuous versus intermittent treatment
	Optimal dosing of high-dose ascorbic therapy
	Duration
	Timing of administration (upon diagnosis of shock, upon initiation of inotropes, when inotrope-refractory shock is diagnosed etc.)
Optimal dosing and duration of thiamine therapy	Dose
	Duration
	Timing of administration
	Single therapy with thiamine versus combined therapy/HAT
Identification of phenotypes more likely to benefit from HAT	Severity scores
	Serum and host transcriptomic biomarkers of oxidative stress, endothelial dysfunction, and organ dysfunction to identify subgroups
	Ascorbic acid serum levels to guide therapy
	Mitochondrial assays to guide thiamine therapy
	Host immune monitoring to guide hydrocortisone therapy
Safety	Safety of mega-dose and high-dose ascorbic acid
	Safety of high-dose thiamine
	Safety of HAT compared to standard care
Efficacy	Impact of HAT therapy, or of its components, on
	Organ dysfunction
	Need for organ support
	Duration of PICU stay
	Survival
	Survival free of organ dysfunction
	Survival free of organ support
	Survival free of PICU
Interventional trials investigating the effect of HAT and HAT components (blinded or open label)	HAT versus standard care
	HAT versus hydrocortisone alone versus standard care
	Ascorbic acid alone versus standard care
	Thiamine alone versus standard care
Generalisability and considerations prior to implementation	Cost effectiveness
	Impact of HAT or HAT components on long-term outcomes such as quality of life or functional status

commonly represented in clinical trials.

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