Original article

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Early hydrocortisone, ascorbate and thiamine therapy for severe septic shock

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Abstract

***Objective*: Septic shock is a devastating physiological state with significant mortality risk. Recently, trials have suggested clinical benefits of adjunctive treatment with iHAT. These agents may reduce oxidative stress, inflammation, mitochondrial dysfunction and endothelial injury in patients with septic shock. The primary objective of this study was to evaluate intensive care unit (ICU) and hospital mortality for patients with septic shock treated with and without intravenous hydrocortisone, ascorbic acid and thiamine (iHAT).**

***Design*: A retrospective cohort study was performed evaluating patients admitted with septic shock requiring vasopressors to the ICU treated with and without iHAT.**

***Setting*: The intensive care unit of a tertiary care academic center in Madison, WI**

***Patients*: Of 3,463 patients admitted to the ICU, 206 met inclusion criteria with 127 treated according to standard care (SC) and 79 receiving additional adjunctive iHAT.**

***Intervention*: Hydrocortisone 50 mg IV q6h, Ascorbic Acid 1500 mg IV q6h and Thiamine 200 mg IV q12h.**

***Measurements and results*: Acute Physiology And Chronic Health Evaluation (APACHE) scores were higher in the SC cohort. Observed ICU mortality was lower in the iHAT cohort compared to SC as was APACHE-adjusted ICU mortality (OR 0.44, p=0.043). APACHE-adjusted ICU mortality was lowest when iHAT was initiated within 6 hours (OR 0.08, p<0.01). Hospital mortality, vasopressor duration, initiation of renal replacement therapy and lengths of stay were not significantly different between cohorts.**

***Conclusion*: There was a time-sensitive improvement in APACHE-adjusted ICU mortality in septic shock patients treated with adjunctive iHAT. The strong temporal benefit of iHAT therapy has important implications towards future studies.**

Key words: Critical care, shock, septic, ascorbic acid, hydrocortisone, thiamine.

Introduction

Sepsis is a life-threatening disease process that impacts 1.7 million patients in the United States annually and carries a mortality rate of up to 45%. (1,2) Despite the remarkable societal burden, limited targeted therapies exist. Current guidelines emphasize rapid identification, effective source control, and empiric antibiotic therapy alongside of early and aggressive management of hypoperfusion with combinations of fluids, vasopressors, and/or inotropes. (3,4) More recently, therapeutic options have expanded to include an emphasize on reversing the metabolic derangements of septic shock, which include widespread inflammation, endothelial dysfunction with ischemia/reperfusion injury, and oxidative stress with mitochondrial dysfunction. (4-8)

One group of medications that may offer synergistic benefits is iHAT therapy, consisting of hydrocortisone, ascorbic acid (vitamin C), and thiamine, all administered intravenously. (9-11) Early clinical data has repeatedly found considerable improvements in mortality with iHAT therapy, (9,11-15) and subsequently many intensivists have insti-

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tuted adjunctive iHAT therapy into the care of patients with septic shock given its potential benefits and favorable safety profile. (9,16)

We performed a retrospective cohort study of patients with septic shock treated with and without adjunctive iHAT therapy in an intensive care unit (ICU) at a single tertiary care academic hospital between January 1, 2018 and June 30, 2019. We hypothesized that critically ill septic patients treated with iHAT therapy would have reduced ICU and 30-day mortality compared to patients who were not treated with this constellation of supplements. Our primary outcome measures were ICU and hospital mortality and Acute Physiology And Chronic Health Evaluation (APACHE)-adjusted mortality rates. Secondary outcome measures included ICU and hospital lengths of stay, vasopressor duration, mechanical ventilator duration, and new renal replacement therapy (RRT) initiation. Planned subgroup analysis included patients who received iHAT "early," within the 6-hour Center for Medicare & Medicaid Services (CMS) sepsis bundle time limit.

Methods

Patient selection

This was an institutional review board approved retrospective cohort study at a tertiary academic medical center. All patients admitted to the main medical-surgical ICU from January 1, 2018 to May 31, 2019 were screened for the diagnosis of sepsis using an ICU patient database compiled by our electronic ICU (E-ICU) service using Philips E-Care Manager™ software (Philips, Andover, MA, USA). The E-ICU service staff has routinely input the clinical and diagnostic data necessary for calculation of APACHE IV scores for all admitted patients since 2008. The E-ICU software then generates, on a quarterly basis, an Excel spreadsheet (Microsoft, Tigard, OR, USA) database of all admitted patients which includes: admitting diagnosis, physician and service, both actual and predicted ICU and hospital mortality, ventilator use and duration of use, and ICU and hospital length of stays (LOS). The database was filtered to include only those patients with an admission diagnosis of sepsis, septic shock, or bacterial pneumonia. A review of the electronic health record (Epic™, Verona, WI) was then performed on all such identified patients to assess if they met the following inclusion criteria for the study as follows: 1) admission to the medical ICU service, 2) a vasopressor requirement within the first 24 hours of admission with a duration of at least 3 hours, 3) a treatment plan which included early anti-infective therapy, 4) no requirement for an open surgical intervention to achieve source control as defined below, 5) if transferred from a referring hospital, arrival to the ICU occurred within 24 hours of initial presentation to the referring hospital, 6) initiation of iHAT therapy occurred within 24 hours of admission to the ICU with a full course administered as defined below, 7) absence of an advanced directive or surrogate decision that limited intensive care therapies within the first 24 hours of ICU admission based on a pre-existing poor prognosis or terminal illness (**Figure 1**). Patients with sepsis caused by obstructive biliary or urologic pathology necessitating interventional but not open-surgical procedures were included.

Standard care and iHAT interventions

Standard treatment of septic shock in all patients was in accordance with the treatment bundle recommended by the 2012 Surviving Sepsis Campaign guidelines. (17) All patients received early, aggressive initial fluid resuscitation targeting 30 ml/kg of crystalloid unless contraindicated, with administration of broad-spectrum antibiotics within 3 hours of the diagnosis of severe sepsis or septic shock. Vasopressor therapy was initiated with norepinephrine for fluid-nonresponsive hypotension to maintain a mean arterial blood pressure (MAP) >65 mmHg and was discontinued when not required to maintain this MAP goal. Steroids were administered at the discretion of the critical care faculty physician, generally for refractory hypotension despite moderate- or high-dose vasopressor requirement. Other cares were within accepted critical care guidelines: lactate was trended and correlated to interval physical examinations to determine ongoing need for resuscitation; lung protective ventilation was instituted with adequate positive end-expiratory pressure; unnecessary use of sedatives was minimized and a daily sedation holiday instituted; and we practiced routine prophylaxis for deep venous thromboembolism and stress ulcers.

Patients in the iHAT cohort all received standard care with the addition of hydrocortisone 50 mg IV every 6 hours, vitamin C in a dose of 1.5 g IV every 6 hours, and thiamine 200 mg IV every 12 hours. Completion of a full course was defined as continuing iHAT until the patient either was liberated from vasopressors, was discharged from the ICU or until 4 days of therapy had elapsed - whichever came first. Patients who never received iHAT, received incomplete courses or were initiated on iHAT more than 24 hours after presentation for sepsis were assigned to the standard care co-

hort. Sepsis presentation time was consistent with the surviving sepsis bundle definitions and defined as the emergency department (ED) listed triage time for patients admitted from the ED and the ICU admission time for patients admitted from the hospital ward. (18)

Data analysis

Retrospective review of the electronic health record and the Philips E-Care Manager™ ICU (E-ICU) database provided all necessary patient data including age, gender, comorbidities, admission source, sepsis source, time to both antibiotics and iHAT therapy, time from initial healthcare facility presentation to ICU admission, discharge location, duration of mechanical ventilation, vasopressor duration, requirement for RRT, and both ICU and hospital lengths of stay and mortalities. APACHE IV scores from the E-ICU database were used to calculate both expected ICU and hospital mortality, ICU and hospital lengths of stay, and initiation and duration of mechanical ventilation. Patients who were discharged directly from the ICU to inpatient hospice care >24 hours from ICU admission were considered an ICU mortality. Vasopressor liberation was defined as freedom from vasopressor use for more than 12 hours. Subgroup analysis was performed for patients who received "early" iHAT therapy (early-iHAT), defined as occurring within the 6-hour CMS sepsis bundle time limit. In addition, outcomes were compared for patients admitted from the in-hospital ED or ward compared to admissions from referring hospitals.

We assessed for survival using the electronic health record with the last date of follow-up on August 15, 2019. Descriptive analyses were conducted using summary statistics, frequencies and proportions. Categorical baseline data was compared between standard care and iHAT patients using a chi-square test and continuous variables compared using Welch's two-sample t-test or using Mann-Whitney U test for non-normally distributed data. Multiple logistic regression was used to estimate ICU and hospital mortality and adjust for risk based on APACHE IV scores. Firth's bias reduction was used in case of separation. (19) Multivariable Cox-proportional hazards models were used to predict the adjusted mortality hazard between the categorized study groups. Changes in vasopressor duration were estimated by fitting general linear models to log-transformed data. Length of stay was modelled using Fine and Gray's competing risk regression. (20) All analyses were conducted using R version 3.5.2. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient selection and baseline characteristics

Of the 3,463 patients admitted to the ICU during the study time period, 639 had a diagnosis of sepsis, septic shock, or bacterial pneumonia. Two hundred and six patients met all subsequent inclusion criteria and were entered in the study. Of these 206 patients, 127 met criteria for the standard care cohort and 79 met criteria for the iHAT cohort (**Figure 1**). The study included five patients in the standard care group who received very late, or very limited iHAT therapy; these patients were placed into the standard care (SC) cohort. **Table 1** compares the baseline characteristics of the cohorts. There were no significant differences in age or gender. There was a higher rate of cancer in the iHAT cohort (26.6% vs 14.2%, p=0.04). The most common source of sepsis in both cohorts was pulmonary with no significant differences in source of sepsis between the groups. Patients were most frequently admitted to the ICU from the emergency department (43.7%) or were transferred from a referring hospital (37.8%) with 18.4% admitted from a hospital ward. Patients transferred from referring hospitals were almost all transferred directly from the presenting hospital ED to our ICU using our institution's regional active air-medical response team. Average time from initial healthcare presentation to ICU admission was similar between cohorts (7.6 vs 7.1 hours, p=0.57). Adjunctive iHAT therapy was initiated an average of 10.9 hours after presentation of septic shock and patients received iHAT therapy for an average duration of 40.7 hours (SD 27.3). All patients in the iHAT cohort received hydrocortisone within 48 hours of ICU admission compared to 31.5% of patients in the SC cohort (p<0.01). There was no statistically significant difference between the cohorts in the need for mechanical ventilation (iHAT 41.7% vs 55.9%, p=0.07).

Outcomes

Comparisons between iHAT and SC cohorts are given as an odds ratio (OR) displayed as OR [95% confidence interval]. Patients in the SC cohort had higher APACHE IV scores (88.2 vs 80.0, p=0.04) but no significant difference in APACHE-predicted ICU mortality (24.0% vs 17.6%, p=0.06). Observed ICU mortality was lower in the iHAT cohort compared to the SC cohort (11.4% vs 26.0%, p=0.02). This relationship held true after adjustment for APACHE scores (OR 0.44 [0.18, 0.97], p=0.043). Hospital mortality was not signif-

icantly different between cohorts (iHAT 26.6% vs 32.3%, p=0.48), nor was APACHE-adjusted hospital mortality (iHAT OR 0.92 [0.47, 1.76], p=0.80) (**Table 2**).

After excluding patients who died in the ICU from each cohort (who could not thereafter receive vasopressors), duration of vasopressor therapy was significantly reduced in the iHAT cohort (median 13.9 vs 24.2 hours, p=0.02) but not after APACHE-adjustment (multiplicative difference compared to SC=0.81 [0.63, 1.04], p=0.09). There were no significant differences in new RRT initiation (14.9% iHAT vs 26.4%, p=0.10), or APACHE-adjusted new RRT initiation (OR 0.62 [0.26, 1.40]). Among surviving patients, neither ICU nor hospital length of stay were significantly different between cohorts (ICU LOS, iHAT median 2.0 vs 2.5 days, p=0.24; hospital LOS, iHAT median 9.5 vs 9.1, p=0.86) (**Table 3**).

On planned subgroup analysis, initiation of iHAT therapy within 6 hours of presentation of sepsis was associated with a reduction in ICU mortality compared to SC, which remained significant after adjusting for APACHE scores (OR 0.08 [0.0, 0.59], p<0.01). There was no such association when iHAT was initiated 6-24 hours after presentation (OR 0.66 [0.27, 1.50], p=0.33) (**Figure 2**). Hospital mortality was not significantly different for either subgroup (<6 hours vs SC: OR 0.79 [0.25, 2.19], p=0.67; >6 hours vs SC: OR 0.99 [0.48, 2.02], p=0.99) (**Figure 2**). Second, there was no overall difference in ICU mortality for all patients based on source of admission (referring hospital vs ED/ward OR 1.05 [0.93, 1.17], p=0.46), or for SC patients alone (referring hospital vs ED/ward OR 0.97 [0.83, 1.13], p=0.68).

Discussion

This retrospective cohort study found a decreased APACHE-adjusted ICU mortality rate when adjunctive iHAT therapy was added to standard care among patients with septic shock. This effect was driven by early (<6 hour) initiation of therapy, consistent with other bundle-based interventions in sepsis. (3) There was no change in hospital mortality between cohorts. Other outcome measures including lengths of stay, ventilator duration, APACHE-adjusted vasopressor duration, and RRT initiation were not different between cohorts.

Our findings of a strong relationship between the timeliness and effectiveness of iHAT therapy towards ICU mortality are crucial and novel. Early initiation of iHAT therapy within typical sepsis bundle timelines was associated with the largest reduction in mortality (**Figure 2**). Most importantly, the impact of treatment delay suggests that randomized and controlled trials may suffer find a decreased magnitude or even lack of effect if delays for consent, enrollment, randomization, and administration are excessive.

It is surprising that our APACHE-adjusted ICU mortality reduction did not result in improved hospital mortality. This is potentially driven by the fact that a considerable proportion of patients who develop sepsis have advanced co-morbidities or are at extremes of age. In this study specifically, our iHAT cohort more frequently had cancer (26.6 vs 14.2%, p=0.04). In these cases, although a larger proportion of patients treated with iHAT may survive the initial insult of septic shock, later decline may occur from other end-stage chronic illness, post-ICU syndrome, or due to secondary infections after surviving their initial insult. Adjunctive therapy, in this case, may have improved short term aberrancies, but not the pathophysiologic baseline that resulted in, or was a result of, septic shock. Further, families may feel compelled to adjust goals of care in light of severity of illness or oncologic prognosis after a challenging ICU stay.

Additionally, the appropriate onset timing and duration of iHAT therapy has yet to be elucidated. It may be that initial benefits from early and aggressive antioxidant therapy are reversed by later decrements due to the loss of crucial oxidant signalling. Oxidants, despite injuring cells at high levels, are important to cellular signalling and stress adaptation. Importantly, they also play a role in activation of various pathways in the innate and adaptive immune response. (21)

The extreme oxidative stress of sepsis causes mitochondrial dysfunction and is evidenced by pathologic depletion of antioxidants. (7,8) Severe depletion of vitamin C is ubiquitous in sepsis and is quantitatively associated with disease severity and mortality. (6,13,22-25) Adequately dosed parenteral regimens (generally 2-3 g/d) of vitamin C predictably corrects deficiency and increase oxidant scavenging in the critically ill. (9,11-15) Notably, enteral regimens are woefully inadequate in the critically ill, as are typical nutritional dosing recommendations. (26) The selected dose has been shown to predictably achieve supratherapeutic levels (27) that remain below typical doses argued to risk pro-oxidant injury. (28) Adequate vitamin C levels directly improve endothelial and mitochondrial function, catecholamine synthesis, and decrease ischemia and reperfusion injury. (28-33) Vitamin C may also improve immune (34,35) and adrenal function. (36,37) Steroids increase vitamin C enteral and cellular absorption, (38,39) treat rela-

tive or absolute adrenal insufficiency and target inflammation and endothelial dysfunction. (40-43) Finally, thiamine deficiency is common in septic shock and supplementation decreases lactic acidosis, supports the mitochondria, and may stabilize the endothelium. (44-47)

Clinical trials assessing vitamin C monotherapy in the critically ill have shown several direct patient benefits including improved SOFA scores, (13) decreased vasopressor requirements, (12) and mortality. (12-14) Combination therapy with iHAT may offer synergistic benefits (28,48) and has shown similarly improved patient outcomes including mortality in some patient populations including patients with septic shock (9,10,15,49) and pneumonia. (11)

Literature to date suggests that iHAT therapy in critically ill patients is well tolerated. Nonetheless, theoretical risks include the risk of a pro-oxidant effect of vitamin C at extremely high doses or in at-risk populations such as sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, and hereditary hemochromatosis. (50-52) Of note, several trials have administered doses in excess of 10 g/day without causing injury. (9,13,14,53) Next, vitamin C causes hyperoxalosis, which may in at risk patients result in nephrolithiasis and obstructive uropathy. (54-56) Finally, with some point of care glucose meters vitamin C can cause a false-high error, resulting in inappropriate insulin administration and hypoglycemia. (57-59)

This study has significant limitations in that it is a single-center, observational "real-world" study employing a retrospective analysis of cohorts with an imbalance in the severity of illness. Severity imbalance may be crucial; some studies have shown benefits only in more severe subsets of patients. (10) Additionally, iHAT therapy was not limited to patients with biomarker aberrancies like those used by Marik et al. (46) Further, iHAT use was non-standardized and frequently delayed after presentation. Other trials with significant delays in therapy had nonsignificant results. (60,61) Finally, physician initiation of iHAT therapy varied markedly. Practice patterns, patient selection, and other unique practice habits and selection bias may have played a role in these results. Notably, we did not observe any complications of therapy in the iHAT cohort, but an additional consideration of early adoption of therapies in a non-prospective manner is that complications are not systematically screened for or audited. Finally, the study included five patients in the standard care group who received very late, or very limited iHAT therapy. Short duration therapy may not offer patient benefit, (10) nor may late "salvage" use, but this is not consistent with intent-to-treat prospective research. Finally, it is notable that in the iHAT cohort there was a reduction in ICU mortality in those patients admitted from the ED/ward, but not from referring hospitals, again, largely from referring EDs. This relationship was not apparent within the SC cohort. Though prehospital care may have driven some changes in outcomes, these patients were also far more likely to receive iHAT therapy in a timely manner.

This retrospective cohort study found a time-sensitive improvement in APACHE-adjusted ICU mortality in septic shock patients treated with adjunctive iHAT therapy. Unfortunately, we did not observe a difference in hospital mortality. This supports emerging literature for the benefit of iHAT therapy in septic shock. The strong temporal benefit of iHAT therapy has important implications towards future studies and future trials should clearly explore the relationship between timeliness of therapy and the magnitude of improvement in outcomes.

Table 1. Demographics and baseline clinical characteristics of cohorts

Characteristic	iHAT therapy	Standard care	p value
Age, years (mean, SD)	64.4 (13.9)	61.1 (16.2)	0.13
Male gender, %	54.4	55.9	0.95
Comorbidities, %			
- Cancer	26.6	14.2	0.04*
- Cardiovascular disease	55.7	49.6	0.48
- Pulmonary disease	22.8	29.1	0.40
- Diabetes	22.8	22.8	0.99
- Organ transplant recipient	13.9	16.5	0.76
- Liver disease	13.9	10.2	0.56
- ESRD	6.3	13.4	0.17
Admission source, %			0.11
- Referring hospital	35.4	39.4	
- ED	51.9	38.6	
- Hospital ward	12.7	22.0	
Source of sepsis[1], %			0.27
- Pulmonary	40.5	46.5	
- Gastrointestinal	20.3	17.3	
- Cutaneous/soft tissue	8.9	15.7	
- Genitourinary	24.1	18.1	
- Other	6.3	2.4	
Time to ICU admission after presentation, hours (mean, SD)	7.6 (5.2)	7.0 (8.5)	0.57
Ventilator initiation, %	41.7	55.9	0.07
Hydrocortisone use[2], %	100	31.5	<0.01*
Time to iHAT therapy after presentation, hours (mean, SD)	10.9 (7.0)	N/A	
iHAT therapy duration, hours (mean, SD)	40.7 (27.3)	N/A	

Legend: ESRD=end stage renal disease; ED=emergency department; ICU=intensive care unit; iHAT=intravenous ascorbate, hydrocortisone and thiamine.
*statistical significance, defined as $p \leq 0.05$.
[1]Sepsis source determination made on admission to intensive care unit.
[2]Intravenous hydrocortisone given during first 48 hours of intensive care unit admission.

Table 2. Primary clinical outcome measures

Outcome	iHAT therapy	Standard care	p value
APACHE IV score[1]	80.0	88.2	0.04*
Predicted ICU mortality, %	17.6	24.0	0.061
Observed ICU mortality[2], %	11.4 (9/79)	26.0 (33/127)	0.02*
APACHE-adjusted ICU mortality[2] OR [95% CI]	0.44 [0.18, 0.97]	(reference)	0.04*
Hospital mortality[2], %	26.6 (21/79)	32.3 (41/127)	0.48
APACHE-adjusted hospital mortality[2] OR [95% CI]	0.92 [0.47, 1.76]	(reference)	0.80

Legend: APACHE IV=Acute Physiology and Chronic Health Evaluation-IV; ICU=intensive care unit; iHAT=intravenous ascorbate, hydrocortisone and thiamine; OR=odds ratio; CI=confidence interval.
*Statistical significance, defined as $p \leq 0.05$.
[1]Scored electronically using admission data.
[2]Mortality includes patients who expired during their stay or were transitioned to a hospice location.

Table 3. Secondary clinical outcome measures

Outcome	iHAT therapy	Standard care	p value
Vasopressor duration[1], hours (median)	13.9	24.2	<0.02*
APACHE-adjusted Vasopressor duration Change[1], [95% CI]	0.81 [0.63, 1.04]	(reference)	0.09
New RRT initiation[2], % (N)	14.9% (11/74)	26.4% (29/110)	0.10
APACHE-adjusted New RRT initiation[2] OR [95% CI]	0.62 [0.26, 1.40]	(reference)	0.26
Ventilator duration, days	3.4	3.3	0.96
APACHE-adjusted Ventilator duration, days	0.29 [-1.0, 1.6]	(reference)	0.66
ICU LOS, days[3] (median)	2.0	2.5	0.24
APACHE-adjusted ICU discharge SHR[4]	1.54 [1.12, 2.12]	(reference)	<0.01*
Hospital LOS, days[3] (median)	9.5	9.1	0.86
APACHE-adjusted Hospital discharge SHR[4]	1.02 [0.73, 1.43]	(reference)	0.91

Legend: APACHE=Acute Physiology and Chronic Health Evaluation; CI=confidence interval; RRT=renal replacement therapy; OR=odds ratio; ICU=intensive care unit; LOS=length of stay; SHR=subdistribution hazard ratios; iHAT=intravenous ascorbate, hydrocortisone and thiamine.

*Statistical significance, defined as $p \leq 0.05$.

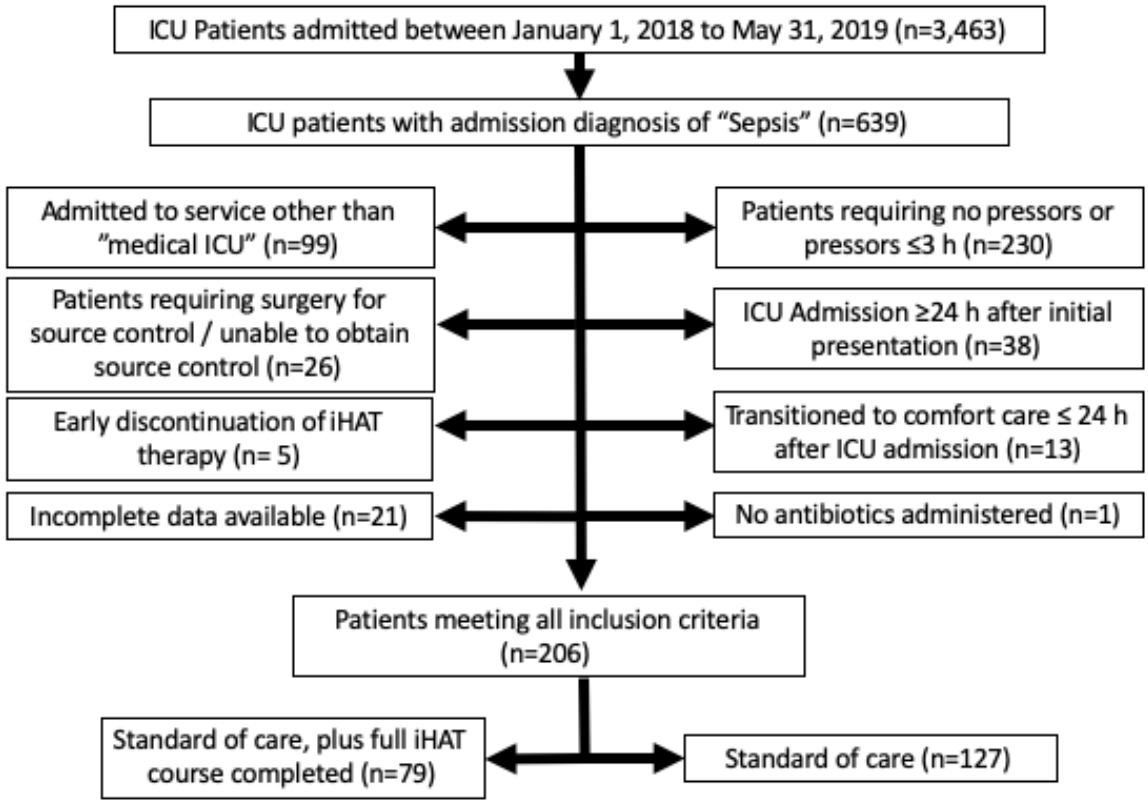
[1]Vasopressor duration excludes patients that died in the ICU. Change is multiplicative relative to standard care: the iHAT cohort were on vasoactives 81% as long as the SC cohort, and this difference was not statistically significant ([95% CI 63%, 104%] p=0.091).

[2]RRT initiation after ICU admission, excluding patients on pre-admission renal replacement therapy.

[3]Medians expressed include only patients who survived the ICU and hospital, respectively.

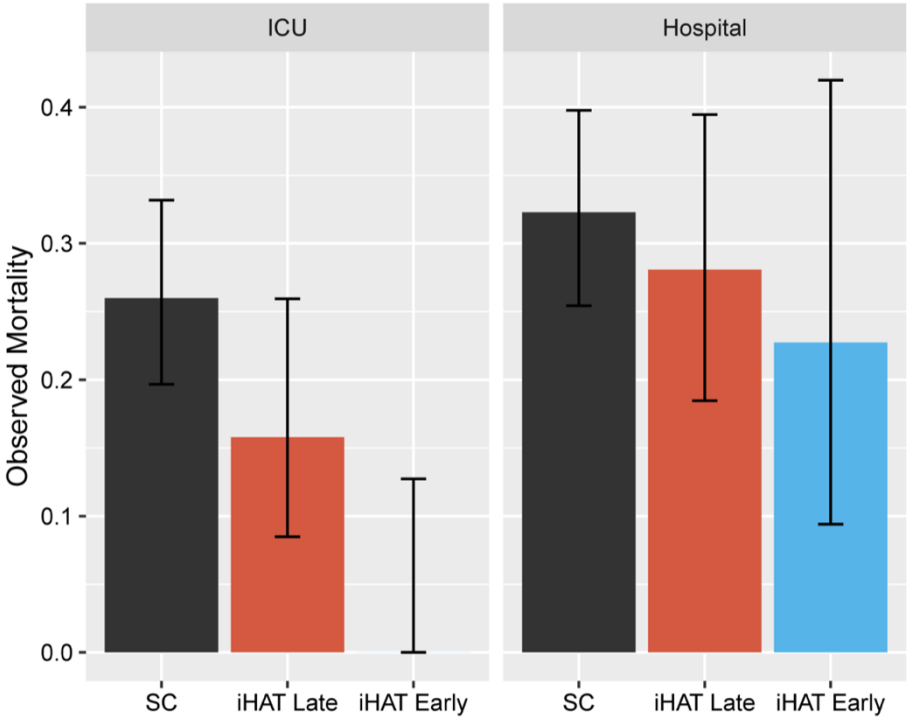
[4]Subdistribution hazard ratios (SHR) >1 indicate increased rate of discharge and therefore shorter length of stay. Mortality was treated as a competing event.

Figure 1. Patient selection flowchart



Legend: ICU=intensive care unit; iHAT=intravenous ascorbate, hydrocortisone and thiamine

Figure 2. ICU and hospital mortality: subgroup analysis



Legend: Comparison of mortality for patients in the standard care (SC) cohort compared to iHAT subgroups. Those that initiated iHAT therapy in <6 hours (iHAT Early; blue) after ICU admission had a significant improvement in ICU mortality versus SC (black); others (iHAT Late; red) did not. There was no difference in hospital mortality in any group. Error bars delineate 90% binomial confidence intervals.

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