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# Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Health-Related Quality of Life in Sepsis

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**Objectives:** Patients who experience sepsis often have long-term effects that may impact health-related quality of life. This study aimed to investigate whether the combination of ascorbic acid, corticosteroids, and thiamine compared with placebo improves health-related quality of life in patients with septic shock.

**Design:** Secondary analysis of the Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis randomized controlled trial (NCT03389555).

**Setting:** Thirteen tertiary-care hospitals in the United States.

**Patients:** Patients who were enrolled in Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis, survived to 90 days post enrollment and were able to be contacted by telephone.

**Interventions:** Patients were randomly assigned to parenteral ascorbic acid (1,500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 hours for 4 days or placebo.

**Measurements and Main Results:** One hundred seventeen patients (59%) survived to 90 days and were administered the Short Form 36 questionnaire; of these, 72 (62%) completed the Short Form 36 (38 [53%] in the intervention group, 34 [47%] in placebo). Sixty-six (92%) completed all survey questions (36 [95%] in the intervention group, 30 [88%] in placebo). There was no significant difference in overall Short Form 36 score between intervention and placebo group (median score: 39.4 [interquartile range, 31.2–45.4] vs 43.2 [37.0–46.7],

respectively,  $p = 0.18$ ). We found no statistically significant difference between the two groups in any of the other health-related quality of life domains used.

**Conclusions:** We found no difference in the health-related quality of life in patients with septic shock treated with a combination of ascorbic acid, corticosteroids, and thiamine compared to placebo.

**Key Words:** ascorbic acid; corticosteroids; quality of life; thiamine; sepsis

In 2017, there were almost 50 million estimated incident cases of sepsis worldwide (1). Although overall sepsis mortality has improved in recent decades, sepsis survivors often suffer from diminished health-related quality of life (2). They commonly experience deficits in terms of their physical, mental, and cognitive health (3), which is thought to be part of a “postsepsis syndrome” that can last from months to years after hospital discharge (3). These deficits often limit mobility and ability to perform the daily activities at the level of one’s presepsis baseline (4). This is so prevalent that some researchers have recommended including health-related quality of life as an endpoint in clinical trials of sepsis (2).

This is a secondary analysis of the Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial (5), a randomized controlled trial in which patients with septic shock were randomized to ascorbic acid, corticosteroids, and thiamine versus placebo. We sought to determine whether quality of life among septic shock survivors at 90 days following enrollment in the ACTS trial (5) was improved in the intervention group compared with placebo.

## METHODS

### Design and Setting

This predefined secondary analysis was based on the ACTS trial (5), a randomized blinded multicenter clinical trial of ascorbic acid, corticosteroids, and thiamine versus placebo for patients with septic shock. The ACTS trial enrolled 200 patients between February 2018 and October 2019 at 14 centers in the United States. Patients were randomly assigned to parenteral ascorbic acid (1,500 mg), hydrocortisone (50 mg) and thiamine

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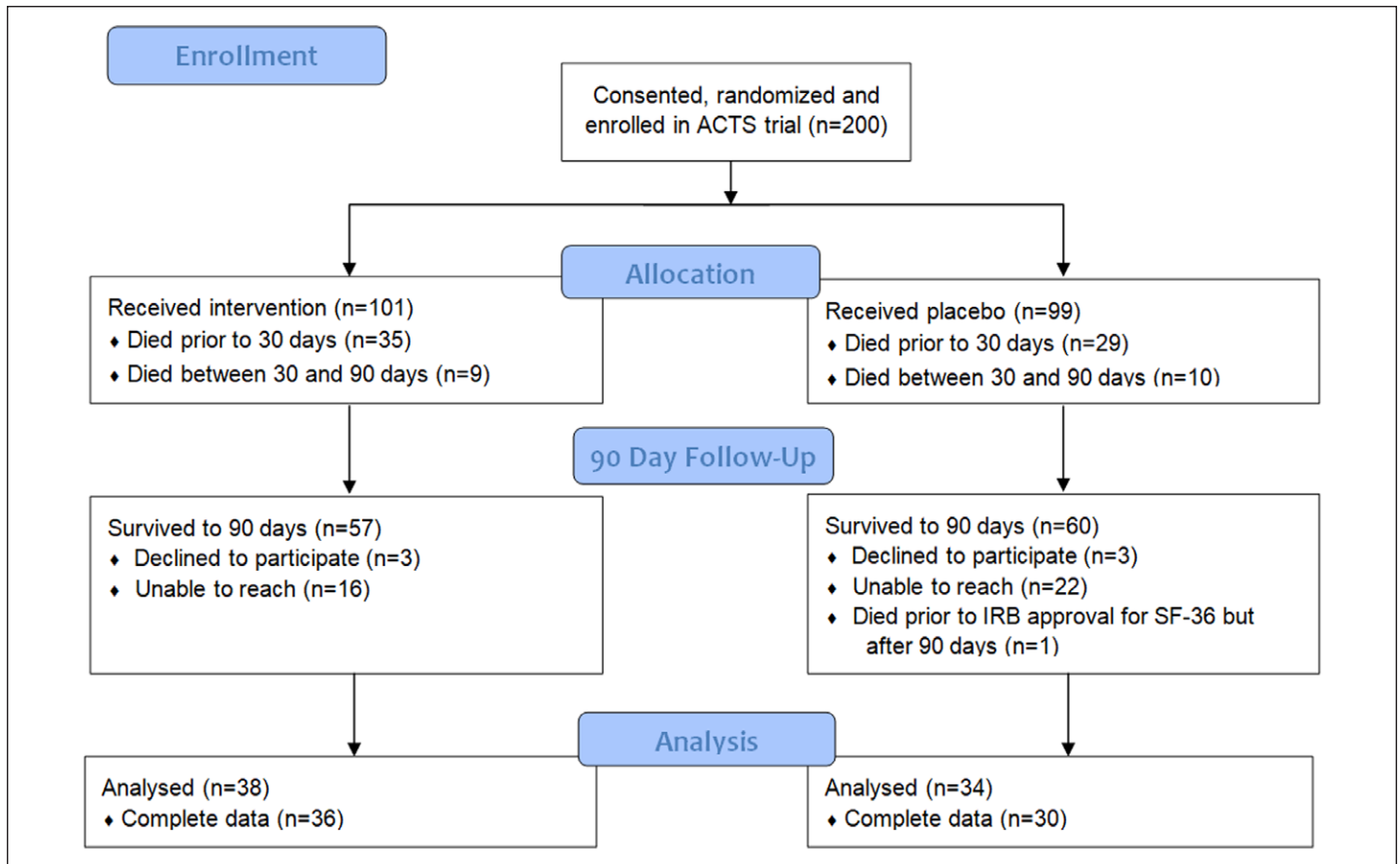
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*Crit Care Expl* 2020; 2:e0270

DOI: 10.1097/CCE.0000000000000270



**Figure 1.** Patient enrollment. ACTS = Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis, IRB = Institutional Review Board, SF-36 = Short Form 36.

(100 mg) or placebo every 6 hours for 4 days. The Committee on Clinical Investigations at Beth Israel Deaconess Medical Center, the Clinical Coordinating Center, approved this study (2017P-000436). The ACTS protocol also was approved by the institutional review boards at each participating medical center.

Patients were eligible for enrollment in ACTS if they had a suspected or confirmed infection, were receiving at least one vasopressor agent due to hypotension thought to be a consequence of sepsis, and were greater than or equal to 18 years old. Patients were enrolled within 24 hours of meeting inclusion criteria. Exclusion criteria included known allergy to ascorbic acid, corticosteroids, or thiamine; clinical indication for ascorbic acid, corticosteroids, and/or thiamine; symptomatic kidney stones within one year of potential enrollment in ACTS; Glucose-6-Phosphate Dehydrogenase deficiency or hemochromatosis; receipt of renal replacement therapy; expectation of survival of less than 24 hours post enrollment; or membership in a protected population in this case either a prisoner or pregnant patient.

## Methodology

All patients who survived to 90 days post enrollment received a follow-up telephone call by either a trained research assistant at the local site or by the Data Coordinating Center (if permission granted by the local Institutional Review Board). All assessors were blinded to treatment arm. Ninety day follow-up data were

entered into a Clinical Research Form in REDCap Cloud ([www.redcapcloud.com](http://www.redcapcloud.com)) dedicated for these results, regardless of where the 90-day follow-up call was performed. Patients who were not able to be reached by telephone were sent a letter proposing a telephone conversation. Patients who did not respond to the letter and who were not reachable by telephone were considered lost to follow-up. All patients who had been discharged prior to 90 days were interviewed over the telephone; patients still hospitalized were interviewed in person if possible.

Patients who were contacted were given the Short Form 36 (SF-36) to measure health-related quality of life. The SF-36 is a validated survey of general quality of life in adults. It measures eight different dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions, as well as one question asking about perceived changes in health. These domains are clustered into two summary scores: the Physical Component Score (PCS) and the Mental Component Score (MCS). Higher scores indicate better health-related quality of life (6). The telephone version of the SF-36 has been validated and used in sepsis (7). All scoring of the SF-36 was done at the Data Coordinating Center. Patients who were not able to be reached were excluded. All available response data were used, and no imputation strategies were performed for missing data.

**TABLE 1. Baseline Cohort Characteristics**

Characteristics	Intervention Arm (n = 38)	Placebo Arm (n = 34)	p
Demographics			
Age (yr), median (IQR)	68 (60–77)	66.5 (56–74)	0.59
Body mass index (kg/m <sup>2</sup> ), median (IQR) <sup>a</sup>	27.3 (24.1–33.7)	27.5 (22.8–31.3)	0.80
Female, n (%)	14 (37)	14 (41)	0.71
Race, n (%)			
Black	3 (8)	4 (12)	0.48
White	27 (71)	28 (82)	
Asian	2 (5)	0 (0)	
Other/unknown	5 (13)	2 (6)	
Not reported	1 (3)	0 (0)	
Ethnicity, n (%)			
Hispanic	1 (3)	1 (3)	0.03
Not Hispanic	31 (82)	33 (97)	
Unknown/not reported	6 (16)	0 (0)	
Past medical history, n (%)			
Coronary artery disease	12 (32)	7 (21)	0.42
Congestive heart failure	4 (11)	4 (12)	> 0.99
Malignancy	6 (16)	11 (32)	0.16
Liver disease	5 (13)	4 (12)	> 0.99
Chronic renal disease, stage 2	0 (0)	0 (0)	0.24
Chronic renal disease, stage 3	3 (8)	0 (0)	
Chronic renal disease, stage 4	1 (3)	1 (3)	
Unknown chronic renal disease stage	0 (0)	1 (3)	
Clinical characteristics			
Primary infectious source, n (%)			
Pneumonia	11 (29)	7 (21)	0.67
Urinary tract infection	3 (8)	5 (15)	
Intraabdominal	14 (37)	12 (35)	
Other	7 (18)	9 (26)	
Unknown	3 (8)	1 (3)	
Volume of IV fluids prior to study drug (mL), median (IQR) <sup>b</sup>	2,057.5 (1,000–3,500)	2,000 (1,200–3,000)	0.64
Baseline cardiovascular Sequential Organ Failure Assessment score, median (IQR)	4 (3–4)	4 (3–4)	0.72
Time from vasopressor initiation to study drug (hr), median (IQR)	9.8 (7.7–16.5)	10.3 (6.2–18.3)	0.66
Mechanically ventilated, n (%)	21 (55)	15 (44)	0.35
Acute respiratory distress syndrome present, n (%)	11 (29)	6 (18)	0.28
Lactate (mmol/L), median, IQR	1.8 (1.3–2.7)	1.5 (1.2–2.9)	0.71
30-d predicted survival, n (%) <sup>c</sup>			
High likelihood	18 (47)	16 (47)	0.51
Uncertain	20 (53)	16 (47)	
Low likelihood	0 (0)	2 (6)	

IQR = interquartile range.

<sup>a</sup>2 patients had unknown body mass indexes; one in the intervention group and one in the placebo group.<sup>b</sup>Volume of IV fluids received in the 12 hr preceding enrollment.<sup>c</sup>At time of enrollment, the physician enrolling the patient is asked to predict 30-d survival.

**TABLE 2. Outcomes**

Health-Related Quality of Life Outcomes, Median (IQR) <sup>a</sup>	Intervention Arm	n	Placebo Arm	n	p
Overall Short Form 36 score	39.4 (31.2–45.4)	36	43.2 (37.0–46.7)	30	0.19
Mental Component Score	48.5 (34.1–58.0)	36	53.8 (41.1–60.9)	30	0.14
Physical Component Score	32.6 (25.8–39.4)	36	29.0 (23.2–39.9)	30	0.83
Dimensions of health					
Physical functioning	40 (0–75)	37	50 (15–80)	33	0.51
Physical role functioning	0 (0–50)	37	25 (0–100)	33	0.26
Emotional role functioning	67 (0–100)	37	50 (0–100)	32	0.59
Energy/fatigue	40 (20–58)	36	48 (33–63)	32	0.15
Emotional wellbeing	68 (52–88)	37	80 (64–92)	31	0.12
Social functioning	63 (38–88)	37	63 (50–100)	33	0.59
Pain	52 (31–62)	37	42 (31–84)	33	0.95
General health	42 (30–57)	37	45 (28–64)	32	0.93

IQR = interquartile range.

<sup>a</sup>The Short Form 36 ranges from 0 to 100, with 100 being optimal health. The average score for residents of the United States is 50.

## Outcomes

The primary outcome was health-related quality of life as measured by the SF-36. As the SF-36 has two main domains, the results were analyzed looking at the overall score, the PCS, and the MCS. This was done to see if there is an effect primarily on the physical or mental aspects of health-related quality of life.

## Statistical Analysis

Data are expressed as means and SD ( $\pm$ ) if the data are normally distributed or median and interquartile range (IQR) if the data exhibited a nonnormal distribution. Raw scores from each of the 36 items were transformed into scores that ranged from 0 to 100 that were standardized to the U.S. population (with 50 representing the average score) (8). Differences in medians between overall SF-36 score, PCS, and MCS by randomization group were analyzed by Wilcoxon rank-sum tests. To compare the standardized scores with the average American population, a one-sample *t* test was used, assuming a mean of 50. All analyses were performed in Stata 14.2 (StataCorp LLC, College Station, TX). A post hoc analysis of the eight domains of the SF-36 was performed using Wilcoxon rank-sum tests. A *p* value of less than 0.05 was considered statistically significant.

## RESULTS

Out of the 117 patients in the ACTS trial alive at 90 days, we were able to reach and interview 72 of them (64%) (Fig. 1). Interviewed and noninterviewed patients were generally similar. However, interviewed patients had significantly more liver disease (13% in the group interviewed compared with 0% in the group not interviewed,  $p = 0.01$ ), fewer urinary tract infections (11% vs 36%), and more intra-abdominal infections (36% vs 18%;  $p = 0.01$ ) as the primary source of sepsis (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A417>).

Of the 72 patients who responded, 38 of them were in the intervention group, and 34 were in the placebo group. Sixty-six patients (92%) answered all 36 questions. All baseline characteristics were equal between the two groups (Table 1).

In terms of overall SF-36 score, there was no significant difference between the intervention and the placebo group (median score, 39.4 [IQR, 31.2–45.4] vs 43.2 [37.0–46.7], respectively,  $p = 0.18$ ). There were also no significant differences between the PCS, the MCS, or any other health-related domains (all  $p > 0.10$ ) (Table 2). The overall and PCS score for respondents was significantly lower than the average score for people residing in the United States ( $p < 0.001$ ). The MCS was not significantly different (Supplemental Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/CCX/A418>).

## DISCUSSION

In this substudy of the ACTS trial, we investigated health-related quality of life by analyzing SF-36 results 90 days after enrollment in survivors. We found that there was no difference in health-related quality of life based on whether the patient was randomized to the intervention or the placebo group. This is consistent with the results found in the Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial, which found no difference in health-related quality of life (as measured by the EuroQol (<https://euroqol.org/>) questionnaire) at 6 months in critically ill patients with septic shock randomized to either hydrocortisone or placebo (9). Additionally, we found that physical health-related quality of life was significantly lower in survivors than the general U.S. population, which supports other work (2, 4, 10). Our finding that the mental component of the SF-36 was comparable with the overall U.S. population also aligns with previous studies (11) that find that physical deficits seem to be more pronounced than mental in terms of self-assessment of health-related quality

of life. One possible explanation for this is that many of the questions that make up the MCS are more subjective than those in the PCS and could potentially be more influenced by changes in the perception of health and quality of life following sepsis (11). Alternately, it could be that sepsis has more of a negative impact on physical domains compared with mental and emotional ones or that patients are more reticent to discuss mental and emotional struggles. Our study has several limitations. First, we did not have a baseline measure of health-related quality of life, so were not able to assess change from baseline. Given that this study included only 36% of the patients who were randomized in the parent trial, the preservation of randomization balance between the treatment and placebo groups may have been lost. Second, our sample only included 36% of the patients initially enrolled in the study. Forty-two percent did not survive to 90 days, and 23% were lost to follow-up. Due to this attrition, these results are potentially not representative of all patients in the trial and are likely complicated by survival bias. Additionally, we only had complete data on 66 patients, which means that the comparison of the MCS and PCS are likely underpowered to find a difference. Finally, our response rate was only 62%, and only 92% of respondents completed the entire SF-36. Perhaps another, simpler scale of health-related quality of life would have led to a higher response and completion rate.

## CONCLUSIONS

Among survivors of sepsis who were enrolled in the ACTS trial, there was no difference in health-related quality of life between the intervention and the placebo treatment group.

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The Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis trial (NCT03389555) was supported, in part, by a grant from the Open Philanthropy Project, a non-profit foundation.

Dr. Grossestreuer reported receipt of grants from Harvard Catalyst Medical Research Investigator Training. Drs. Donnino, Moskowitz, and Berg reported

receipt of grants from the National Institutes of Health. The remaining authors have not disclosed any potential conflicts of interest.

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