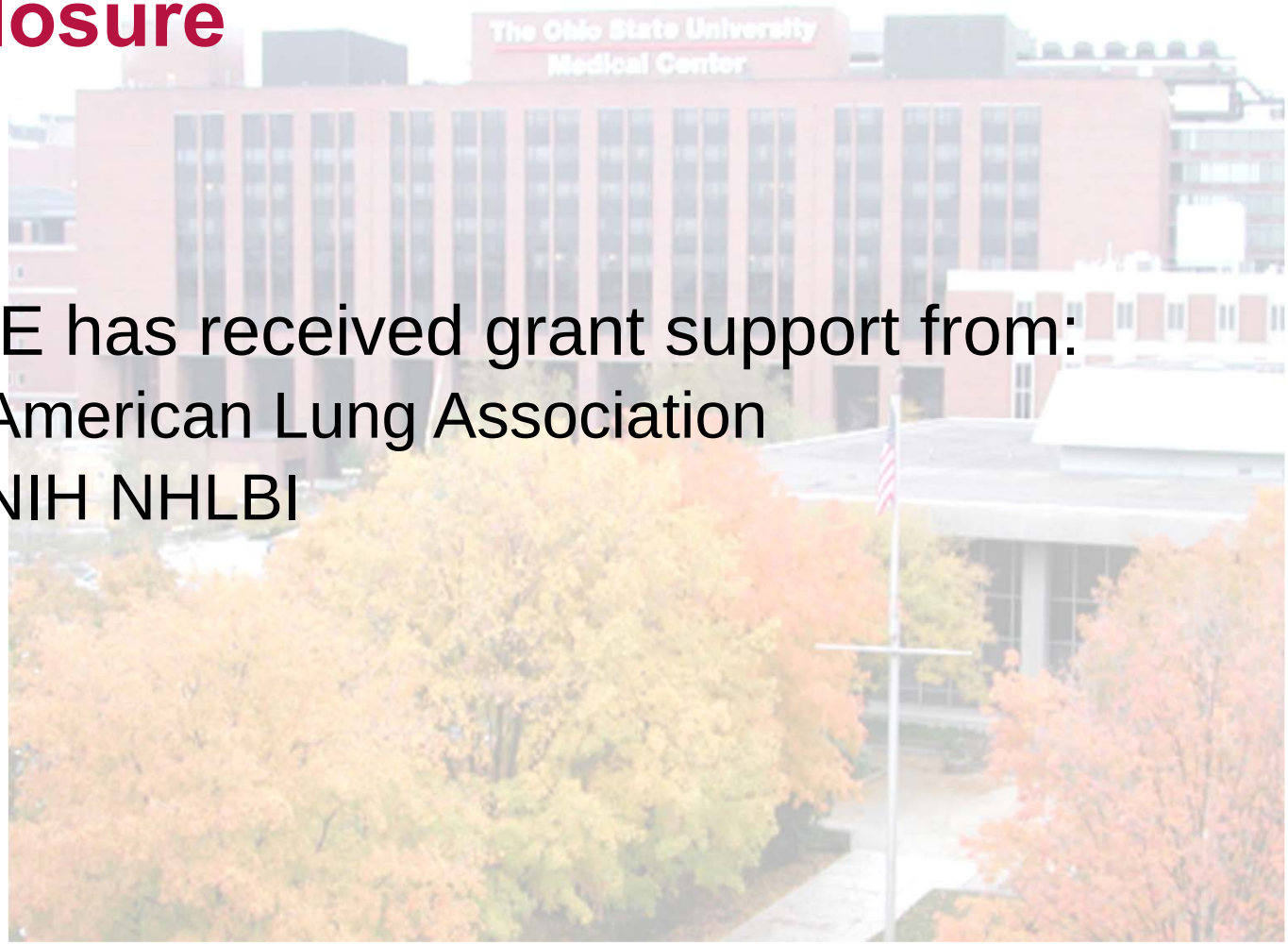
Fluid Resuscitation in Septic Shock

Matthew Exline MD MPH
November 2015

Wexner Medical Center

Disclosure



- MCE has received grant support from:
  - American Lung Association
  - NIH NHLBI

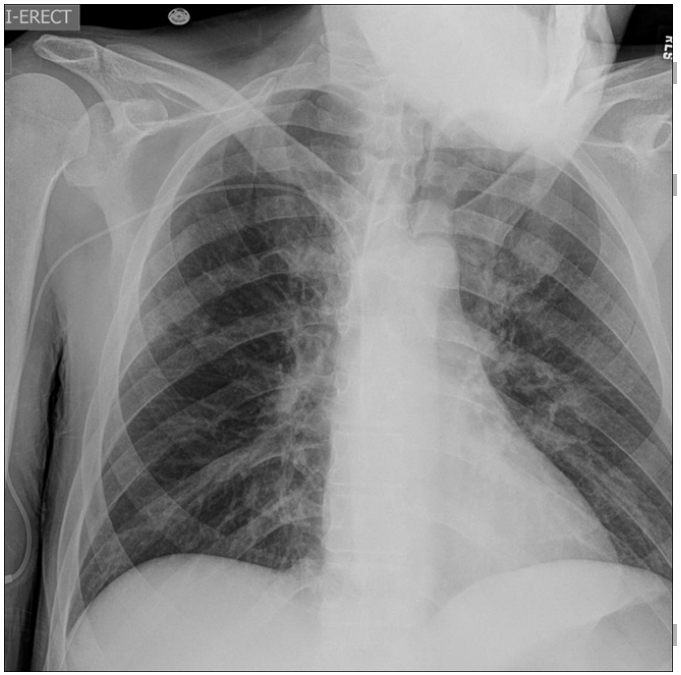
Objectives

- Identify common presentation of septic shock
- Identify common missed opportunities in septic shock
  - Why do we fear fluid resuscitation
- Understand core measures for CMS for septic shock
- Assessing fluid resuscitation

A bad run at dialysis

- 58 yo history of CAD and ESRD presents from his dialysis unit
- He endorses a 2 day history of URI symptoms
- His dialysis was terminated early for low blood pressure and he was sent to the ED
- Temp 95^{8} HR 101 RR 22 BP 89/54
- 92% SpO_2 on room air
- CBC reveals a white count of 8,600

Our Patient



- Patient identified as a septic alert in ED.
- Vanco and pip/tazo given
- Resident ordered a 250 cc bolus of 0.9NS
  - “I don’t want to overload him”
  - This is repeated for a total of 750cc
- In ED, he deteriorates from resp standpoint
  - Requires bipap and xfer to ICU

Where do they come from?

- Recognition often focuses on patients from community into ER, but…

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  - Up to 50% of sepsis is hospital-acquired

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  - Up to 50% of sepsis is hospital-acquired
  - Up to 25% of sepsis is ICU-acquired

JAMA 1995, **274**(12):968

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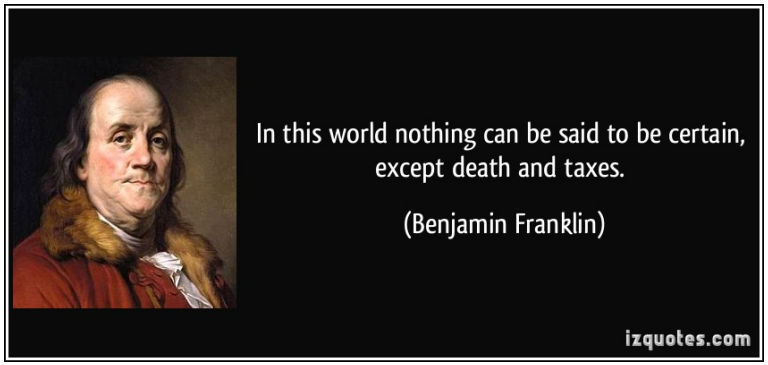
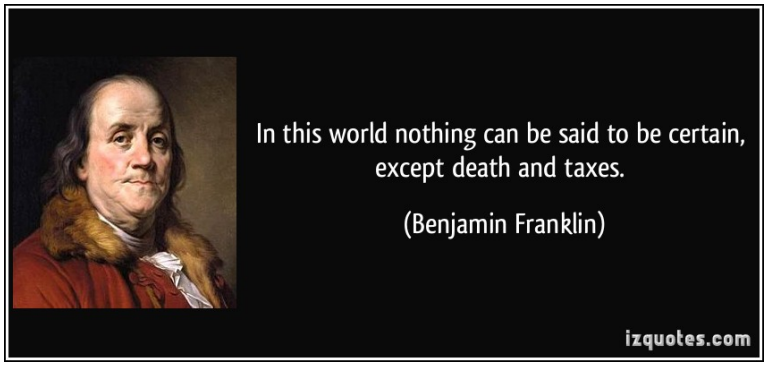
What do we need to achieve in sepsis?



- CMS Mandated Targets for Hospitals
  - Measure lactate
  - Obtain cultures prior to antibiotics
  - Administer antibiotics
  - Administer 30ml/kg fluid for hypotension or elevated lactate
  - Apply vasopressors
  - Assess volume status
  - Repeat lactate

What do we need to achieve in sepsis?



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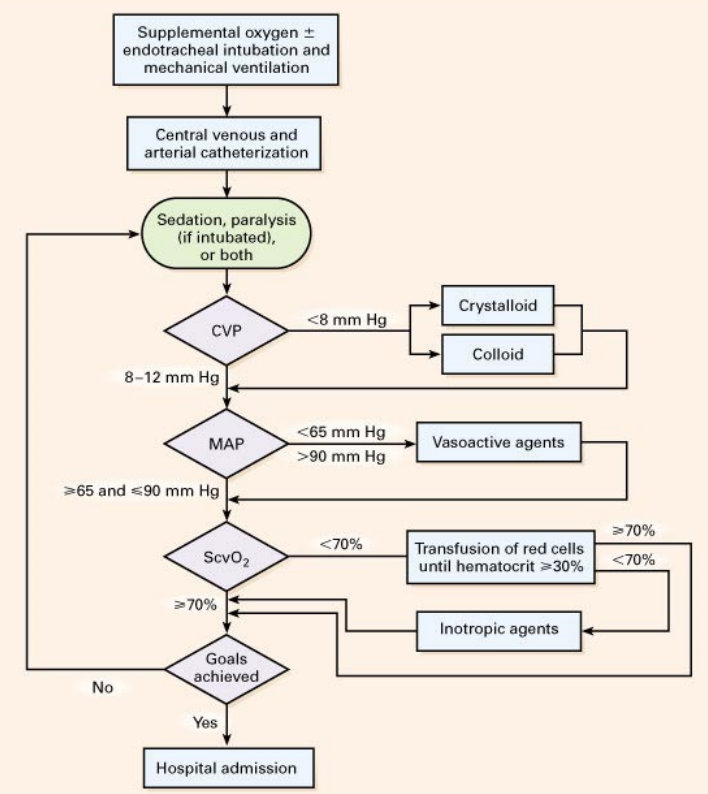
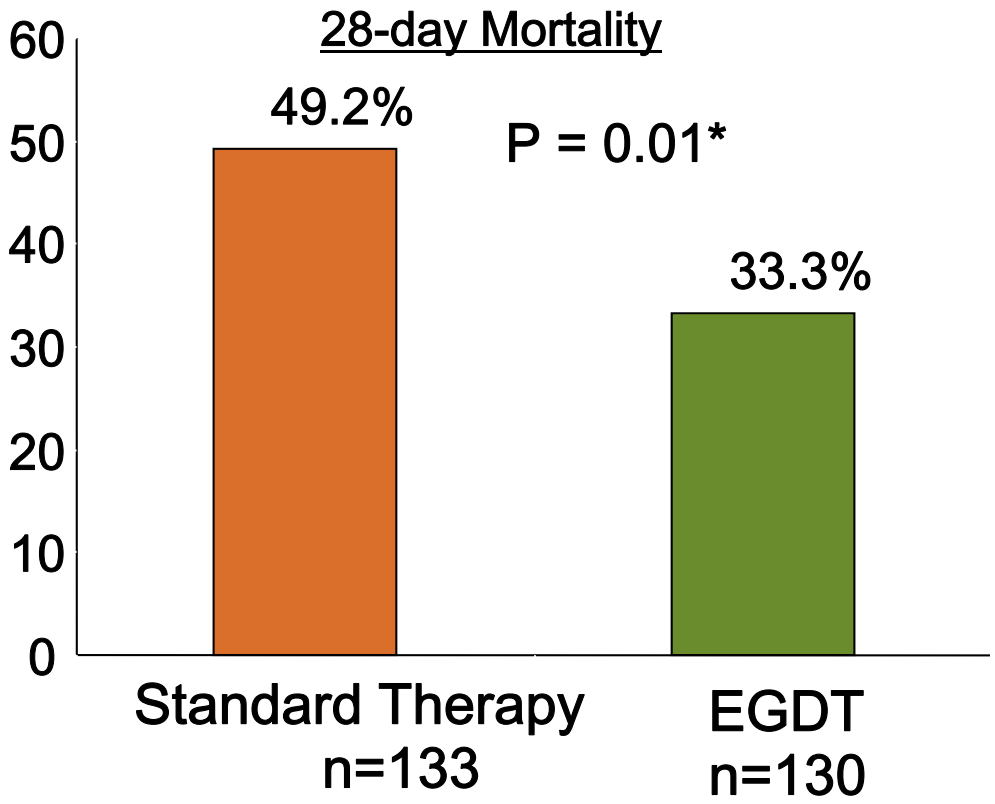
Why did CMS Choose These Targets?





Limitations

- Single center and a single group of investigators
- Is the whole protocol necessary?

N Engl J Med 2001;345:1368-77.

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The NEW ENGLAND JOURNAL of MEDICINE

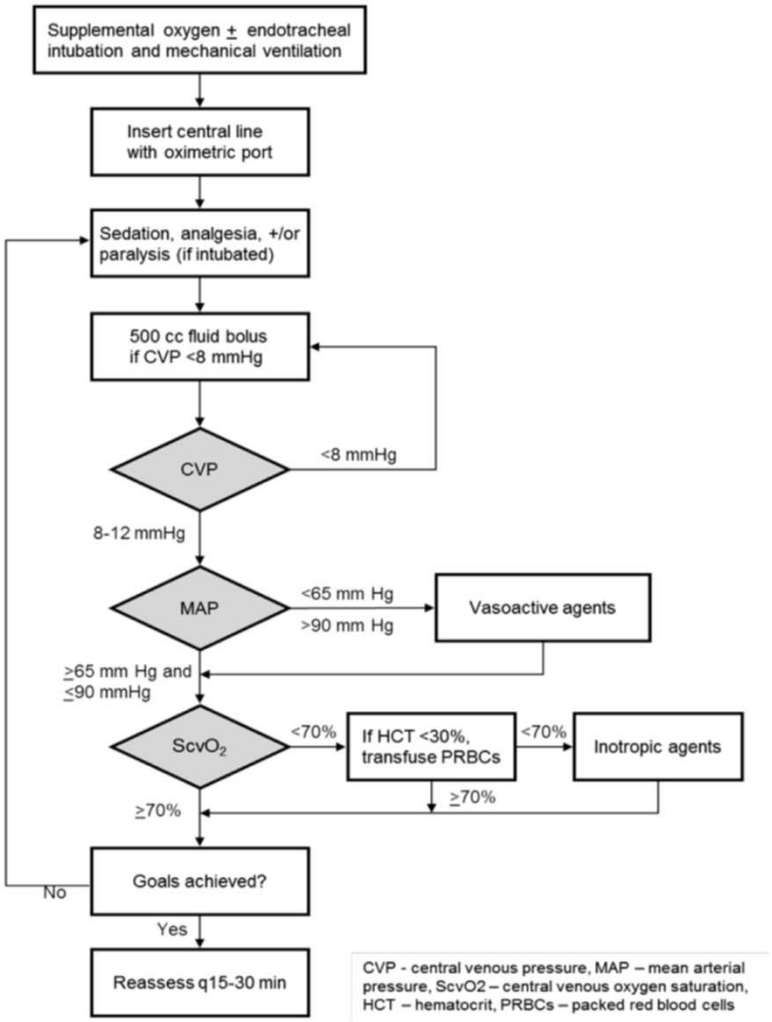
ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

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

The ProCESS Investigators*

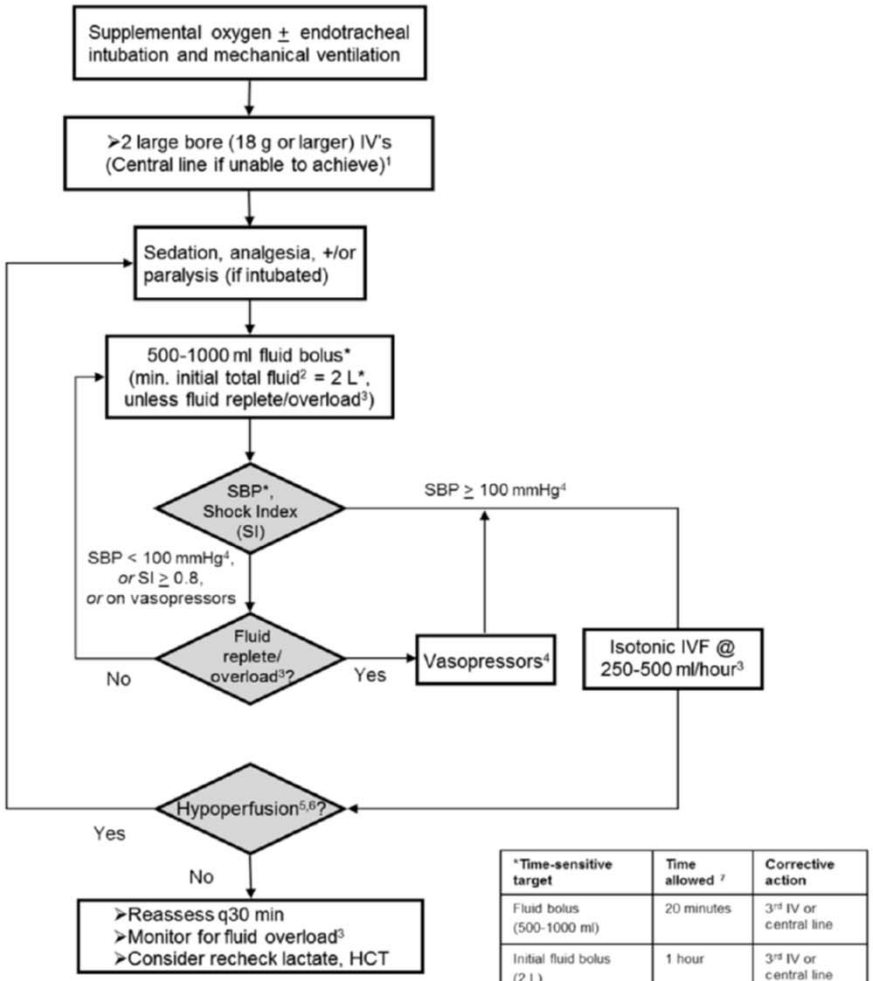
- 3 Arms (Rivers, “standard”, usual care)
- N = 1341 patients
- 31 ER departments
- Inclusion:
  - Sepsis suspected
  - >=2 SIRS criteria
  - Shock (BP < 90 after fluids or lactate > 4)

Figure S1. – Protocol for early goal-directed therapy (EGDT)



CVP - central venous pressure, MAP – mean arterial pressure, ScvO2 – central venous oxygen saturation, HCT – hematocrit, PRBCs – packed red blood cells

Figure S2. – Protocol for Standard Therapy.



*Time-sensitive target	Time allowed [7]	Corrective action
Fluid bolus (500-1000 ml)	20 minutes	3rd IV or central line
Initial fluid bolus (2 L)	1 hour	3rd IV or central line
SBP ≥ 100 mmHg	1 hour	Vasopressors

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What Did They Actually Do?

Table S4. – Resuscitation and processes of care from baseline to 72h.[a]

Intervention	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual care (N=456)	p-value[g]
Pre-randomization				
Intravenous fluids[b] – mL	2254 ± 1472	2226 ± 1363	2083 ± 1405	0.15
Fluids per body weight (mL/kg)	30.5 ± 22.3	29.2 ± 19.1	28 ± 21	
Vasopressor use[c]	84 (19.1)	75 (16.8)	69 (15.1)	0.28
Dobutamine use	0 (0)	0 (0)	0 (0)	
Blood transfusion	5 (1.1)	7 (1.6)	9 (2.0)	0.63
Mechanical ventilation	60 (13.7)	65 (14.6)	63 (13.8)	0.93
Intravenous antibiotics	332 (75.6)	343 (76.9)	347 (76.1)	0.91
Corticosteroids	41 (9.3)	42 (9.4)	38 (8.3)	0.82
Activated protein C	0 (0)	0 (0)	0 (0)	
Randomization to hour 6[d]				
Resuscitation elements				
Central venous catheterization	411 (93.6)	252 (56.5)	264 (57.9)	<0.0001
Central venous oximeter catheterization[e]	409 (93.2)	18 (4.0)	16 (3.5)	<0.0001
Intravenous fluids – mL	2805 ± 1957	3285 ± 1743	2279 ± 1881	<0.0001
Vasopressor use	241 (54.9)	233 (52.2)	201 (44.1)	0.003
Dobutamine use	35 (8)	5 (1.1)	4 (0.9)	<0.0001
Blood transfusion	63 (14.4)	37 (8.3)	34 (7.5)	0.001

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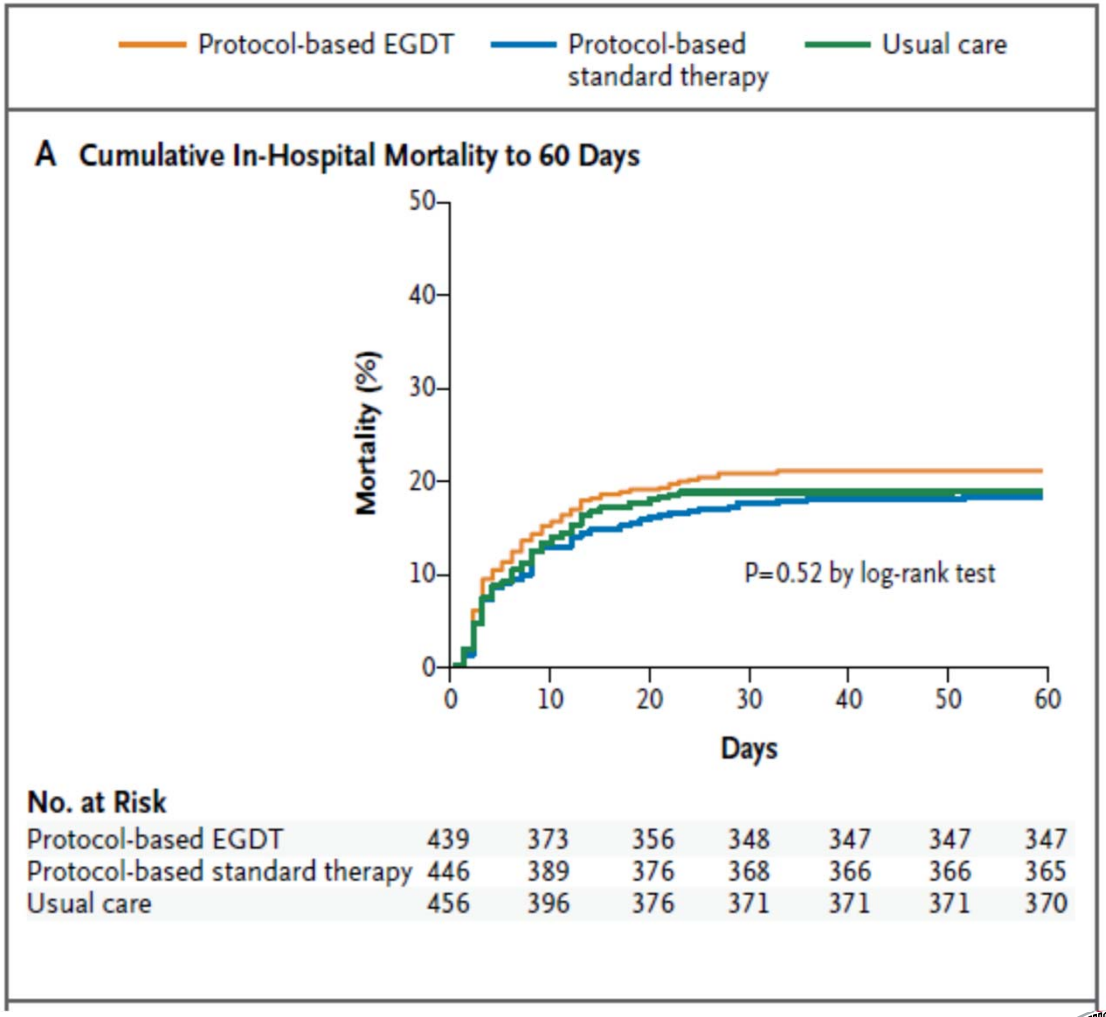
Did they help?



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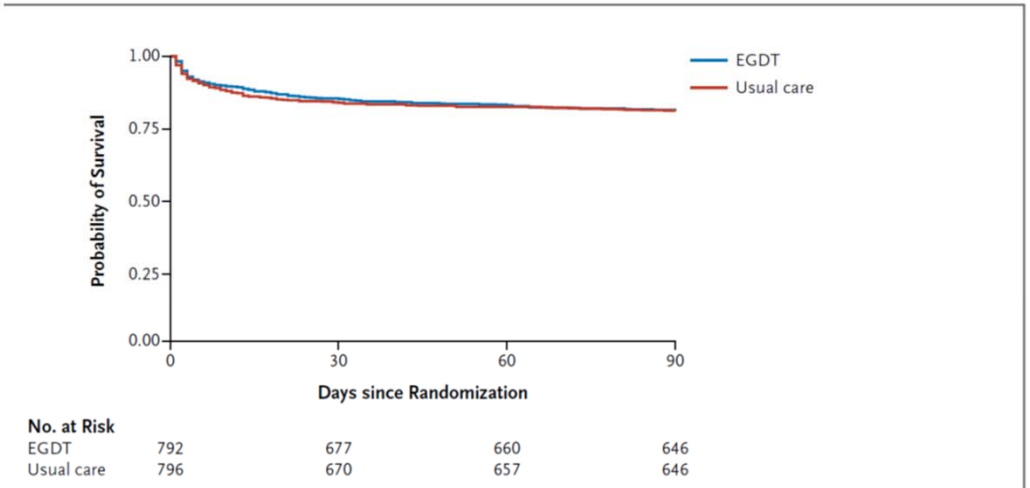
ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

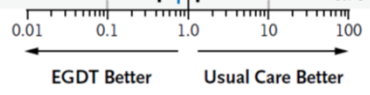
Are we sure EGDT doesn't work?

Pretty sure…



B Subgroup Analyses

Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Overall	147/792 (18.6)	150/796 (18.8)			
Country					0.38
Australia	126/677 (18.6)	132/679 (19.4)	0.95 (0.72–1.24)	0.70	
New Zealand	13/67 (19.4)	8/69 (11.6)	1.84 (0.71–4.76)	0.21	
Other	8/48 (16.7)	10/48 (20.8)	0.76 (0.27–2.13)	0.60	
Age					0.15
<65 yr	61/393 (15.5)	50/387 (12.9)	1.24 (0.83–1.85)	0.30	
≥65 yr	86/399 (21.6)	100/409 (24.4)	0.85 (0.61–1.18)	0.33	
APACHE II					0.98
<25	114/720 (15.8)	114/718 (15.9)	1.00 (0.75–1.32)	0.98	
≥25	33/72 (45.8)	36/78 (46.2)	0.99 (0.52–1.88)	0.97	
Invasive mechanical ventilation					0.25
Yes	19/71 (26.8)	23/64 (35.9)	0.65 (0.31–1.36)	0.25	
No	128/721 (17.8)	127/732 (17.3)	1.03 (0.78–1.35)	0.84	
Refractory hypotension					0.50
Yes	90/554 (16.2)	97/557 (17.4)	0.92 (0.67–1.26)	0.60	
No	57/238 (23.9)	53/239 (22.2)	1.11 (0.72–1.69)	0.65	
Hypofusion					0.27
Yes	99/365 (27.1)	93/369 (25.2)	1.10 (0.79–1.54)	0.55	
No	48/427 (11.2)	57/427 (13.3)	0.82 (0.55–1.24)	0.35	
IV fluid volume before randomization					0.41
≥20 ml/kg	106/574 (18.5)	104/572 (18.2)	1.02 (0.76–1.37)	0.90	
<20 ml/kg	28/181 (15.5)	35/181 (19.3)	0.76 (0.44–1.32)	0.33	



Really sure?

- PROMISE
- 1260 pts with septic shock in UK
- 90-day mortality
  - EGDT 29.5%
  - Usual Care 29.2%
- EGDT increased cost

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

N ENGL J MED 372;14 NEJM.ORG APRIL 2, 2015

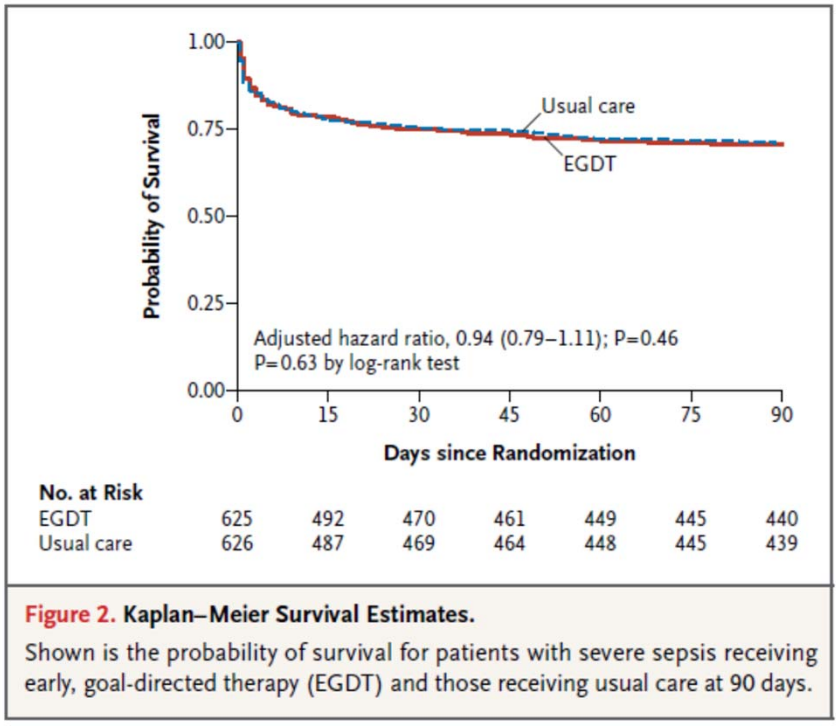


Figure 2. Kaplan–Meier Survival Estimates.
Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

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So EGDT Doesn't Work?

- Recent studies didn't demonstrate harm from EGDT, just a failure to demonstrate an improvement compared to our usual care
- Our usual care in 2015 reflects most of the principles demonstrated in the Rivers trial in 2000
- Resuscitation bundles for sepsis are essential, but likely clinician assessment of resuscitation can substitute for EGDT
  - CMS has now relaxed the requirement for CVP / ScvO2 from septic shock bundle

How are we going to maximize sepsis care?

- Focus on the patients, not the CMS bundle
- Identification is key
- Default to the best practice
  - Make it easy to do the right thing
- Guidance for clinicians
  - Order sets
  - Note template for sepsis

1st we need to recognize sepsis

- Early signs of sepsis
  - Fever or chills
  - Mental status changes (dizziness, confusion, or reduced consciousness)
  - Tachycardia
  - Tachypnea or short of breath
  - Reduction in urine output
  - Changes in blood pressure (high or low)
- Clock starts at the 1st signs of sepsis

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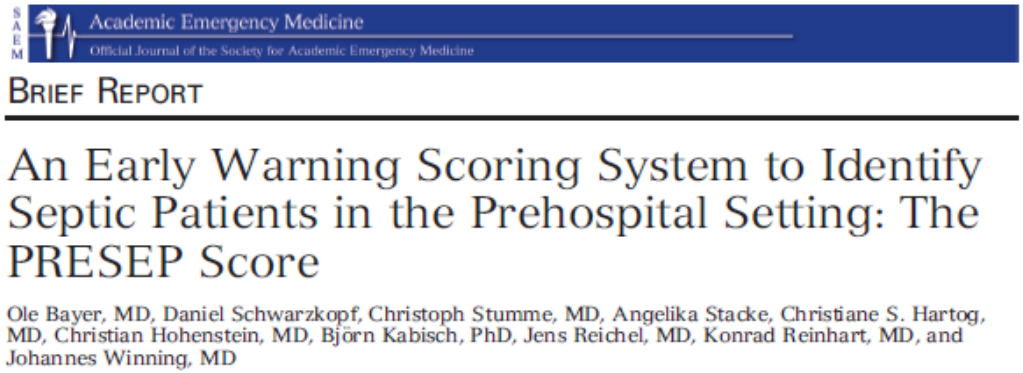
How to find sepsis outside of hospital?
PRESEP Score

Sign	Points
Fever	4
Hypothermia	1
HR > 90	2
RR > 22	1
SaO2< 92	2
SBP < 90	2
≥ 4 points has high likelihood of sepsis	



Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

BRIEF REPORT

An Early Warning Scoring System to Identify Septic Patients in the Prehospital Setting: The PRESEP Score

Ole Bayer, MD, Daniel Schwarzkopf, Christoph Stumme, MD, Angelika Stacke, Christiane S. Hartog, MD, Christian Hohenstein, MD, Björn Kabisch, PhD, Jens Reichel, MD, Konrad Reinhart, MD, and Johannes Winning, MD

How to find sepsis outside of ER?

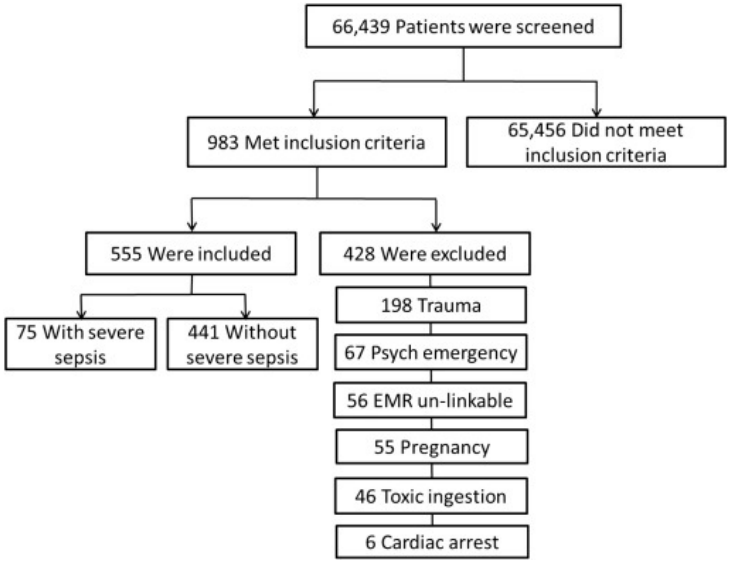


Table 7
Final predictive model

Final predictive model (n = 441)			
Predictor variable	Odds ratio	95% CL	*P*
Age (y), tertiles			
<40	Reference	–	–
50-59	4.28	1.20-15.38	.03
≥60	2.19	0.56-8.66	.26
Nursing home transport (Y/N)	4.73	2.01-11.13	<.001
EMD complaint: sick person (Y/N)	3.04	1.45-6.37	<.01
Hot tactile temperature (Y/N)	2.90	1.35-6.23	<.01
SBP, per 1-mm-Hg increase	0.96	0.93-0.99	<.01
O_2 saturation, per 1% increase	0.95	0.91-0.99	<.01

Abbreviations: CL, confidence limit; Y/N, yes/no.

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Prehospital recognition of severe sepsis: development and validation of a novel EMS screening tool☆

Carmen C. Polito, MD, MS [a,*], Alex Isakov, MD, MPH [b], Arthur H. Yancey II, MD, MPH [b], Duncan K. Wilson, MD [c], Blake A. Anderson, MD [d], Ingrid Bloom, MD [b], Greg S. Martin, MD, MS [a], Jonathan E. Sevransky, MD, MS [a]

Criteria:

- HR > 90
- RR > 20
- SBP<110

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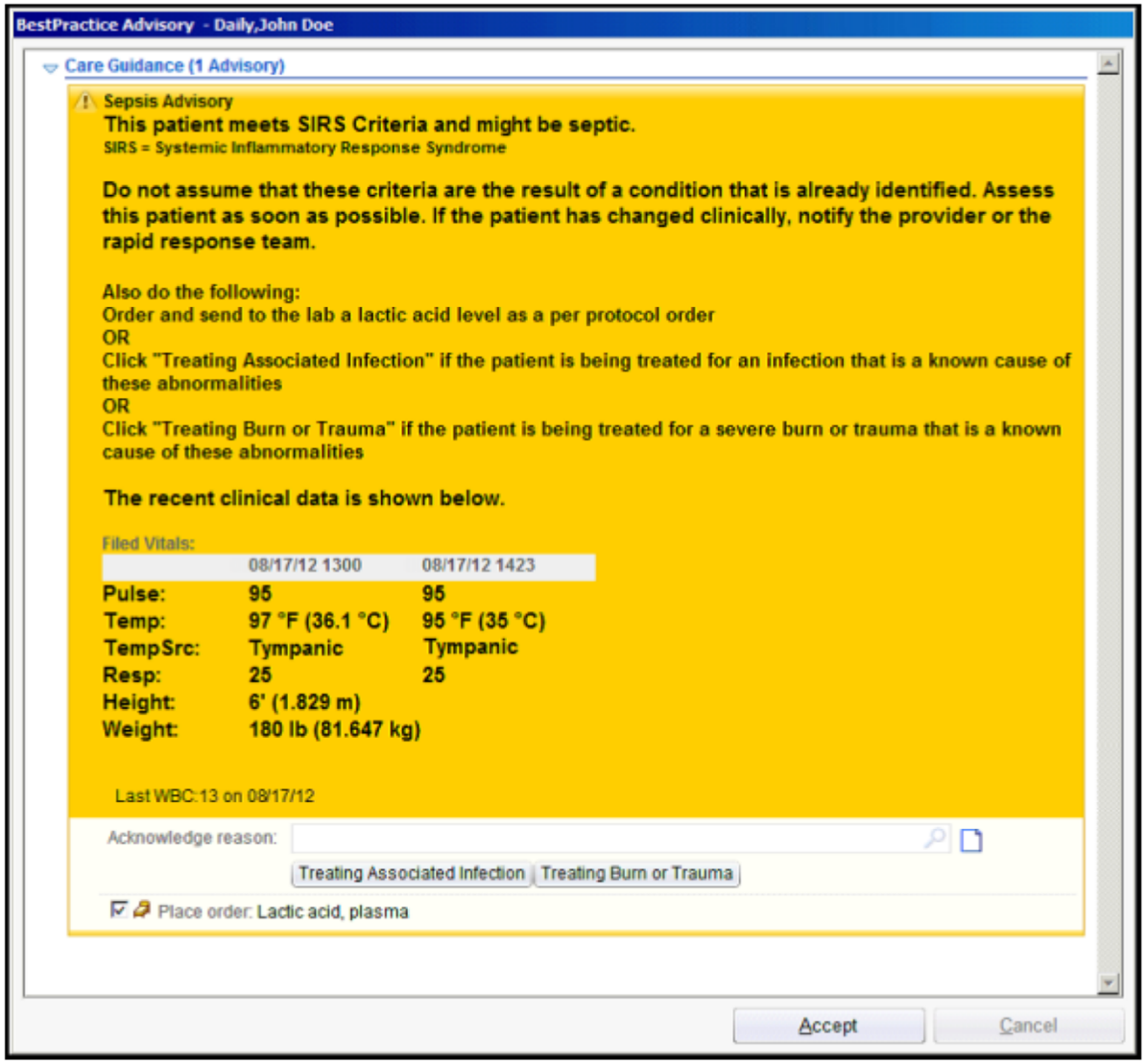
23

Can EMR Help Us?



- Sepsis Alert from EPIC
- Prompts treatment for infection and initial lactate

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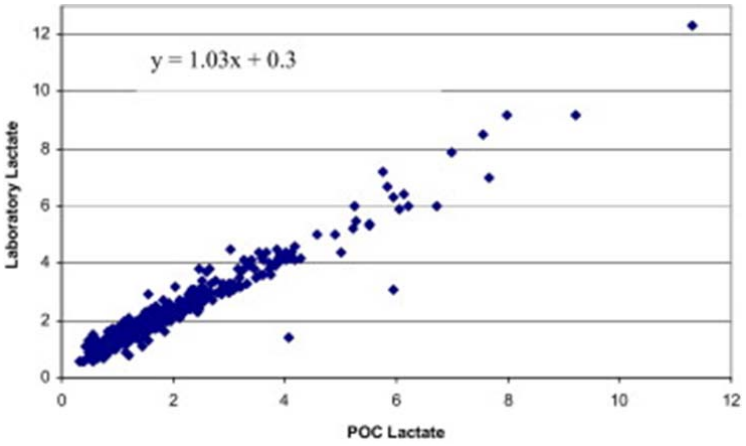
Why is measuring lactate so important?

- Septic Shock Defined as Hypotension or Lactate > 4 mmol/L

POC or lab lactate fine



Point-of-care lactate comparable with laboratory lactate level.

How does lactate help?

Lactate Group (mmol/L)	Compliant Lactate Measured ≤ 6 hr				Noncompliant Lactate Measured > 6 hr			
	No Hypotension		Hypotension		No Hypotension		Hypotension	
	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]	Total, *n* (Died *n*/%)	OR[a] (95% CI) [*p*]
≤ 2 (referent)	1,302 (301/23.1)	1.00	5,158 (1,423/27.6)	1.00	369 (109/29.5)	1.00	1,407 (417/29.6)	1.00
> 2 to ≤ 3	1,009 (242/24.0)	1.04 (0.87–1.24) [0.661]	3,241 (991/30.6)	1.16 (1.05–1.27) [0.002]	143 (46/32.2)	1.20 (0.94–1.52) [0.143]	613 (222/36.2)	1.33 (1.11–1.60) [0.002]
> 3 to ≤ 4	693 (158/22.8)	0.99 (0.80–1.21) [0.891]	2,274 (718/31.6)	1.21 (1.09–1.35) [< 0.001]	72 (27/37.5)	1.41 (1.06–1.88) [0.018]	356 (150/42.1)	1.73 (1.39–2.16) [< 0.001]
> 4	996 (289/29.0)	1.38 (1.16–1.65) [< 0.001]	5,272 (2,344/44.5)	2.10 (1.93–2.27) [< 0.001]	107 (55/51.4)	2.25 (1.78–2.85) [< 0.001]	719 (421/58.6)	3.42 (2.87–4.07) [< 0.001]

OR = odds ratio.

[a]Odds ratio based on generalized estimating equation population-averaged logistic regression model.

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[a]Odds ratio based on generalized estimating equation population-averaged logistic regression model.

What do we need to do when we find Severe Sepsis?

- Within 3 hours
  - Initial lactate
  - Blood cultures
  - Broad spectrum antibiotics
- Within 6 hours
  - Repeat lactate (if initial was elevated)

What do we need to do when we find Septic Shock?

- Within 3 hours
  - 30 cc/kg INITIAL FLUID bolus
- Within 6 hours (if hypotension / lactate elevated)
  - Start vasopressors
  - Repeat volume status / tissue perfusion check

IHIS Sepsis Order Set

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Give the Right Amount of Volume

240 ml

350 ml

591 ml

1000 ml

2645 ml

My Septic Need!!!

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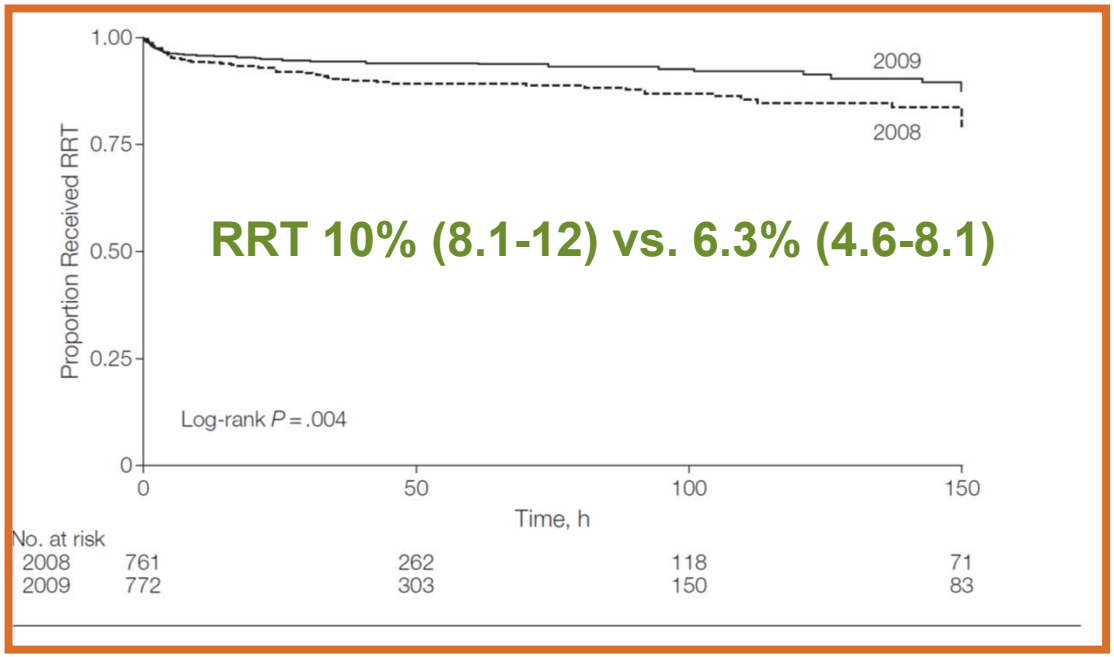
What Fluids Should I Give?

- Change Cl^--rich to Cl^--poor fluid
- Reduced AKI, ARF, and RRT
- No change to mortality or LOS improvement



1566 JAMA, October 17, 2012—Vol 308, No. 15

Cl^--rich: 0.9% saline, succinylated gelatin solution, or 4% albumin
Cl^--poor: lactated solution, Plasma-Lyte 148, or Cl^--poor 20% albumin

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What Fluids Should I Give? UPDATE!

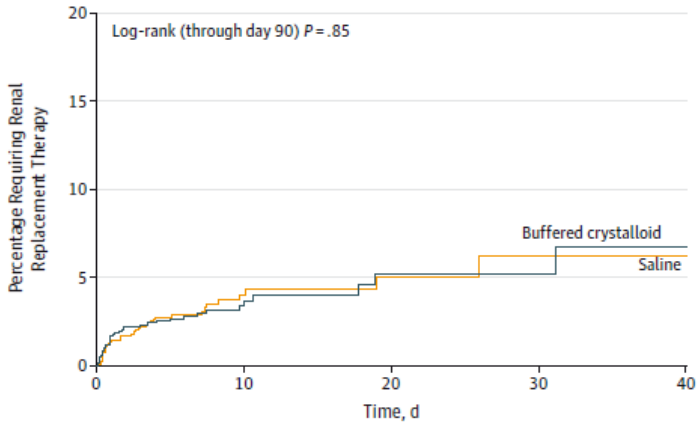
Normal Saline 0.9%

versus

Plasma-Lyte 148
(Buffered crystalloid)

- No difference in AKI or need for RRT

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial



No. at risk

Buffered crystalloid	1152	341	134	62	36
Saline	1110	310	124	64	28

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

JAMA 2015

What do I do if my patient is still in Shock?

- Reassess Volume Status
- What are you missing?
  - Reassess Antibiotics
  - Look for Source of Infection
    - Lines
    - Abscess
- Start Vasopressors

How do I assess volume?
The CMS Way

Exam by MD / APP with:

- VS
- Cardiopulm exam
- Cap refill
- Peripheral pulse eval
- Skin Exam

Documentation of 2 of the following:

- CVP
- Central venous oxygen
- Bedside CV ultrasound
- Passive Leg Raise or Fluid Challenge

Must be done within 6 hours is hypotension persists

What should I do if they are volume up?
Start Pressors (6 hours)

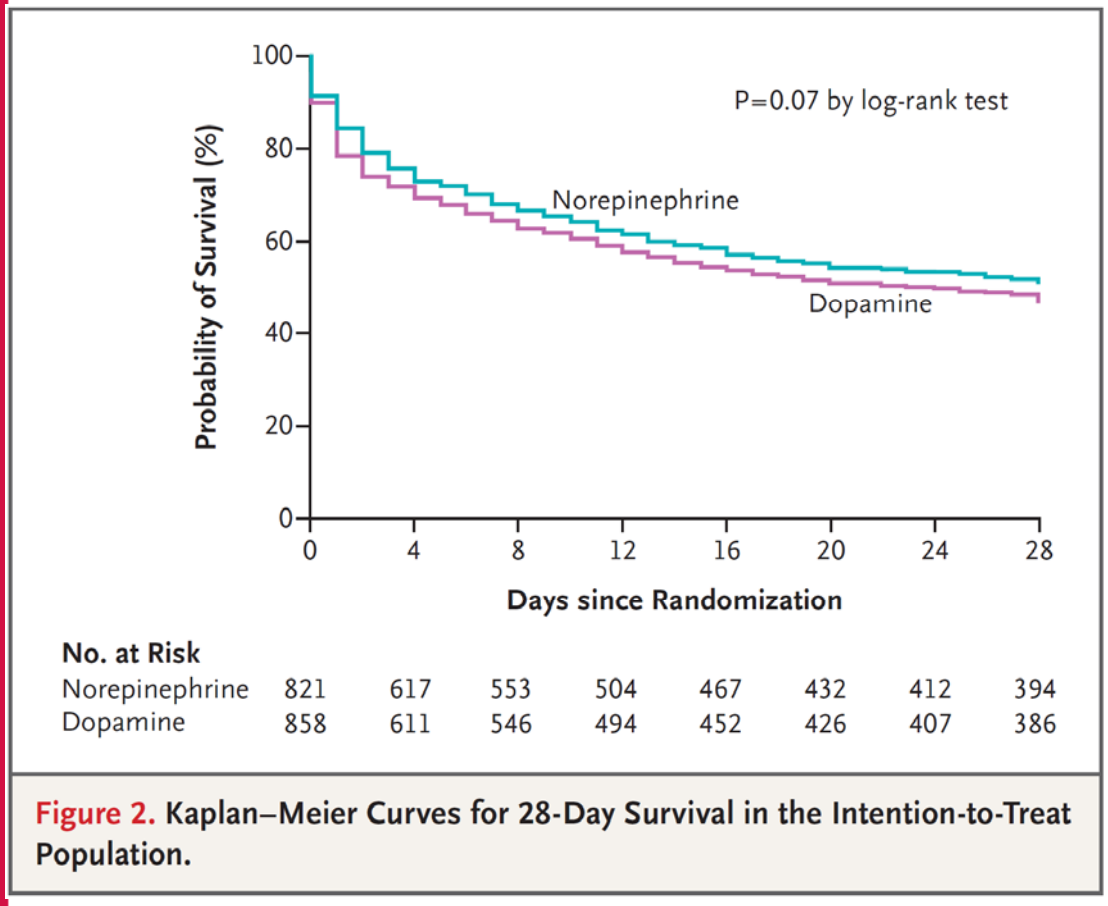
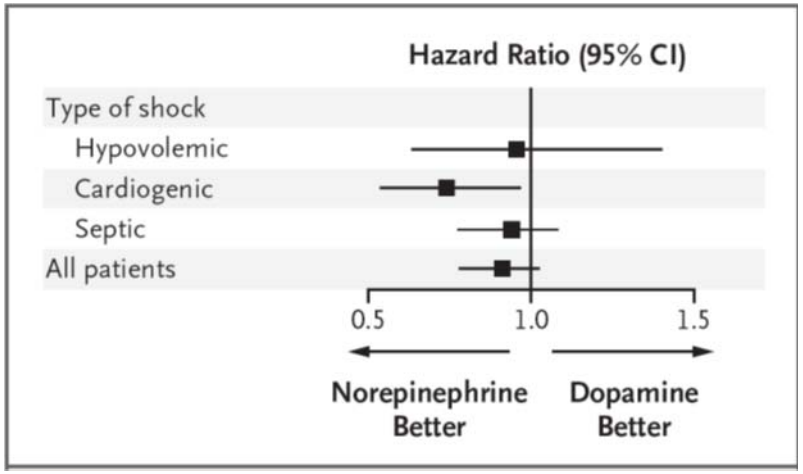


Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.



- Less tachycardia versus dopamine
  - May be better tolerated in cardiac patients

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So why do we use Norepinephrine?

TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

Norepinephrine compared with dopamine in severe sepsis

Patient or population: Patients with severe sepsis
Settings: Intensive care unit
Intervention: Norepinephrine
Comparison: Dopamine
Sources: Analysis performed by Djillali Annane for Surviving Sepsis Campaign using following publications: De Backer D. *N Engl J Med* 2010; 362:779–789; Marik PE. *JAMA* 1994; 272:1354–1357; Mathur RDAC. *Indian J Crit Care Med* 2007; 11:186–191; Martin C. Chest 1993; 103:1826–1831; Patel GP. *Shock* 2010; 33:375–380; Ruokonen E. *Crit Care Med* 1993; 21:1296–1303

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				
	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]	

[a]The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval, RR = risk ratio.
[b]Strong heterogeneity in the results ($I^2 = 85\%$), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.
[c]Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.

Is it safe to give pressors through IV?

shm Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

ORIGINAL RESEARCH

Safety of Peripheral Intravenous Administration of Vasoactive Medication

Jose Cardenas-Garcia, MD[1]*, Karen F. Schaub, BS[1], Yuly G. Belchikov, PharmD[2], Mangala Narasimhan, DO[1], Seth J. Koenig, MD[1], Paul H. Mayo, MD[1]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Hofstra North Shore–Long Island Jewish School of Medicine, Hempstead, New York; [2]Clinical Pharmacy Services, Department of Pharmacy, Westchester Medical Center, Valhalla, New York.

TABLE 4. Frequency, Highest Dose, and Complications of Vasoactive Medication Administered via PIV Access

Norepinephrine	
Interventions	506
Dose, μg/kg/min, mean ± SD	0.70 ± 0.23
PIV access extravasations	16
Dopamine	
Interventions	101
Dose, μg/kg/min, mean ± SD	12.7 ± 5.23
PIV access extravasations	3
Phenylephrine	
Interventions	176
Dose, μg/kg/min, mean ± SD	3.25 ± 1.69
PIV access extravasations	0

NOTE: **Abbreviations:** PIV, peripheral intravenous; SD, standard deviation.

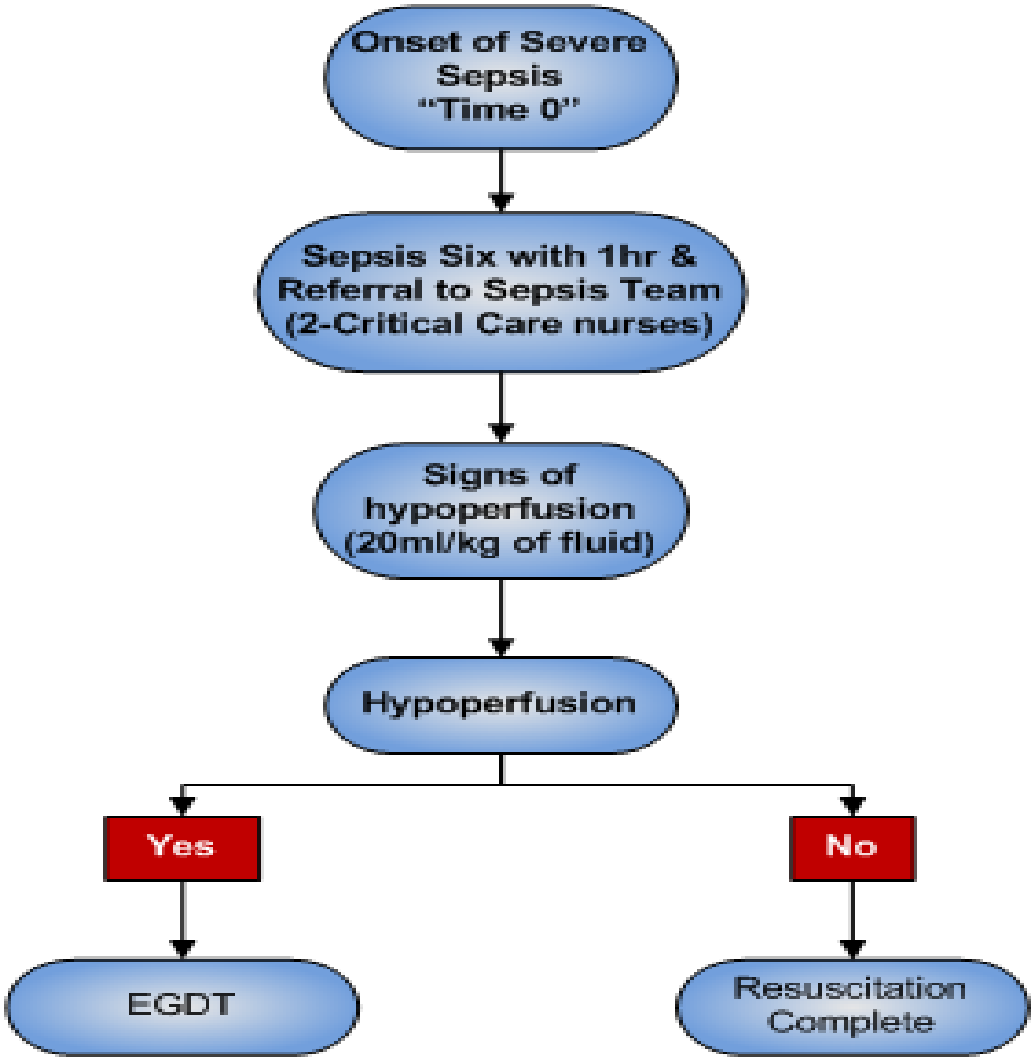
Sepsis Six and the Severe Sepsis Resuscitation Bundle

Daniels et. Al.

- Prospective observational cohort study-500 bed acute general hospital
- Assess the impact of the Surviving Sepsis Campaign resuscitation bundle (SSCRB) and the “sepsis six”
- Sepsis six (1hr of onset of severe sepsis)
    1. Deliver high flow oxygen
    2. Blood cultures
    3. Administer empiric antibiotics
    4. Start resuscitation fluids
    5. Measure serum lactate & complete blood count
    6. Accurate urine output measurement

Sepsis Six and the Severe Sepsis Resuscitation Bundle

Daniels et. Al.



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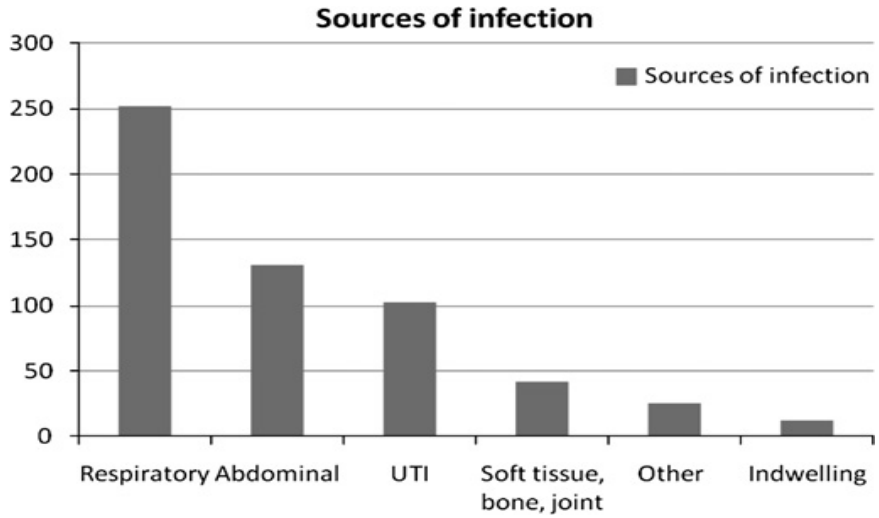
Sepsis Six and the Severe Sepsis Resuscitation Bundle

Daniels et. Al.

- 567 patients –eligible for Sepsis Six and SSCRB
  - Median modified early warning score (MEWS): 6 (0-15)
  - 71.7% (303/423) hypoperfused patients received fluid challenge
    - Shock reversed 65% of cases
  - Shock mortality 64.5% vs. 17.1%



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Sepsis Six and the Severe Sepsis Resuscitation Bundle

Daniels et. al.

- Sepsis team
  - Resuscitation bundle (72.9% vs. 23.4%, p<0.001)
  - Mortality (25.5% vs. 38.4%, p<0.001)

No Shock Cohort

Cohort	N (%)	Mortality day 28 (%)
No intervention	**192 (34)**	**23.3**
Resuscitation Bundle (RB) only	**18 (3.2)**	**11.1**
Sepsis Six + RB	**143 (25.3)**	**4.2**

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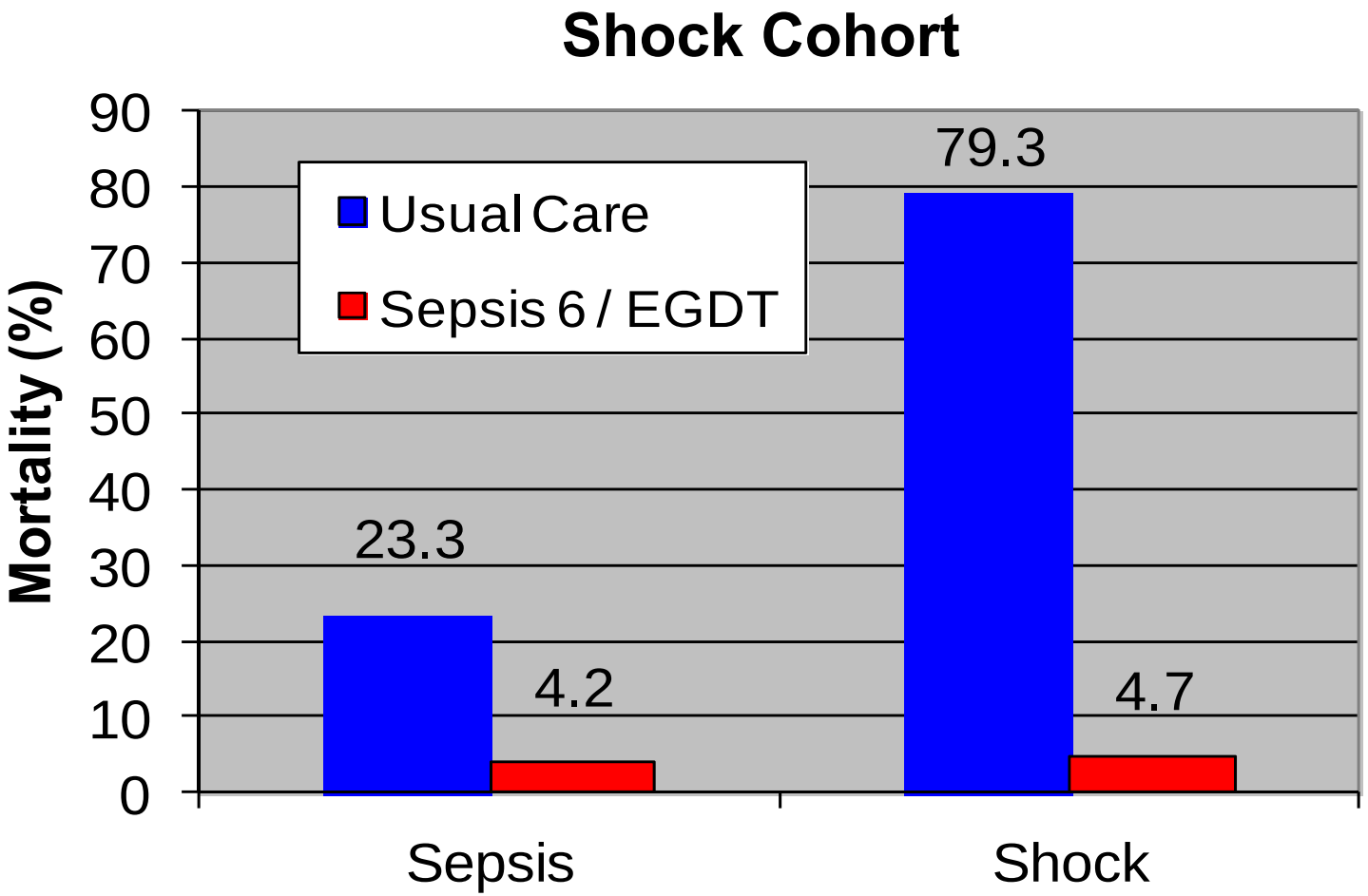
Emerg Med J 2011; 507-512

Sepsis Six and the Severe Sepsis Resuscitation Bundle

Daniels et. al.



Emerg Med J 2011; 507-512

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The Sepsis Six

- Prospective observational cohort
- Assess the impact of the Surviving Sepsis Campaign resuscitation bundle (SSCRB) and the “sepsis six”
- Sepsis six (1hr of onset of severe sepsis)

Table 5 Individual sepsis six interventions and outcomes

Therapy	Mortality when not achieved (%)	Mortality when achieved (%)	Frequency achieved (%)	p Value
High flow oxygen	43.1	31.8	74.3	0.014
Blood cultures	49.1	26.3	63.0	<0.0001
Antibiotics	45.4	28.1	61.6	<0.0001
Fluids	44.8	30.0	67.7	<0.0001
Lactate	43.4	30.9	69.1	0.004
Urine output	42.9	31.0	68.8	0.006

Emerg Med J 2011; 507-512

What can be done prior to ER?

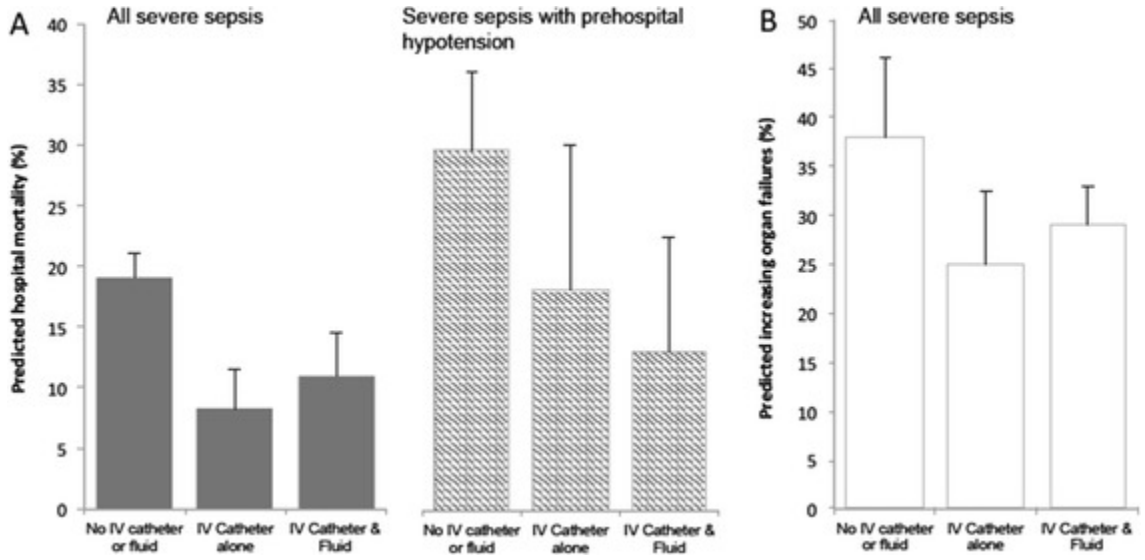
Seymour *et al. Critical Care* 2014, **18**:533
http://ccforum.com/content/18/5/533

CRITICAL CARE

RESEARCH Open Access

Prehospital intravenous access and fluid resuscitation in severe sepsis: an observational cohort study

Christopher W Seymour[1,2*], Colin R Cooke[3,4], Susan R Heckbert[5], John A Spertus[6], Clifton W Callaway[7], Christian Martin-Gill[7], Donald M Yealy[7], Thomas D Rea[8,9] and Derek C Angus[2,10]



Our Patient

- Worsening mental status and respiratory status
- Eventually weaned off non-invasive after 2 days

Could we do it better?

Next Day

- 64 yo status post K-P transplant presents with 1 day history of nausea / vomiting
- VS AF 123 80/40 22 SpO2 90% on room air
- Abdomen was distended and tender without rebound

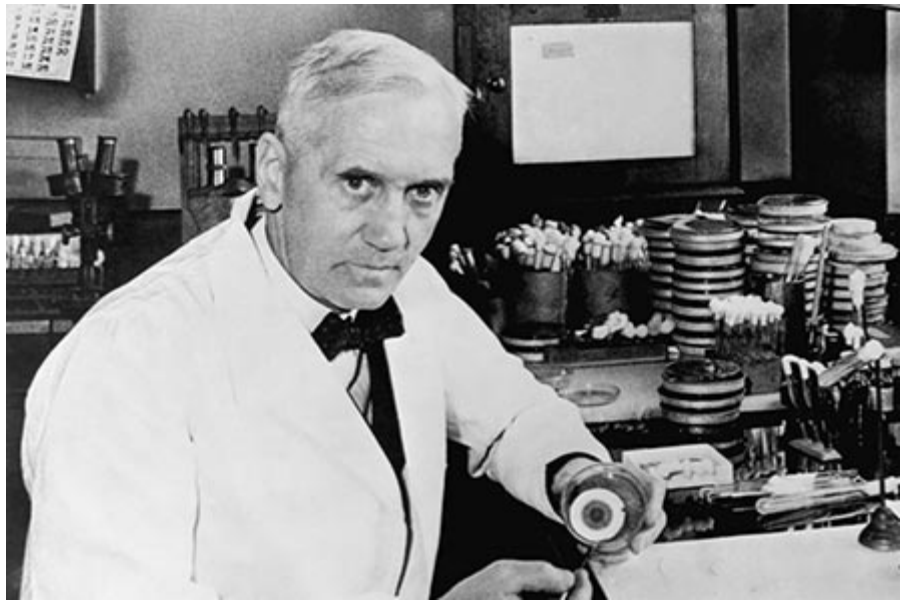
What did we do?

- Initial lab work revealed acute kidney injury
- Patient identified as a suspected infection
  - Antibiotics given within 1 hour of presentation
  - Lactate checked (2.2)
  - Blood cultures obtained
  - Surgery evaluated in ED (dx with partial SBO)
- Persistent given 2 liter initial bolus (close)
- Repeat lactate 2.4 (done for shock)
- Started on norepinephrine drip

How'd it turn out?

- Despite concern about his volume status, a total of 7 liters given in first 12 hours
- Clinical exam remained unchanged
- He never required more than 4 LPM of oxygen
- He was off pressors with improved renal function by the morning!

Questions?



"Everything you need to know about the treatment of sepsis you learned in 1928."

fake quote Alexander Fleming

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