Vitamin C and Concomitant Therapies in Sepsis

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Objectives

1. Describe the mechanism of action of vitamin C as it relates to the pathophysiology of sepsis
2. Summarize the current literature available regarding vitamin C in sepsis
3. Select appropriate guideline recommendations for the treatment of vitamin C in Sepsis

Background

- Despite various efforts and changes in the standards of care for the management of sepsis and septic shock in recent years, mortality rates remain high
  - A recent meta-analysis showed 30-day sepsis mortality was 24.4% and 90-day sepsis mortality was 32.2%[1]
    - Septic shock mortality was higher with a 30-day mortality of 34.7% and a 90-day mortality of 38.5%
- According to the Joint Commission, sepsis is one of the most expensive diseases to treat at $17 billion annually with 750,000 Americans diagnosed with sepsis each year[2]
  - Exploration of new therapies is necessary to improve sepsis outcomes

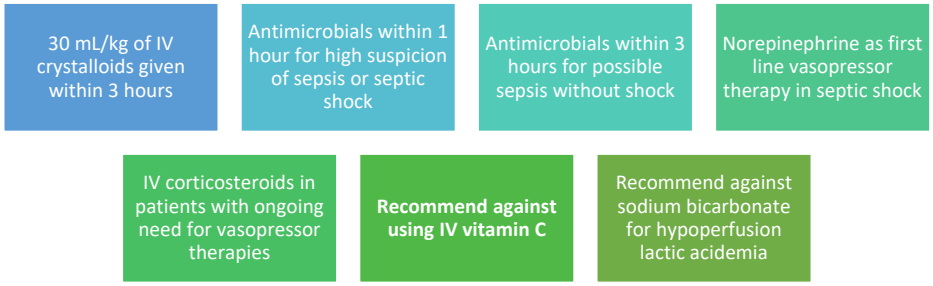
Guidelines

Surviving Sepsis 2021[3]

Definitions and diagnosis criteria:

- Sepsis:
  - 2 or more SIRS criteria
  - suspected or confirmed source of infection
- Septic Shock: circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality
  - vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater
  - serum lactate level greater than 2 mmol/L in the absence of hypovolemia
- qSOFA no longer recommended – SIRS, NEWS, or MEWS preferred for diagnosis

Figure 1. Treatment recommendations



Pathophysiology of Sepsis and Vitamin C Mechanism of Action

- Pathophysiology of sepsis[4]:

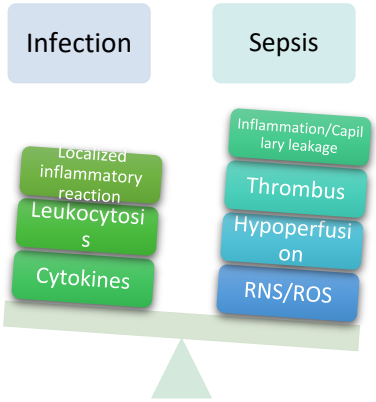


Figure 2. Sepsis is a dysregulated inflammatory response to infection involving circulatory and cellular metabolism abnormalities which can lead to life-threatening organ failure**.** Changes in vascular integrity leads to capillary leakage, microvascular thrombus, hypotension, and hypoperfusion**.** The production of reactive nitrogen species (RNS) and reactive oxygen species (ROS) damage intercellular junctions and cellular membranes.

The proposed role of vitamin C in sepsis[4,5,6]

Table 1. Summary of pathophysiology and vitamin C mechanisms in sepsis

	Pathophysiology	Mechanism
Inflammation	Release of inflammatory cytokines such as IL-1, TNF, IL-17, and IL-6 bind receptors activating NFKB signaling for more cytokines and chemokines to be released	Inhibits NFKB pathway reducing cytokine, chemokine, and other inflammatory mediator production
Antioxidant	Overwhelming production of ROS/RNS leads to oxidative stress causing attacking and apoptosis of endothelial cells, glycocalyx shedding, and damage of intercellular junctions	Scavenger of reactive species
Thrombus formation	Tissue factor activates coagulation cascade and platelets Downregulation of thrombomodulin leading to excess thrombin generation	Increase in thrombomodulin and decrease in platelet activation and tissue factor expression
Hypoperfusion/ capillary leakage	Inducible nitric oxide synthase activation Endothelial nitric oxide synthase downregulated Excess nitric oxide causing vasodilation ROS and RNS released by immune and endothelial cells cause increased oxidative stress and apoptosis of endothelial cells, glycocalyx shedding, and damage of intercellular junctions causing refractive vascular permeability, capillary leakage, and hypotension	Increases eNOS and decreases INOS to preserve tight junctions
Endogenous catecholamines	Dopamine β-hydroxylase and peptidylglycine α-amidating monooxygenase use vitamin C as a co-factor to produce epinephrine and vasopressin Depletion of vitamin C leads to reduced catecholamine production	Acts as co-factor for catecholamine synthesis

Outcome Assessment

Appropriateness of Primary Outcomes:

- **SOFA-score has been correlated with mortality[7]**
- **Thrombomodulin (TM) is a transmembrane glycoprotein in blood vessels regulating coagulation and inflammation[8]**
    - Binds thrombin causing it to activate protein C limiting thrombin generation
    - Anti-inflammatory properties through inhibition of proinflammatory protein
    - Loss of TM during sepsis leads to thrombin activation as proinflammatory and profibrotic mediator
- **Time alive and free of vasopressors at 7 days**
    - Patients with septic shock are initiated on vasopressors which are associated with worse outcomes versus patients who do not need vasopressors (sepsis)
- **Mortality at longest follow up[9]**
    - Septic shock has a high mortality rate as previously mentioned
    - Morbidity and worsened pre-existing conditions are also impacted by sepsis leading to re-hospitalization within the first 90 days after discharge
    - Interventions improving short-term mortality may worsen long-term mortality so need to assess longest follow up remains

Secondary Endpoints and Subgroups:

- Renal dysfunction and cardiac abnormalities are appropriate based on the multiorgan failure commonly seen in sepsis
- Time to drug administration is appropriate based on guideline recommendations and evidence showing improved outcomes with early intervention
- Length of hospital stay is appropriate for assessing burden of disease

Table 2. Guideline referenced trials

Guideline Referenced Trials						
	Study Design	**Population**	**Intervention**	**Endpoints**	**Statistics**	**Results**
The CITRIS-ALI Trial[10]	Randomized, double blind, placebo-controlled trial	Patients with sepsis and ARDS	Vitamin C IV 50 mg/kg vs Placebo x 96h or until discharge from ICU or death	**Primary:** mSOFA score at 96h, CRP and thrombomodulin at 168h **Secondary:** all-cause mortality, ventilator free days, and ICU free days at day 28, hospital-free days at day 60. At hours 0, 48, 96, and 168 they measured oxygen index, VE-40, and SOFA score components	-170 patients total for 80% power and 2-sided alpha < 0.05 -Mixed linear model used for primary endpoint -Kaplan-Meier analysis for mortality -Wilcoxon test for survival curves	-Mortality at day 28 was 46.3% in placebo vs 29.8% in vit c, P = 0.03 -Kaplan- Meier curves significantly different by Wilcoxon test, P = 0.01 -ICU- free days to day 28 was 10.7 in vit c vs 7.7 in placebo. 95% CI. 0.3-5.9; P =0.03 -Hospital-free days 22.6 in vit c and 15.5 in placebo, 95% CI, 0.3-13.8; P = 0.04
The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients: A Systematic Review with Meta-analysis of Randomized Controlled Trials[11]	Cochrane systematic review	ICU and cardiac surgery patients; 6 studies included sepsis patients	Any type of vitamin C formulation and regimen	**Primary:** Mortality at longest follow up **Secondary:** AKI, supraventricular arrhythmia, ventricular arrhythmia stroke, length of ICU stay, and length of hospital stay	-P < 0.05 significant -Dichotomous variables OR calculated -Continuous variables assessed with standardized mean difference -Heterogeneity assessed using Chi-square -Publication bias assessed using funnel plots	No statistically significant differences in ICU stay, hospital stay, or survival for ICU patients

The ACTS Trial[12]	Multicenter, randomized, double-blinded, placebo-controlled superiority trial	Septic shock patients	Ascorbic acid (1500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 hours for 4 days or until intensive care unit (ICU) discharge	**Primary:** change in SOFA score between enrollment and 72h follow up **Secondary:** kidney failure (KDIGO), all-cause mortality after first 30 days, ventilator free days during first 7 days, shock free days during first 28 days, all-cause mortality to ICU discharge, all-cause mortality to hospital discharge, posthospitalization disposition, 72h change in SOFA components, and delirium on day 3 (CAM-ICU) **Subgroup:** baseline SOFA score, lactate, time to drug administration, and predicted 30-day survival by enrolling clinician	-2-sided alpha of 0.05 and $P < 0.5$ considered significant -Sample size of 200 giving > 99% power -Primary outcome analyzed using linear mixed effects Covariates included age, sex, treatment group, time, and interaction between treatment group and time -Survival to 30 days assessed using Kaplan-Meier and Cox proportional hazards controlling for site -Linear regression used for continuous, nonlongitudinal outcomes -Quantile regression used for ventilator, shock, and ICU free days -Subgroups analysed using relevant interaction term -Sensitivity analysis including only patients with SOFA score at 72 hours and assigning a 20% increase SOFA score for death prior to 72 hours	-No differences in primary outcome -Shock-free days with 5 days in tx group and 4 in placebo (AMD 1; 95% CI, 0.2-1.8) -No significant ADRs reported

The VITAMINS Trial[13]	Multicenter, open label, parallel group, randomized controlled trial	Septic shock patients based on Sepsis-3 criteria	**Tx:** 1.5g IV vit c q6h, hydrocortisone 50 mg IV q6h, thiamine 1200 mg IV q12h **Control:** IV hydrocortisone 50 mg q6h; could potentially receive thiamine based on prescribers discretion	**Primary:** Time alive and free of vasopressors at 7 days **Secondary:** 28-day, 90-day, ICU, and hospital mortality, 28-day cumulative vasopressor-free days, 28-day cumulative mechanical ventilation-free days, 28-day renal replacement therapy–free days, change in SOFA score at day 3, 28-day ICU free-days, and hospital length of stay **Exploratory:** AKI (meeting KDIGO criteria) and vasopressor dose over 10 days	-180 patients for 90% power with 2-sided alpha of 0.05 to detect 25 hours vasopressor free -P < 0.05 significant -Wilcoxon rank sum test for primary outcome -Sensitivity analysis for APACHE III score, lactate levels, WBCs, and milrinone use -Survival time analyzed with Cox proportional hazards regression and presented using Kaplan-Meier curves -Post-hoc analysis for duration of vasopressor use assessed using Cox proportional hazards, censoring for patients who died before resolution of shock -Post hoc analysis for primary outcome performed on lactate, SOFA score, vasopressor dose, and hydrocortisone prior to enrollment	-211 patients included -No statistically significant difference in primary outcome -Change in SOFA score at day 3 was significantly greater in the intervention group than in the control group (median, –2 [IQR, –4 to 0] vs –1 [IQR, –3 to 0], respectively; difference, –1.0 [95% CI, –1.9 to –0.1]; P = .02) -No significant difference in exploratory outcomes -Post hoc analysis showed no significant difference between groups for death or vasopressor re-dependence

Clinical Question:

Despite various updates in sepsis treatment, the mortality rates of sepsis are still high.

Does vitamin C in sepsis improve patient outcomes such as mortality, organ dysfunction, and use of ventilators and vasopressors?

Should guidelines reassess their stance based on new studies?

Table 3: The VICTAS Randomized Clinical Trial

Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator and Vasopressor-Free Days in Patients With Sepsis The VICTAS Randomized Clinical Trial[14]		
Design	Multicenter, randomized, double-blind, adaptive-sample-size, placebo-controlled trial	
Patient Selection	Inclusion Criteria: • 18+ • Acute respiratory failure or cardiac dysfunction caused by proven or suspected infection with planned ICU admission	Exclusion Criteria: • Weight <40kg • Cardiac or respiratory failure due to cause other than sepsis • Unable to randomize within 24 hours of onset of sepsis • DNI status • Hospitalization > 30 days • Chronic hypoxemia requiring O2 • Chronic cardiac problems requiring home support • Use of vit C > 1g/d within 24 hours of first episode of organ dysfunction • Kidney stones • Pregnancy or breastfeeding • Prisoner
Treatments	Vitamin C 1.5g, thiamine 100 mg, and hydrocortisone 50 mg within 4 hours of randomization and then every 6 hours up to 96 hours, death, or discharge from ICU	
Outcomes	**Primary:** Ventilator and vasopressor free days (VVFDs) in first 30 days following randomization **Secondary:** Mortality within 30 days from randomization	**Exploratory:** ICU mortality, ICU and hospital length of stay, ICU delirium and coma-free days, renal-replacement therapy at day 30, change between pre-randomization and day 4 SOFA score **Safety**: nephrolithiasis, hemolysis, hypersensitivity, injection site reactions
Patient Population	• N = 501 • Baseline characteristics of the population included an average age of 62, average SOFA score of 9, APACHE II score of 27, and most common source of infection in both groups was listed as lung, then UTI, then blood • The treatment group had more patients intubated (69.6% vs 63.6%) while the control group had more patients on high flow oxygen (19.2% vs 12%)	
Results	See table 3a below	
Statistics	• Early termination of the trial resulted from funding changes leaving the study potentially underpowered o N = 2000 needed to detect a 25% mortality difference and 1.5 VVFDs which was voted as clinically meaningful by the executive committee • Primary outcome assessed using Wilcoxon rank sum test	
Study Assessment	The combination of vitamin C, hydrocortisone, and thiamine did not impact ventilator or vasopressor days in patients with sepsis. Mortality, SOFA score, and length of stay were similar between groups as well as coma/delirium-free days and kidney replacement therapy. None of the outcomes of this trial were statistically significant in either an intention to treat analysis or the per protocol analysis.	
	Strengths: • Clinically relevant outcomes assessed • Administered treatment to groups within 28 hours of sepsis onset (earlier than previous trials) • Exclusion criteria improve internal validity	Limitations: • Early cessation of trial – may have been underpowered • Steroids used in control group may have pushed results towards null hypothesis • All other management relied on the discretion of the treatment team
	Internal validity: • Poor, while timing and dosing of interventions was specific, other management not well documented	External validity: • Good, based on the baseline disease states (chronic illnesses) and age, this population represents the overall population experiencing sepsis well

Table 3a: Results of The VICTAS Trial

Primary Outcome	Intervention (N = 252)	Control (n= 249)	Difference (95% CI)	p value
Time alive and free of ventilator and vasopressors, median (IQR), d	25 (0-29)	26 (0-28)	-1 (-4 to 2)	0.85
Secondary Outcomes	**Intervention (N = 252)**	**Control (n= 249)**	**Difference (95% CI)**	**p value**
30-day all-cause mortality, no. (%)	56 (22%)	60 (24%)	-0.019 (-0.055 to 0.093)	0.619
ICU Mortality, No. (%)	52 (20.6)	49(19.7)	0.9 (-0.8 to 6.1)	0.79
Mortality at 180 days, No. (%)	102 (40.5)	94 (37.8)	2.7 (-11.3 to 5.8)	0.53
Change in SOFA score, median (IQR)	5 (3-7)	5 (2-7)	0.0 (-1.0 to 0.0)	0.10
Length of ICU stay, median (IQR), d	4 (2-8)	4 (2-8)	0.0 (-2.0 to 1.0)	0.82
Length of hospital stay, median (IQR), d	10 (6-17)	9 (5-17)	1.0 (-3.0 to 2.0)	0.66
Coma/delirium-free days, median (IQR)	4 (2-5)	4 (2-5)	0.0 (0.0 to 1.0)	0.45
Kidney replacement therapy-free days, median (IQR)	30 (0-30)	30 (0-30)	0.0 (0.0 to 0.0)	0.58

Table 4: Vitamin C for ≥ 5 Days is Associated with Decreased Hospital Mortality in Sepsis Subgroups: A Nationwide Cohort Study

Vitamin C for ≥ 5 Days is Associated with Decreased Hospital Mortality in Sepsis Subgroups: A Nationwide Cohort Study[15]		
Design	Retrospective cohort study performed in Korea from 1/2017-12/2019 with data taken from the National Health Insurance Service identifying patients based on ICD-10 codes for infection and organ dysfunction. Septic shock was identified using either ICD-10 codes or administration of vasopressors	
Patient Selection	Inclusion Criteria: • Age ≥ 18 • Sepsis based on Sepsis-3 criteria • Admission to ICU	Exclusion Criteria: • Age < 18 • Pregnancy or related condition • Palliative care • Cardiac arrest • Multiple ICU admissions
Treatments	Patients with 1 dose of "high dose" IV vitamin C charged were in treatment group and patients without charges were in control group • The daily dose of vitamin C was not calculated but suspected to be 6g/day based on previous Korean studies • ICD-10 codes for vitamin C included ascorbic acid 100 mg, 500 mg, 5 g, 10 g, and 25 g	
Outcomes	**Primary:** In hospital mortality	**Secondary:** 90-day mortality, vasopressor days, ventilator days, ICU length of stay, hospital length of stay, and hospital cost
Patient Population	• N = 72,654 • Baseline characteristics: mean age 70.7 years, 55% male, Charlson Comorbidity Index 3, 31% pulmonary infection, 13% had a GI tract infection, and 13% had a GU tract infection, 50% of patients in each group had septic shock, and 30% of patients were on a ventilator	
Results	See table 4a below	
Statistics	• Continuous data assessed using Student's t-test or Kruskal-Wallis • Categorical data assessed using chi-square or Fisher's exact • Propensity matching for differences in vitamin C administration but similar measured variables	
Study Assessment	Compared with patients who received vitamin C for 1–2 or 3–4 days, those treated for ≥ 5 days showed statistically significant lower hospital and 90-day mortality rates. An increase in ventilator and vasopressor days was seen with the use of vitamin C as well as length of ICU and hospital stay. Forest plots for combinations demonstrated that vitamin C alone (5 days or longer) or the combination of vitamin C (any duration) plus thiamine (any duration) was significantly associated with decreased mortality. However, any combination of vitamin C and corticosteroids, regardless of thiamine use, was significantly associated with increased mortality.	
	Strengths: • Large sample size • Patients well matched in each group • Assessment of various durations and combinations	Limitations: • Unknown dosing of vitamin C • Potential confounding variables including unknown appropriateness of antibiotics, fluid maintenance, vasopressor standards, etc. • Concomitant therapies unknown • Sepsis was defined as infection and organ dysfunction in the same admission – may have had time difference • Lack of time stamps on medication
	Internal validity: • Poor, unknown vitamin C dosing and timing of administration of medications	External validity: • Poor, unknown if patients truly had sepsis

Table 4a: Results for Vitamin C for ≥ 5 Days is Associated with Decreased Hospital Mortality in Sepsis Subgroups: A Nationwide Cohort

Primary Outcome	Vitamin C (n=36,327)	Control (n=36,327)	Difference (95% CI)	p value
Hospital mortality, No. (%)	6209 (17.1)	6538 (18.0)	- 0.9 (-1.3 to -0.5)	<0.001
Secondary Outcomes	**Vitamin C (n=36,327)**	**Control (n=36,327)**	**Difference (95% CI)**	**p value**
90-day mortality, No. (%)	9226 (25.4)	9820 (27.0)	-3.2 (-3.8 to -2.6)	<0.001
Vasopressor days, mean (SD)	2.9 (2.3)	2.7 (2.0)	0.12 (2.0 to 2.1)	0.002
Ventilator days, mean (SD)	9.5 (18.8)	8.2 (15.7)	1.4 (1.3 to 1.5)	<0.001
Length of stay, mean (SD), days				
ICU	10.6 (17.5)	8.6 (14.2)	2.02 (2.0 to 2.1)	<0.001
Hospital	27.1 (41.6)	21.0 (22.1)	6.0 (5.9 to 6.1)	<0.001
Hospital costs, mean (SD), U.S $1000	13.3 (19.0)	12.1 (25.2)	1.19 (1.18 to 1.2)	<0.001

Table 5.: Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit[16]		
Design	Randomized, placebo-controlled, double blind superiority trial performed internationally in Canada, France, and New Zealand from 11/14/2018 to 7/19/2021	
Patient Selection	Inclusion Criteria: • 18+ years • Proven or suspected infection receiving any dose of vasopressor • Admission to ICU within 24 hours of enrollment	Exclusion Criteria: • More than 24 hours of intensive care unit admission • Known Glucose-6-phosphate dehydrogenase deficiency pregnancy • Known allergy to vitamin C • Known kidney stones within the past 1 year • Receipt of intravenous vitamin C during the current hospitalization (unless incorporated in parenteral nutrition) • Expected death or withdrawal from life-sustaining therapy within 48h
Treatments	IV vitamin C bolus of 50 mg/kg (200mg/kg/day) in D5 or NS over 30-60 minutes every 6 hours for 96h or until discharge from ICU	
Outcomes	**Primary:** Composite of death or persistent organ dysfunction (receipt of vasopressors, mechanical ventilation, or renal replacement therapy) at day 28	**Secondary:** days without organ dysfunction in ICU up to 28, mortality at day 28 and 6 months, quality of life at 6 months (EQ-5D-5L questionnaire), organ failure at days 2-4, 7, 10, 14, and 28 (SOFA), inflammation biomarkers (IL1 beta and TNF alpha), lactate, endothelial injury (thrombomodulin and angiopoeitin-2) at days 3 and 7
Patient Population	• N = 863 • Baseline characteristics of patients included were mean age of 65, most common infectious source of pulmonary infection, and baseline SOFA score in the vitamin C group was 10.2 and in the placebo group was 10.1	
Results	No statistically significant differences found when composite broken down	
Statistics	• Intention-to-treat population assessed for primary analysis • Logistic regression model assessed primary outcome • Mixed linear effects assessed SOFA score over time, analysis of covariance assessed inflammation biomarkers, and other continuous outcomes analyzed using t-tests or Wilcoxon rank-sum	
Study Assessment	Vitamin C was shown to increase the composite outcome of death or persistent organ failure in patients with sepsis in the ICU. There was also a higher incidence of death at 6 months and hypoglycemia in the vitamin C group. There was a slight reduction in stage 3 AKI in the vitamin C group but no differences in SOFA score or EQ-5D-5L score. Subgroup analyses showed that the primary outcome was more likely in patients receiving vitamin C for female patients, patients with a frailty score 1-4, patients with a lower predicted risk of death, and patients not meeting sepsis-3 criteria for septic shock.	
	Strengths: • Clinically relevant endpoints • Intervention is appropriate based on previous studies • Multicenter, randomized, double blinded	Limitations: • Results do not align with previous trials • No data regarding appropriate standard of care • Lacking US involvement
	Internal validity: • Poor, many confounders may have played a role in outcomes including comorbidities and other treatment received such as antibiotics, fluids, choice of vasopressor, etc.	External validity: • Good as far as inclusion/exclusion criteria focusing on including patients meeting septic shock definition and preventing adverse reactions to study drug o Broad patient population expected o Difficult to assess true validity with lack of patient comorbidity characteristics

Table 5a.: Results of Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit

Primary Outcome	Vitamin C	Control	Difference (RR, 95% CI)
Death or persistent organ dysfunction at 28 days, no./total no. (%)	**191/429 (44.5)**	**167/434 (38.5)**	**1.21 (1.04 to 1.40)**
Death	152/429 (35.4)	137/434 (31.6)	1.17 (0.98 to 1.40)
Persistent organ dysfunction	39/429 (9.1)	30/434 (6.9)	1.30 (0.83 to 2.05)
Vasopressor use	8/429 (1.9)	6/434 (1.4)	1.36 (0.48 to 3.85)
Mechanical Ventilation	25/429 (5.8)	19/434 (4.4)	1.31 (0.74 to 2.30)
Renal-replacement therapy	24/429 (5.6)	18/434 (4.1)	1.35 (0.73 to 2.5)

Primary Literature Summary

Table 6. Primary literature since guideline update

Trial	Interpretation
VICTAS Trial (Sevransky et al. 2021)	Vitamin C, thiamine, hydrocortisone impact on ventilator and vasopressor use in ARDS or cardiac dysfunction: • No statistically significant differences
Vitamin C ≥ 5 days (Jung et al. 2022)	Vitamin C Duration: • ≥ 5 days reduced hospital and 90-day mortality as compared to 1-2 and 3-4 days • Any duration vs placebo reduced in hospital mortality by 0.9% and 90-day mortality by 3.2% Vitamin C in combination: • Vitamin C + Thiamine reduced hospital mortality compared to no vitamin C • Vitamin C + Steroid increased hospital mortality compared to no vitamin C
IV Vitamin C in the ICU (Agarwal et al. 2022)	Vitamin C alone • Increased risk of composite of death and organ dysfunction at 28 days

Table 7. Outcome comparison across all studies

Guideline Referenced Trials					
	Mortality	**SOFA Score**	**Vasopressor Use**	**Ventilator Use**	**Renal Outcomes**
CITRIS-ALI (Fowler et al. 2019)	↓	↔	↔	↔	N/A
Meta-analysis (Putzu et al. 2019)	↔	N/A	N/A	N/A	↔
ACTS (Moskowitz et al. 2020)	↔	↔	↓	↔	↔
VITAMINS (Fuji et al. 2020)	↔	↓	↔	↔	↔
Post-Guideline Publications					
VICTAS (Sevransky et al. 2021)	↔	↔	N/A	N/A	↔
Vitamin C ≥ 5 days (Jung et al. 2022)	↓	N/A	↑	↑	N/A
IV Vitamin C in the ICU (Agarwal et al. 2022)	↔	↔	↔	↔	↔

Final Recommendations and Place in Therapy

Vitamin C is an inexpensive therapy that works through various mechanisms including in the inflammation and thrombotic pathways. This leads to the theory that repleting vitamin C during sepsis may enhance outcomes such as mortality, vasopressor use, intubations, and organ failure. Primary literature reviewed shows inconsistent outcome data, treatment dosing, duration, and background treatment. Confounding variables come into play including unknown appropriateness of antibiotic treatment, fluid resuscitation, and vasopressor choice as well as unknown baseline characteristics and comorbidities. Based on presented data and the data in the Surviving Sepsis 2021 Guideline, I agree with the current recommendations against vitamin C use in sepsis. More consistent, prospective standardized trials are needed with treatment plans and clinically significant outcomes.

The Pharmacists Role:

- Assess appropriateness of indications on vitamin C orders
- Provide data regarding safety and efficacy of vitamin C use
- Ensure appropriate initial therapy and timing of sepsis medications

Assessment Questions

1. **Categorize the following patient into the category of no sepsis, sepsis, septic shock, or other:**

   Patient presents with complaint of productive cough, fever, and chills for 6 days. Patient is hypotensive and receives a 30 mL/kg bolus of LR. Vitals are as follows: BP 94/48, HR 112, RR 27, O2 sat. 86%, Temp. 102.1. Labs are drawn and are as follows: Na 137, K 4.2, Ca 9.3, Mg 2.1, Phos 2.4, SCr 3.2, BUN 46, Lactate 5, AST 63, ALT 56

   a. **No sepsis**
   b. **Sepsis**
   c. **Septic shock**
   d. **Other**

2. **Fill in the blank. A proposed mechanism of vitamin C in sepsis is _____.**
   a. **Decreased production of nitric oxide**
   b. **Upregulation of alpha-1 receptors**
   c. **Downregulation of beta-1 receptors**
   d. **Increased production of vasopressin/dopamine**

3. **Which of the following is a true statement regarding the current data of vitamin C in sepsis:**
   a. **Vitamin C showed a reduction in ventilator use**
   b. **Vitamin C use for 1-2 days showed a reduction in mortality**
   c. **Vitamin C had a significant reduction in SOFA score**
   d. **Vitamin C showed an increase in ICU and hospital stay**

References:

1. Bauer, M., Gerlach, H., Vogelmann, T. *et al.* Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. *Crit Care* **24,** 239 (2020). https://doi.org/10.1186/s13054-020-02950-2
2. Reducing sepsis mortality. Center for Transforming Healthcare. https://www.centerfortransforminghealthcare.org/improvement-topics/reducing-sepsis-mortality/ Accessed August 7, 2022.
3. Evans, L., Rhodes, A. Alhazzani, W., *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine: November 2021 - Volume 49 - Issue 11 - p e1063-e1143 doi: 10.1097/CCM.0000000000005337
4. Kuhn SO, Meissner K, Mayes LM, Bartels K. Vitamin C in sepsis. Curr Opin Anaesthesiol. 2018 Feb;31(1):55-60. doi: 10.1097/ACO.0000000000000549. PMID: 29176375; PMCID: PMC5996765.
5. Carr AC, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? Crit Care. 2015 Nov 27;19:418. doi: 10.1186/s13054-015-1131-2. PMID: 26612352; PMCID: PMC4661979.
6. Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. Antioxid Redox Signal. 2013 Dec 10;19(17):2129-40. doi: 10.1089/ars.2013.5401. Epub 2013 Jun 25. PMID: 23682970; PMCID: PMC3869437
7. Gupta V, Karnik ND, Agrawal D. SOFA Score and Critically Ill Elderly Patients. J Assoc Physicians India. 2017 Jul;65(7):47-50. PMID: 28792169.
8. Levi M, Van Der Poll T. Thrombomodulin in sepsis. Minerva Anestesiol. 2013 Mar;79(3):294-8. Epub 2012 Dec 17. PMID: 23241735.
9. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. JAMA. 2018 Jan 2;319(1):62-75. doi: 10.1001/jama.2017.17687. PMID: 29297082; PMCID: PMC5839473.
10. Fowler A, Truwit JD, Hite D, et.al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure. The CITRIS-ALI randomized clinical trial. JAMA 2019;322(13):1261-70.
11. Putzu A, Daems AM, Lopez-Delgado JC, et al. The effect of vitamin C on clinical outcome in critically ill patients: A systematic review with meta-analysis of randomized controlled trials. Crit Care Med. 2019; 47:774–783
12. Moskowitz A, Huang DT, Hou PC, Gong J, Doshi PB, Grossestreuer AV, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020;324:642–50.
13. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA. 2020;323:423–31
14. Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, et al. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS randomized clinical trial. JAMA. 2021;325:742–50
15. Jung, SY., Lee, MT., Baek, M.S. et al. Vitamin C for ≥ 5 days is associated with decreased hospital mortality in sepsis subgroups: a nationwide cohort study. Crit Care 26, 3 (2022). https://doi.org/10.1186/s13054-021-03872-3
16. Arnav Agarwal, John Basmaji, Shannon M. Fernando, Fang Zhou Ge, Yingqi Xiao, Haseeb Faisal, Kimia Honarmand, Mathieu Hylands, Vincent Lau, Kimberley Lewis, Rachel Couban, François Lamontagne, Neill K. J. Adhikari. (2022) Parenteral Vitamin C in Patients with Severe Infection: A Systematic Review. NEJM Evidence 50.

Optimal Timing of Corticosteroids in Septic Shock

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Learning Objectives

1. Explain potential mechanisms of action by which corticosteroids may exert their therapeutic effect in septic shock.

2. Identify the appropriate corticosteroid drug, dose, route, and frequency if indicated for septic shock.

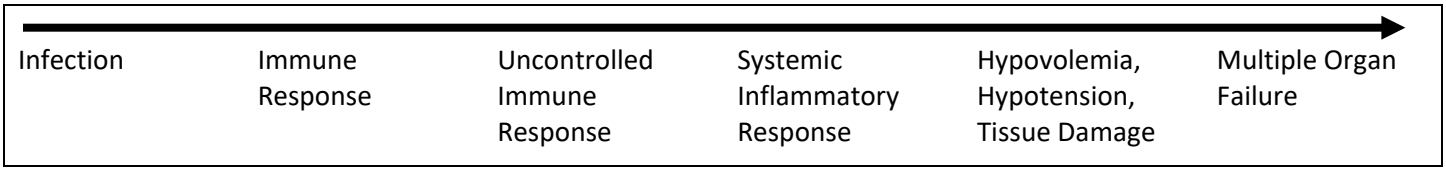
3. Select the appropriate time to initiate corticosteroids in septic shock based on time from shock onset and concurrent therapies in use.

Background

Septic Shock[1-3]

- As defined per the Sepsis-3 criteria, septic shock is the requirement for vasopressors to maintain a mean arterial pressure (MAP) ≥65mmHg and a serum lactate >2mmol/L despite adequate volume resuscitation
    - 30-day mortality in septic shock is about 35%

Pathophysiology[4,5]



Basic Elements of Septic Shock Treatment[6,7]

- Antimicrobials
    - Sepsis arises from an uncontrolled host response to infection, thus antimicrobials provide prompt treatment of infection along with source control as indicated
    - Strong mortality benefit, especially with rapid use in septic shock
    - Not without harms – resistance, use in non-infectious cases, or adverse reactions
    - Reassess for presence of infection or non-infectious causes of illness
- Volume Resuscitation
    - Aimed at the correction of relative or absolute hypovolemia
        - Suggested 30ml/kg IV crystalloid fluid within first 3 hours
    - Supports tissue perfusion through restoration of circulating blood volume
    - Potential to cause volume overload
    - Continual reassessment of volume status is necessary to guide resuscitation
- Vasopressors
    - Norepinephrine (NE) primarily exerts its effects through alpha-1 agonism to cause vasoconstriction and is 1st-line vasopressor based on SOAP II trial
    - Benefit of vasopressors is supporting end-organ perfusion through vasoconstriction by targeting a MAP ≥65mmHg
    - Harms are numerous: tachyarrhythmias, increased myocardial oxygen demand, and ischemia (e.g. peripheral, digital, mesenteric, splanchnic) plus complications of central lines

Corticosteroids in Septic Shock

- Mechanism of Action[8-10]
  - Glucocorticoid effects: attenuate the immune response and regulate metabolic activity
    - Benefit in septic shock may be suppression of unchecked immune response, but harm is hyperglycemia
  - Mineralocorticoid effects: promote sodium reabsorption in renal tubules
    - Benefit in septic shock is support of correction of hypovolemia, but harm is hypernatremia
  - Vascular effects
    - In septic shock, corticosteroids may help restore vasopressor responsiveness and/or improve vascular tone
- Relative Potency[11]

	Glucocorticoid Activity	Mineralocorticoid Activity
Cortisol	1	1
Hydrocortisone	1	0.8
Prednisone	4	0.8
Methylprednisolone	5	0.5
Fludrocortisone	10	125
Dexamethasone	25	0

- Corticosteroid adverse effects – observed in septic shock populations[6,10,12-14]
  - Hyperglycemia, hypernatremia, new septic shock or superinfection, weakness/frailty after ICU admission
- Steroids result in quicker resolution of shock
  - Benefit realized initially with a trial in 2002 by Annane and colleagues,[13] then later supported by the CORTICUS trial in 2008[12]
  - Recent landmark trials:

APROCCHSS[10]

Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med.* 2018;378(9):809-818.

Objective: Evaluate the effect of drotrecogin alfa (activated protein C), low-dose steroids, and their combination on septic shock treatment

Design: prospective, randomized, multicenter, double-blind, placebo-controlled trial

- 2x2 factorial design changed to 2 arms after drotrecogin alfa was withdrawn from the market

Eligibility:

- Included if receiving norepinephrine/epinephrine (NE/EPI) $\geq$0.25mcg/kg/min for 6-24 hours to treat septic shock and SOFA $\geq$3 for 2 organ systems

- Excluded if otherwise indicated to receive steroids plus other exclusions

Intervention: hydrocortisone 50mg IV bolus every 6 hours and fludrocortisone 50mcg tablet enterally once daily for 7 days

Study Population Patient Characteristics:

- 1241 randomized
- Demographics: male=66.6%, age 66$\pm$16 years
- SOFA = 12$\pm$3
- Community-acquired infection = 76.6%
- Site of infection: lung = 59.6%
- Mechanical ventilation = 91.8%
- Vasopressor dose (mcg/kg/min):
  NE=1.08$\pm$1.63
  EPI=2.01$\pm$4.88

Primary Outcome - death from any cause at 90 days (intention-to-treat):

- Placebo, n=308 (49.1%) vs steroids, n=264 (43%)
- RR = 0.88 (95% CI 0.78-0.99, p=0.03)

Secondary Outcomes:

Outcome	Placebo	Steroids	RR (95% CI)	p-value
Death from any cause at 28 days, n (%)	244 (38.9)	207 (33.7)	0.87 (0.75-1.01)	0.06
Death from any cause at hospital discharge, n (%)	284 (45.3)	239 (39.0)	0.86 (0.76-0.98)	0.02
Vasopressor-free days to day 28, mean±SD	15±11	17±11	---	<0.001
Ventilator-free days to day 28, mean±SD	10±11	11±11	---	0.07
Organ failure-free days to day 28, mean±SD	12±11	14±11	---	0.003
Blood glucose ≥150mg/dL at least once by day 7, n (%)	520 (83.1)	547 (89.1)	1.07 (1.03-1.12)	0.002

Strengths:
- SOFA score was part of enrollment criteria
- Sample size calculation assumed 45% mortality
- Utilized a power of 95%
- Thorough reporting of antimicrobial, fluid utilization, and vasopressors
- Resolution of shock findings are consistent with other studies

Limitations:
- Trial was altered from its original intent
- Delay in publication compared to when study conducted
- Primary endpoint of 90 days

Conclusion:
- Authors' Conclusion: Corticosteroid use resulted in lower mortality at 90 days and at ICU and hospital discharge than placebo.
- Evaluator Conclusions:
    - In a cohort of patients with septic shock, representative of more historical mortality rates, corticosteroids might reduce mortality.
    - Corticosteroid use was associated with 2 more days liberated from vasopressor use than placebo.

ADRENAL[14]

Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med.* 2018;378(9):797-808.

Objective: Test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock

Design: prospective, randomized, multicenter, double-blind, placebo-controlled

Eligibility:

- Included if receiving vasopressors or inotropes for over 4 hours, respiratory support through CPAP, BiPAP, or mechanical ventilation, and documented or strong suspicion of infection.

- Excluded if inclusion criteria were met over 24 hours ago, had another indication for steroids, plus other exclusions

Intervention: hydrocortisone 200mg IV infusion over 24 hours until ICU discharge, max of 7 days

Study Population Patient Characteristics: n=3713

Characteristic	Placebo	Steroids
Age – years, mean±SD	62.7±15.2	62.3±14.9
Male, %	61.3	60.4
APACHE II, median (IQR)	23 (18-29)	24 (19-29)
Site of infection = lung, %	36.5	33.8
Catecholamine dose >15mcg/min, %	55.3	53.5

Primary Outcome - death from any cause at 90 days (modified intention-to-treat):

- Placebo, n=526 (28.8%) vs steroids, n=511 (27.9)%
- HR = 0.95 (95% CI 0.82-1.10, p=0.5)

Secondary Outcomes:

Outcome	Placebo	Steroids	RR (95% CI)	p-value
Death from any cause at 28 days, n (%)	448 (24.3)	410 (22.3)	0.89 (0.76-1.03)	0.13
Days alive and out of hospital, median±SD	38.6±32.4	40±32	1.45 (-0.59 to 3.49)	0.16
Time to resolution of shock, days (IQR)	4 (2-9)	3 (2-5)	1.32 (1.23-1.41)	<0.001
Blood transfusion, n (%)	773 (41.7)	683 (37.0)	0.82 (0.72-0.94)	0.004
Time to cessation of initial ventilation strategy, days (IQR)	7 (3-24)	6 (3-18)	1.13 (1.05-1.22)	<0.001
Total adverse events, n (%)	6 (0.3)	27 (1.1)	---	0.009

Strengths:

- Sample size calculation assumed 33% mortality
- Study population reflects current state of septic shock management better
- Resolution of shock findings are consistent with other studies
- Subgroup analyses for primary outcome

Limitations:

- Reporting and protocolization of antimicrobial therapy or fluid resuscitation
- Reporting of glycemic and other adverse events
- Primary endpoint of 90 days
- Possibility of type II error

Conclusion:

- Authors' Conclusion: A continuous infusion of HC did not result in lower mortality at 90 days than placebo.
- Evaluator Conclusion:
  - In a cohort of patients with septic shock with an overall mortality rate similar to current practice, HC did not significantly reduce 28-day or 90-day mortality.
  - Time to resolution of shock was 1 day shorter in patients receiving HC versus placebo.

- 2021 Surviving Sepsis Campaign Guidelines
  - Steroids suggested if persistent vasopressor requirement to treat septic shock
    - Described as being on vasopressors for at least 4 hours and receiving NE or EPI ≥0.25mcg/kg/min
  - Hydrocortisone 50mg IV every 6 hours or 200mg IV infusion over 24 hours per day

What is the optimal timing of corticosteroids in septic shock?

"Comparison of Early Versus Late Initiation of Hydrocortisone in Patients With Septic Shock in the ICU Setting"[15]

Objective

- Evaluate the impact of early versus late initiation of low-dose hydrocortisone (HC) in patients with septic shock

Design

- Multi-center (3 hospitals in Jacksonville, FL), retrospective (July 1, 2014 – August 31, 2019), observational
- Cohorts: stratified by time to HC initiation from vasopressor initiation
  - Early: ≤12 hours
  - Late: >12 hours

Eligibility Criteria

Inclusion Criteria

- Age ≥ 18 years
- ICD-9/10 diagnosis of septic shock
- Received:
  - Continuous vasopressor infusion
  - IV hydrocortisone ≤300mg/day
  - Empiric IV antibiotics

Exclusion Criteria

- Corticosteroid use in past 30 days
- PMH of adrenal insufficiency
- Cardiac vasoplegia syndrome
- Cardiac arrest in past 30 days
- Pregnancy
- Incarceration

Outcomes

Primary

- Time to vasopressor discontinuation

Secondary

- In-hospital mortality
- ICU length of stay (LOS)
- Hospital LOS
- Maximum NE-equivalent dose required
- Total insulin requirements

Statistical Analyses

- Sample size of 120 per cohort to detect a mean difference of 12 hours
- Primary outcome: Wilcoxon log rank test
  - Effect of time to HC initiation was analyzed with multivariate regression
- Other
  - Chi-square or Fisher exact test for categorical data
  - Mann-Whitney U test or student's t-test for continuous data
- Propensity score (PS) matched cohort was derived for further analyses

Results

Baseline Characteristics

Characteristic – Unmatched Cohort	Early (n=125)	Late (n=115)
Age – years, median (IQR)	68.9 (60.4-77.5)	68.5 (60.5-77.8)
Male, n (%)	68 (54.4)	61 (53.0)
Lactic acid (mg/dL), median (IQR)	5.0 (3.1-9.6)	3.3 (1.9-7.3)
SOFA score, median (IQR)	13 (10-15)	12 (8-15)
Site of infection = lung, n (%)	62 (49.6)	51 (44.4)
MAP (mmHg) at vasopressor initiation, median (IQR)	59 (52-63)	63 (57-68)
NE-equivalent dose (mcg/min) at steroid initiation, median (IQR)	20 (9-30)	12 (5-24)

Primary Outcome

- Time to vasopressor discontinuation: 40.7 hours in early cohort vs 60.6 hours in late cohort (p=0.002)
  - Multivariate linear regression: each hour hydrocortisone is delayed associated with 52.8 more minutes of vasopressor use (p <0.001)
  - Post-hoc subgroup analyses: obesity (BMI >30kg/m^2), history of hypertension, and NE-equivalent dose (>15mcg/min)
    - each subgroup confirmed the primary outcome (p <0.05)

Secondary Outcomes – PS matched cohort

	Early (n=99)	Late (n=99)	p-value
In-hospital mortality, n (%)	42 (42.4)	48 (48.5)	0.3918
ICU LOS, days	3.6 (1.8-9.2)	5.1 (3-9.9)	0.0147
Hospital LOS, days	8.9 (2.6-15.2)	10.9 (5.5-17.9)	0.0220
Maximum NE-equivalent dose, mcg/kg/min	0.5 (0.2-0.8)	0.4 (0.2-0.7)	0.6221
Total insulin from vasopressor initiation, units	12 (0-60)	11 (0-76)	0.8384

*statistical significance, whether met or not, was also demonstrated in unmatched cohort for each secondary endpoint

Evaluation

Strengths

- Internal validity strengthened with propensity score matched and subgroup analyses
- External validity strengthened by acuity and mortality similar to other literature
- Benefit of early corticosteroid use is able to overcome intervention bias

Limitations

- Retrospective data
- Reporting of antimicrobial therapy or fluid resuscitation
- Dichotomization of timing to steroid initiation
- Inclusion of hydrocortisone doses up to 300mg/day
- Evaluation of blood glucose control with surrogate endpoint of insulin use

Conclusions

Authors'

- Earlier initiation of hydrocortisone is associated with improved time to discontinuation of vasopressors and shortened ICU and hospital length of stay

Evaluator

- Mortality in study is above normal for general septic shock population
- Poor reporting of antimicrobial therapy or fluid resuscitation
- Vasopressor duration reduced by about 20 hours
- ICU and hospital LOS reduced by 1.5 and 2 days, respectively

"Evaluation of the Initiation Timing of Hydrocortisone in Adult Patients With Septic Shock"[16]

Objective

- Compare vasopressor duration and mortality in patients with septic shock who received hydrocortisone, based on timing after shock onset

Design

- Single center: Cleveland Clinic Main Campus
- Retrospective: January 2011 – November 2017
- Observational
- Stratification per timing of hydrocortisone initiation from the start of vasopressors: 0-6 hours, 6-12 hours, 12-24 hours, 24-48 hours and 48 hours

Eligibility Criteria

Inclusion Criteria

- Age ≥18 years
- Septic shock with NE use for >12 hours
- At least 2 consecutive doses of IV hydrocortisone after initiation of vasopressors

Exclusion Criteria

- Multiple systemic steroids (fludrocortisone use was allowed)
- Missing data from electronic medical record necessary for outcome assessment

Outcomes

Primary

- Compare vasopressor duration according to time to hydrocortisone initiation

Secondary

- Association of the timing of steroid initiation with vasopressor duration
- Dichotomized study population to ≤24 hours versus >24 hours for association with vasopressor duration
- ICU and hospital mortality and LOS

Statistical Analyses

- Primary endpoint: Kruskal-Wallis test
  - Defined as days alive and free of vasopressors at 28 days
- Multivariate linear regression for association of timing of steroid initiation with vasopressor duration
  - Adjusted for lactate, NE dose as steroid initiation, and APACHE II score (plus other significant variables)
- Comparison of ≤24 hours versus >24 hours: Chi-square
- Mortality outcomes: multivariate logistic regression

Results

Baseline Characteristics

Characteristic (at steroid initiation)	Total Population (n=1470)
Age – years, mean±SD	61±15
Male, n (%)	804 (54.7)
APACHE III score, mean±SD	104.3±33.6

	0-6hr (n=567)	6-12hr (n=231)	12-24hr (n=260)	24-48hr (n=195)	>48hr (n=217)	p value
Lactate (mmol/L), mean±SD *at steroid initiation	4.6±4.0	4.9±4.5	3.9±3.6	3.9±3.7	3.1±3.0	<0.01
NE dose (mcg/min), mean±SD *at steroid initiation	23.6±20.2	26.6±23.0	25.0±23.8	23.7±22.3	19.2±19.5	<0.01
Hydrocortisone dose in first 24 hours (mg), mean±SD	215.8±62.9	214.8±55.1	217.5±64.7	210.3±54.8	221.7±79.6	0.73

Primary and Secondary

	0-6hr (n=567)	6-12hr (n=231)	12-24hr (n=260)	24-48hr (n=195)	>48hr (n=217)	p-value
Days alive and free from vasopressors at 28 days	3.3 (0-26.2)	1.9 (0-25.2)	1.9 (0-25.7)	0 (0-25.4)	0 (0-23.4)	0.39
ICU mortality, n (%)	244 (43.0)	108 (46.8)	120 (46.2)	94 (48.2)	105 (48.4)	0.58
Hospital mortality, n (%)	275 (48.5)	121 (52.4)	137 (52.7)	107 (54.9)	128 (59.0)	0.10
ICU LOS (days), mean±SD	11.1±15.3	11.6±12.4	13.2±15.6	13.6±12.5	18.9±16.8	<0.01
Hospital LOS, mean±SD	21.2±26.2	20.6±18.8	22.7±21.0	22.5±19.9	27.3±21.3	<0.01

Multivariate Linear Regression – Days alive and free of vasopressors

	Beta Coefficient (95% CI)	p value
0-6hr vs >48hr	2.75 (0.84-4.65)	0.005
6-12hr vs >48hr	2.47 (0.23-4.71)	0.03
12-24hr vs >48hr	2.31 (0.16-4.45)	0.04
24-48hr vs >48hr	1.36 (-0.94-1.28)	0.25

Multivariate Logistic Regression – ICU mortality

	Odds Ratio (95% CI)	p value
0-6hr vs >48hr	0.59 (0.41-0.85)	0.004
6-12hr vs >48hr	0.59 (0.38-0.91)	0.02
12-24hr vs >48hr	0.75 (0.5-1.13)	0.17
24-48hr vs >48hr	0.82 (0.53-1.28)	0.39

Evaluation

Strengths

- Stratification (0-6hr, 6-12hr, etc.) allows for greater granularity when evaluating data
  - Multivariate and subgroup analyses
- Consistency of results with other literature
- External validity of study applies to population of higher acuity than previously studied
- Benefit of early corticosteroids is able to overcome intervention bias

Limitations

- Retrospective data
- Reporting of antimicrobial therapy or fluid resuscitation
- Choice of primary endpoint
- No evaluation of adverse effect of steroids

Conclusions

Authors'

- Initiation of hydrocortisone within the first 12 hours appears to confer more benefit than initiation after 12 hours

Evaluator

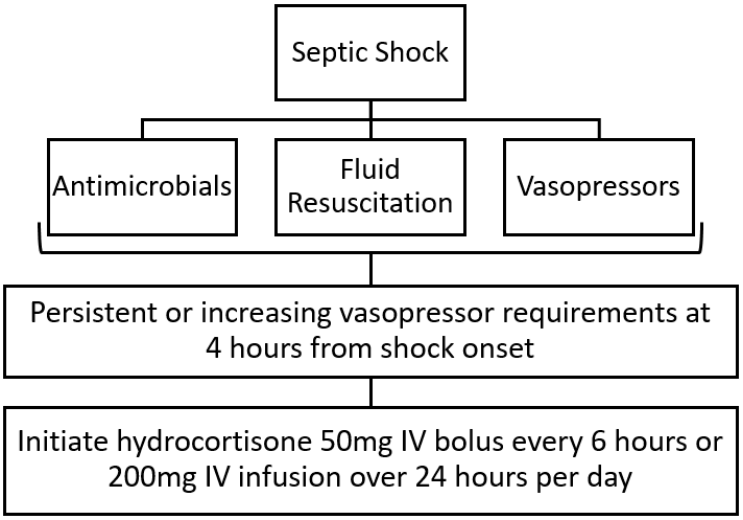
- Mortality in study is above normal for general septic shock population
- Poor reporting of antimicrobial therapy or fluid resuscitation
- Early initiation spared patients of about 1.9 to 3.3 days worth of vasopressor utilization
- ICU and hospital LOS reduced with early initiation

Conclusions

Overall: Corticosteroid therapy is optimally timed when implemented at 4 hours after shock onset in patients with persistent or rising vasopressor requirements

- Randomized controlled trials provide consistent support for the clinical benefit that steroids result in quicker resolution of shock.
    - Trial population differences distort the precision of this and other outcomes such as mortality or LOS
- Retrospective studies were able to reaffirm quicker resolution of shock in real-world setting among populations that are reasonably similar to randomized trials.
    - Such studies were able to apply greater scrutiny to the effect of when steroids are administered for how effective they are in achieving reductions in vasopressor use

Treatment Algorithm



Considerations if original corticosteroid timing goal not achieved:	
Within 24 hours from shock onset	Recommend initiating corticosteroids over delaying therapy since benefits in shock resolution are optimized with early use, rather than reservation for salvage therapy
Past 24 hours from shock onset	Consider corticosteroid therapy since harms of longer vasopressor requirements likely outweigh harms of corticosteroid therapy, even if vasopressor duration-reducing benefits of corticosteroids may be slightly diminished

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
2. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. *Crit Care*. 2020;24(1):239. Published 2020 May 19.
3. Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. *Crit Care*. 2019;23(1):196. Published 2019 May 31.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851.
5. Sardinha J, Lehmann C, Kelly M. Targeting the Endocannabinoid System to Treat Sepsis. *Signa Vitae*. 2013. 8(1);9-14.
6. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181-1247.
7. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779-789.
8. Taves MD, Gomez-Sanchez CE, Soma KK. Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. *Am J Physiol Endocrinol Metab*. 2011;301(1):E11-E24.
9. Annane D. The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update. *Front Endocrinol (Lausanne)*. 2016;7:70. Published 2016 Jun 20.
10. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med*. 2018;378(9):809-818.
11. Heming N, Sivanandamoorthy S, Meng P, Bounab R, Annane D. Immune Effects of Corticosteroids in Sepsis. *Front Immunol*. 2018;9:1736.
12. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
13. 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(7):862-871.
14. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med*. 2018;378(9):797-808.
15. Ragoonanan D, Allen B, Cannon C, Rottman-Pietrzak K, Bello A. Comparison of Early Versus Late Initiation of Hydrocortisone in Patients With Septic Shock in the ICU Setting. *Ann Pharmacother*. 2022;56(3):264-270.
16. Sacha GL, Chen AY, Palm NM, Duggal A. Evaluation of the Initiation Timing of Hydrocortisone in Adult Patients With Septic Shock. *Shock*. 2021;55(4):488-494.

Fluid Balance in Septic Shock Following Initial Resuscitation

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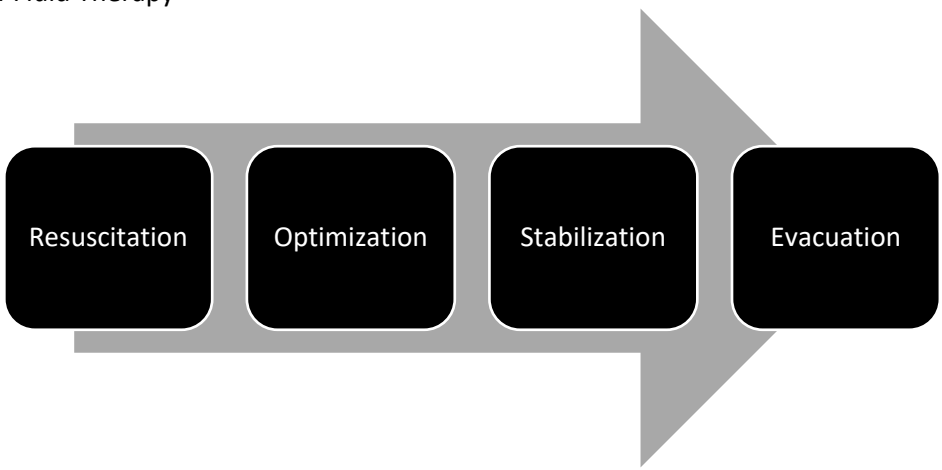
- **Objectives**
  - Identify harms of fluid overload in patients with septic shock
  - Describe appropriate measures of fluid status in patients with septic shock
  - Describe current literature regarding fluid administration following initial resuscitation in septic shock

- **Background**
  - Definitions[1]

Sepsis	Septic Shock
• Life-threatening organ dysfunction caused by dysregulated host response to infection	• Sepsis with underlying circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality • Characterized by hypotension and hypoperfusion refractory to fluids and requiring vasopressors

  - Treatment Overview[2]
    - Antibiotics
    - Fluids
    - Vasopressors
    - Inotropes
    - Glucocorticoids
    - Supportive care: stress ulcer prophylaxis, glycemic control, VTE prophylaxis, nutritional support
  - Role of Fluids[1, 2]
    - Stages of Fluid Therapy



    - Initial Fluid Resuscitation[1]
      - IV fluids to improve circulation and perfusion
      - 30 mL/kg IBW of IV crystalloid fluids administered within the first 3 hours[1]
        - Based on observational evidence but widely accepted and currently best practice
          - Inadequate fluid resuscitation resulted in increased mortality, delayed resolution of hypotension and increase ICU stay
        - Recently downgraded to a weak recommendation in the Surviving Sepsis Guidelines
        - Guidelines suggest the use of dynamic measures to guide fluid resuscitation, guiding fluid resuscitation with decrease in serum lactate and using capillary refill time to as an adjunct measure

- Pathophysiology[2]
  - Actual and/or relative intravascular volume depletion
  - IV fluids correct volume depletion and increase preload
  - Increasing cardiac output
  - Improving blood flow and perfusion
- Fluids After Initial Resuscitation[2-4]
  - The optimization and stabilization phases
  - More difficult to assess
    - Certain patients may benefit from further fluids
    - 50% of patients are not fluid responsive
    - Risk of volume overload
  - Pathophysiology
    - Volume overload: > 10% fluid accumulation from time of admission
    - Capillary leakage causing large amounts of intravascular to shift out
    - Negative impacts due to increased intracardiac pressures, organ edema and arterial vasodilation
    - Can result in worsened clinical outcomes

- **Harms of Fluid Overload**
  - Includes: [3, 5]

Acute kidney injury (AKI)	Electrolyte disturbances	Respiratory failure
Prolonged ventilation	Increased organ failure	Increased mortality

  - Primary Literature Support
    - A Higher Fluid Balance in the Days After Septic Shock Reversal Is Associated with Increased Mortality: An Observational Cohort Study[6]
      - Methods
        - Retrospective observational cohort study
        - Adult patients with septic shock that had been reversed (serum lactate < 2 mmol/L and weaned off vasopressors)
        - Aim was to find association with fluid balance and mortality in days following septic shock reversal
        - Logistic regression was used in that analysis and possible confounders were adjusted for
      - Results
        - N = 636

	Per 10 mL/kg increase fluid balance	Positive fluid balance
Hospital Mortality	1.70 (1.40-2.07)	3.39 (2.35-4.90)
ICU Mortality	3.18 (1.90-5.32)	3.46 (2.29-5.23)
30-day Mortality	2.09 (1.64-2.67)	5.33 (3.52-8.08)
90-day Mortality	1.79 (1.38-2.32)	3.57 (2.49-5.12)
1-year Mortality	1.53 (1.17-2.01)	x

        - Increased mortality with fluid balance > 50 mL/kg
        - The study also found that AKI was more common in patients with increased fluid balance
      - Conclusions
        - Limited since retrospective observational study
        - Strengths include a larger cohort with similar characteristics, specifically focuses on fluid after initial resuscitation and confounders were adjusted for
        - Study shows that positive fluid balance increases mortality

- Fluid Balance Correlates with Clinical Course of Multiple Organ Dysfunction Syndrome[7]
  - Methods
    - Retrospective observational cohort study
    - Objective was to determine if cumulative fluid balance (CFB) was associated with sepsis induced multiorgan dysfunction syndrome (MODS)
  - Results
    - N = 104
    - 72-hour fluid balance: survivors was 1066.7 ml vs non-survivors at 3067.7 ml (p= 0.001)
    - 72-hour fluid balance: MODS was 873.1 ml vs no MODS at 2409.8 ml (p= 0.016)
    - 72-hour CFB > median increased risk of MODS
      - Univariate OR 2.69 (1.11-6.51, p= 0.033)
      - Multivariate OR 3.67 (1.18-11.40, p= 0.024)
    - 72-hour CFB > median increased risk of 28-day mortality
      - Univariate OR 1.80 (1.21-2.69, p= 0.033)
      - Multivariate OR 4.13 (1.134-12.66 p= 0.013)
  - Conclusions
    - Limited since small retrospective observational cohort study
    - 72-hour CFB can be used as a predictor for development of MODS and mortality in patients with septic shock with higher fluid balance leading to increased risk of MODS and mortality

- **Active Learning #1**
  - What patient outcomes have been identified in patients with septic shock that are volume overloaded? Select all that apply:
    A. Electrolyte disturbances
    B. Acute kidney injury
    C. Decreased mortality
    D. Respiratory failure

- **Fluid Measures** [1-3]
  - Static measures
    - Physical exam: weight, heart rate, blood pressure, edema, skin temperature
    - Capillary refill time
    - Jugular venous pressure (JVP)
    - I&Os
    - Lactate
    - Central venous pressure (CVP)
    - Overall not as accurate, more measures of fluid status rather than flud responsiveness
  - Dynamic measures
    - Changes in stroke volume and cardiac output in response to passive leg raise or fluid boluses
    - Pulse pressure variation (PPV)
    - Systolic pressure variation (SVV)
    - Inferior vena cava variation
    - End-expiratory occlusion testing

- **Active Learning #2**
  - Which is a dynamic measure of fluid responsiveness recommended by the Surviving Sepsis Campaign Guidelines?
    A. Passive leg raise with measure of change in stroke volume
    B. Capillary refill time
    C. Lactate > 4 mmol/L
    D. Central venous pressure

- **Guidelines Recommendations[1]**
  - Surviving Sepsis Campaign Guidelines
    - There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation

- **Literature Review**
  - Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study[9]
    - Methods
      - Prospective randomized pilot study
      - Following initial resuscitation received usual care or targeted fluid minimization (TFM)
      - With TFM a fluid challenge was completed with 500 mL NS and leg raise to deem if fluid responsive
      - Fluid responsive patients received fluids while fluid non-responders fluids were limited as much as possible
    - Results
      - Fluid balance by day 3: TFM 1,952 mL vs 3,124 mL, p= 0.20
      - Fluid balance by day 5: TFM 2,641 mL vs 3,616 mL, p= 0.40
      - Similar rates of RRT, vasopressor and ventilator use, and in-hospital mortality
    - Conclusions
      - Small pilot study
      - Used appropriate dynamic measures, though fluid boluses result in fluid accumulation
      - Protocol guided fluid assessment possible
      - No significantly different outcomes
      - Larger studies are needed

  - Restricting Volumes of Resuscitation Fluid in Adults with Septic Shock After Initial Management: the CLASSIC Randomized, Parallel-group, Multicentre Feasibility Trial[8]
    - Methods
      - Randomized parallel-group, multicenter feasibility trial
      - After initial resuscitation received standard care or restrictive fluid protocol
      - The restrictive group only received fluids with severe hypoperfusion including lactate > 4, MAP < 50, mottling beyond the edge of the kneecap, urinary output < 0.1ml/kg IBWwith 2 hours randomization
    - Results
      - Significantly reduced fluid volumes:
        - Day 5: -1.2 L
        - ICU stay: -1.4 L
      - Significantly less worsening of AKI OR 0.46 (0.23-0.92, p= 0.03) in the restrictive group
      - No significant difference in ischemic events OR 0.32 (0.08-1.27, p= 0.11) and 90-day mortality OR 0.71 (0.36-1.40, p= 0.32)

- Conclusions
  - Small study
  - Underpowered
  - No dynamic measures used
  - Restrictive protocol reduced fluid volumes
  - Showed potential clinical benefit
  - Paved the way for future trials

- Fluid Response Evaluation in Sepsis Hypotension and Shock[4]
  - Multicenter, randomized, unblinded clinical trial
  - Objective: To determine if fluid administration guided by dynamic assessments of fluid responsiveness in patients with septic shock will improve outcomes
- Outcomes
  - Primary endpoints:
    - Fluid balance
  - Secondary endpoints:
    - RRT, ventilator use, length ICU stay, vasopressor use and SCr changes
  - Inclusion and exclusion criteria:
    - Inclusion
      - Patients with sepsis or septic shock
      - Anticipated ICU admission
      - Refractory hypotension
      - Enrollment within 24 hours hospitalization
    - Exclusion
      - > 3 L IV fluids prior to randomization
      - Do not resuscitate order
      - Transferred from another hospital
      - Active hemorrhage, acute cerebral vascular event, acute coronary syndrome or acute pulmonary embolism, major cardiac arrythmias, drug overdose, trauma or burns
        - Due to altered fluid requirements
  - Methods
    - Randomized at 2:1 ratio to receive:
      - Usual care – fluids administered based on medical team discretion
      - Intervention – fluid administration based on fluid responsiveness
        - Fluid responsive if passive leg raise and change in stroke volume >10%
      - Full protocol algorithm – Appendix 1
  - Baseline characteristics

	Intervention Group	Usual Care Group
Mean Age	61.8 years	62.7 years
Female Gender	61.40%	31.70%
SIRs Criteria	2.7	2.8
BMI	26.5 kg/m2	25.3 kg/m2
qSOFA	1.9	2.1
Serum Lactate	3.6	3.8
Hospital Arrival	5.2 hrs	4.4 hrs
Fluid Following Arrival	2.4 L	2.2 L

  - Results
    - N = 150 patients

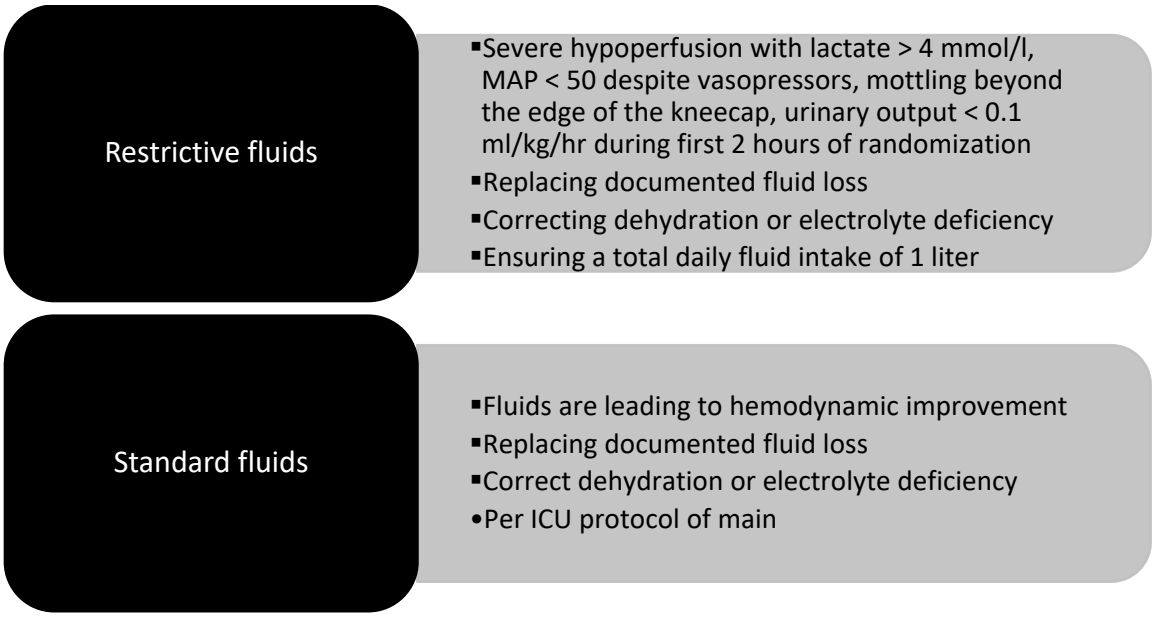
	Intervention Group	Usual Care Group	Treatment Difference	P value
Mean Fluid Balance at 72 hours or ICU Discharge	0.65 ± 2.85 L	2.02 ± 3.44 L	-1.37 L	0.021
RRT Requirement	5.1%	17.5%	-12.4%	0.042
Ventilator Use	17.7%	34.1%	-16.42%	0.044
Discharge Home	63.9%	43.9%	20%	0.035

        - Non-significant differences:
            - Length of ICU stay
            - Hours of vasopressor use
            - Change from baseline serum creatinine
            - ADRs
            - Number of ICU readmissions
            - Mortality rate
            - Incidence of major cardiovascular end points (CV death, nonfatal MI, nonfatal stroke)
    - Strengths and limitations
        - Strengths
            - Use of dynamic measures
            - Total body volume measured
            - Clear protocol
        - Limitations
            - Gender unequal in groups
            - Takes into account resuscitation and subsequent fluid administration
            - Large confidence interval within fluid data
            - Responsive if SV change > 10% vs > 15%
    - Conclusions
        - Fluid balance was significantly reduced in the fluid responsiveness guided fluid administration group
            - Dynamic measures are effective
            - Even with higher diuretic use and RRT in the standard treatment group
        - Reduced fluid balance led to improved outcomes and no additional safety concerns
        - More studies still needed

- **Active Learning #3**
    - In the FRESH Trial protocol, patients were deemed fluid responsive following a passive leg raise if change in stroke volume was _____
        A. < 5%
        B. 5-10%
        C. > 10%

    - Restriction of Intravenous Fluid in ICU Patients with Septic Shock (CLASSIC Trial)[10]
        - International, randomized, open label clinical trial
        - Objective: To determine if restrictive versus liberal fluid management following initial fluid resuscitation decreased poor outcomes in patients with septic shock
        - Outcomes
            - Primary endpoints:
                - 90-day mortality
            - Secondary endpoints:
                - Serious ADEs, serious ADRs, days Alive without support and days alive out of hospital

- Inclusion and exclusion criteria
  - Inclusion
    - ≥ 18 years old
    - ICU with septic shock
    - Onset of shock within 12 hours
  - Exclusion
    - Life threatening bleed
    - Acute burns > 10% of BSA
    - Pregnancy
- Methods
  - Randomized at a 1:1 ratio to receive:



  - Restrictive fluids only could give 250 to 500 mL boluses while there was no limit on standard fluids administered
  - Enteral and oral fluids, nutrition and medication administration fluids were allowed in both groups
  - Crystalloid fluids were recommended with albumin only after abdominal paracentesis
  - All other clinical decisions were up to the providers, including diuretic use
- Baseline characteristics

Baseline Characteristics	Restrictive Fluid Group	Standard Fluid Group
Median Age	71 years	70 years
Male Gender	59.90%	58.20%
Predicted 90-day Mortality	40%	40%
GI Source	36.80%	38.30%
Body Weight	77 kg	78 kg
Plasma Lactate	3.8	3.9
Highest NE Dose	0.25 ug/kg/min	0.23 ug/kg/min
Fluid Prior Randomization	3.2 L	3 L

- Results

	Median IV fluids	Median Total Fluids	Cumulative Fluid Balance
Restrictive Fluids	1,796 mL	10,433 mL	1,645 mL
Standard Fluids	3,811 mL	12,747 mL	2,368 mL
Difference	-2,013 mL	-2,314 mL	-723 mL

	90 Day Mortality	Serious Adverse Events	Serious Adverse Reactions	Median Days without Life Support	Median Days Alive and Out of Hospital
Restrictive Fluids	42.3%	29.4%	4.1%	77	21
Standard Fluids	42.1%	30.8%	4.1%	77	33
Difference	0.1 (-4.7 to 4.9)	-1.7 (-7.7 to 4.3)	-0.1 (-2.8 to 2.6)	0 (-11 to 11)	-12 (-30 to 6)
Relative Risk	1.00 (0.89 to 1.13)	0.95 (0.77 to 1.15)	0.99 (0.50 to 1.93)	-	-
P Value	0.96	0.46	0.95	0.84	0.84

- Strengths and limitations
  - Strengths
    - Multicenter and geographic diversity
    - Well balanced baseline characteristics between groups
    - Standard fluid amount similar to other trials
  - Limitations
    - Restrictive fluid protocol violated more
    - No dynamic variables; static measures used
    - Small difference in cumulative balance
    - Standard group ICU protocol differed by location
- Conclusions
  - Researchers concluded that restrictive IV fluid administration following initial resuscitation did not reduce mortality or other clinical outcomes
  - Though administration of fluid was not based on recommended dynamic measures

- **Conclusions**[2, 3, 5]

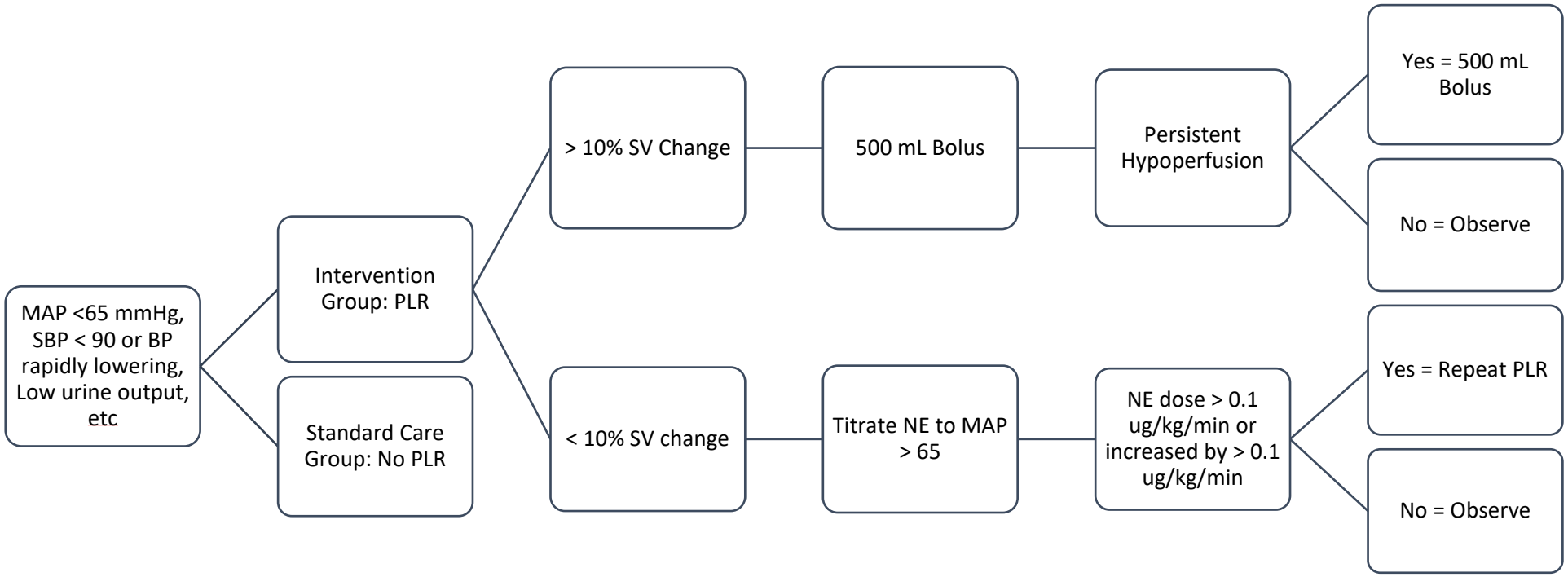
CLASSIC	Both Trials	FRESH
• Static measures • Intervention CFB 1.6 L • Larger trial • Clear protocol	• Randomized control trial • Similar Standard care CFB • Small differences in fluids	• Dynamic measures • Intervention CFB 0.65 L • Smaller trial • Protocol not as well defined

  - No exact amount of fluids needed
  - Patient specific
  - Appropriate dynamic and static measures
  - Prevent fluid overload and its harms
  - Pharmacist role in assessing appropriate use of fluids as well as management of use of diuretics and ultrafiltration moving toward evacuation resulting in patient have a negative fluid balance

References:

1. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-1247. doi:10.1007/s00134-021-06506-y
2. Brown RM, Semler MW. Fluid Management in Sepsis. J Intensive Care Med. 2019;34(5):364-373. doi:10.1177/0885066618784861
3. Bissell BD, Mefford B. Pathophysiology of Volume Administration in Septic Shock and the Role of the Clinical Pharmacist. Ann Pharmacother. 2020;54(4):388-396. doi:10.1177/1060028019887160
4. Douglas IS, Alapat PM, Corl KA, et al. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial. Chest. 2020;158(4):1431-1445. doi:10.1016/j.chest.2020.04.025
5. Besen BA, Taniguchi LU. Negative Fluid Balance in Sepsis: When and How?. Shock. 2017;47(1S Suppl 1):35-40. doi:10.1097/SHK.0000000000000701
6. Van Mourik N, Geerts BF, Binnekade JM, et al. A Higher Fluid Balance in the Days After Septic Shock Reversal Is Associated With Increased Mortality: An Observational Cohort Study. Crit Care Explor. 2020;2(10):e0219. Published 2020 Sep 23. doi:10.1097/CCE.0000000000000219
7. Huang AC, Lee TY, Ko MC, et al. Fluid balance correlates with clinical course of multiple organ dysfunction syndrome and mortality in patients with septic shock. PLoS One. 2019;14(12):e0225423. Published 2019 Dec 2. doi:10.1371/journal.pone.0225423
8. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomized, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-1705. doi:10.1007/s00134-016-4500-7
9. Chen C, Kollef MH. Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study. Chest. 2015;148(6):1462-1469. doi:10.1378/chest.15-1525
10. Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med. 2022;386(26):2459-2470. doi:10.1056/NEJMoa2202707

Appendix 1 – The FRESH Trial Treatment Algorithm[4]



Abbreviations
MAP = mean arterial pressure
SBP = systolic blood pressure
PLR = passive leg raise
SV = stroke volume
NE = norepinephrine