The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

- 3723 patients at 138 hospitals in seven countries (all patients from the PROCESS, PROMIS and ARISE trials)
- Prior to randomization >92% of patients were identified early, and provided the 3 hour bundle (including 2L of fluid and antibiotics-given within 70 minutes of presentation to ED)
- No difference in 90 day mortality between EGDT and Usual Care groups
- Authors stated: "It remains possible that general advances in the provision of care for sepsis and septic shock, to the benefit of all patients, explain part or all of the difference in findings between the trial by Rivers et al. and the more recent trials"

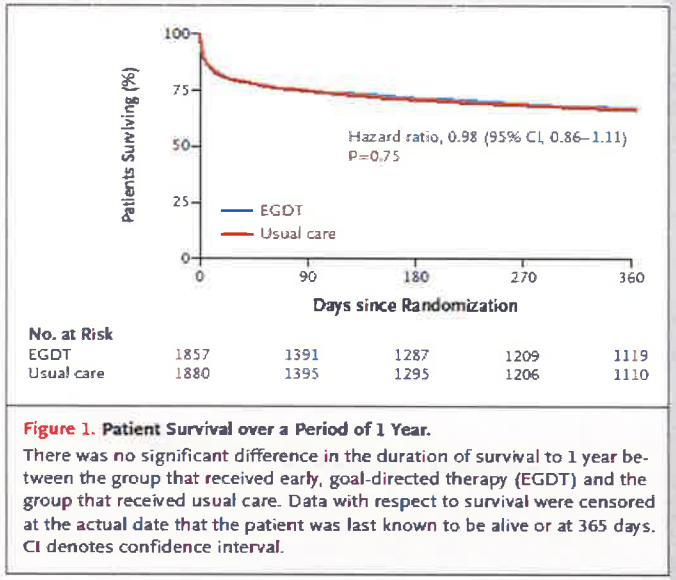


Figure 1. Patient Survival over a Period of 1 Year.
There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

NEJM , March 21, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

- In 2013, New York began requiring hospitals to follow protocols for the early identification
- April 2014 to June 30, 2016
- 49,331 patients at 149 hospitals
- 82.5% had the 3-hour bundle completed within 3 hours (median time was 1.3 hrs)
- Longer time to completion of the 3 hour bundle was associated with higher risk-adjusted in-hospital mortality as well as longer time to administration of antibiotics (14% higher for both)

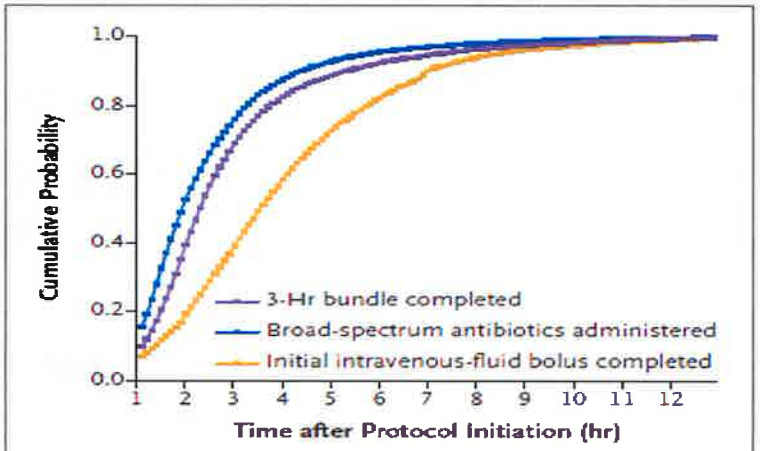
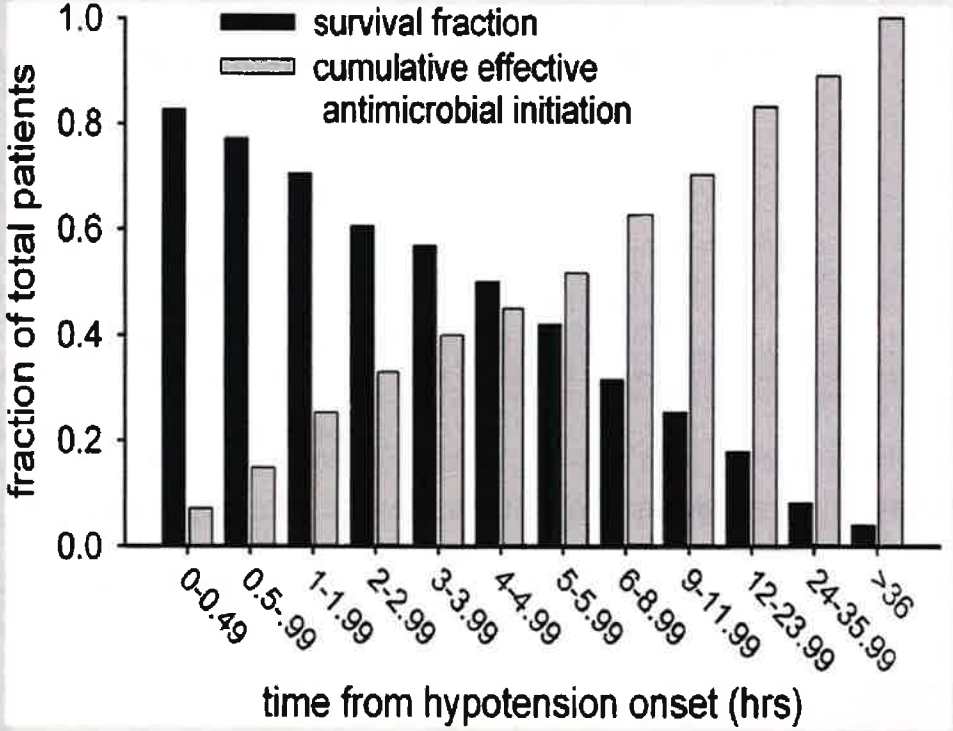


Figure 1. Cumulative Probability of Completion of the 3-Hour Bundle, Administration of Broad-Spectrum Antibiotics, and Completion of the Initial Intravenous-Fluid Bolus after the Time That the Sepsis Protocol Was Initiated.

The 3-hour bundle for the care of patients with sepsis or septic shock had to include receipt of the following care within 3 hours: obtaining of a blood culture before the administration of antibiotics, measurement of the serum lactate level, and the administration of broad-spectrum antibiotics; however, protocols could be tailored by each hospital. We also assessed the time to the administration of broad-spectrum antibiotics and the time to the completion of an initial bolus of intravenous fluids.

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock



CCM 2006 Vol. 34 No.6

***2,154 septic shock patients**

***Effective antimicrobial administration within the 1st hour of documented hypotension was associated with increased survival in patients with septic shock.**

***Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6% (range 3.6-9.9%)**

Antibiotics are Key

ORIGINAL ARTICLE

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

Vincent X. Liu[1], Vikram Fielding-Singh[2], John D. Greene[1], Jennifer M. Baker[1], Theodore J. Iwashyna[3,4], Jay Bhattacharya[5], and Gabriel J. Escobar[1]

[1]Kaiser Permanente Division of Research, Oakland, California; [2]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California; [3]Center for Clinical Management Research, VA Ann Arbor Health System, Ann Arbor, Michigan; [4]Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; and [5]Primary Care and Outcomes Research, Stanford University, Stanford, California

American Journal of Respiratory and Critical Care Medicine Volume 196 Number 7 | October 1 2017

Each elapsed hour between presentation and antibiotic administration was associated with a 9% increase in the odds of mortality with sepsis of all severity strata

Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients

Bristol B. Whiles, BS1; Amanda S. Deis, MS1; Steven Q. Simpson, MD2
Critical Care Medicine. April 2017. Vol 45. Number 4

- Each hour until initial antimicrobial administration was associated with a 8% increase in progression to septic shock.
- Patients who progressed to shock had significant increase in hospital LOS (18.7 days vs 9.66 days) and mortality (30.1% vs 7%)

Antibiotics Challenges

- Appropriate initial antibiotics
  - Guide for providers recommending the appropriate antibiotic based on whether hospital or community acquired, source and your hospitals antibiogram
- Turnaround time---from indication to hanging
  - ED vs ICU vs Floor
- Understand your current process and where the gaps are
- Make antibiotics rapidly available
- Factors that showed delay administration
  - Higher APACHE, older, presence of co-morbidities, HLOS before hypotension, dx of pneumonia, admin to academic hospitals & transfer from medical wards

Amaral ACKB, et al. Crit Care Med;2016;44:2145-2153

Fluid Boluses

- How fast should they be given?
  - Gravity or pressure bag not by infusion pump
- What about dialysis patients?
- What about patients with CHF or low EF?

Fluid bolus is given rapidly, IV wide open, pressure bag if necessary; goal is 500ml every 15-30 minutes

One liter of normal saline adds **275 ml** to the patient's plasma volume

Heart Failure—Going to Flood My Patient Not Based in Evidence

- Rivers et al Study: % Ventilated Patients

	Hours after start of Therapy		
	0-6	7-72	0-72
Standard Therapy	53.8%	16.8%	70.6%
Early Goal Directed Therapy	53%	2.6%	55.6%
P Value		<.001	0.02

Chronic coexisting conditions-CHF:
Control 30.2%
EGDT 36.7%

N Engl J Med 2001;345:1368-1377

Early Fluid Resuscitation is Key

INFECTIOUS DISEASE/ORIGINAL RESEARCH

Association of Fluid Resuscitation Initiation Within 30 Minutes of Severe Sepsis and Septic Shock Recognition With Reduced Mortality and Length of Stay

Daniel Leisman, BS*; Benjamin Wie, BA; Martin Doerfler, MD; Andrea Bianculli, BA; Mary Frances Ward, RN, MS; Meredith Akerman, MS; John K. D'Angelo, MD; Jason A. Zemmel D'Amore, MD

*Corresponding Author. E-mail: deleisman@gmail.com.

[Ann Emerg Med. 2016;■:1-14.]

↑ mortality with later fluid administration 13.3% (30 minutes) versus 16.0% (31 to 60 minutes) versus 16.9% (61 to 180 minutes) versus 19.7% (>180 minutes)

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality
A Retrospective Cohort Study

Sarah J. Lee , MD , MPH ; Kannan Ramar , MBBS , MD ; John G. Park , MD , FCCP ; Ognjen Gajic , MD , FCCP ; Guangxi Li , MD ; and Rahul Kashyap , MBBS

CHEST OCTOBER 2 0 1 4]

After adjusting for confounders, the higher proportion of total fluid received within the first 3 hrs was associated with decreased hospital mortality

Early Fluid Resuscitation is Key

Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Values

Vincent X. Liu[1,2], John W. Morehouse[2], Gregory P. Marelich[2], Jay Soule[2], Thomas Russell[2], Melinda Skeath[3], Carmen Adams[3], Gabriel J. Escobar[1,2], and Alan Whippy[2]

[1]Kaiser Permanente Division of Research, Oakland, California; [2]The Permanente Medical Group, Oakland, California; and [3]Kaiser Foundation Hospitals and Health Plan, Oakland, California

American Journal of Respiratory and Critical Care Medicine Volume 193 Number 11 | June 1 2016

Decrease in hospital mortality was observed primarily in patients with heart and/or kidney failure ($p<0.04$) who received at least 2 Liters fluid resuscitation for severe sepsis with lactate between 2.1-3.9

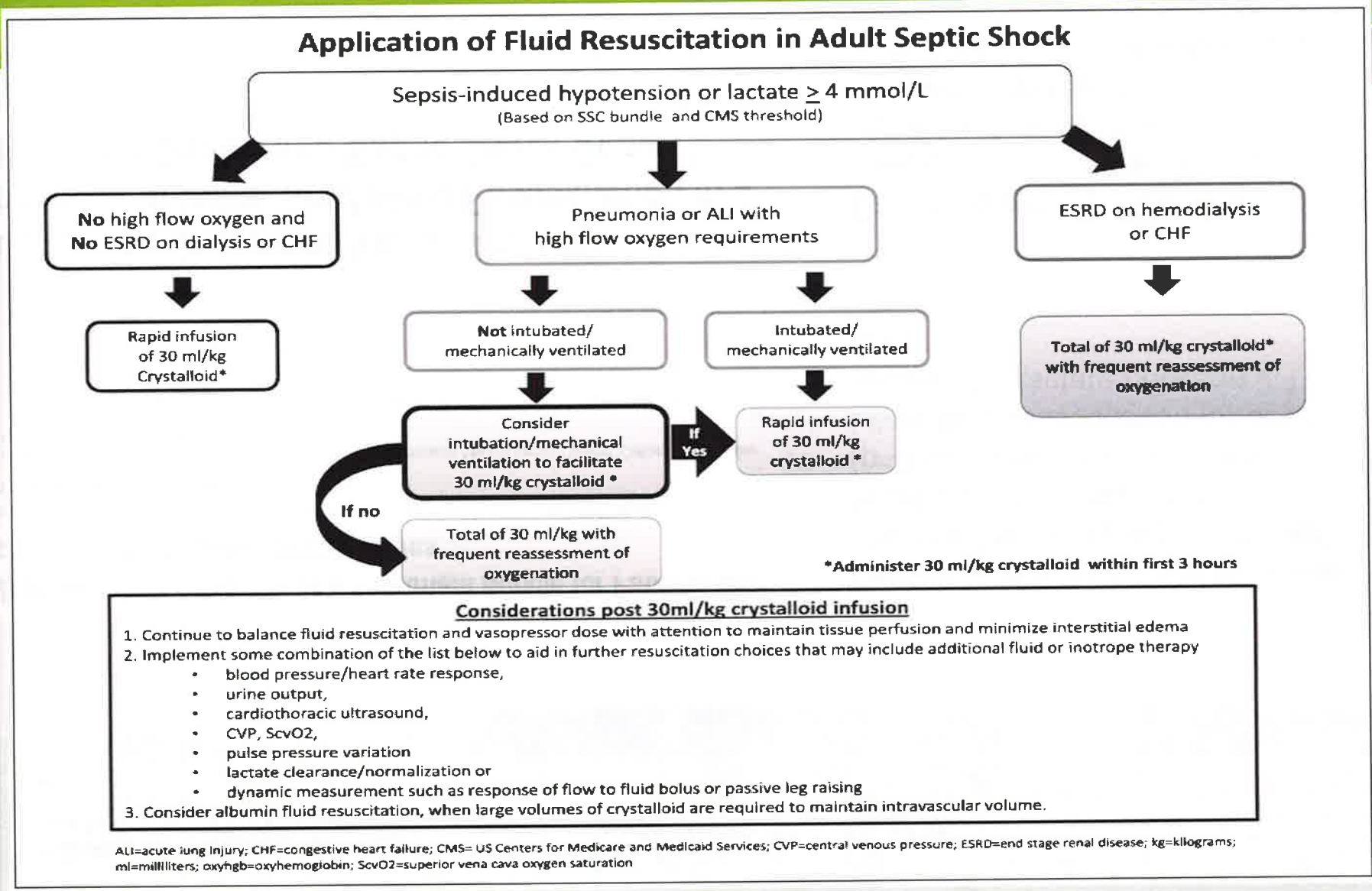
Patterns and Outcomes Associated With Timeliness of Initial Crystalloid Resuscitation in a Prospective Sepsis and Septic Shock Cohort*

Daniel E. Leisman, BS[1,2,3]; Chananya Goldman, MD[4]; Martin E. Doerfler, MD[4,5]; Kevin D. Masick, PhD[5]; Susan Dries, RN, PhD[6]; Eric Hamilton, BA[6]; Mangala Narasimhan, DO[7]; Gulrukh Zaidi, MD[7]; Jason A. D'Amore, MD[1]; John K. D'Angelo, MD[1,2]

Critical Care Med October 2017 • Volume 45 • Number 10

Early fluid initiation (30-120 minutes) was associated with significantly lower hospital mortality, mechanical ventilation, ICU admission, LOS and ICU days & no harm seen to the patients

Application of Fluid Resuscitation in Adult Septic Shock



User's Guide to the 2016 Surviving Sepsis Guidelines Dellinger, CCM published ahead of print 1-2017

Repeat Lactate Strategies

- Repeat lactate can be drawn anytime after fluid bolus
- Reflex lactate for any initial lactate greater than 2
- 2nd lactate order included when first one is ordered

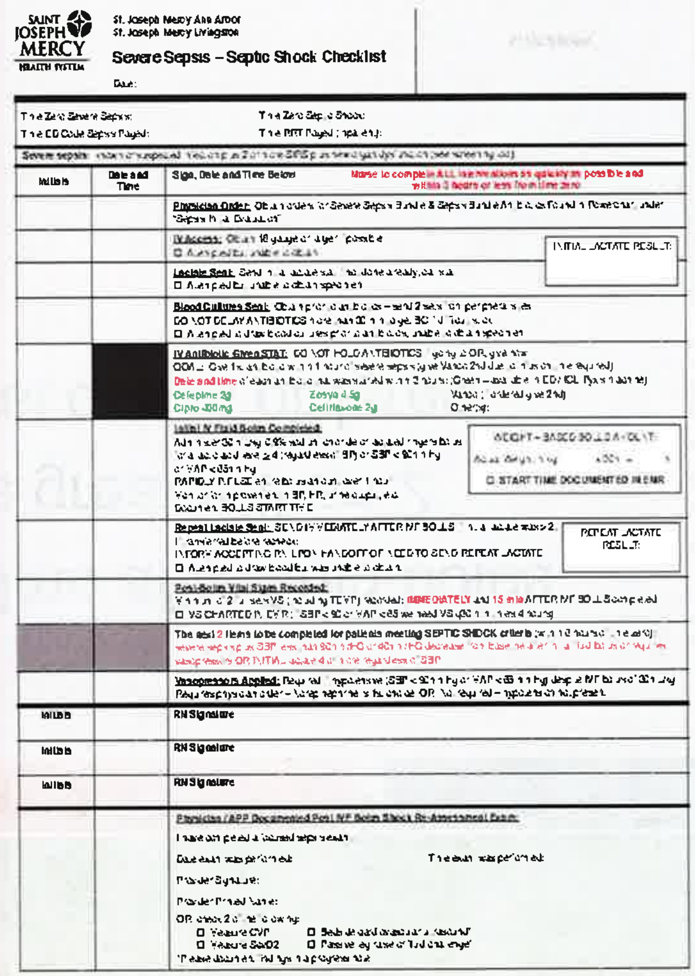
Reassessment

Requirement changes in July, 2018 for CMS

- Still a requirement for physician/APP to reassess volume status and tissue perfusion, just no requirement to state how that reassessment occurred or what the outcome of the assessment was
- IE: " perfusion reassessed; "sepsis reassessment done"
- Only need to do one out of 2 of the reassessment measurement (CVP, ScvO2, Echo, dynamic responsiveness)

Strategies to comply with documentation requirements

- Standard provider note or dot phrase
- Expect that whomever orders the 30ml/kg fluid bolus is responsible for the reassessment documentation
- Part of a sepsis checklist


SAINT JOSEPH MERCY HEALTH SYSTEM
St. Joseph Mercy Ann Arbor
St. Joseph Mercy Livingston
Severe Sepsis – Septic Shock Checklist
Date:
Initials | Date and Time | Sign, Date and Time Below
INITIAL LACTATE RESULT:
Cefepime 2g | Zosyn 4.5g
Cipro 400mg | Ceftriaxone 2g
REPEAT LACTATE RESULT:
Initials | RN Signature
Initials | RN Signature
Initials | RN Signature

Other Challenges and Barriers

- Antibiotic stewardship
- Executive support
- Physician buy-in
- New sepsis definitions

Role of Executive Sponsor

- Review project plans
- Review results from first team meeting
- Identify anticipated barriers that senior leader can help address
- Enlist support and help AND ASK for a sponsor to be assigned to the project

Challenges with Physician Buy In

- Cook book medicine
- "I know I can treat them better" or "I have been treating this patient my whole career"
- " I don't have enough time"

Strategies to Address Buy In

- Use hospital sepsis mortality data and nationally data to show it makes up the majority of deaths
- Strong informal leaders connect individually
- Identify who's opinion they would respect and provide discussion or feedback
- Individual physician data on patients treated including bundle compliance
- Quick turn around time on data to change behavior

Challenges: New Sepsis Definitions

Sep-2 Definitions (used by CMS and coders)

- **Infection**
- **Sepsis:** infection plus 2 or more SIRS
- **Severe Sepsis:** infection plus 2 or more SIRS plus new organ dysfunction
- **Septic Shock:** severe sepsis with a lactic acid greater than or equal to 4mmol/L OR continued hypotension (systolic BP<90 or 40mmHg decrease from their baseline) after initial fluid bolus (30ml/kg)

Sepsis 3:

Singer et al, JAMA 2016. PMID: 26903338

- **Sepsis is:** 'life-threatening organ dysfunction caused by a dysregulated host response to infection'
  - Sepsis-3 does away with:
    - SIRS criteria (sepsis is pro- and anti-inflammatory)
    - Severe sepsis (sepsis = the old severe sepsis)
    - Antiquated concepts: sepsis syndrome; septicemia
- **Sepsis:** infection plus 2 or more SOFA (Sequential Organ Failure Assessment) points
- **Septic shock:** vasopressor-dependent hypotension + lactate >2

Sepsis-3 includes clinical criteria to predict life-threatening disease

qSOFA: (have 2 or more of these, then evaluate for SOFA)

Respiratory Rate≥ 22

Altered Mental Status

Systolic BP ≤ 100mmHg

SOFA

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Challenges with New Sep-3 Definitions

- SIRS not part of the definition:
  - the most appropriate use for SIRS is that its presence prompts an immediate search for both infection, as its possible source, and organ dysfunction, as its possible companion
- Late recognition
  - "sepsis is a problem only when life-threatening organ dysfunction is already present fails to recognize the spectrum of the illness, minimizes the importance of infection to its evolution and as its principal driver and devalues systemic host response as a harbinger of the onset of organ failure"
- Doesn't recognize 'cryptic shock'
- People will begin to use qSOFA as a screening tool
  - qSOFA and SOFA are predictors of mortality; they are not test of early sepsis at risk to progress to organ failure
- Only their predictive ability for morality and prolonged ICU stay have been evaluated, not their utility in reducing mortality

Simpson, S. Chest. January 2018 SIRS in the Time of Sepsis-3

"As the physician say of hectic fever, that in the beginning of the malady it is difficult to detect but easy to treat, but in the course of time, having been neither detected nor treated in the beginning, it becomes easy to detect but difficult to treat"

Niccolo Machiavelli, 14th Century

Simpson, S. Chest. January 2018 SIRS in the Time of Sepsis-3

Surviving Sepsis Campaign

Surviving Sepsis Campaign Responds to Sepsis-3

March 1, 2016

Implications of the New Definitions for Screening and Management

For hospitals who have prepared for the transition, screening for early identification and treatment of patients with *sepsis* (formerly called *severe sepsis*) should continue essentially as has been previously recommended by SSC.

Step 1: Screening and Management of Infection

The appropriate first step in screening should be identification of infection. Hospitals should continue to use signs and symptoms of infection to promote the early identification of patients with suspected or confirmed infection.

In those patients identified as having infection, management should begin by obtaining blood and other cultures as indicated, administering tailored antibiotics as appropriate, and simultaneously obtaining laboratory results to evaluate the patient for infection-related organ dysfunction.

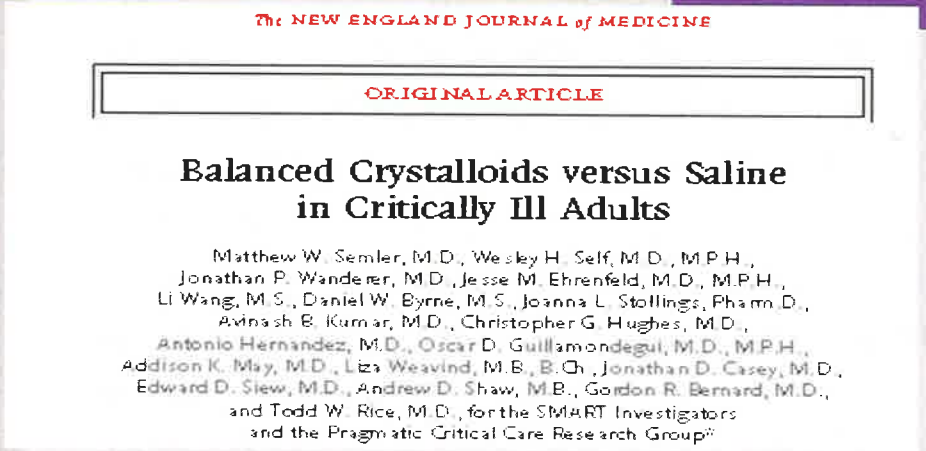
Step 2: Screening for Organ Dysfunction and Management of *Sepsis* (formerly called *Severe Sepsis*)

Step 3: Identification and Management of Initial Hypotension

In those patients who have infection and hypotension or a lactate level greater than or equal to 4 mmol/L, providing 30 mL/kg crystalloid with reassessment of volume responsiveness or tissue perfusion should be implemented. The six-hour elements of care should be completed. For the six-hour bundle, repeat lactate level is also recommended if initial lactate level was greater than 2 mmol/L.

Coming Attractions!!

Recent Studies

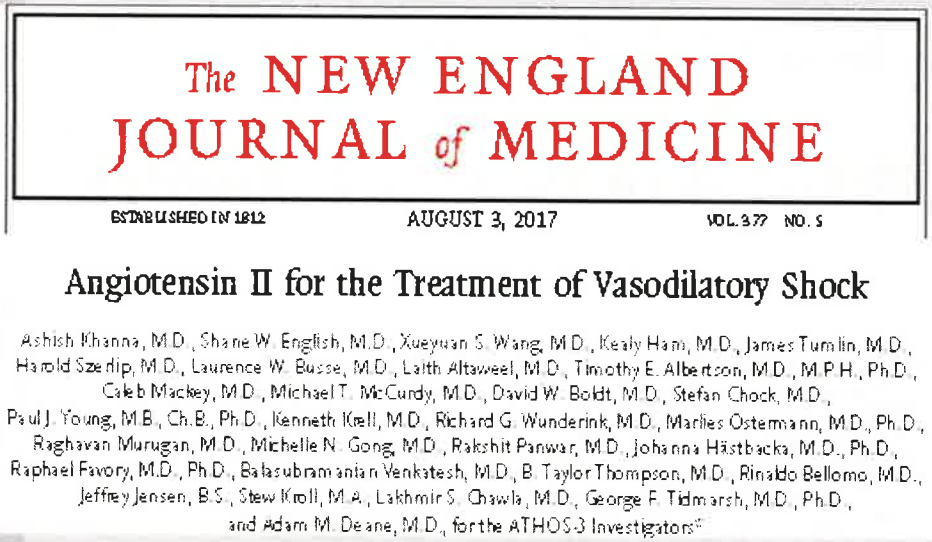


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 3, 2017 VOL. 377 NO. 5

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D., Kealy Ham, M.D., James Tumlin, M.D., Harold Szerlip, M.D., Laurence W. Busse, M.D., Laith Altaweel, M.D., Timothy E. Albertson, M.D., M.P.H., Ph.D., Caleb Mackey, M.D., Michael T. McCurdy, M.D., David W. Boldt, M.D., Stefan Chock, M.D., Paul J. Young, M.B., Ch.B., Ph.D., Kenneth Krell, M.D., Richard G. Wunderink, M.D., Marlies Ostermann, M.D., Ph.D., Raghavan Murugan, M.D., Michelle N. Gong, M.D., Rakshit Panwar, M.D., Johanna Hästbacka, M.D., Ph.D., Raphael Favory, M.D., Ph.D., Balasubramanian Venkatesh, M.D., B. Taylor Thompson, M.D., Rinaldo Bellomo, M.D., Jeffrey Jensen, B.S., Stew Kroll, M.A., Lakhmir S. Chawla, M.D., George F. Tidmarsh, M.D., Ph.D., and Adam M. Deane, M.D., for the ATHOS-3 Investigators*

Use of balanced fluids in critically ill adults resulted in a lower rate of the composite outcome of death from any cause, new renal replacement therapy or persistent renal dysfunction than use of saline

Angiotension II effectively increases blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors