Prehospital *treatment* of sepsis

Christopher W. Seymour, MD MSc

The CRISMA Center
Assistant Professor of Critical Care Medicine & Emergency Medicine
University of Pittsburgh School of Medicine

CRITICAL CARE MEDICINE

CRISMA CENTER

Disclosures

- Received funding from:
  NIH NIGMS, SCCM, AHA, MedicOne, SIS
- Consulting fees from Beckman Coulter, Edwards Inc.
- Member, Surviving Sepsis Campaign, ATS representative
- Member, 2016 Third International Sepsis Definitions Task Force

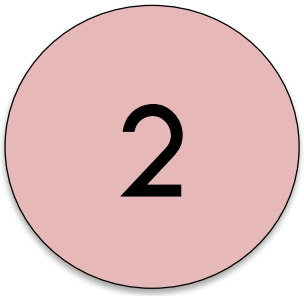
Caveats

- I am not an EMS clinician
- Involved in prehospital sepsis treatment trial (CIHR, PI: Scales, PITSTOP) planning to enroll in 2018
- Intensivist at UPMC-Mercy in Pittsburgh, PA

Objectives

- What did we discuss last lecture
  - Definitions, criteria
- What are the main tenets of sepsis treatment
- What can we do NOW during prehospital care
- What will we do in the FUTURE
- Questions

Sepsis is everywhere.



million US cases each year

percent of US healthcare spending

Gaieski et al. Crit Care Med, 2014
Singer et al., JAMA, 2016

Sepsis defined

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathophysiology, management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathophysiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement.

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.

Editorial page 1

Author Video Interview and Author Audio Interview and JAMA Report Video at jama.com

Related articles pages 1 and 1

CME Quiz at jamanetworkcme.com and CME Questions jma160009

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Sepsis Definitions Task Force members are the authors listed above.

Corresponding Author: Clifford S. Deutschman, MD, MS, Departments of Pediatrics and Molecular Medicine, Hofstra-Northwell School of Medicine, Feinstein Institute for Medical Research, 269-01 76th Ave, New Hyde Park, NY 11040 (cdeutschman@snhs.edu).

JAMA. 2016;315(8):1-10. doi:10.1001/jama.2016.0287

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

- Infection
- Organ dysfunction
- Life threatening
- Dysregulated host response

Singer et al., JAMA, 2016

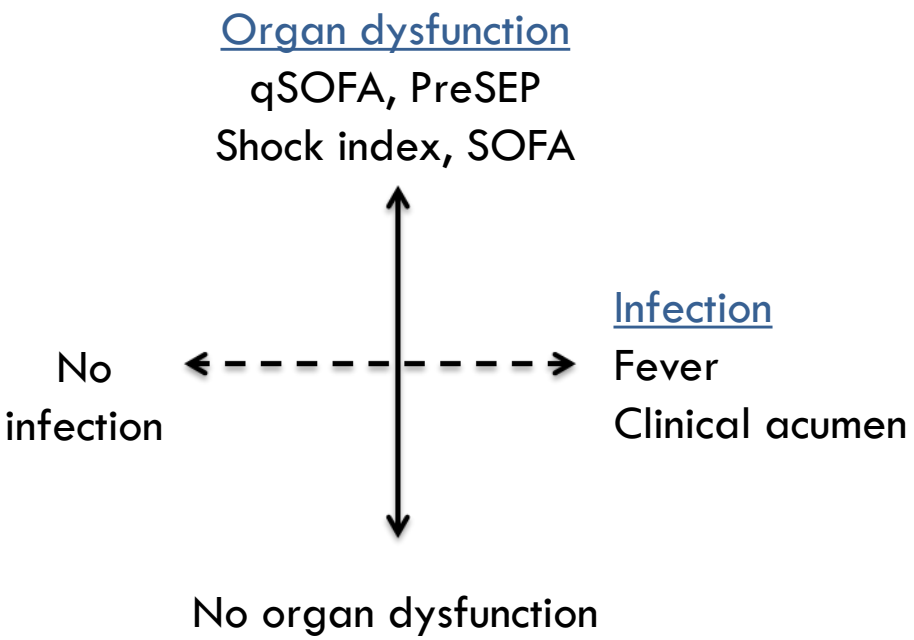
Clinical criteria for sepsis

- Infection plus 2 or more SOFA points above baseline

Prompt to consider sepsis outside the ICU

- Infection plus 2 or more qSOFA points

Finding sepsis in prehospital care



Conclusions – last time

- Sepsis is an enormous pubic health problem
- New sepsis definitions released in 2016
- Clinical suspicion for infection remains a challenge
- New tools such as qSOFA may be prompts but are not adequately sensitive
- New and old biomarkers – good for research – not yet ready for prime time

So now what?

I've found a septic patient, what can we do…

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
- Fluid bolus therapy

Source control

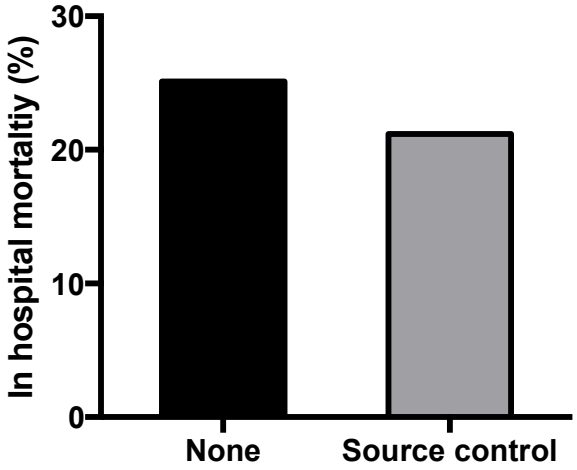
All those physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area.

John Marshall

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

Marshall et al. *Crit Care Clin*, 2009

Source control, 2



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)

Martinez et al. *Crit Care Med*, 2016

Source control,3

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).

Dellinger et al., *Crit Care Med*, 2012

Timely administration of antibiotics

Clinical practice guidelines and CMS

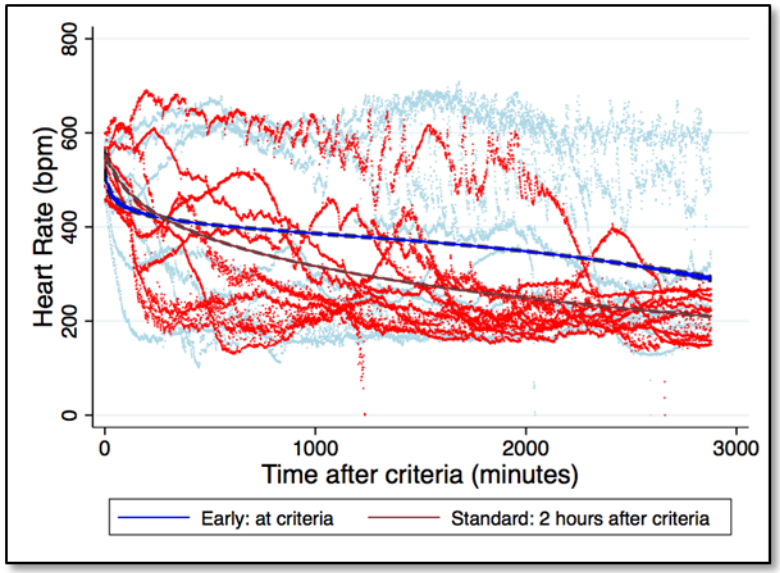
1. We recommend the administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock (strong recommendation; moderate quality of evidence).

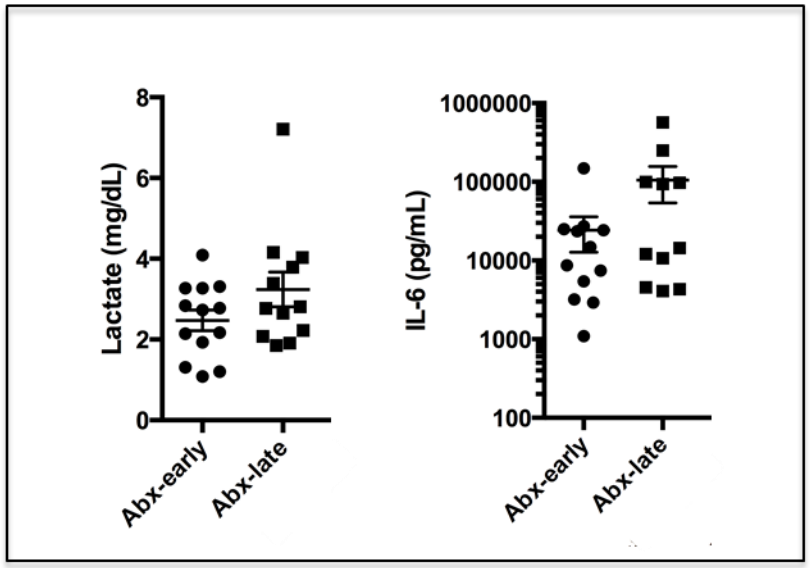
Rhodes, Evans et al., *Crit Care Med*, 2017

Example of preclinical data

Mice with CLP polymicrobial sepsis **and** physiologic deterioration, test early vs late antibiotic administration

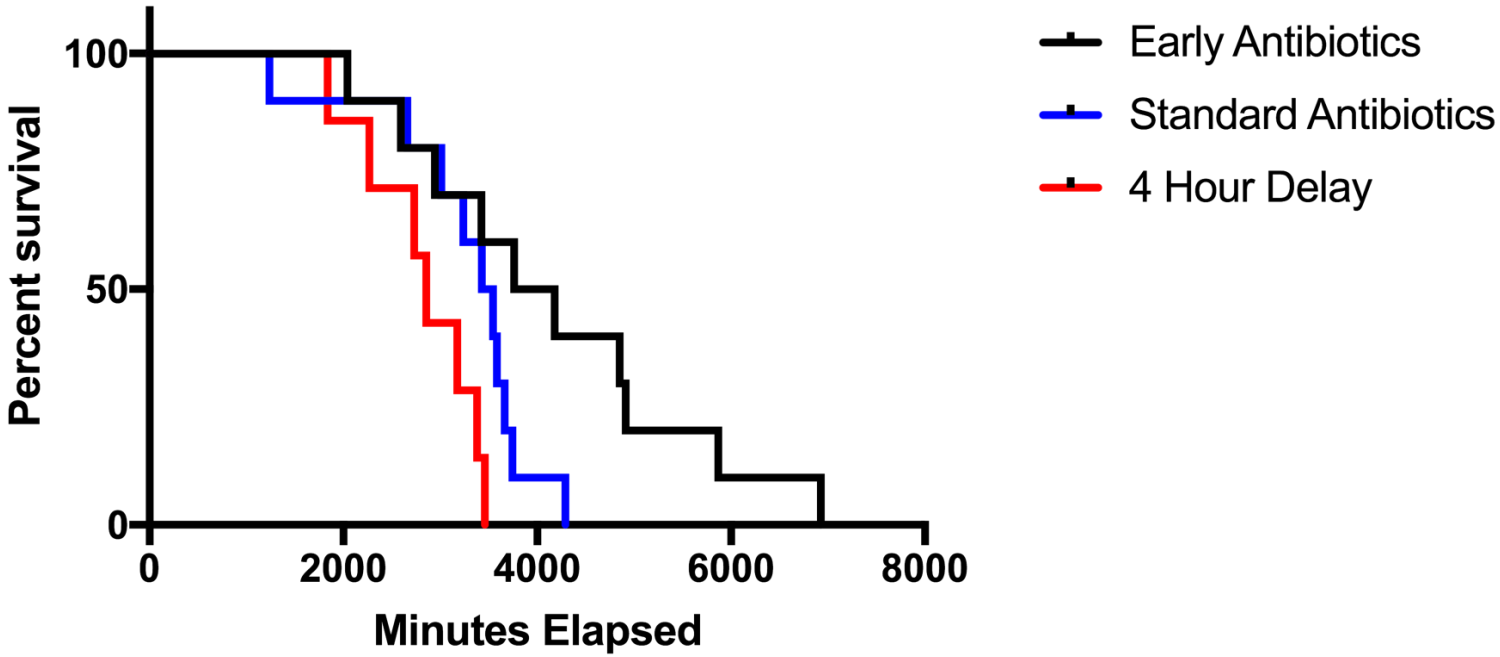
- Measure 24 hr biomarkers
- Survival





Lewis et al. *Crit Care Med*, 2016

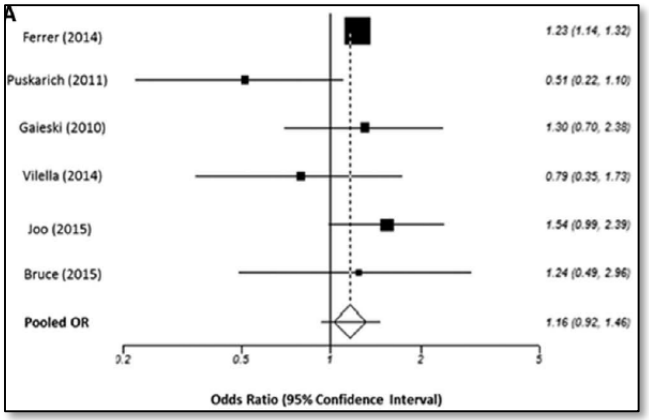
Example of preclinical data, 2



Lewis et al. *unpublished data*

Meta analysis → not so fast

- **No benefit from antibiotics administered with 3 hours of ED arrival**
- **Unintended consequences?**
  - Adverse effects
  - Burden on clinical team
  - Over-use, resistance
- **No randomized clinical trial**



Sterling et al., *Crit Care Med*, 2015

Mandated Care

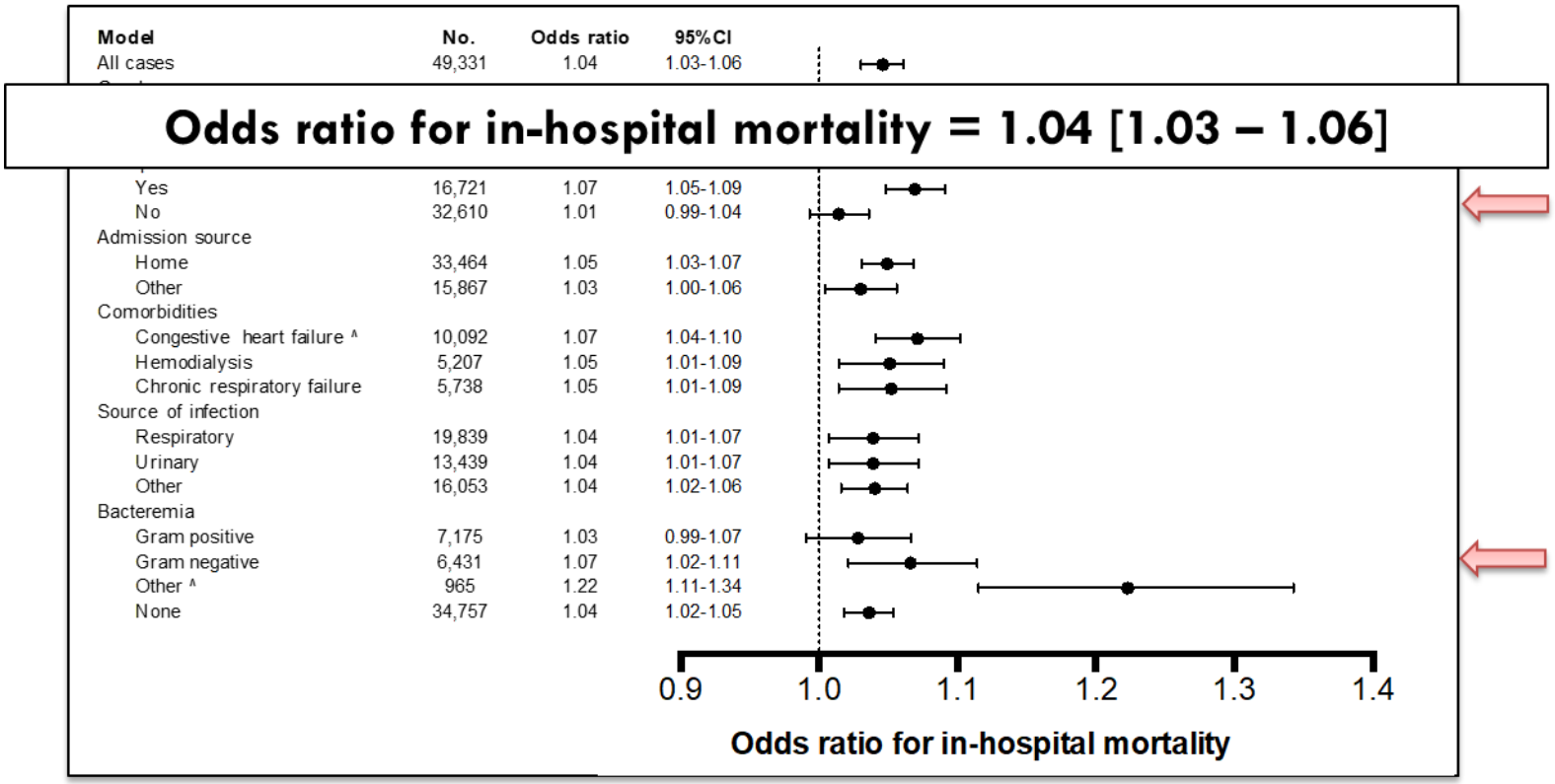
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

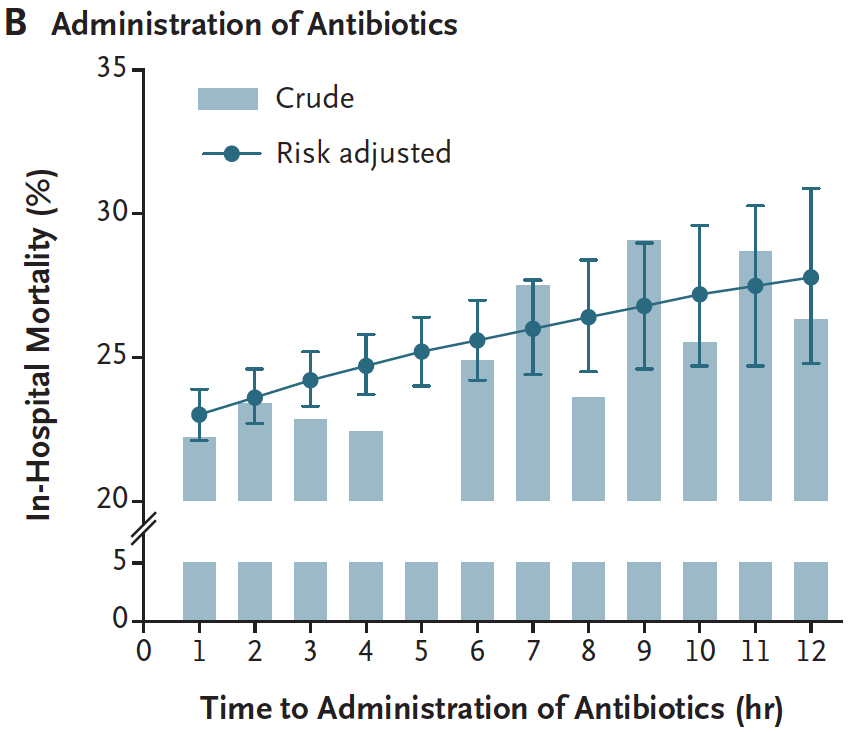
Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

Time to antibiotics administered in New York State



CRITICAL CARE MEDICINE CRISMA CENTER NEW YORK STATE

Risk of death



*Predictive margins from average of independent variables

Recommendations

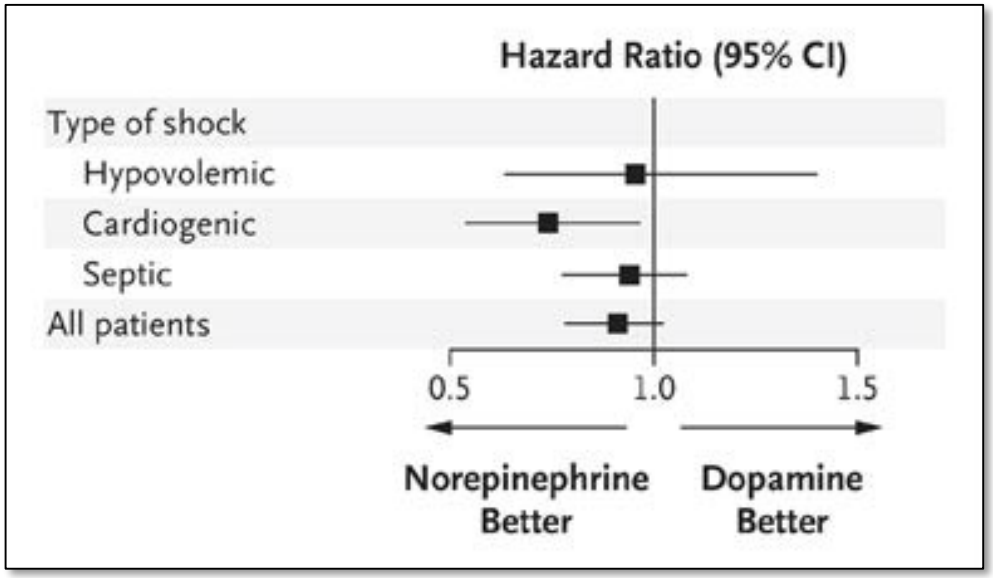
Guideline	Severe Sepsis	Septic shock
Surviving Sepsis Campaign, 2012 *	1 hr of recognition	1 hr of recognition
CMS SEP1 bundle	3 hr of recognition	3 hr of recognition

* Strong recommendation, moderate quality of evidence

Dellinger et al. *Crit Care Med*, 2011
https://www.acep.org/content.aspx?id=104615

Hemodynamic support

(vasopressors for shock)



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

De Backer et al. *N Engl J Med*, 2010

Hemodynamic support, 2

- 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) Assumed Risk	Corresponding Risk	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
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[b,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[b,c]	

Dellinger et al. *Crit Care Med*, 2012

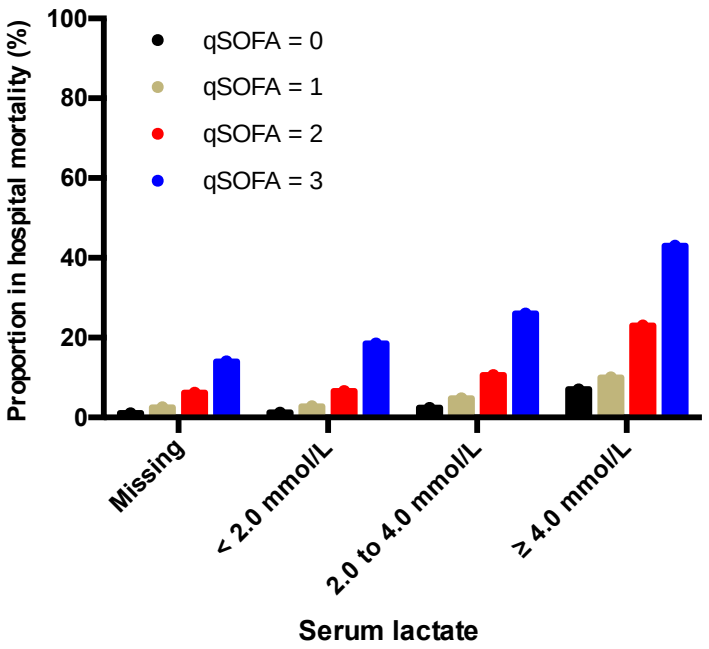
Recommendations, 2

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

Dellinger et al. *Crit Care Med*, 2012

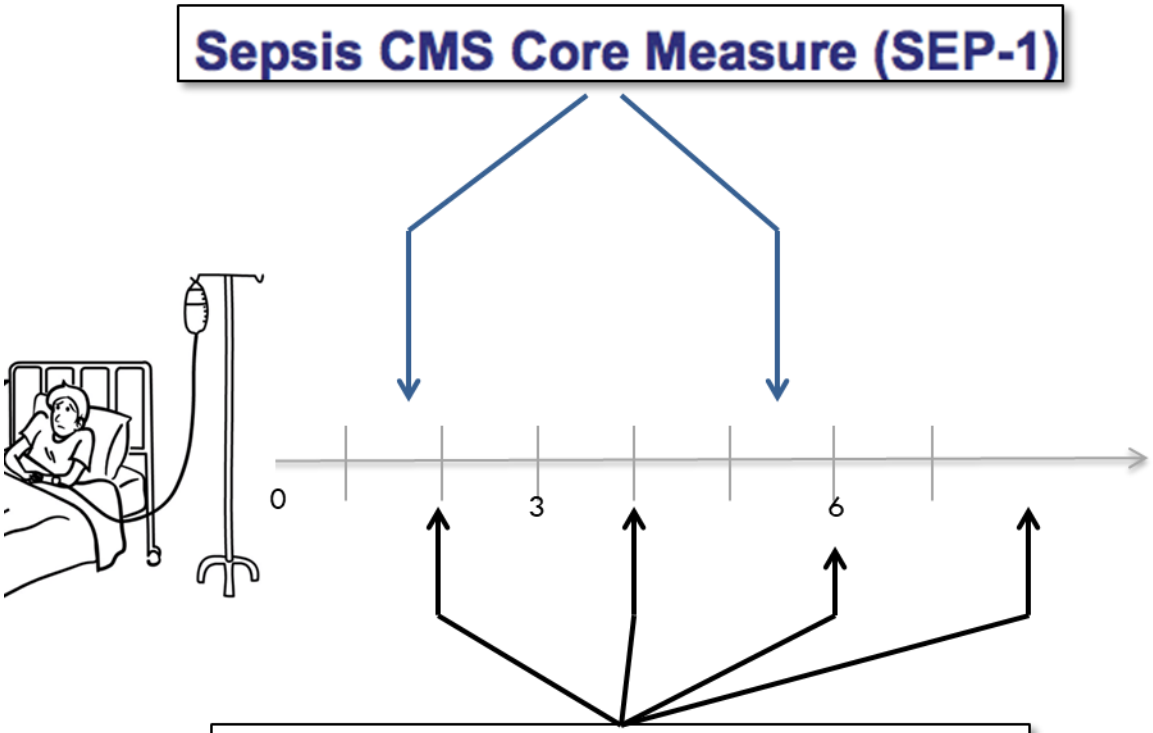
Serum lactate measurement

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



Seymour et al. *JAMA*, 2016

Serum lactate measurement, 2



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. Jansen[1], Jasper van Bommel[1], F. Jeanette Schoonderbeek[3], Steven J. Sleeswijk Visser[4], Johan M. van der Klooster[5], Alex P. Lima[1], Sten P. Willemsen[2], and Jan Bakker[1], for the LACTATE study group*

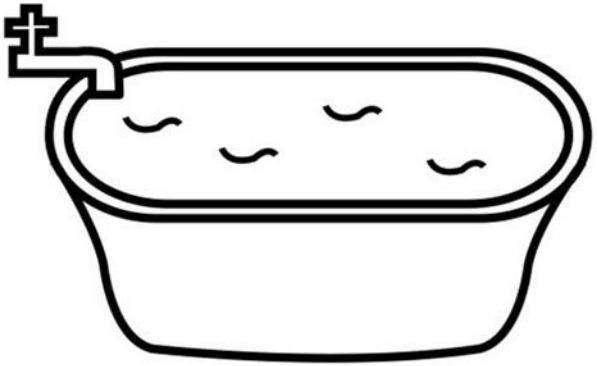
Measure every 2 hrs during guided resuscx protocol
49% reduction in odds of death

Recommendations, 3

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

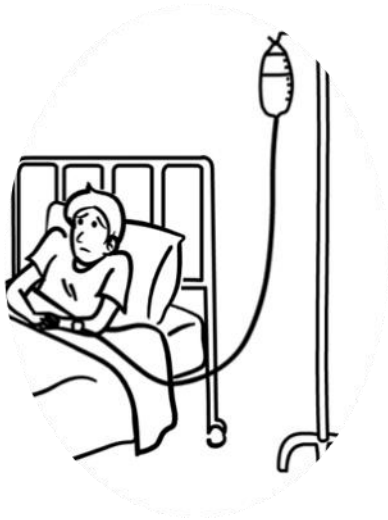
Reassessment after a change

Turn the dial →



→ Check the water temp

Intervene on sepsis →



→ Check on the patient

Reassessment after a change, 2

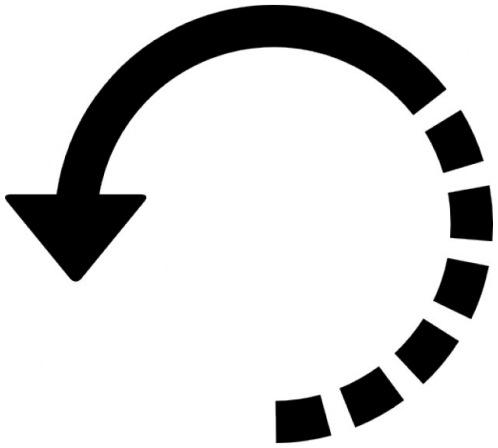
Source	Recommendation	Evidence
CMS SEP1 bundle	Assessment of volume status, tissue perfusion	"Best practice"

Focused physical exam must include:

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

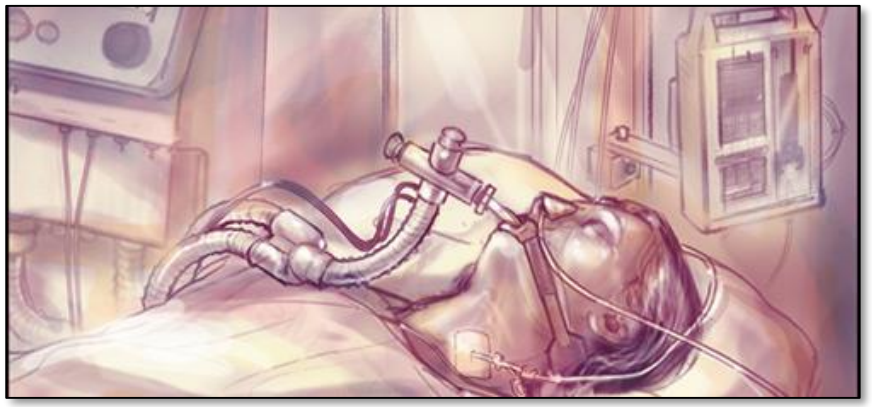
OR any two of the following:

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



Intravenous fluids

- **Ubiquitous intervention in acute medicine**
  - Drug like any other from pharmacy
- **Millions of unit administered to patients each day**
  - Hypovolemic shock
  - Dehydration
  - Many others



History of IV fluid use

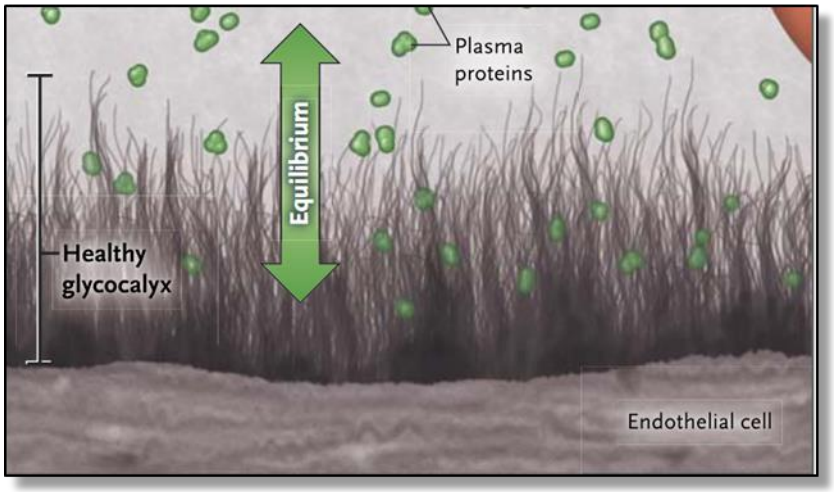
- **Robert Lewins, alkalinized salt solution for cholera in 19th century**
  - Nearly 200 years ago, but still relevant
  - A treatment before its time

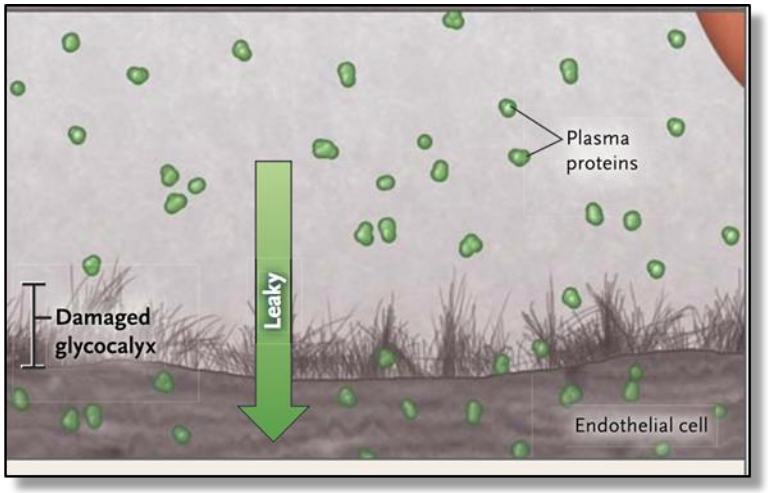
> "The very remarkable effects of this remedy require to be witnessed to be believed. Shortly after the commencement of the injection the pulse, which was not perceptible, gradually returns; the eyes, which were sunk and turned upwards, are suddenly brought forward, and the patient looks round as if in health, the natural heat of the body is gradually restored, the tongue and breath, which were in some cases at the tempera- ture of 79 and 80, rise to 88 and 90, and soon become natural, the laborious respiration and oppression of weight of the chest are relieved ... the whole countenance assumes a natural healthy appearance"

Andreson et al. *Lancet*, 1832

Physiology of fluid resuscitation

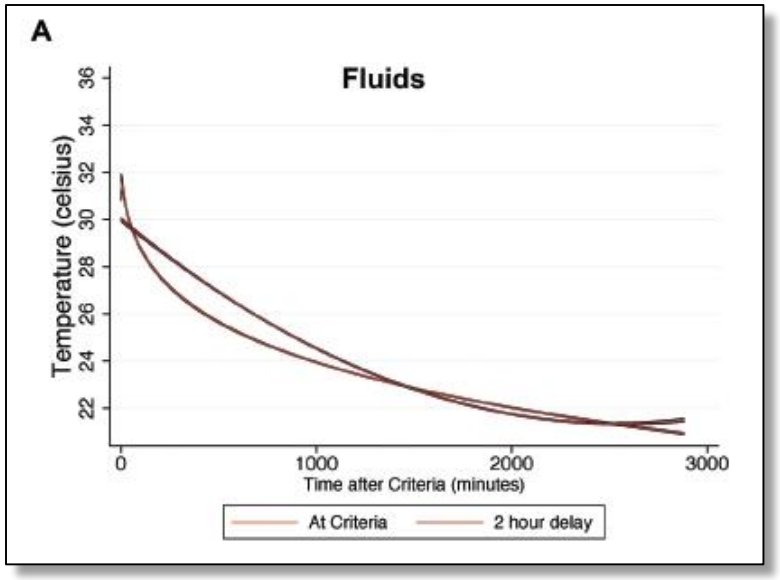
- Altered membrane permeability in critically ill patients
  - Endothelial glycocalx loses integrity
  - Increased interstitial edema
  - Particularly in surgical trauma and sepsis





Myburgh et al. *NEJM*, 2013

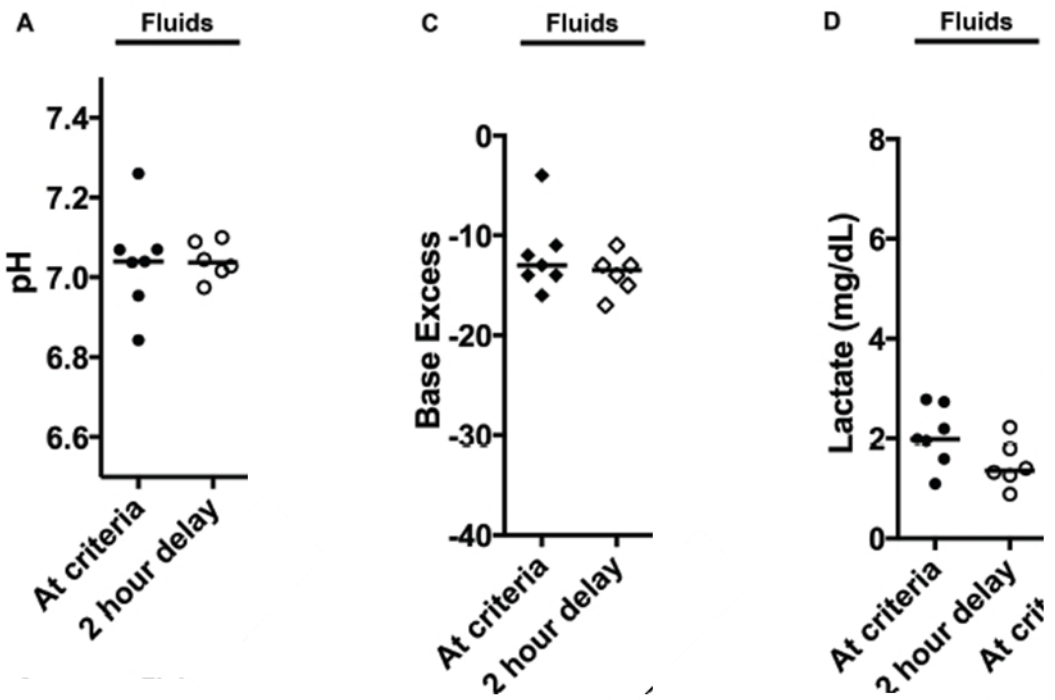
Comparison of early vs. 2 hour delayed fluids



No difference in heart rate or temperature trajectory

Lewis et al., *under review*, 2017

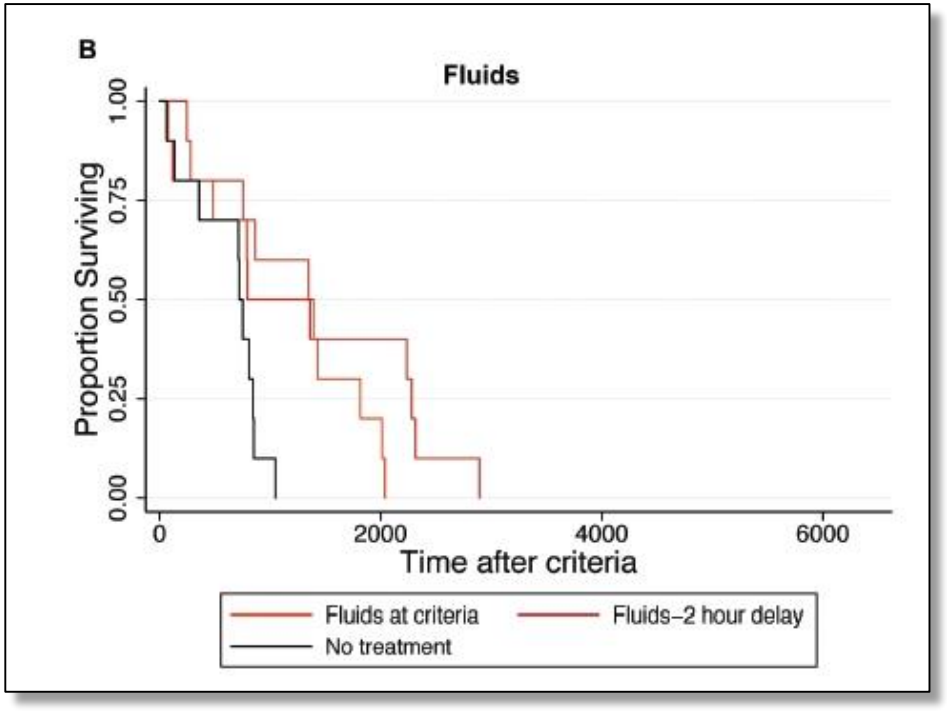
Comparison of early vs. 2 hour delayed fluids, [2]



No significant difference in pH, base excess, or lactate with earlier fluids

Lewis et al., *under review*, 2017

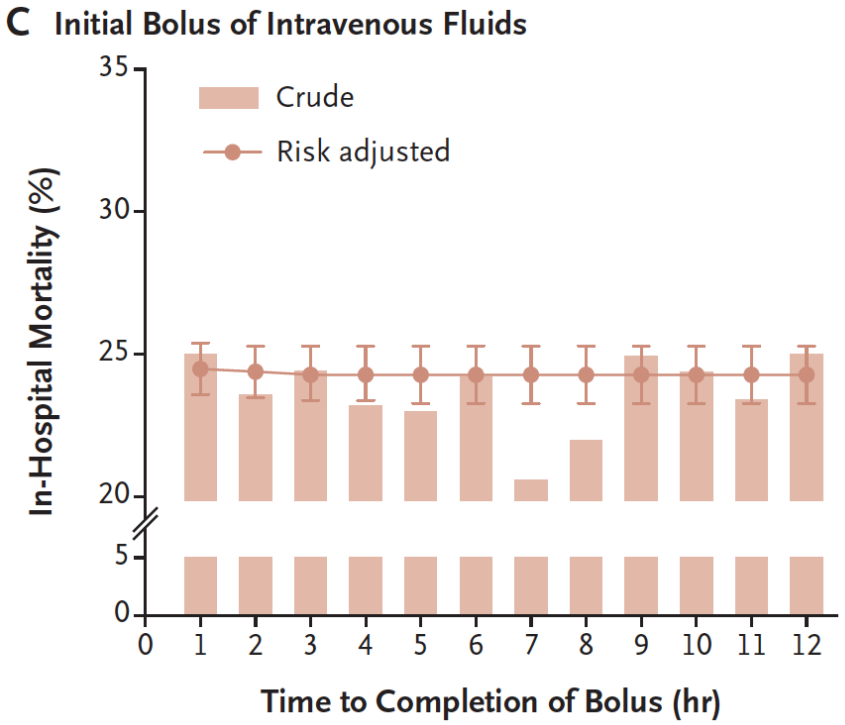
Comparison of early vs. 2 hour delayed fluids, [3]



No significant difference in survival

Lewis et al., *under review*, 2017

Risk of death, 2



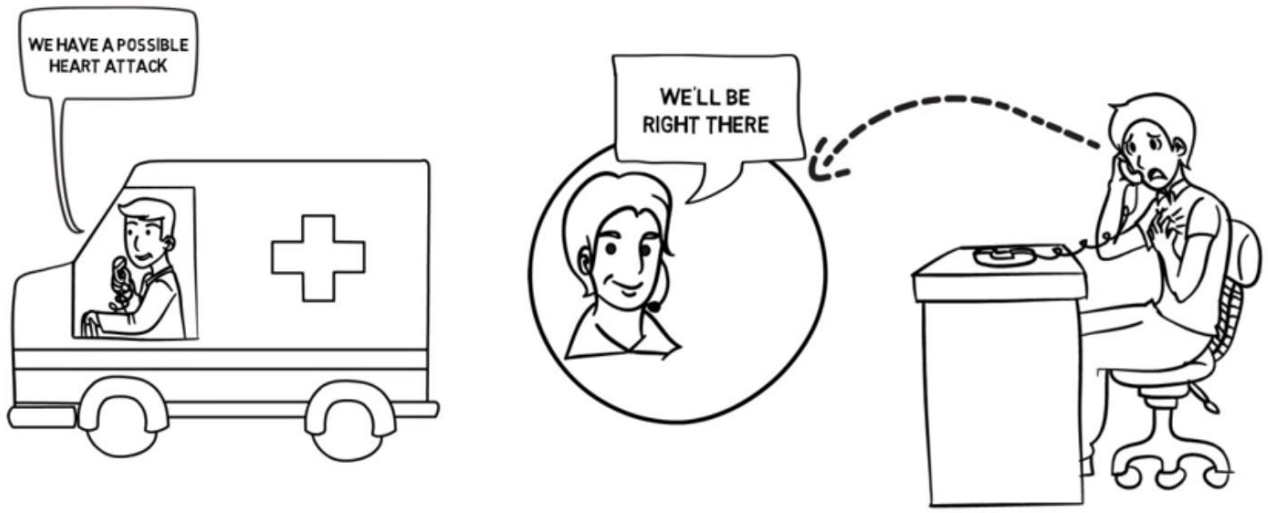
*Predictive margins from average of independent variables

Recent national policies reinforce fluids

- **Centers for Medicare and Medicaid bundle for sepsis (SEP1)**
  - All severe sepsis or septic shock patients must receive a fluid bolus of 30cc/kg of crystalloid fluids
  - Hospitals must report all cases, compliance with fluid bolus completion

- **Controversial**
  - No exclusions for ESRD
  - No exclusions for CHF

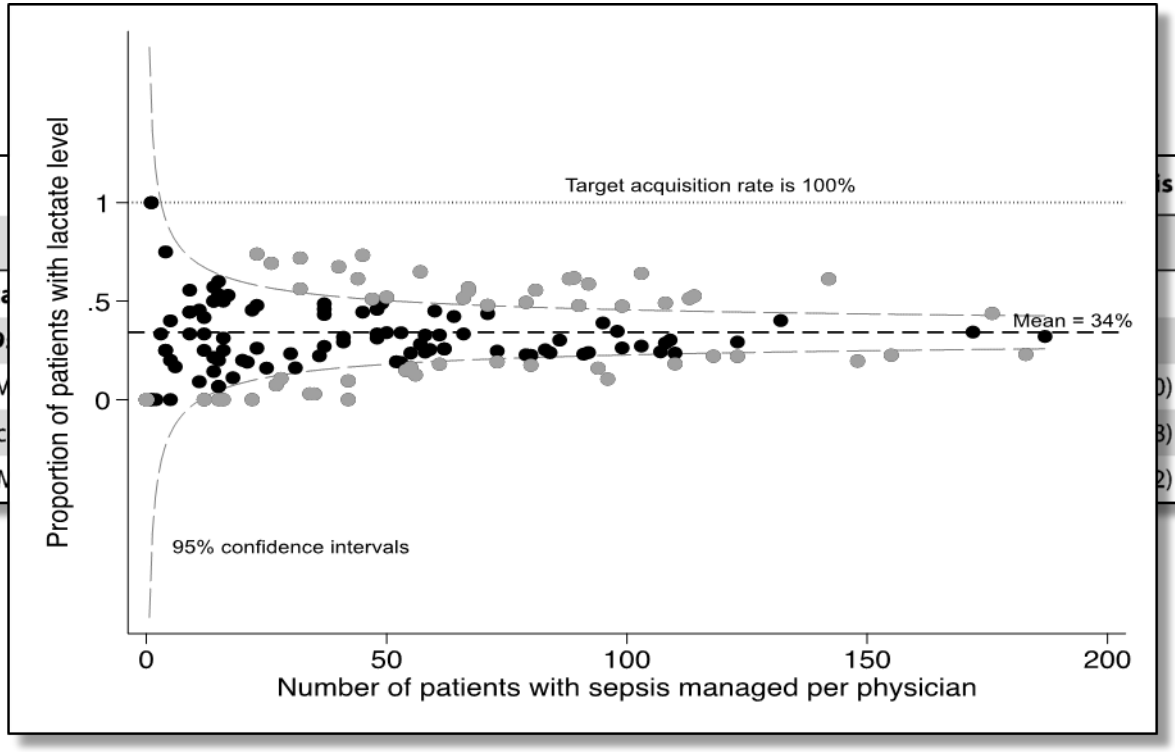
What for prehospital?



Advanced notification

- Modeled after STEMI and stroke alert systems
- Mostly small before / after studies testing activation of sepsis teams
- No large cluster RCT
- Proposed to speed process measures at the hospital
  - Source control
  - Antibiotic administration
  - Hospital fluids

What about destination for sepsis?

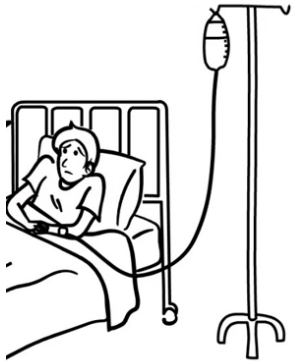


	>60 Cases
No. of Hospita	1162 (33.32)
Odds Ratio (9	
Unadjusted M	1.0 [Reference]
Demographic	1.0 [Reference]
Multivariate M	1.0 [Reference]

Shahul et al., *PlosOne*, 2014
Mohan, *unpublished*

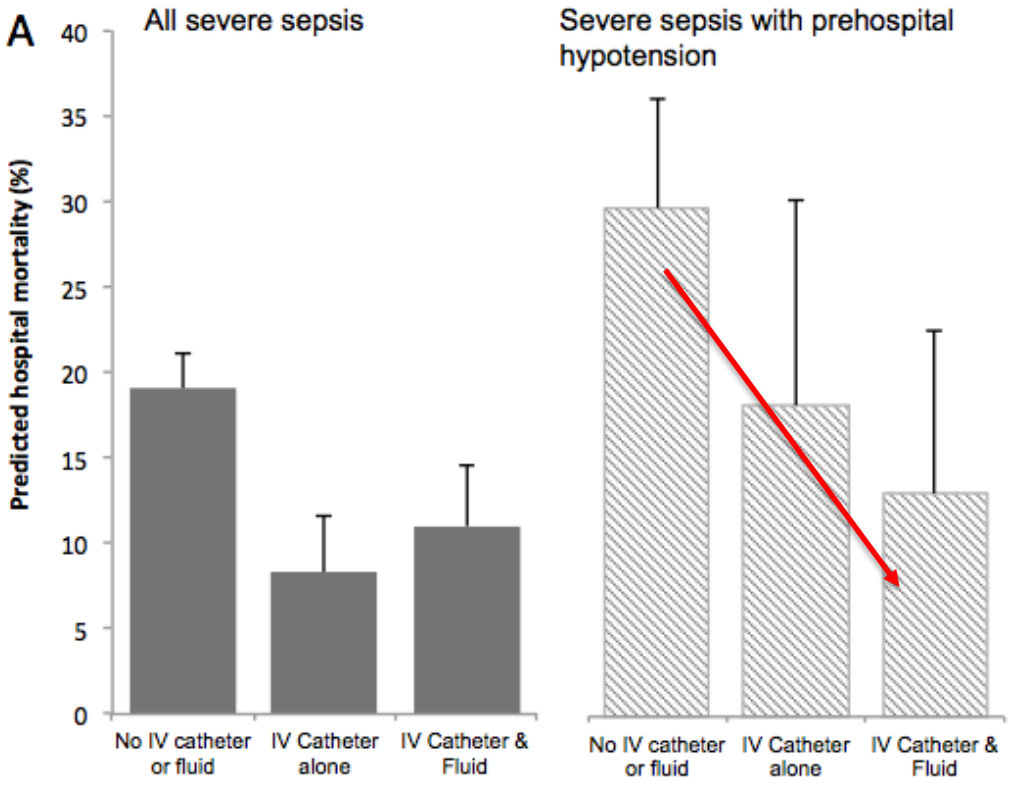
Direct treatment with fluids

- Prehospital fluids
- No RCTs yet
- Observational studies in large cohorts

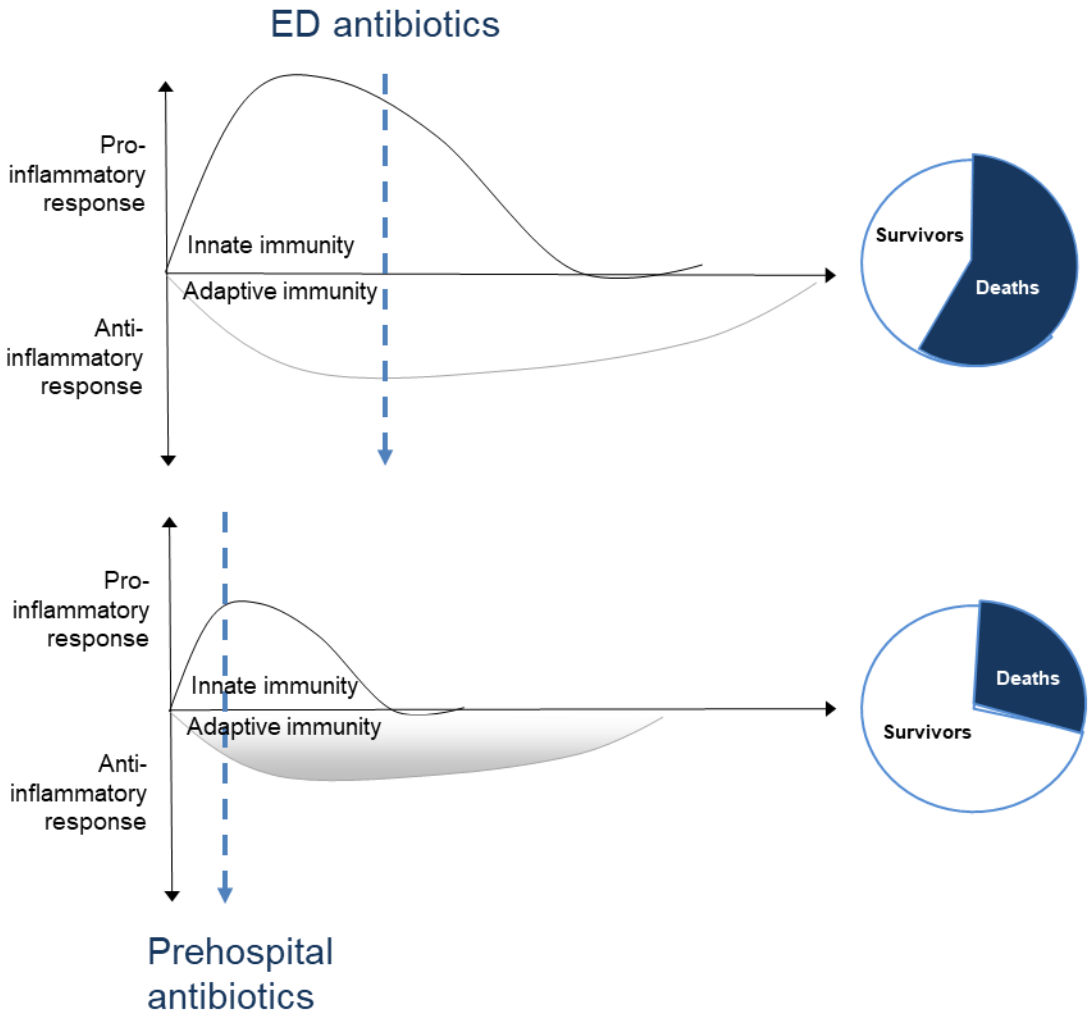


Model	+ Catheter, no fluid OR (95%CI)	+ Catheter, + fluid OR (95%CI)
Unadjusted	1.27 (0.71, 2.27)	2.05 (1.71, 2.46)
Partial adjustment: demographics & prehospital physiology *	0.98 (0.52, 1.86)	1.27 (0.98, 1.62)
Full adjustment **	0.31 (0.17, 0.57)	0.45 (0.23, 0.89)
Sensitivity analyses: ^		
Prehospital hypotension (SBP <=110mmHg)	0.40 (0.08, 2.07)	0.26 (0.08, 0.85)
Advanced life support only	0.24 (0.14, 0.38)	0.31 (0.15, 0.66)

What can we do?



Other treatments?



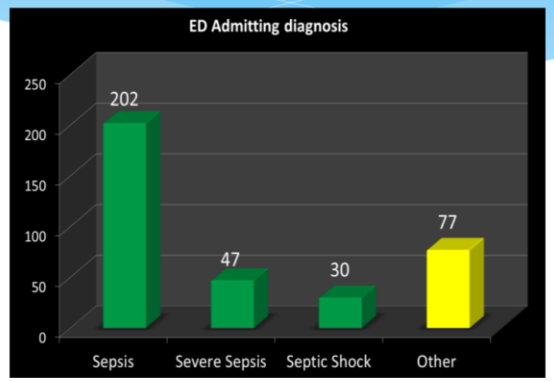
Prehospital antibiotics

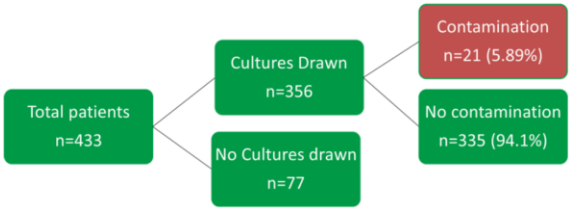
- Recommended blood cultures before treatment
- Appropriate vs. aggressively timed
  - Which drug(s)?
  - What dose?
- Who is the right population to target?
- Are we allowed to do this?

Better preclinical and clinical data required

Demonstration project in EMS

* 356 Blood cultures collected from 433 patients
* Patient demographics included 55.3% male and mean age of 65
* Most common admitting diagnosis was Sepsis 202/356 (56.7%)



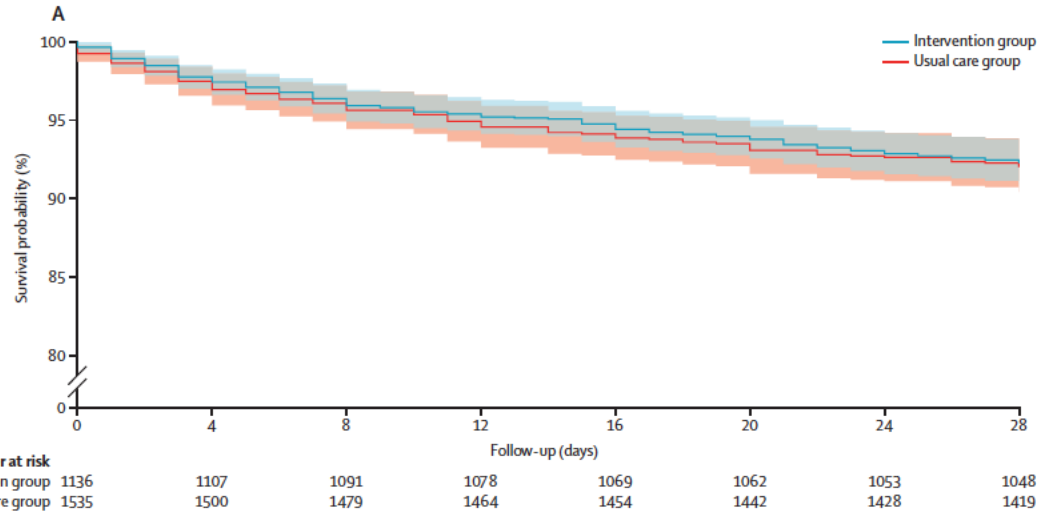


Walchuk et al, *Prehosp Emerg Med,* 2016

Randomized trial in Europe

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

*Nadia Alam, Erick Oskam, Patricia M Stassen, Pieternel van Exter, Peter M van de Ven, Harm R Haak, Frits Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A M Duineveld, Rishi S Nannan Panday, Mark H H Kramer, Prabath W B Nanayakkara, on behalf of the PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands**



So now what? Take home…

- Awareness and recognition is most important
- Consider advanced notification, don't be shy
- Follow existing protocols for fluids (shock)
- No role for antibiotics (for now)

European, Canadian, and US trials either funded or under review to generate a larger evidence base

Questions