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Sepsis: The Controversies Never Stop

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Disclosures

- I have no disclosures, conflicts of interest related to this subject or talk

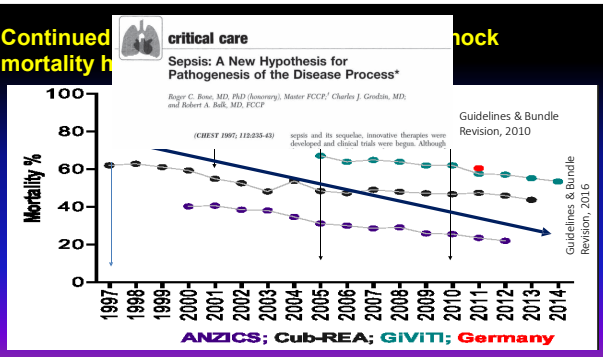
Lecture Objectives

- Review key studies related to sepsis and septic shock
- Discuss the current issues about septic shock related to
  - What is the importance of 30 and 60 day mortality
  - Recognition of septic patient, what's new
  - Concepts of antibiotics & intravenous fluids in sepsis/shock
  - Steroids for the septic patient, where have we been and where are we going
  - Possible adjuvant therapies for sepsis and shock are they ready for prime time

The Guideline: Map

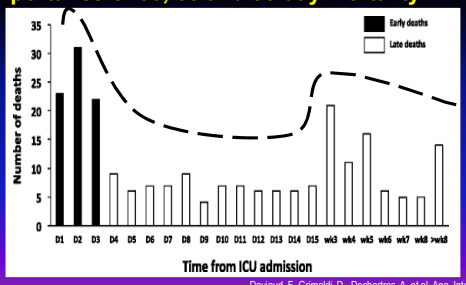
1. Defining the disease
2. Broad-spectrum antibiotics
3. Fluid resuscitation
4. Inotropes
5. Corticosteroids
6. Adjunct treatments

Continued … hock mortality h…



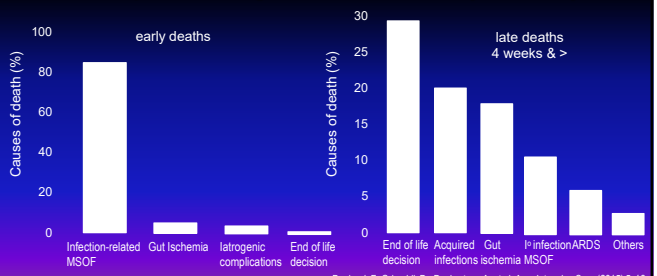
Shankar-Hari, Manu et al. "Judging quality of current septic shock definitions and criteria." *Critical Care* 19 (2015): 1-5.

Timing and causes of death in septic and septic shock
The importance of 30, 60 and 90 day mortality



Daviaud, F., Grimaldi, D., Dechartres, A. et al. Ann. Intensive Care (2015) 5: 16. https://doi.org/10.1186/s13613-015-0058-8

Timing and causes of death in septic shock
The concept of looking at 30, 60 and 90 day mortality



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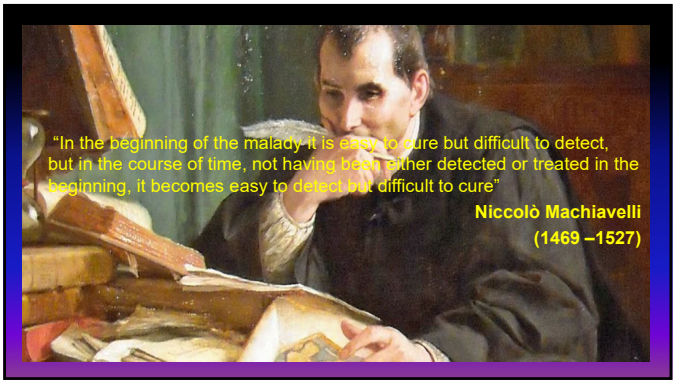

Revisited the 1992 definitions found the SIRS criteria to be useful but not specific and therefore

- Sepsis was defined as infection and 'some' of the following:
  - General variable: fever (temp > 38.3°C), hypothermia (temp< 36°C), heart rate > 90% beats/min, tachypnea, altered mental status, significant edema (+ fluid balance > 20 ml/Kg over 24 hours), hyperglycemia (glucose > 120 mg/dL in the absence of diabetes)
  - Inflammatory variable: leukocytosis(WBC >12 cells/μL), leukopenia (WBC <4 cells/μL), bandemia (>10% immature forms), C-reactive protein > 2 s.d. above normal value, Pro-calcitonin > 2 s.d. above normal value
  - Hemodynamic variables: Arterial hypotension (SBP<90 mmHg, MAP > 70, or SBP decrease > 40 mmHg), SvO2< 70%, Cardiac index > 3.5 L/min

Levy MM, et al. Crit Care Med. 2003 Apr; 31(4):1250-6.

Sepsis Redefined - The Third International Definitions for Sepsis and Septic Shock (Sepsis-3)

- Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection
- Organ dysfunction identified as an acute change in total SOFA score ≥ 2 points consequent to the infection
- Septic shock is sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level > 2 mmol/L despite adequate volume resuscitation

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552.
Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10

The assessment of patients with infection

- Retrospective evaluation of 148,907 patients at UPMC with suspected infection (cultures obtained and antibiotics initiated)
- Multivariable regression used to explore the performance of 21 bedside & laboratory criteria for patients inside and outside ICU

Ability to predict mortality among patients with possible infection outside the ICU

Test	Area under ROC curve	Sensitivity for mortality	Specificity for mortality
SIRS ≥ 2	0.76	64%	65%
SOFA ≥ 2	0.79	68%	67%
qSOFA ≥ 2	0.81	55%	84%

The assessment of patients with infection

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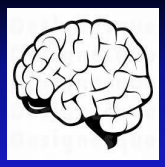
Sepsis-3 guidelines recommend the use of the quick SOFA (qSOFA) score, using only three criteria:



Criteria:	Altered Mental Status	Respiratory Rate	Systolic blood pressure
Value:	Change from baseline	> 22 /minute	BP < 100 mm Hg

q SOFA Points		Predicted mortality
	0	< 1 %
	1	2 - 3 %
	>2	> 10 %

Sepsis Redefined - The Third International Definitions for Sepsis and Septic Shock (Sepsis-3)

- Operationally, sepsis can be identified whenever infection is known or suspected and clinical criteria defining organ dysfunction are met.
- The recommended criteria to assess organ dysfunction are included in the Sequential Organ Failure Assessment (SOFA) score.
- SOFA Score assigns a value of 0-4 for each of six organ systems assessed: respiratory, coagulation, hepatic, cardiovascular, central nervous, and renal, with increasing scores for more severe dysfunction (online SOFA score calculators are available) https://www.mdcalc.com/sofa-quick-sofa-qsofa-sepsis

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552.
Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10

Sepsis Definitions

	Previous Definitions	Sepsis-3 SCCM Definition 2016
SIRS	Screening tool for patients with infection to identify sepsis (> 2 of 4 criteria)	Removed
Quick SOFA	N/A	Risk stratification tool for patients with suspected infection to predicted poor outcomes
Sepsis	1992: SIRS + infection 2003: Sepsis plus "some" variable	Life threatening organ dysfunction caused by a dysregulated host response to infection
Severe Sepsis	Sepsis complicated by organ dysfunction	Removed
Septic Shock	Sepsis with hypotension despite adequate fluid resuscitation	Sepsis with persisting hypotension requiring vasopressor to maintain MAP > 65 mmHg and having a serum lactate level > 2 mmol/L despite adequate volume resuscitations

Singer, et al. JAMA. 2016 Feb 23; 315(8):801-10.
Levy MM, et al. Crit Care Med. 2003 Apr; 31(4):1250-6.

The Guideline: Map

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4. Inotropes
5. Corticosteroids
6. Adjunct treatments

2013 to current 2016 SSC Bundles in Response to New Evidence

http://www.survivingsepsis.org/sitecollectiondocuments/ssc_bundle.pdf

2013 Surviving Sepsis Campaign Bundles
1. Measure serum lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/Kg of crystalloid fluid for hypotension or lactate > 4 mmol/L
To be completed within 6 hours
1. Apply vasopressors for hypotension that does not respond to initial fluid administration to maintain MAP > 65 mmHg
2. Measure central venous pressure (CVP) Measure central venous oxygen saturations ($Scvo_2$)
3. Re-measure lactate if initial lactate elevated

Dellinger, et al. Intensive Care Med.2013Feb;39(2):165-228.

3 Hour Bundle
1. Measure serum lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/Kg of crystalloid fluid for hypotension or lactate > 4 mmol/L
6 Hour Bundle
1. Apply vasopressors for hypotension that does not respond to initial fluid administration to maintain MAP > 65 mmHg
2. Re-asses volume status and tissue perfusion if persistent hypotension after initial fluids
3. Re-measure lactate if initial lactate elevated

Rhodes A, et al. CritCare Med. 2017 Mar;45(3):486-552.

Current 2016 SSC Bundles in Response to New Evidence

- Recommend administration of IV antimicrobials as soon as possible after recognition of sepsis within one hour
- Empiric broad-spectrum therapy with one or more antimicrobials to cover likely pathogens
- Narrow antimicrobials once pathogen identification and sensitivities are established

3 Hour Bundle
1. Measure serum lactate level
2. Obtain blood cultures prior to administration of antibiotics
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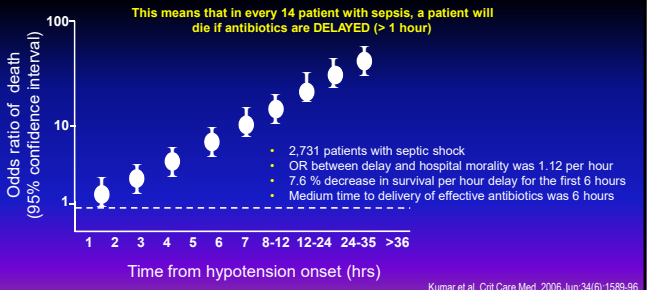
Dellinger, et al. Intensive Care Med.2013Feb;39(2):165-228.
http://www.survivingsepsis.org/siteCollectionDocuments/ssc_bundle.pdf

The effects of antibiotics on survival



Kumar et al. Crit Care Med. 2006 Jun;34(6):1589-96.
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.

Early Goal-Directed Therapy for Sepsis: A Novel Solution for Discordant Survival Outcomes in Clinical Trials

- **Random-effect & Bayesian hierarchical analysis**
- **Patients with sepsis and septic shock**
- **Methods:**
  - **31 observational studies (n = 19,998 patients)**
  - **6 randomized studies (n = 4,342 patients)**

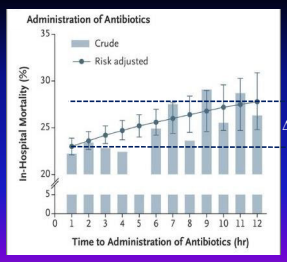
No effect on mortality: age, country, hospital location, era, systolic pressure, mean arterial pressure, lactate level, bundle compliance, amount of fluid administered, and hemodynamic goal achievements.

Covariate Factor (No of Studies)	Relative Risk	95% CI	*P* value
Antibiotics < 3 hours (n= 10)	0.09	0.03 – 0.27	<0.001
Antibiotics 4 hours (n= 16)	0.16	0.06 – 0.39	0.0001
Antibiotics 6 hours (n= 20)	0.20	0.09 – 0.45	0.0001
Time to first antibiotics (n = 15)	1.22	1.09 – 1.36	0.006

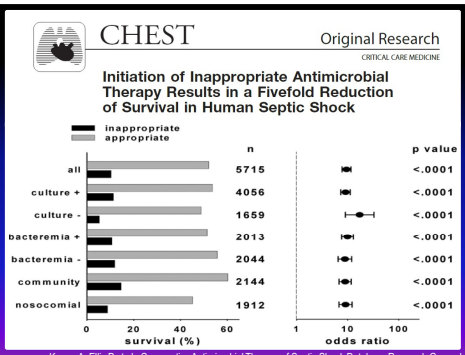
Andre Kalil; Daniel Johnson; Steven Lisco; et al. Early Goal-Directed Therapy for Sepsis: A Novel Solution for Discordan
Survival Outcomes in Clinical Trials. Critical Care Medicine. 2017; 45(4):607–614

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

- Data on sepsis and septic shock from New York hospitals over a 2 year period (NYSDOH data)
- *Enrollment:*
  - Sepsis protocol initialed within 6 hours in emergency room
  - All items in a 3-hour bundle completed (BC, lactate, antibiotics)
  - 49,331 patients at 149 hospitals, of which (82.5%) completed 3-hour bundle
  - Median time to complete bundle was 1.30 hours
    - Median time for antibiotics 0.95 hours
    - Median time for IV fluid completion 2.56 hours



Seymour CW, Gesten F,Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376(23):2235-2244.



Kumar A, Ellis P, et al.; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009 Nov;136(5):1237-48

The Guideline: Map

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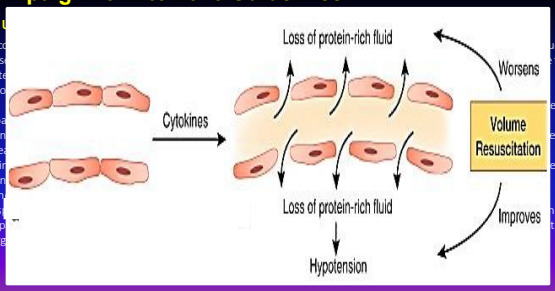
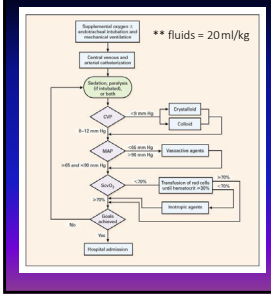
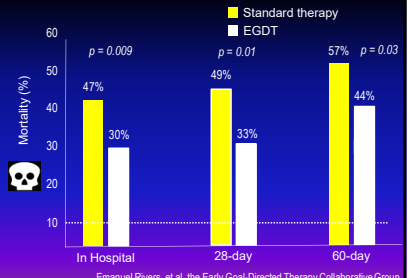
Hemodynamic goals of therapy: Surviving sepsis campaign 2012 to 2016 Guidelines



EGDT: fluid resuscitation is a life saving & time sensitive intervention, regardless of the monitoring device





Emanuel Rivers, et al. the Early Goal-Directed Therapy Collaborative Group. N Engl. J Med 2001; 345:1368-1377.

PROCESS, ARISE AND PROMISE Clinical Trials

Reference	# of Patients	Intervention	Primary outcome	Results
EGDT (Rivers et al. 2001, NEJM	263	Single center (Henry Ford Hospital): EGDT vs. standard care	In-hospital mortality Secondary endpoint: 60-day mortality	30.5% vs. 46.5% (p = 0.009) 44.3% vs. 56% (p = 0.03)
Reference	**# of Patients**	**Intervention**	**Primary outcome**	**Results**
PROCESS[2] (2014 NEJM)	1,341	31 EDs in the US: protocolized EGDT vs. protocol-based standard vs. usual care	60-day mortality	21% (EGDT), 18.2% (standard), 18.9% (usual) (p = 0.83)
ARISE[3] (2014 NEJM)	1,600	51 centers in Australia or New Zealand: EGDT vs. usual care	90-day mortality	18.6% vs. 18.8% (p = 0.9)
PROMISE[4] (2015 NEJM)	1,260	56 hospitals in England: EGDT vs. usual care	90-day mortality	29.5% vs. 29.2% (p = 0.9)

Process Investigators, et al. N Engl J Med 2014 May 1;370(18):1683-93.
ARISE Investigators, et al. N Engl J Med 2014 Oct 16;371(16):1496-506.
Mouncey PR, et al. N Engl J Med 2015 Apr 2;372(14):1301-11.

	ProCESS	ARISE	ProMISe
Title	A Randomized Trial of Protocol-Based Care for Early Septic Shock	Goal-Directed Resuscitation for Patients with Early Septic Shock	Protocolised Management in Sepsis (ProMISe)
Location	U.S. 31 Emergency Departments	Australia/New Zealand 51 Emergency Departments	U.K. Multi-Center
Population	1935 adult subjects with septic shock (refractory hypotension or LA ≥ 4mmol/L)	1600 adult sepsis subjects with septic shock (refractory hypotension or LA ≥4mmol/L)	1260 adult sepsis subjects with septic shock (refractory hypotension or LA ≥4mmol/L)
Intervention	EGDT	EGDT	EGDT
Control	Protocol-Based Care (no CVC) Usual Care	Usual Care	Usual Care
Primary Outcome	60 Day Mortality	90 Day Mortality	90 Day Mortality
Primary Outcome Result (relative risk)	EGDT 21% Protocol Based 18.1% Usual Care 18.9%	EGDT 18.6% Usual Care 18.8%	EGDT 30% Usual Care 29%
Publication Date	May 2014	October 2014	Mar 2014
Journal	NEJM	NEJM	NEJM

Adapted from:
Yealy DM et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 2014; 370:1683-1693.
Peake SL et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. N Engl J Med 2014; 371:1496-1506.
Power GS et al., The Protocolized Management in Sepsis (ProMISe) trial statistical analysis plan. Crit Care Med; 2013Dec;15(4):311-7.

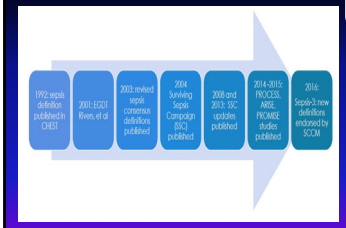
Why did these newer EGDT never find a difference compare to usual care?

Intervention	Protocol-based EGDT	Protocol-based standard therapy	Usual Care	P-value
Pre-intervention				
Fluids	2,254 mL ± 1,472 mL	2,226 mL ± 1,363 mL	2,083 mL ± 1,405 mL	0.15
Antibiotics	75.6%	76.9%	76.1%	0.91
Randomization to hour 6				
Central venous catheter	93.6%	56.5%	57.9%	< 0.0001
Central venous oximeter	93.2%	4%	3.5%	< 0.0001
Antibiotics	97.5%	97.1%	96.9%	0.9
Vasopressor use	54.9%	52.2%	44.1%	0.003
Dobutamine use	8%	1.1%	0.9%	< 0.001
Blood transfusions	14.4%	8.3%	7.5%	0.001

ARISE Investigators, et al. N Engl J Med. 2014 Oct 16;371(16):1496-506.

Example from the ARISE study: No difference in fluid resuscitation, early antibiotics but more central lines, vasopressors, inotropes and blood transfusions

Why did these newer EGDT never find a difference compare to usual care?

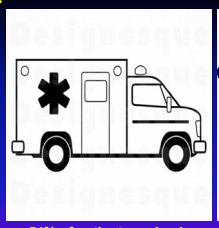


- Early recognition of sepsis and hypotension in all 3 trials
- Early aggressive fluid resuscitation in all 3 trails = was at least 30 ml/kg in the first 6 hours
- Severity of disease was HIGER in EGDT study, Rivers, 2001
- "Usual care" contained elements of EGDT since studies were conducted in an era where protocolized sepsis management was considered the standard of care

Adapted from:
Yealy DM et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 2014; 370:1683-1693.
Peake SL et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. N Engl J Med 2014; 371:1496-1506.
Power GS et al., The Protocolized Management in Sepsis (ProMISe) trial statistical analysis plan. Crit Care Med; 2013 Dec;15(4):311-7.

Association between early intravenous fluids provided by paramedics and subsequent in-hospital mortality among patients with sepsis.

Total 1,871 patient with presumed sepsis



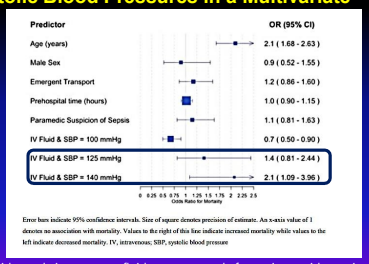
54% of patient received IV fluid from paramedics

Overall in-hospital mortality of 28.2% (n = 528)

Lane DJ, Wunsch H, Saskin R, et al. Association between early intravenous fluids provided by paramedics and subsequent in-hospital mortality among patients with sepsis. *JAMA Netw Open*. 2018;1(8):e185845

Changes in Odd of Mortality With Intravenous Fluid Treatment at Different Initial Systolic Blood Pressures in a Multivariate Model

Median volume provided was 500 ml.

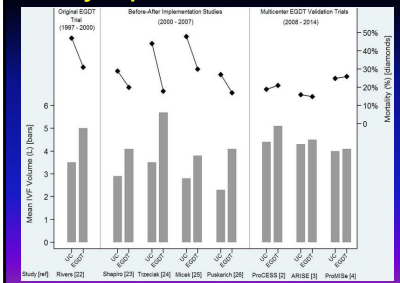


Error bars indicate 95% confidence intervals. Size of square denotes precision of estimate. An x-axis value of 1 denotes no association with mortality. Values to the right of this line indicate increased mortality while values to the left indicate decreased mortality. IV, intravenous; SBP, systolic blood pressure

Meaning: Clinicians may consider early intravenous fluid treatment only for patients with sepsis and low initial blood pressure.

Lane DJ, Wunsch H, Saskin R, et al. Association between early intravenous fluids provided by paramedics and subsequent in-hospital mortality among patients with sepsis. *JAMA Netw Open*. 2018;1(8):e185845

Liberal versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial



2016 UPDATE:RESUSCITATION

Resuscitation from sepsis-induced hypo-perfusion includes at least 30 mL/kg of IV crystalloid fluid given within the first 3 hours

After initial resuscitation, additional fluids guided by frequent reassessment to hemodynamics

Suggest dynamic over static variables be used to predict fluid responsiveness

Self WH, Semler MW, Bellomo R, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. *Ann Emerg Med*. 2018;72(4):457–466.

The Guideline: Map

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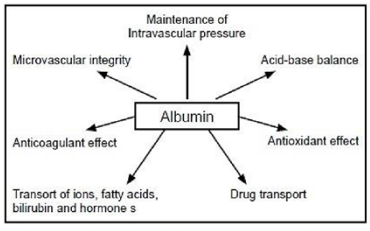
2016 Current Surviving Sepsis Campaign Recommendations: Fluids Types

- **Crystalloids** as fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation)
- Recommend either **balanced crystalloids or saline** for fluid resuscitation of patients with sepsis or septic shock (weak recommendation)
- Initial fluid challenge in patients with **sepsis-induced tissue hypo-perfusion**; 30 mL/kg of crystalloids (Grade 1C)
- **Albumin** in the fluid resuscitation of septic shock when patients *require substantial amounts* of crystalloids (Grade 2C)

Albumin in the fluid resuscitation of septic shock when patients *require substantial amounts* of crystalloids (Grade 2)



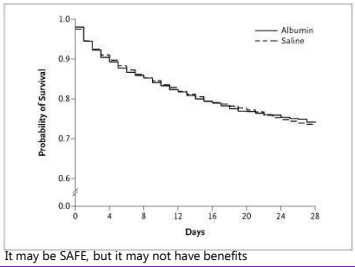
Physiological effects of exogenous albumin.

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

- **SAFE study**, NEJM 2004: A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit
- 6,997 ICU patients requiring fluid administration to increase intravascular volume (17% trauma, 18% severe sepsis)
- Primary outcome: no difference in 28-day mortality between albumin and saline (20.9% vs. 21.1%, p = 0.87)
- No difference in duration of mechanical ventilation, length of ICU stay
- Conclusion: For ICU patients requiring fluid resuscitation, there is no difference in the studied outcomes comparing albumin to normal saline

Finfer S, Bellomo R, Boyce N, et al. The SAFE Study Investigators. N Engl. J Med 2004;350:2247-2256.

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit



Equivalent clinical outcomes:

New single-organ and multiple-organ failure (P = 0.85).

 # days spent in the ICU (6.5±6.6 in the albumin group and 6.2 ± 6.2 in the saline group, P=0.44),

Days spent in the hospital (15.3 ± 9.6 and 15.6±9.6, respectively; P=0.30),

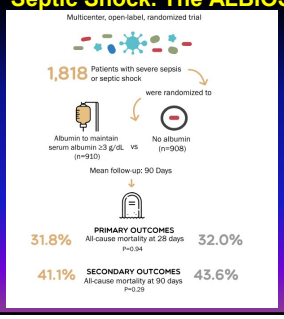
Days of mechanical ventilation (4.5 ± 6.1 and 4.3±5.7, respectively; P=0.74),

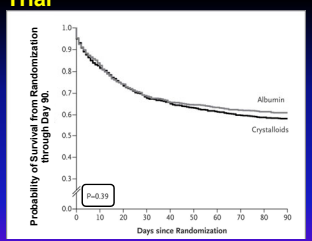
Days of renal-replacement therapy (0.5 ± 2.3 and 0.4 ± 2.0, respectively; P=0.41).

It may be SAFE, but it may not have benefits

Finfer S, Bellomo R, Boyce N, et al. The SAFE Study Investigators. N Engl. J Med 2004;350:2247-2256.

Albumin Replacement in Patients with Severe Sepsis or Septic Shock. The ALBIOS Trial





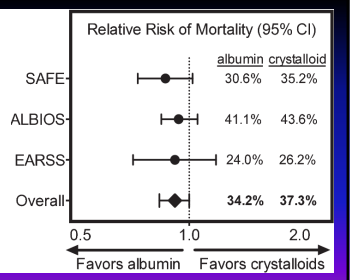
In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days.

Pietro Caironi P et al. N Engl J Med 2014; Volume 370(15):1412-1421.

Summary of Albumin in Critically ill Patients

Summary

Despite the studies having various design flaws, the meta-analysis suggest a possible small benefit, However, the clinical significance (absolute difference in the pooled results of 34 % vs 37 %) is NOT remarkable!



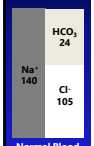
Semler, Matthew W. and Todd W. Rice. "Sepsis Resuscitation: Fluid Choice and Dose." Clinics in Chest Medicine 37 2 (2016): 241-50.

Again, What type of fluids to use?

2016 Current Surviving Sepsis Campaign Recommendations: Fluids Types

- **Crystalloids** as fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation)
- Recommend either **balanced crystalloids or saline** for fluid resuscitation of patients with sepsis or septic shock (weak recommendation)
- Initial fluid challenge in patients with **sepsis-induced tissue hypo-perfusion**; 30 mL/kg of crystalloids (Grade 1C)
- **Albumin** in the fluid resuscitation of septic shock when patients *require substantial amounts* of crystalloids (Grade 2C)

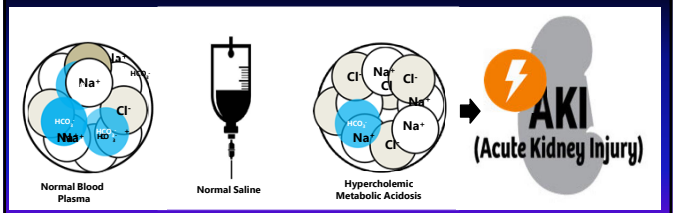
Surviving sepsis campaign guideline authors recommend that clinicians restore euvolemia *initially*, and then more cautiously as the patient stabilizes



	Normal Saline (0.9% NaCl)	Lactated Ringer's	Plasma-Lyte
Sodium (Na)	154 mmol/L	130 mmol/L	140 mmol/L
Chloride (Cl)	154 mmol/L	109 mmol/L	98 mmol/L
Potassium (K)	none	4 mmol/L	5 mmol/L
Calcium (Ca)	none	1.5 mmol/L	none
Magnesium (Mg)	none	none	3 mmol/L
Lactate	none	28 meq (28 mmol/L)	none
Acetate	none	none	27 mmol/L
Gluconate	none	none	23 mmol/L
Tonicity	Hypertonic (308 mOsm/L)	Hypotonic (276 mOsm/L)	Isotonic (294 mOsm/L)
Cost	$2 / liter	$4 / liter	$12 / liter

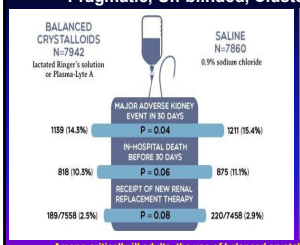
- "Give as much fluid as you need and NOT one drop more"
- Evidence that a sustained positive fluid balance during ICU stay is harmful
- Authors do not recommend, therefore, that fluid be given beyond initial resuscitation without some estimate of the likelihood that the patient will respond positively

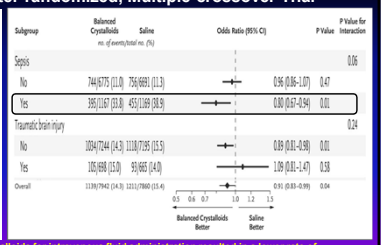
Fluid be given beyond initial resuscitation without some estimate of the likelihood that the patient will respond positively



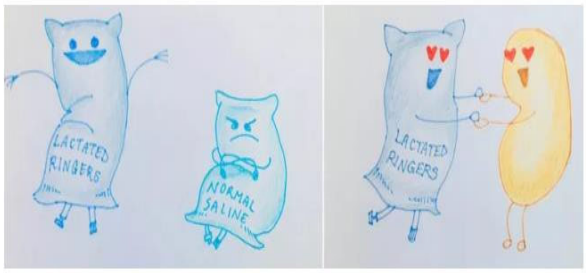
Balance Crystalloids verse Saline in Critically ill Adults The SMART Trial

Pragmatic, Un-blinded, Cluster-randomized, Multiple-crossover Trial





Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal–replacement therapy or persistent renal dysfunction than the use of saline. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018;378:829-839.



Lactated ringers superior for kidneys?

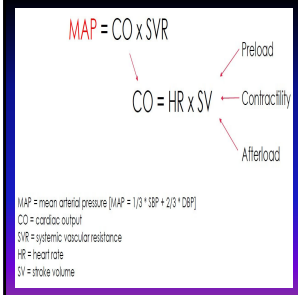
Summary on Fluid in Sepsis

- Certainly, in favor of balanced solutions, the ~ 1% reduction in mortality seen in SMART follows the trend observed in both SPLIT and SALT STUDIES.
- Studies of the critically-ill.
  - In SPLIT, 87 of 1152 patients [7.6%] in the buffered crystalloid group and 95 of 1110 patients [8.6%] in the saline group died in the hospital; while not statistically-significant, it is certainly of clinical note. Looked at 90 day mortality
  - The SALT trial demonstrated a 30 day mortality of 15% in those randomized to saline [n= 454] and 13.8% in those randomized to balanced solutions [n = 520].
- SUMMARY: of the three trials reveal, in totality, 9614 critically-ill patients randomized to balanced solutions and 9,424 patients randomized to saline with 30 [or 90] day mortality rates of 10.2% and 11.0%, respectively.

The Guideline: Map

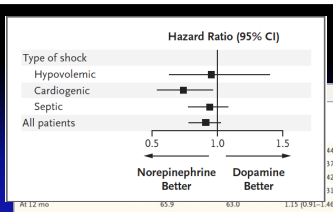
1. Defining the disease
2. Broad-spectrum antibiotics
3. Fluid resuscitation
4. Inotropes
5. Corticosteroids
6. Adjunct treatments

2016 Updated Recommendations for Vasopressors



- **Norepinephrine as the first-choice vasopressor [strong recommendation)**
- **Suggest adding EITHER vasopressin (up to 0.03 units/min) OR epinephrine to norepinephrine with the intent of raising MAP to target [weak recommendation]**
- **Vasopressin (up to 0.03 units/min) may be added with the intent to decrease norepinephrine dosage**
- **Dopamine as alternative vasopressor agent to norepinephrine only in selected patients (low risk of tachyarrhythmias or absolute/relative bradycardia) [weak recommendation]**

- Multicenter RCT
- Randomized >800 patients to each:
  - Norepinephrine
  - Dopamine
- Inclusion criteria = fluid unresponsive shock
  - Septic – 62%
  - Cardiogenic – 17%
  - Hypovolemic – 16%



			P Value
			0.07
			0.24
			0.10
			0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46) 0.34

Adverse events			
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	

DeBacker et al. NEJM 2010

What is Norepinephrine First Line?

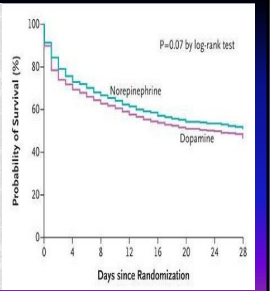
- **SOAP II study 2010**: Comparison of dopamine and norepinephrine in the treatment of septic shock
- 1,689 patients requiring vasopressor support for shock despite fluid challenge (60% septic, 20% cardiogenic, 15% hypovolemic) randomized to receive dopamine or norepinephrine
- Primary outcome: 28-day mortality was not differnet between the two groups (52.5% vs 48.5%, p = 0.1); no difference in secondary outcomes: ICU or hospital length of stay, 6 and 12-month mortality
- Dopamine group had more arrhythmias, mostly atrial fibrillation, compared to norepinephrine (24.1% vs. 12.4%, p< 0.0010)
- Pre-specified subgroup of cardiogenic shock showed higher 28-day mortality with dopamine (p = 0.030)

SOAP II Study. De Backer D et al. N Engl. J Med 2010; 362:779-789.

What is Norepinephrine First Line?

Dopamine vs Norepinephrine

- Multicenter, randomized controlled trial
  - 859 dopamine patients
  - 821 norepinephrine patients
- No differences at baseline or rate of death (52.5% vs 48.5%, p = 0.10)
  - Subgroup analysis showed increased risk of death in dopamine patients with cardiogenic shock (p = 0.03)
- More arrhythmic events among the patients treated with dopamine (207 [24.1%]) than those treated with norepinephrine (102 [12.4%]), p < 0.001
- **No difference in rate of death**
- **Dopamine was associated with a greater number of adverse events**

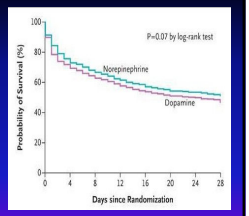


SOAP II Study. De Backer D et al. N Engl. J Med 2010; 362:779-789.

Norepinephrine Compared with Dopamine in Sepsis

Outcomes	illustrative Comparative Risk (95% CI) Assumed Risk	Corresponding Risk	no. of Participants (studies)
	Dopamine	Norepinephrine	
Short-term mortality	530 per 1000	482 per 1000	2,643 (6 studies)
Adverse events (arrhythmias)	229 per 1000	82 per 1000	1,031 (2 studies)
Malignant arrhythmias	39 per 1000	15 per 1000	1,951 (2 studies)

Adverse events			
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	



Sources: Analysis Surviving Sepsis Campaign. NEJM 2010; 362: 779-789.
Marik PE JAMA 1994;272:1354-1357.
Martin C, Chest 1993; 103:1826-1831.
Patel GR, Shock 2010; 33:375-380.
Ruckonen E. Crit Care Med 1993; 21:1296-1303.

Vasopressin vs. Norepinephrine in Patients with Septic Shock

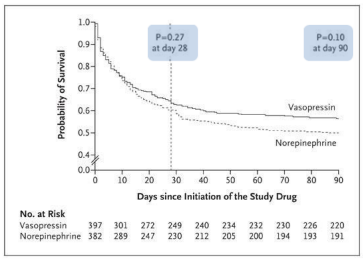
- Vasopressin constricts vascular smooth muscle directly through actions on the V1 receptor and indirectly by decreased nitric oxide mediated vasodilation
- Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (*relative physiologic deficiency*)
- Physiologic vasopressin replacement (low dose continuous infusion) may be effective in raising blood pressure in patients refractory to other vasopressors
- Vasopressin is NEVER monotherapy in treatment of septic shock, always adjunctive

Russell JA et al. N Engl. J Med 2008;358:877-887.

Vasopressin vs. Norepinephrine in Patients with Septic Shock

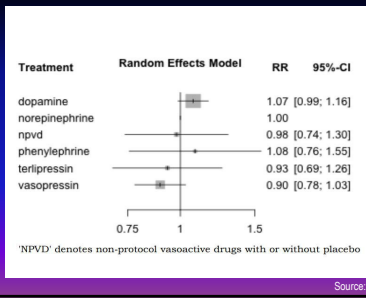
VASST Trial

- Multicenter, randomized double-bind trial of 778 septic shock patients (396 vasopressin and 382 norepinephrine patients)
- **No significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate**
  - 35.4% vs 39.3%, p = 0.26
- 90-day mortality (43.9% vs 49.6%, p = 0.11)
- No differences in the overall rates of serious adverse events (10.3% and 10.5%, p = 1.00)



Russell JA et al. N Engl. J Med 2008;358:877-887.

Pressor Mortality Benefit as it Related to Risk

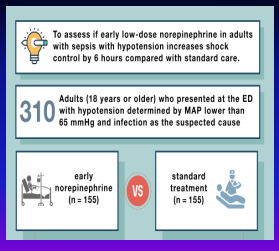


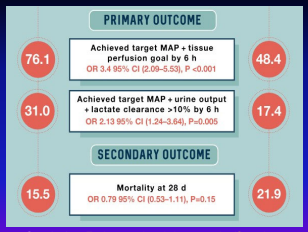
Pressor Mortality Benefit?

- No differences in mortality outcomes in any of 28 studies comparing different vasopressors or combinations
- Network forest plot comparing vasopressor regimens vs norepinephrine from 22 studies
  - p = 0.97
  - RR > 1 indicates increased mortality risk
  - RR < 1 indicates reduced mortality risk

Source: Gamper G, et al. Cochrane Database of Syst Rev 2016;2:1-88.

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial





Conclusion: Early norepinephrine was significantly associated with increased shock control by 6 hours.

Permpikul C et al. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care Med 2019;199(9):1097-1105.

The Guideline: Map

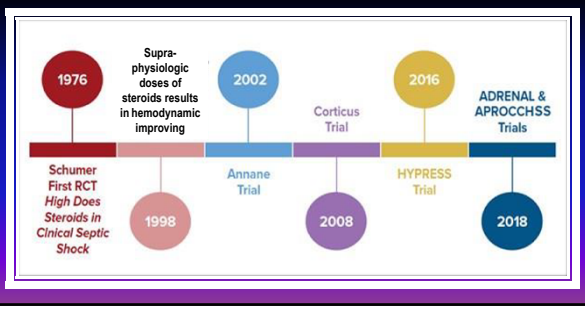
1. Defining the disease
2. Broad-spectrum antibiotics
3. Fluid resuscitation
4. Inotropes
5. Corticosteroids
6. Adjunct treatments

2016 Updated Recommendations for Vasopressors

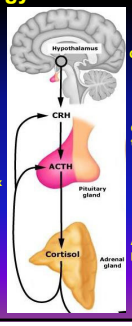
- Recommend against using IV hydrocortisone to treat septic shock patients *if adequate fluid resuscitation* and vasopressor therapy are able to restore hemodynamic stability
- If hemodynamic stability not achievable, recommend IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence)
- Random cortisol levels have not been demonstrated to be useful relative adrenal insufficiency (an inadequate stress response)
- Suggest tapering steroids when vasopressors are no longer needed

Sprung DL, AnnaneD, KehD, et al. N EnglJ Med 2008 Jan 10;358(2):111-24.
Rhodes A, et al. CritCare Med. 2017 Mar;45(3):486-552.

The History of Corticosteroids in Sepsis & Septic Shock



Physiology of the adrenal gland



CRH produced by hypothalamus

CRH stimulates pituitary gland to produce ACTH

ACTH stimulates adrenals to produce cortisol

Cortisol exerts a negative feedback on production of CRH and Cortisol

Metabolic:
- Stimulates gluconeogenesis, decrease glucose utilization
- Decreases protein synthesis and increases catabolism
- Increases lypolysis and oxidation of fatty acids

Cardiovascular:
- Increases blood pressure
- Increases sensitivity of vasculature to catecholamines & angiotensin II

Anti-inflammatory effects:
- Reduces circulating T, B lymphocytes, esinophils, monocytes and neutrophils at sites of inflammation
- Decreases production of cytokines & chemokines
- Increased production of microphage migration inhibitory factor

When to suspect adrenal insufficiency

- Shock poorly responding to fluids and vasopressors especially septic shock
- Catecholamine-dependant shock
- Prolonged mechanical ventilation
- Sudden deterioration of seriously ill patients with DIC, traumatic shock, severe burns or sepsis may be due to adrenal hemorrhage or infarction

Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definition for Sepsis (Sepsis-3). JAMA. 2016;315:801-810.
Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne). 2016;7:70.
Bollaert P,Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998;26(4):645-650.
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.
Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.

- Currently based on random cortisol levels and delta cortisol after high dose ACTH stimulation test

Issues:

- Free cortisol is of more physiological importance but normal levels in acute illness not established, test not widely available
- Low dose ACTH stimulation test thought to be more physiologic and sensitive but limited data
- Delta cortisol assess ability of adrenal cortex to produce cortisol but does not confirm integrity of HPA axis
- Above tests do not evaluate resistance at end organ level

Types Adrenal insufficiency

Primary adrenal insufficiency
- Congenital:
  - CAH
  - Adrenal hypoplasia congenital
  - Familial glucocorticoid deficiency
  - Adrenoleukodystrophy
  - Autosomal recessive deficiency
- Acquired:
  - Infectious diseases
  - Infiltrative processes
  - Autoimmune adrenalitis/lymphocytic hypophysitis
  - Neoplasms
  - Exogenous steroids

Secondary adrenal insufficiency

Critical illness related corticosteroid insufficiency

Is inadequate cellular corticosteroid activity for the severity of the patients illness

Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definition for Sepsis (Sepsis-3). JAMA. 2016;315:801-810.
Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne). 2016;7:70.
Bollaert P, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998;26(4):645-650.
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.
Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.

The confusing basis of steroids in sepsis

- Some studies showed non survivors of severe sepsis have random cortisol level > 20 mcg/dl (552 nmol/l) but incremental increase < 9 (248) after ACTH stim test
- Others found that non-survivors had lower random cortisol level compared to survivors
- Lower levels of cortisol and high ACTH associated with severe disease and poor outcome

Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definition for Sepsis (Sepsis-3). JAMA. 2016;315:801-810.
Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne). 2016;7:70.
Bollaert P, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998;26(4):645-650.
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.
Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.

- Annane et al. used stim test to assess high dose ACTH stim test:
  - Baseline < 10 (276) or delta cortisol < 9 (248) were best predictors of adrenal insufficiency
  - Best predictor of normal adrenal response is baseline > 44 (1214) or increase > 17 (464)

Different criteria in literature include:
- **Delta cortisol after high dose ACTH stim test < 9 (248)**
- **Baseline cortisol < 5 (138)**
- **Baseline cortisol < 7 (193)**
- **Basal cortisol< 20 (552), Delta cortisol < 9 (248)**
- **Delta cortisol < 9 (193)**
- **Peak < (baseline x 2)**

Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patient with Septic Shock

2002

Annane Trial

N=300

N=229 N=70

Nonresponders
Placebo 115
Steroid 114

Responders
Placebo 34
Steroid 36

Methods
- Double blinded
- Randomized
- Parallel-groups (corticotropin test responders vs non-responders)
- 19 French ICUs

Intervention
50 mg IV boluses of hydrocortisone q6hrs **AND** one 50 ug fludrocortisone tablet QD **OR** placebo for 7 days

THE BOTTOM LINE
There was no significant effect of steroids on mortality in responders, but among nonresponders (patients with septic shock and adrenal insufficiency) low dose steroids do reduce 28 day mortality and vasopressor dependence time. The number needed to treat to save one life at 28 days was 7 people.

Secondary Outcomes	Steroid	Placebo
Mortality at end of ICU stay	58%	70%
Mortality at 1 year follow up	68%	77%
Vasopressor Therapy discontinuation at 28 days	57%	40%
Median time to Vasopressor Therapy Discontinuation	7 days	10 days

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.

Hydrocortisone Therapy for Patients with Septic Shock; CORTICUS Study Group

Corticus Trial

2008

N=500

Methods
- 52 medical and surgical ICUs in 9 countries
- Randomized, Double-blind, Placebo controlled
- Intention to treat, interim, and post hoc subgroup analyses

Intervention
50 mg of IV hydrocortisone q6hrs **THEN** tapered **OR** placebo

RESULTS
No significant difference in 28-day mortality in patients who did not have a response to corticotropin was identified.
Hydrocortisone: 49 of 125 died (39.2%)
Placebo: 39 of 108 died (36.1%)

Secondary Outcome	Steroid	Placebo
Time to Reversal of Shock (all patients)	3.3 days	5.8 days
Time to Reversal of Shock (response to corticotropin)	2.8 days	5.8 days
Time to Reversal of Shock (no response to corticotropin)	3.9 days	6.0 days

Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.

Effect of Hydrocortisone on Development of Shock Among Patients with Severe Sepsis: HYPRESS Trial

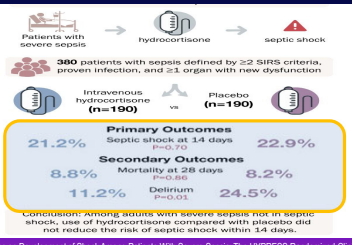
OBJECTIVE: **To determine whether hydrocortisone therapy in patients with severe sepsis prevents the development of septic shock.**

2016

HYPRESS Trial

Methods
- Multicenter; 34 ICUs in German Community and University Hospitals
- Placebo-controlled
- Double-blind, randomized controlled trial

Intervention
IV hydrocortisone 200 mg/day for 5 days **THEN** sequentially tapered for 5 days **OR** placebo



Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. JAMA. 2016;316(17):1775–1785.

Adjunctive Glucocorticoid in Patients with Septic Shock: ADRENAL Trial Investigators

ADRENAL & APROCCHSS Trials

2018

RESULTS

No significant difference in 90-day mortality was identified in the 6 prespecified subgroup analyses (sex, admission type—medical/surgical, catecholamine dose, site of sepsis, APACHE II score, and time from shock onset to randomization)

Hydrocortisone: 511 of 1832 died (27.9%)

Placebo: 526 of 1826 died (28.8%)

Secondary Outcomes	Steroid	Placebo
Time to Resolution of Shock	3 days	4 days
Time to Discharge from ICU	10 days	12 days
Duration of Mechanical Ventilation	6 days	7 days
Blood Transfusion	37%	41.7%

N=3658

N=1832 Steroid

N=1826 Placebo

A LINE

nfusion of hydrocortisone did NOT result in lower 90-day mortality. Steroid use apid resolution of shock, shorter inpatient ICU time, and lower incidence of blood

Venkatesh B et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797-808.

Adjunctive Glucocorticoid in Patients with Septic Shock: ADRENAL Trial Investigators

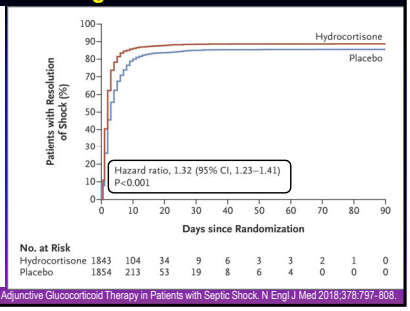
ADRENAL & APROCCHSS Trials

2018

N=3658

N=1832 Steroid

N=1826 Placebo



Venkatesh B et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797-808.

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. CRICS-TRIGERSEP Network

ADRENAL & APROCCHSS Trials

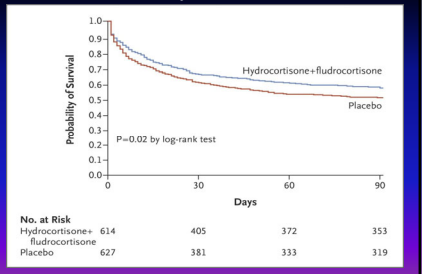
2018

- Patients = 1,241, RCT
- Activated Protein C removed
- Sick patients

Included fludrocortisone
- 90 day mortality benefit
- > hyperglycemia

Conclusion:
- In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo.

Figure :Survival.



Annane D et al. N Engl J Med 2018;378:809-818.

Summary: Adjunctive Glucocorticoid in Patients with Septic Shock

- Comparison of benefit and harm
  - In patients with shock = steroids likely are helpful
  - Resolution of shock maybe important
  - Hydrocortisone 200 mg /d is recommended
  - If needed give, no testing required

The Guideline: Map

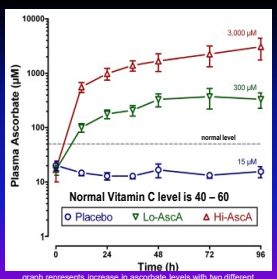
1. Defining the disease
2. Broad-spectrum antibiotics
3. Fluid resuscitation
4. Inotropes
5. Corticosteroids
6. Adjunct treatments

Ascorbic Acid, Thiamine, and Hydrocortisone: Targeted Therapy for the Management of Septic Shock

- Potent anti-oxidant/free radical scavenger
- Coenzyme for many biological reactions (including catecholamine synthesis)
- Preserve/restore endothelial integrity
- Synergistic with steroids: restores glucocorticoid receptor function

Fowler AA, et al. J Transl Med.2014;12:32.
Marik, et al. Chest 2017;151(6):1229-1238.

Sub-therapeutic Ascorbic Acid Levels in Septic Shock



graph represents increase in ascorbate levels with two different treatment doses compared to placebo

- Normal vitamin C level is 40 – 60
- Study demonstrated plasma ascorbate levels were below normal in all septic patients at enrollment
- Dose level with supplementation

Fowler AA, et al. J Transl Med. 2014;12:32.

Wide Interest in a Vitamin C Drug Cocktail for Sepsis

- The Marik Cocktail:
- Enrollment: >18 year old + Severe sepsis/Septic shock + Procalcitonin >2 ng/mL + < 24h from admission:
- Medication: Vitamin C (1.5g q6h), Thiamine (200 mg q12h) and Hydrocortisone (50mg q6h)
- Design: Retrospective, Observational, Before and After Study, Single Tertiary Academic Center (Norfolk General Hospital)
- No significant differences in baseline characteristics.

Kuhn SO, Meissner K, Mayes LM, Bartels K. Vitamin C in sepsis. Curr Opin Anaesthesiol. 2018;31(1):55–60.
Rubin R. Wide Interest in a Vitamin C Drug Cocktail for Sepsis Despite Lagging Evidence. JAMA. Published online July 03, 2019322(4):291–293.
Marik, Paul E. et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock CHEST, Volume 151, Issue 6, 1229 - 1238

Potential to have huge impact on sepsis related morbidity and mortality

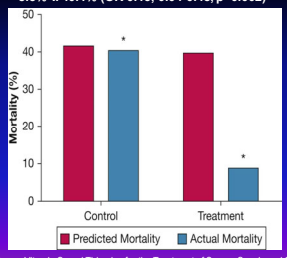
Design:

Retrospective, before-after study of 47 consecutive septic patients treated with IV ascorbic acid, thiamine, and hydrocortisone compared to 47 control patients

Results:

Hospital mortality 8.5% in the treatment group vs. 40.4% in control (p = 0.002). Mean duration of vasopressor therapy 18.3 hours vs. 54.9 hours (p < 0.001)

Primary Outcome Hospital mortality: 8.5% v. 40.4% (OR 0.13, 0.04-0.48, p=0.002)



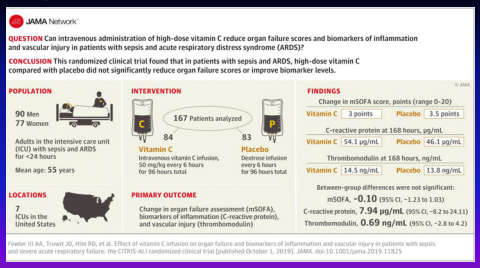
Marik, Paul E. et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock CHEST, Volume 151, Issue 6, 1229 - 1238

Vitamin C Drug Cocktail for Sepsis Treatment Protocol

Ascorbic Acid	• 1500 mg IV every 6 hours • For 4 days
Thiamine	• 200 mg IV every 12 hours • For 4 days
Hydrocortisone	• 50 mg IV every 6 hours* • Tapered at prescriber discretion

*Stress dose hydrocortisone initiated if fluid resuscitation and vasopressor therapy are unable to achieve hemodynamic stability

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



Fowler III AA et al. The CITRIS-ALI Randomized Clinical Trial. JAMA. 2019;322(13):1261-1270. doi:10.1001/jama.2019.11825

Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial

- Multicenter RCT
- Randomized (150 in each):
  - Angiotensin II
    - Dose started at 20 ng/kg/min up to max 300 ng/kg/min
  - Placebo
- Titrated over 3 hours, kept other vasopressors steady
- After 3 hours, other vasopressors titrated to goal MAP >65mmHg

Table 2. Primary and Secondary End Points.*

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

Khanna A et al. "Angiotensin II for the Treatment of Vasodilatory Shock". New Engl J Med. 2017.377:419-30.

Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial

Clinical Question

In patients with severe vasodilatory shock requiring high-dose catecholamines, does angiotensin II result in improvement in mean arterial pressure (MAP) compared to placebo?

Bottom Line

In patients with severe vasodilatory shock (MAP 55-70 despite 0.2ug/kg/min norepinephrine or equivalent), administration of angiotensin II is associated with a 45% absolute increase in MAP response (defined as MAP increase ≥ 10mmHg or MAP > 75mmHg) when compared to placebo.

- In ATHOS-3, 70% of patients who received angiotensin II met criteria for a MAP response (a 45% absolute increase compared to placebo). There was an associated significant reduction in catecholamine doses in patients receiving angiotensin II.

Key Points

Summary

- In summary, ATHOS-3 provides fairly compelling evidence that angiotensin II is safe and effective in reducing peripheral vasodilation and improving hemodynamics in severe vasodilatory shock. Further studies are needed to determine whether the effects of angiotensin II translate into improved morbidity and mortality in this condition.

Khanna A et al. "Angiotensin II for the Treatment of Vasodilatory Shock". New Engl J Med. 2017.377:419-30.

Conclusions

In accordance with the 2016 SCCM Sepsis Guidelines for management of patients such as this, the literature supports the following statements:

Antibiotics — **Timing and accuracy are vital**

Fluids — **Given when hypotensive, at 30 mg/kg**

Start with 0.9% saline, >4 liters consider changing

Steroids — **Give if fluids didn't work = 200mg/day with fludrocortisone**