

SEPSIS PROTOCOL DESIGN

Management

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Disclosures

- Received funding from:

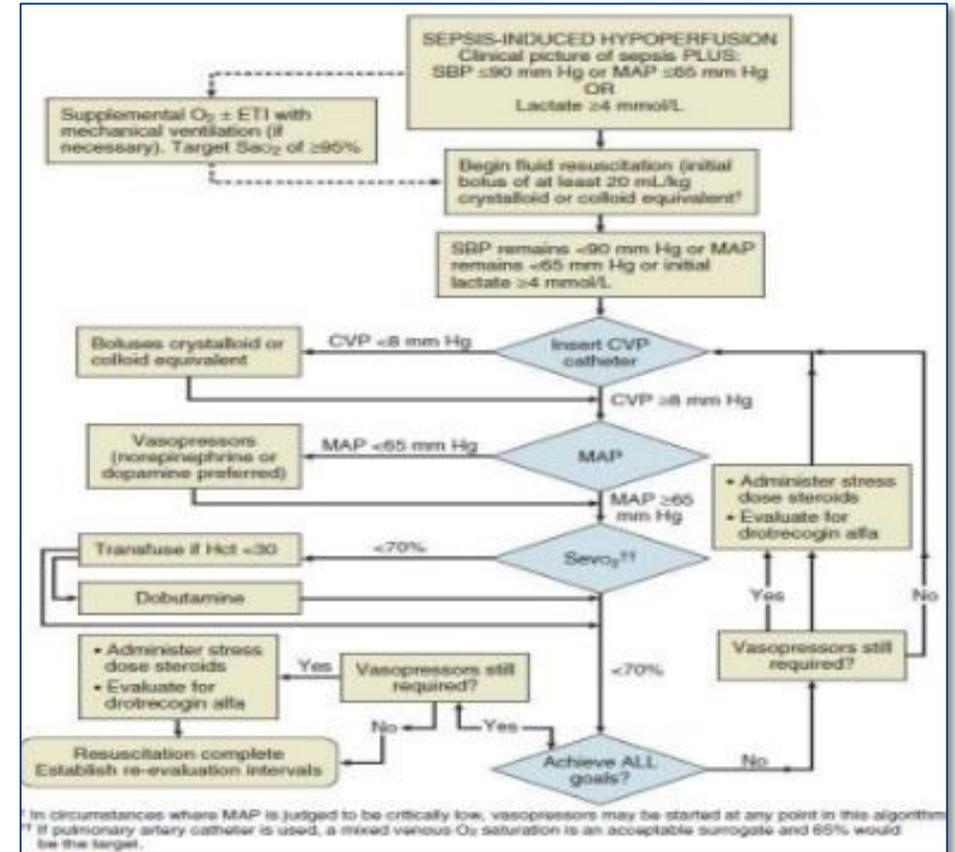
NIH NIGMS, SCCM, AHA, MedicOne, SIS
- Consulting fees from Beckman Coulter, Edwards, Cytovale
- Member, Surviving Sepsis Campaign, ATS representative

Caveats

- I use sepsis protocols in my clinical care in a mixed medical-neuro ICU
- We will discuss elements of management, not whether they should individually be regulated
- Prompt consideration of what your local hospital is or is not already doing for sepsis

Agenda

- Review where to find evidence for elements of a sepsis protocols
- Some elements of state-of-the-art management
- Illustrative example



Where do we look?



Policy mandates

Clinical Review & Education

Review

Septic Shock

Advances in Diagnosis and Treatment

Christopher W. Seymour, MD, MSc; Matthew R. Rosengart, MD, MPH

Systematic reviews

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

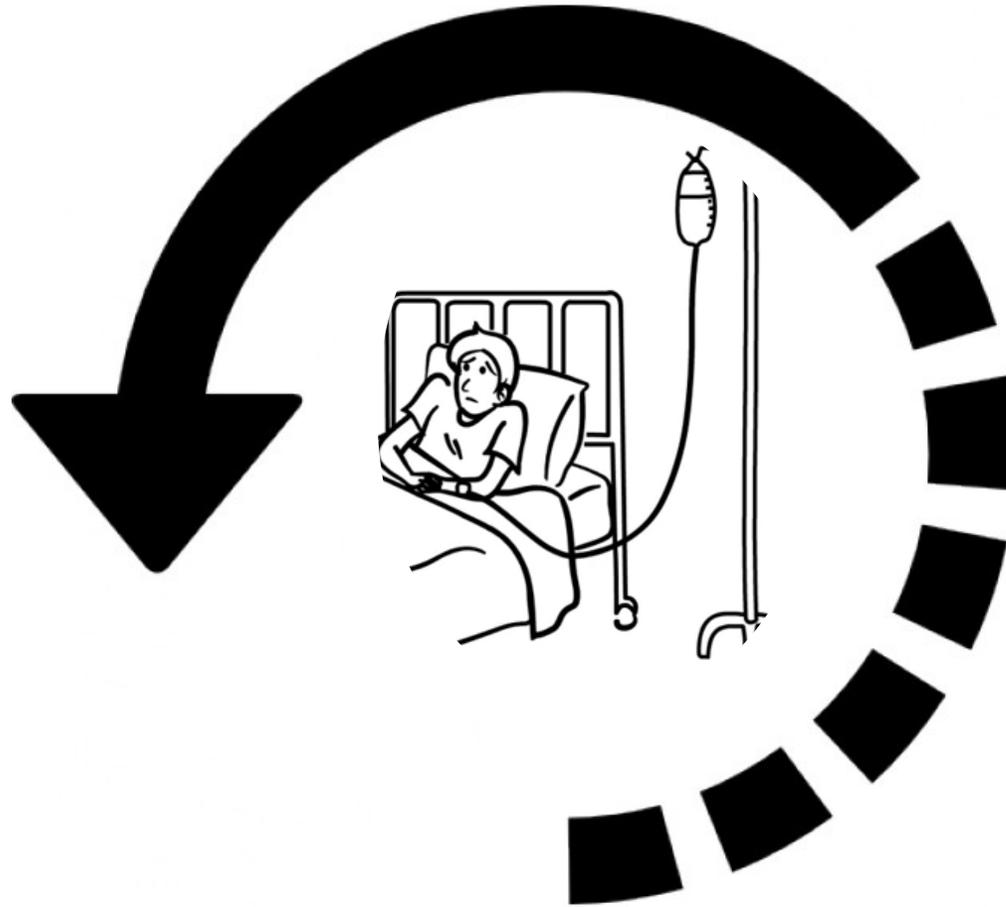
Primary research

Surviving Sepsis Campaign: International
Guidelines for Management of Severe Sepsis
and Septic Shock: 2012

Clinical guideline statements



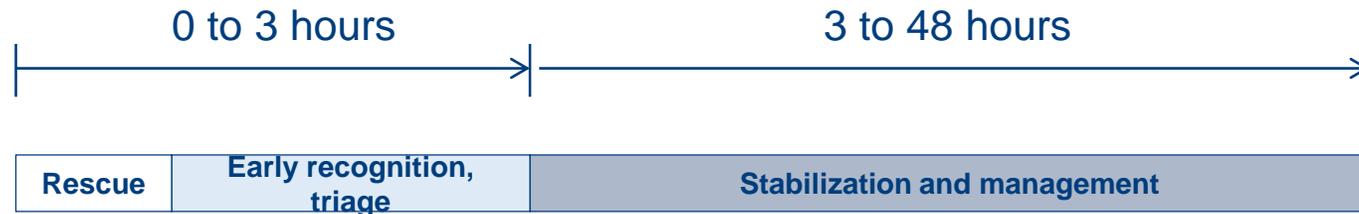
Where do we look?



STOPPING SEPSIS
Saving Lives in Pennsylvania

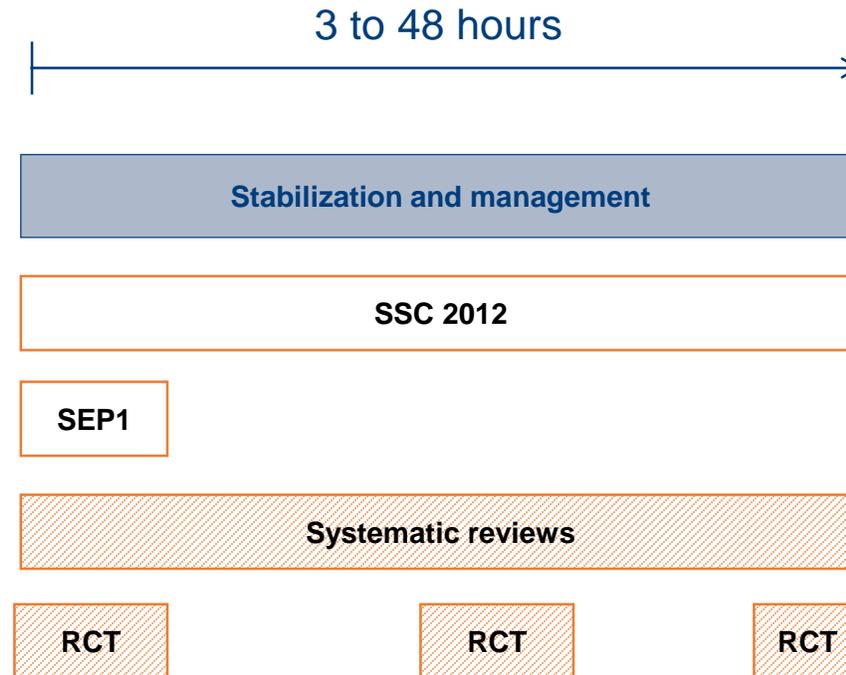


Sense of time across sources



- Surviving Sepsis Campaign 2012
- SEP1 bundle from CMS
- *JAMA* algorithm, 2015
- RCTs

Sense of time across sources



Primary elements of management (after recognition and risk stratification)

- Identification and control of sepsis source
- Timely administration of antibiotics
- Hemodynamic support for shock w/ appropriate monitoring
- Explicit use of serum lactate

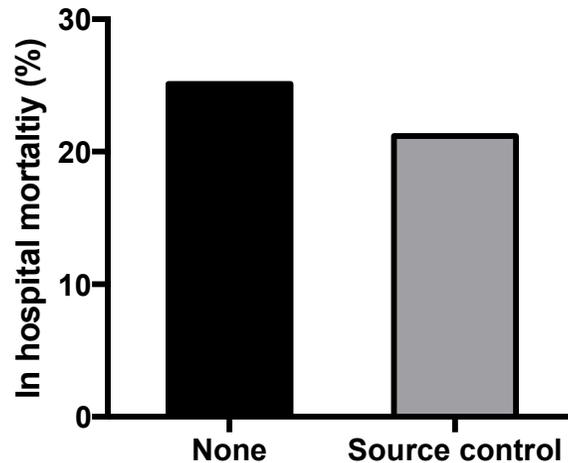
Source control

All those physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area.

John Marshall

- Drainage of closed space infection, liquid
- Debridement or physical removal of infected tissue/device
- Abdomen, chest, skin, soft tissue

Source control

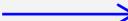


99 Medical – surgical ICUs
3,663 patients severe sepsis,
septic shock
2011 – 2013

OR for source control: 0.81
(95%CI: 0.65, 0.99, p=0.04)

Source control

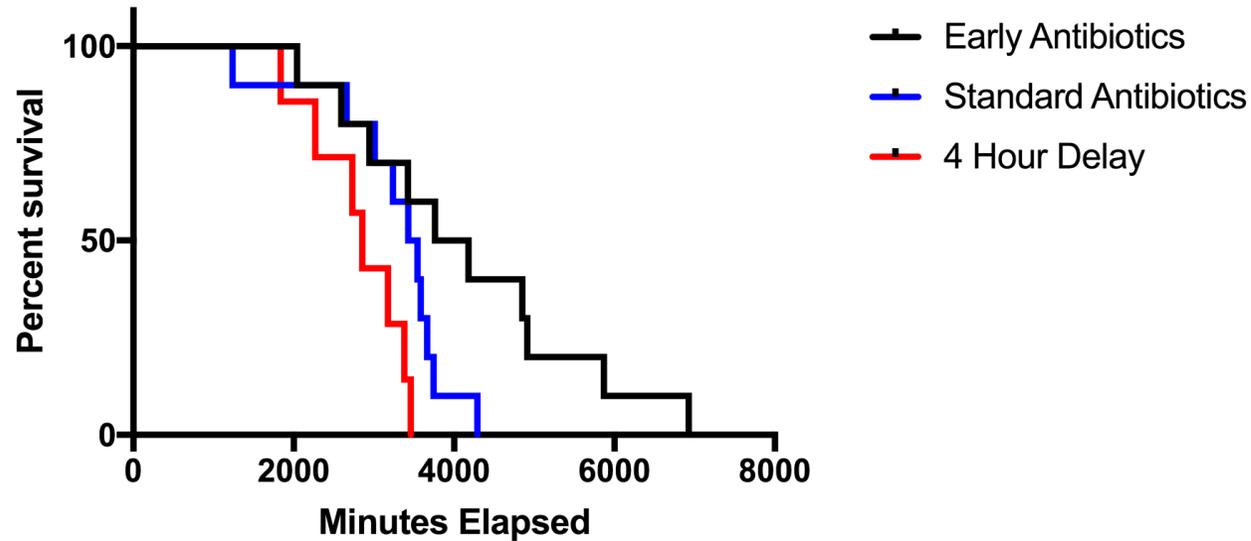
E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C). 
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

Timely administration of antibiotics

- General concept:
Shorter time to appropriate antibiotic therapy saves lives
- Varying data about what time cutoffs for what patients

Timely administration of antibiotics



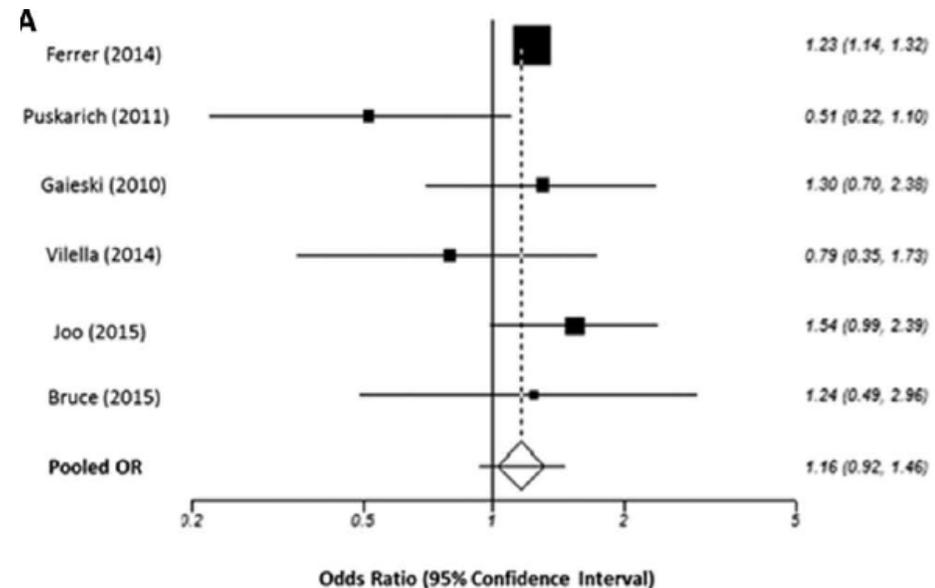
Timely administration of antibiotics

Meta analysis of >6 studies

18,000 patients

OR for in hospital mortality if more than 3 hrs =

1.16 (95% CI:0.92, 1.46)



STOPPING SEPSIS

Saving Lives in Pennsylvania



CRITICAL CARE MEDICINE

CRISMA



pennsylvania

DEPARTMENT OF HEALTH

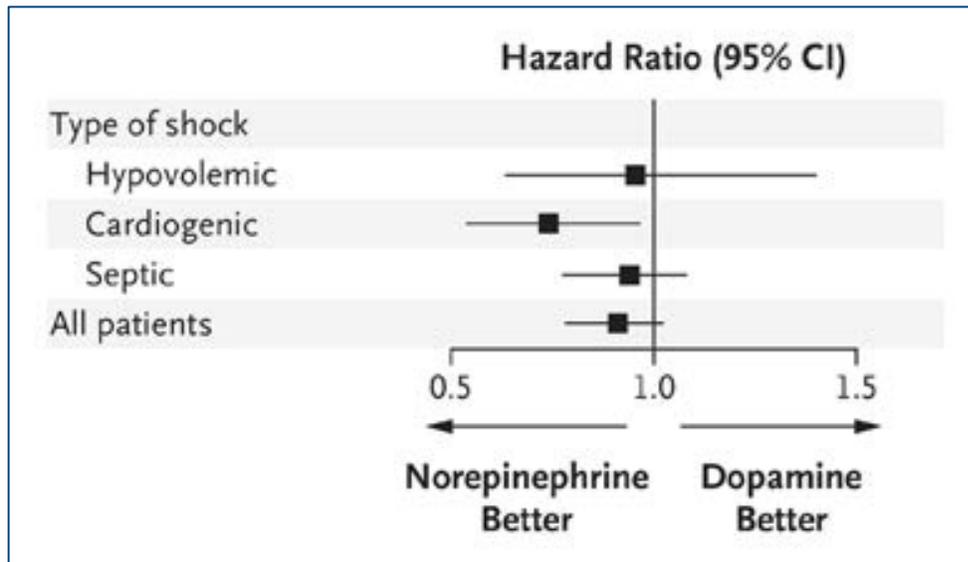
Sterling et al. *Crit Care Med*, 2015

▶ Recommendations

Guideline	Severe Sepsis	Septic shock
Surviving Sepsis Campaign, 2012 *	1 hr of recognition	1 hr of recognition
CMS SEP1 bundle	3 hr of recognition	3 hr of recognition

* Strong recommendation, moderate quality of evidence

▶ Hemodynamic support (vasopressors for shock)



- SOAP II trial
- 1,044 septic shock
- More arrhythmias in dopamine vs. norepinephrine

Hemodynamic support

- Not specified in CMS SEP1 bundle
- Appropriate for patients with septic shock (defined?) who are not responsive to initial fluid challenge

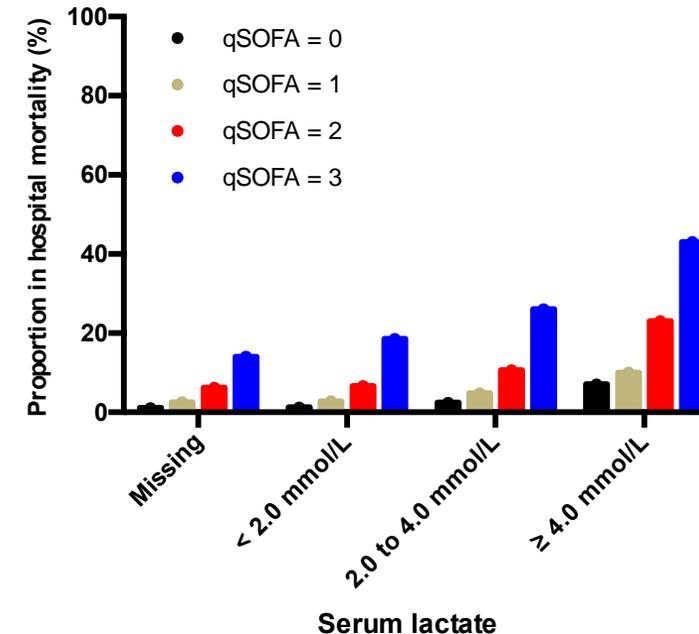
Outcomes	Illustrative Comparative Risks ^a (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE) Comments
	Assumed Risk	Corresponding Risk			
Short-term mortality	Dopamine	Norepinephrine	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊕ moderate ^{a,c}
	530 per 1000	Study population 482 per 1000 (440 to 524)			
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊕ moderate ^{a,c}
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊕ moderate ^{a,c}

Recommendations

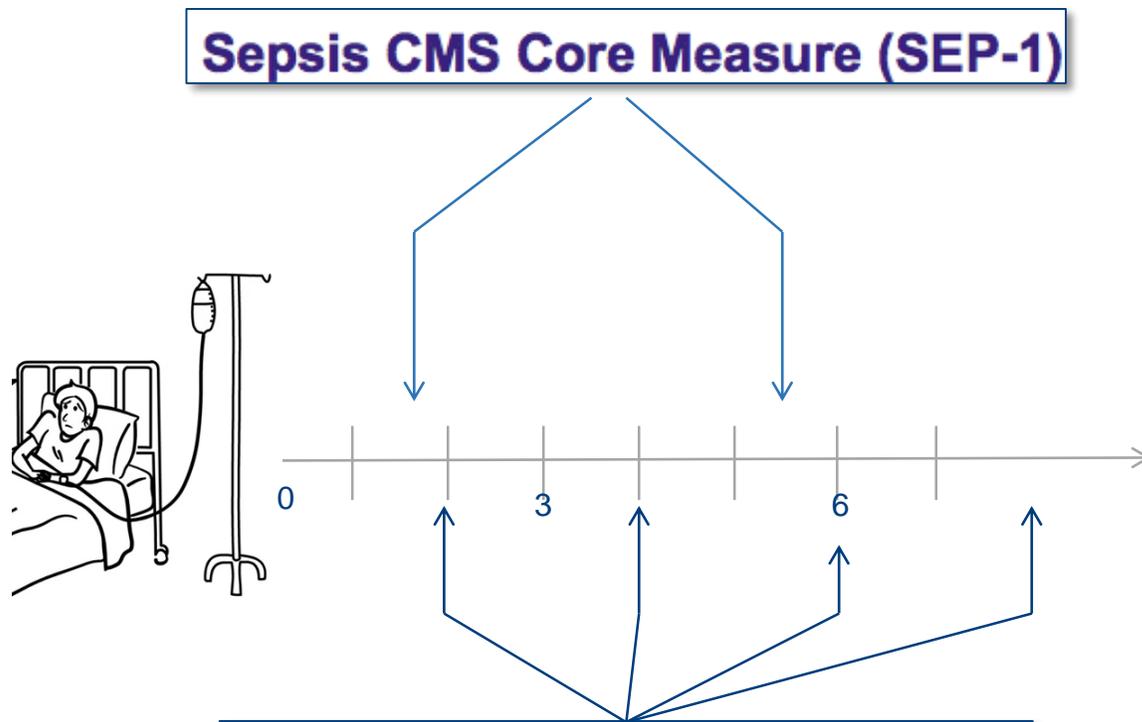
Vasopressor choice	Role	Quality of evidence
Norepinephrine	Primary	Moderate
Epinephrine	Secondary	Low
Vasopressin	Adjunct, norepi sparing	Moderate
Dopamine	Primary if bradycardia	Low

Serum lactate measurement

- Prognostic marker for low organ / tissue perfusion
- Robust association in more than > 100 cohorts
- Not a diagnostic marker
- Unclear role in management protocols



Serum lactate measurement



Sepsis CMS Core Measure (SEP-1)

Measure within 3 hrs
Repeat within 6 hrs

Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen¹, Jasper van Bommel¹, F. Jeanette Schoonderbeek³, Steven J. Sleswijk Visser⁴, Johan M. van der Klooster⁵, Alex P. Lima¹, Sten P. Willemsen², and Jan Bakker¹, for the LACTATE study group*

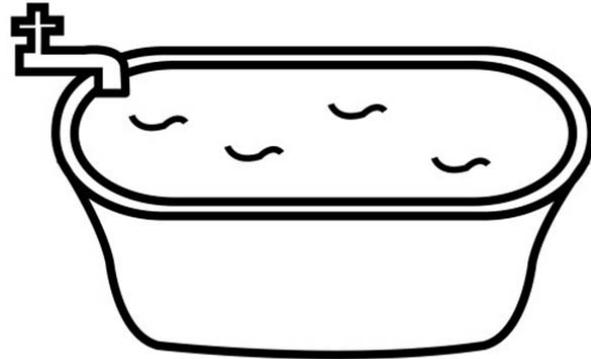
Measure every 2 hrs during guided resuscx protocol
49% reduction in odds of death

Recommendations

Lactate measurement	Purpose	Timing	Recommended by..
First measurement	Help determine if shock present or not	Triage or immediate at sepsis recognition	SSC – dx criteria SEP1, mandated
Repeat measure	Response to initial resuscitation	Minimum- 2 hrs Max – 6 hrs	SSC, low quality SEP1, mandated RCTs, improve mortality

Reassessment after a change

Turn the dial →



→ Check the water temp

Intervene on sepsis →



→ Check on the patient

Reassessment after a change

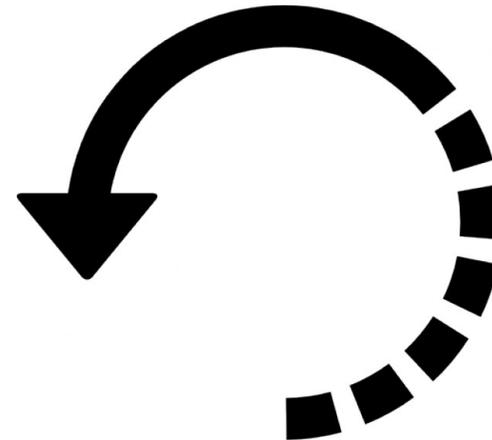
Source	Recommendation	Evidence
CMS SEP1 bundle	Assessment of volume status, tissue perfusion	“Best practice”

Focused physical exam must include:

- Vital signs
- Cardiopulmonary exam
- Capillary refill
- Peripheral pulse evaluation
- Skin exam

OR any two of the following:

- Central venous pressure
- Central venous oxygen
- Bedside cardiovascular ultrasound
- Passive leg raise or fluid challenge



What have we not covered

- **Hemodynamic monitoring**

- Invasive
- Non-invasive

Static

Dynamic measures

- **Adjuncts**

- Corticosteroids
- Sedation
- Ventilator support

IVIg

Nutrition

- **Intravenous fluids**

- Type
- Dose

Denouement

Putting this all together

Clinical Review & Education

Review
Septic Shock
Advances in Diagnosis and Treatment

Christopher W. Seymour, MD, MSc, Matthew R. Rosengart, MD, MPH

IMPORTANCE Septic shock is a clinical emergency that occurs in more than 230 000 US patients each year.

OBSERVATIONS AND ADVANCES In the setting of suspected or documented infection, septic shock is typically defined in a clinical setting by low systolic (<90 mm Hg) or mean arterial blood pressure (<65 mm Hg) accompanied by signs of hypoperfusion (eg, oliguria, hyperlactemia, poor peripheral perfusion, or altered mental status). Focused ultrasonography is recommended for the prompt recognition of complicating physiology (eg, hypovolemia or cardiogenic shock), while invasive hemodynamic monitoring is recommended only for select patients. In septic shock, 3 randomized clinical trials demonstrate that protocolized care offers little advantage compared with management without a protocol. Hydroxyethyl starch is no longer recommended, and debate continues about the role of various crystalloid solutions and albumin.

CONCLUSIONS AND RELEVANCE The prompt diagnosis of septic shock begins with obtaining a medical history and performance of a physical examination for signs and symptoms of infection and may require focused ultrasonography to recognize more complex physiologic manifestations of shock. Clinicians should understand the importance of prompt administration of intravenous fluids and vasoactive medications aimed at restoring adequate circulation, and the limitations of protocol-based therapy as guided by recent evidence.

Supplemental content at jama.com
CME Quiz at jamaevidence.com and CME Questions page 725

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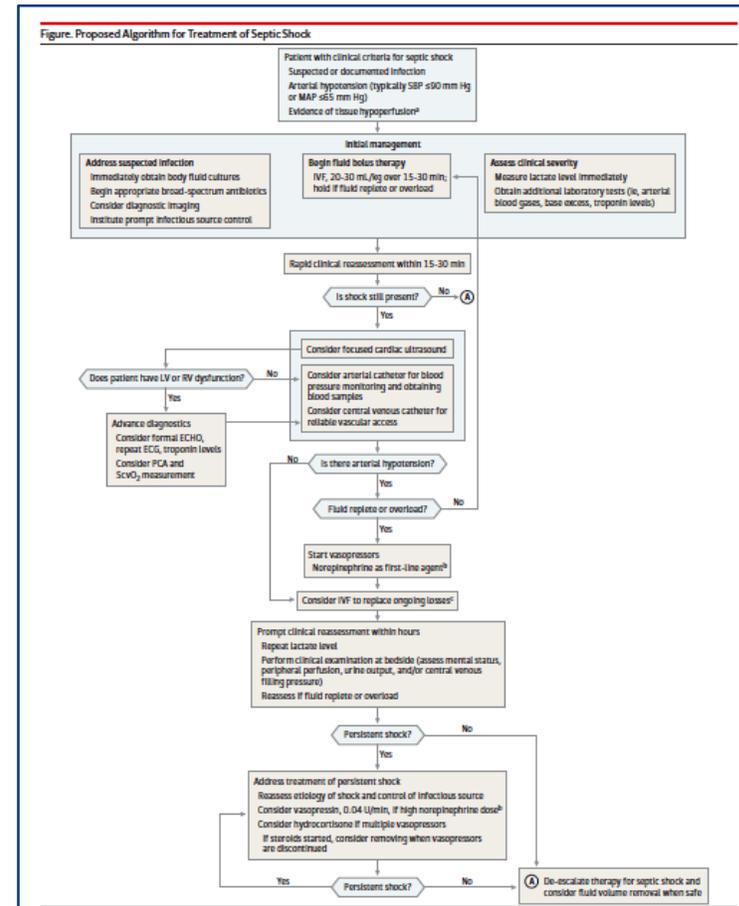
JAMA. 2015;314(7):708-717. doi:10.1001/jama.2015.7885

Shock is life-threatening circulatory failure with inadequate tissue perfusion.¹ The typical presentation is hypotension (low systolic <90 mm Hg) or mean arterial blood pressure (<65 mm Hg) accompanied by clinical signs of hypoperfusion. Historically, shock was attributed to a neurologic response to injury, vasomotor changes to the circulation, or a problem of missing blood.² By the mid-20th century, Blalock and Weil organized shock into distinct constructs: cardiogenic, obstructive, hypovolemic, or vasogenic.^{3,4} Although these categories are valuable teaching concepts, the diagnosis of shock is far more complex. We focus this review on septic shock, which is the most common cause of noncardiogenic shock and has several of the Blalock and Weil physiologic constructs at the same time.⁵ Septic shock occurs in more than 230 000 US patients each year, with more than 40 000 US deaths annually. A recent Burden of Diseases article found that primary risk factors for septic shock (ie, infection) is the fifth leading cause of years of productive life lost due to premature mortality.⁶ Given the public health burden, we review advances in diagnosis, treatment, and areas of uncertainty in septic shock from January 2010 to June 2015.

Methods

We performed a review of the MEDLINE and the Cochrane Database of Systematic Reviews from 2010 to 2015 using specific search strategies. Our primary search used the terms shock, septic shock, diagnosis, and treatment, among others. We provide search strings and Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in eAppendix (in the Supplement). We restricted articles to adult (age >= 18 years) human data reported in the English language only. We screened articles published between January 1, 2010, and June 1, 2015, and excluded opinion articles, commentaries, case series, and cohort studies—focusing on randomized clinical trials (RCTs), meta-analyses, systematic reviews, and clinical practice guidelines. After screening 8329 titles and abstracts, more articles were identified for full-text review, after which manual review of bibliographies generated additional references. A total of 181 articles were manually reviewed, of which 35 were selected with relevant content (eFigure in the Supplement). We selected only articles deemed to provide major advances in the diagnosis or treatment of septic shock. We considered sources of bias in these articles

708 JAMA August 18, 2015 Volume 314, Number 7 jama.com



Wrapping up

- **Many steps to state of the art sepsis care**
- **Core elements include:**
 - Initial recognition, risk stratification
 - Source control
 - Antibiotics
 - Lactate measurement
 - Fluids
 - Hemodynamic support
 - Re-assessment