Fluid Resuscitation and Monitoring in Sepsis

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Learning Objectives

- Compare and contrast fluid resuscitation strategies in septic shock
- Discuss available fluid resuscitation monitoring tools used to guide therapy
- Review literature surrounding protocol based sepsis management

Disclosures

- I have no conflicts of interest or disclosures as they relate to this presentation

Protocol Based Management is BETTER

CON Perspective

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

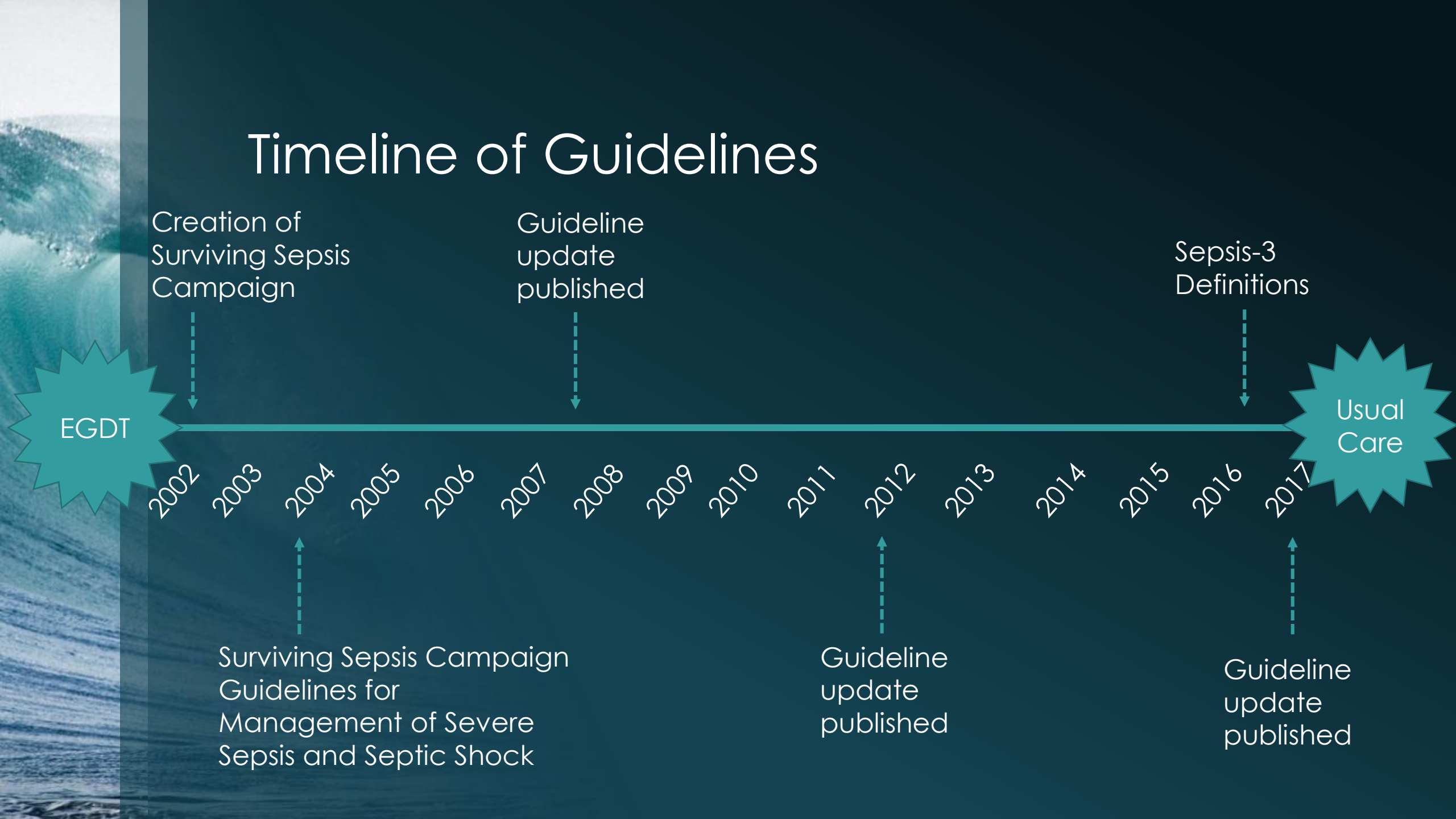
EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

- 2001 results published in NEJM
- Revolutionary 6-hour resuscitation bundle
  - Administration of intravenous fluids, vasopressors, inotropes, and red cell transfusions
- EGDT reduced hospital mortality by 26%
- Prompted world-wide adoption of EGDT

Sepsis Care Gold Standard

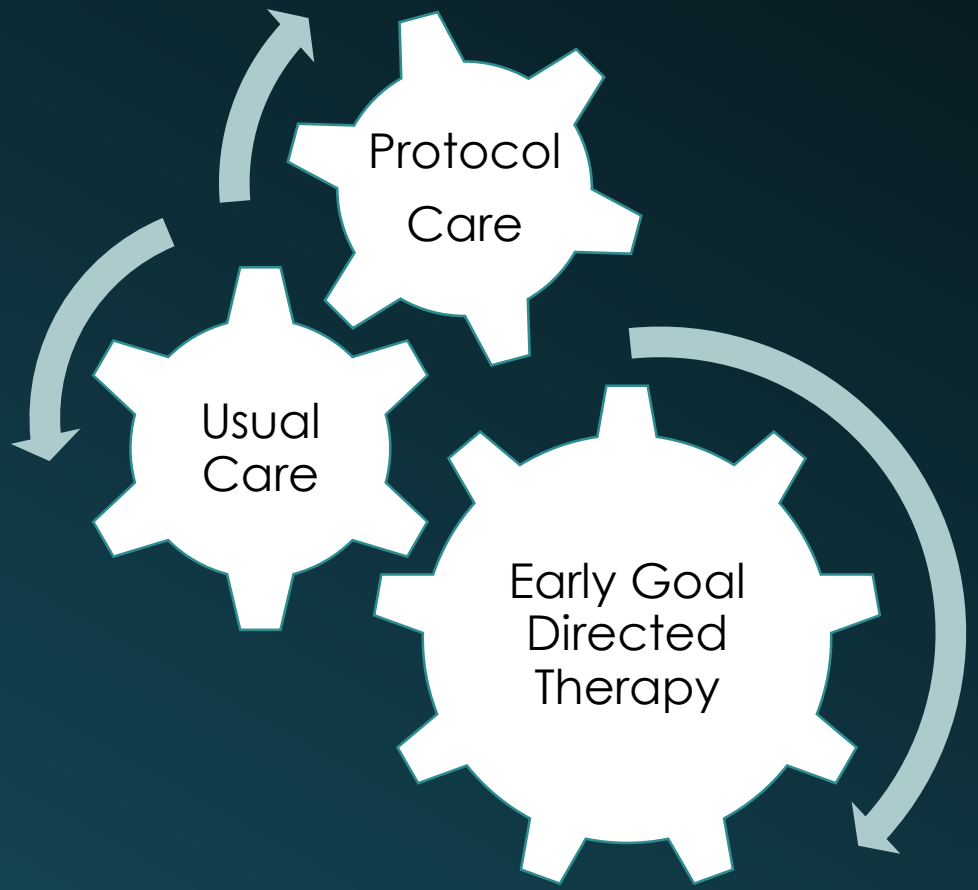
Rivers N Engl J Med. 2001; 345(19):1368-77

Timeline of Guidelines



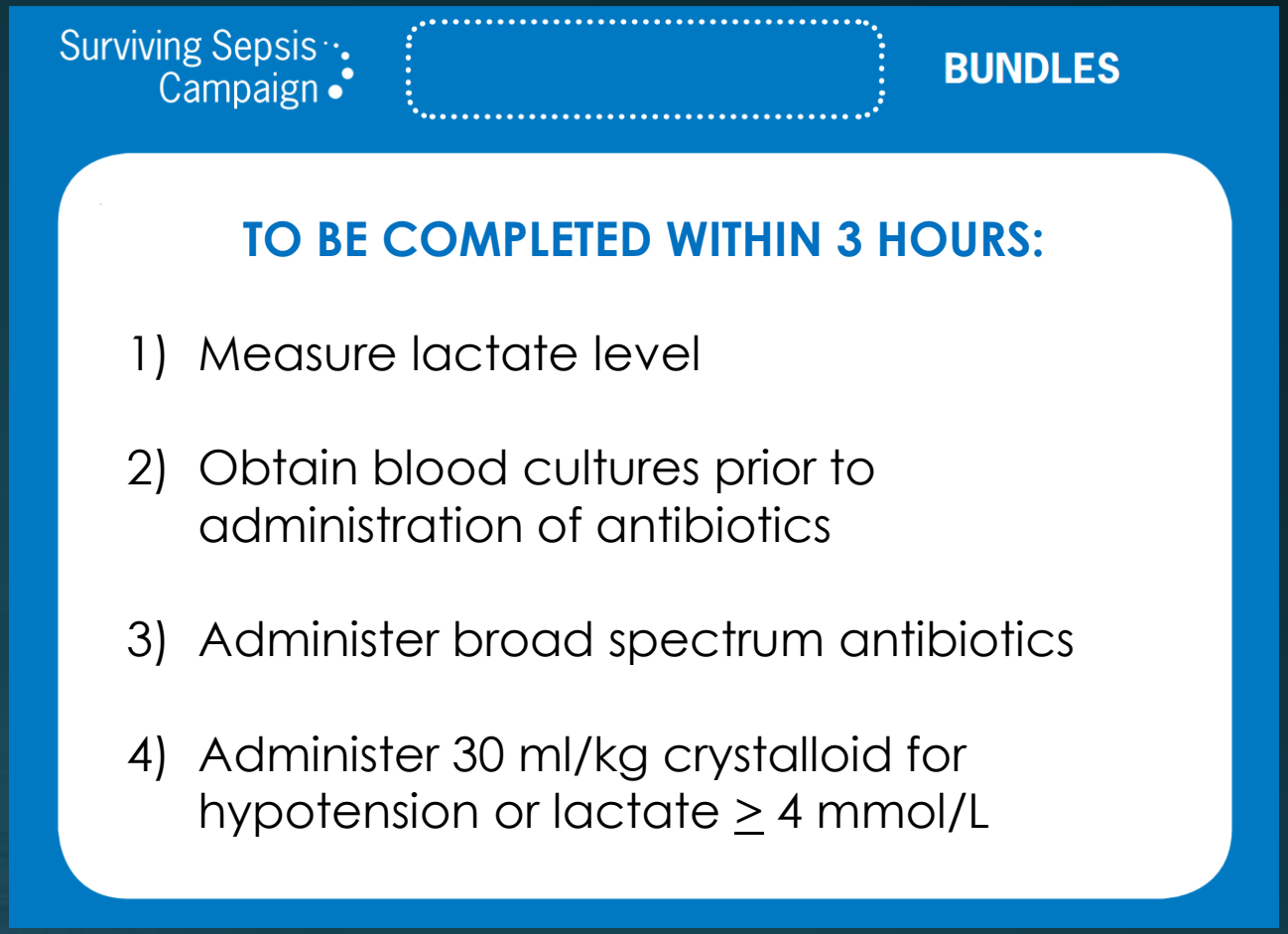
Early Goal Directed Therapy: A Concept

- EGDT provides us with a construct on how to understand resuscitation
  - **Start EARLY**
    - Detection and Risk Stratification
  - **Give ANTIBIOTICS**
    - Within the first hour
  - **Restore PERFUSION PRESSURE**
    - In some patients, a little more or less may be required!
- These concepts are still important today



Rivers N Engl J Med. 2001; 345(19):1368-77

3 Hour Bundles Emphasize EGDT



Singer M et al. JAMA. 2016; 315(8):801-10

Antimicrobials and Survival in Septic Shock

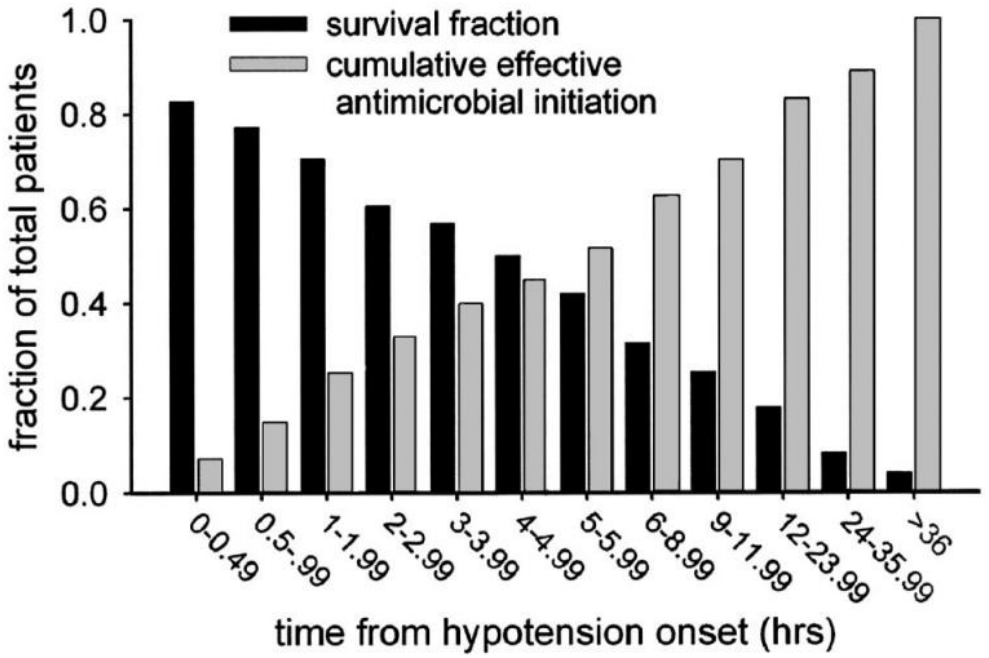


Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Kumar et al. Crit Care Med 2006. 34(6):1589-1596

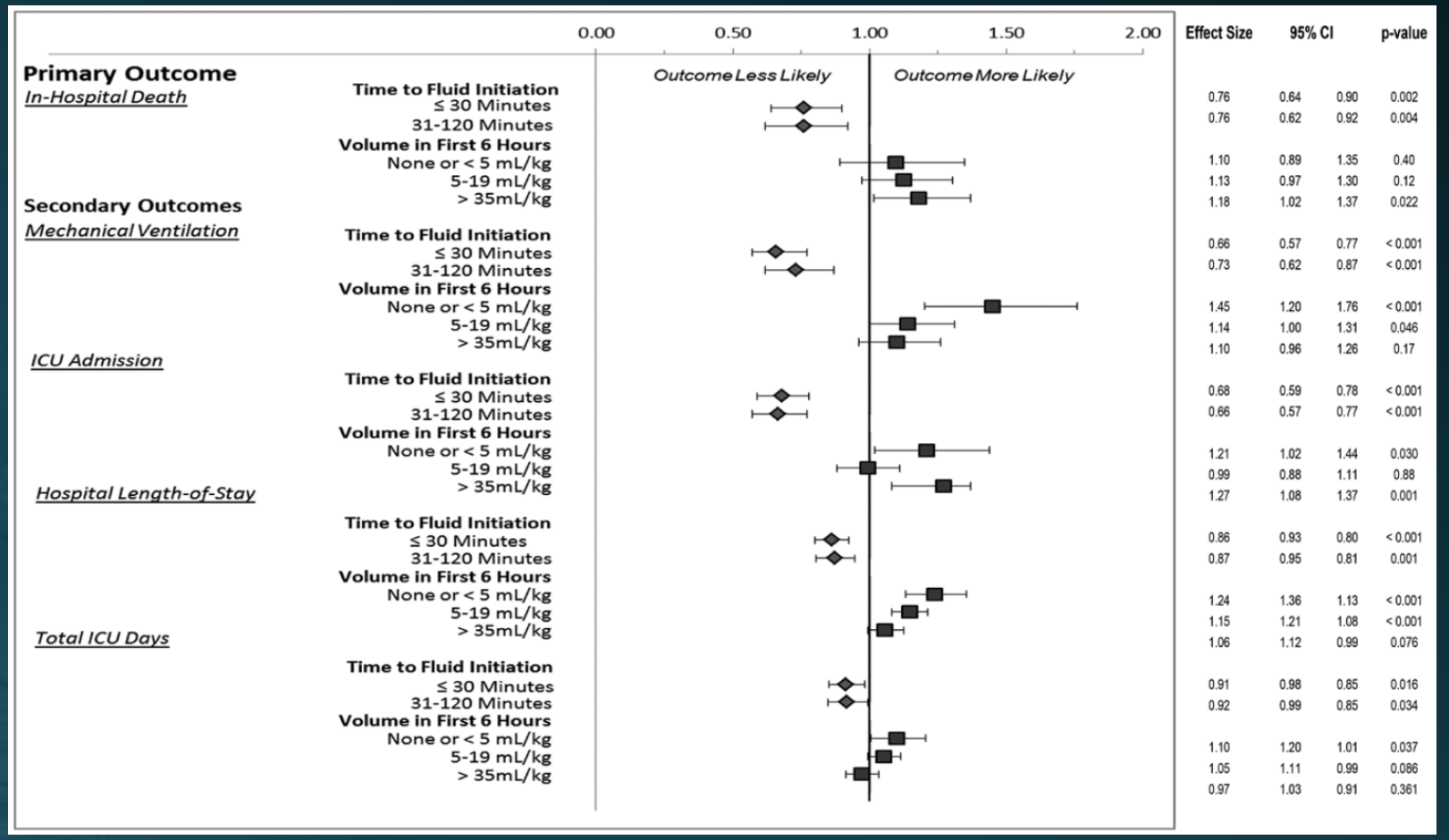
Patterns and Outcomes Associated With Timeliness of Initial Crystalloid Resuscitation in a Prospective Sepsis and Septic Shock Cohort*

Daniel E. Leisman, BS[1,2,3]; Chananya Goldman, MD[4]; Martin E. Doerfler, MD[4,5]; Kevin D. Masick, PhD[6]; 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]

- Examined the impact of timing of fluid resuscitation in 11,182 septic patients at 9 tertiary and community hospitals
- Fluid initiation in less than 30 and 31-120 minutes compared to > 120 minutes was associated with significantly lower:
  - Hospital mortality
  - Mechanical ventilation
  - ICU admission
  - ICU days
  - Hospital length of stay

Leisman et al. Crit Care Med 2017;45:1596-1606

Timeliness of Initial Crystalloid Resuscitation



Leisman et al. Crit Care Med 2017;45:1596-1606

Early Antimicrobials and Fluid

- EGDT set the stage for timely antibiotics and giving enough fluid

	RIVERS		ProCESS			ARISE		PROMISE	
	EGDT	Standard	EGDT	Protocol	Usual Care	EGDT	Usual Care	EGDT	Usual Care
Baseline IV fluids	20-30 mL/kg		30.5 mL/kg	29.2 mL/kg	28 mL/kg	34.6 mL/kg	34.7 mL/kg	1890 mL	1965 mL
mL Fluids administered 0 – 6 hours	4981 ± 2984	3499 ± 2438	2805 ± 1957*	3285 ± 1743*	2279 ± 1881*	1964 ± 1415*	1713 ± 1401*	2226 ± 1443	2022 ± 1271
Time to Antimicrobials	--	--	Time to randomization 187 min			70 minutes (38 -114)	67 minutes (39-110)	--	--
Antimicrobial administration	89% within 6 hours		76% pre-randomization 97% within 6 hours			100% pre-randomization		100% pre-randomization	
APACHE II	21.4	20.4	20.8	20.6	20.7	15.4	15.8	18	17
CVC	100%	100%	93.6%	56.5%	57.9%	90%	70.3%	92.1%	50.9%
Mechanical Ventilation 0-72	55.6%	70.6%	36.2%	34.1%	29.6%	22.2%	22.4%	27.4%	28.5%

Compliance with Protocols Improves Quality of Care

TABLE 2. Patient Clinical Characteristics Across Low- and High-Compliance Sites for Resuscitation Bundle

Characteristic	Low compliance resuscitation *n* = 11,609 (39.0%)		High compliance resuscitation *n* = 17,861 (61.0%)		Total *n* = 29,470		
	n	%	*n*	%	*n*	%	*p*[a]
Nosocomial infection	3,389	29.2	4,138	23.2	7,527	25.5	< 0.001
Septic shock	7,635	65.8	10,823	60.6	18,458	62.6	< 0.001
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	***p*[b]**
Sepsis severity score	58	42–74	51	36–67	53	37–69	< 0.001
Hospital LOS, days	15	7.4–29	12	6.4–23	13	6.8–26	< 0.001
ICU LOS, days	6.4	2.9–14	4.6	2.0–9.8	5.1	2.5–11	< 0.001
LOS prior to ICU, days[c]	0.28	0.05–2.2	0.17	0.04–1.1	0.2	0.05–1.4	< 0.001

Levy M, et al. Crit Care Med 2015; 43:3-12

Compliance with Protocols Improves Mortality

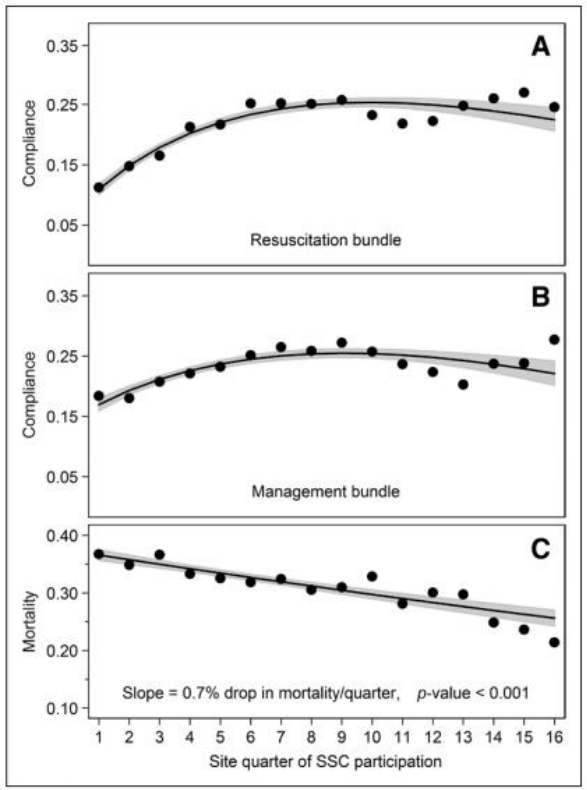


Figure 1. Resuscitation **(A)** and management **(B)** Surviving Sepsis Campaign (SSC) bundle compliance and hospital mortality **(C)**. All panels are based on an unadjusted generalized estimating equation population-averaged logistic regression model where circles represent observed values, lines are based on the regression, and shaded areas are the 95% CIs.

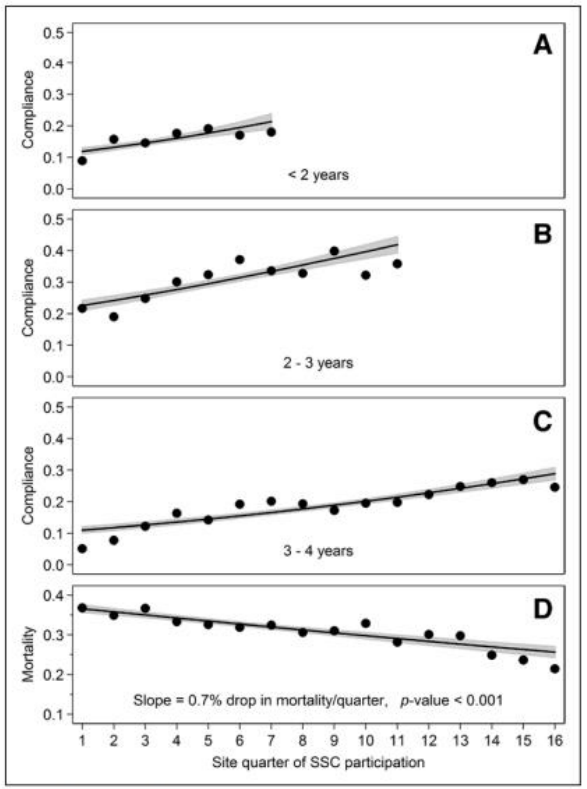
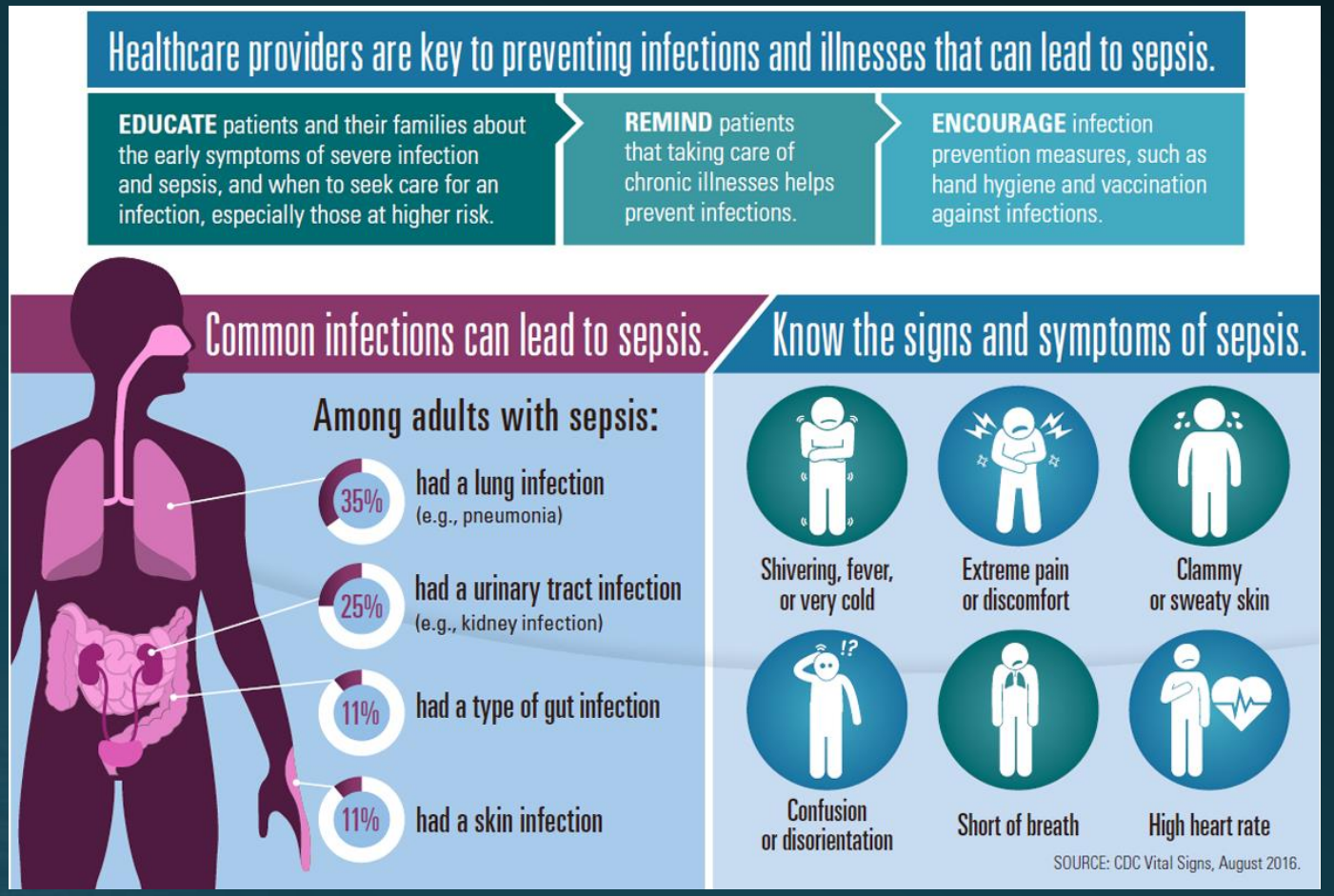


Figure 2. Resuscitation compliance by duration of years of Surviving Sepsis Campaign (SSC) participation (< 2 years, **A**; 2 to < 3 years, **B**; 3–4 years, **C**) and hospital mortality (panel **D**). All panels are based on an unadjusted generalized estimating equation population-averaged logistic regression model where circles represent observed values, lines are based on the regression, and shaded areas are the 95% CIs.

Levy M, et al. Crit Care Med 2015; 43:3-12

Early Detection and Risk Stratification



https://www.cdc.gov/vitalsigns/sepsis/index.html

Early Detection and Risk Stratification

- Early recognition and treatment decreases sepsis mortality
- Lack of recognition prevents timely therapy
- Utilize Surviving Sepsis Campaign bundles
- All of the trials to date have all utilized techniques for early detection

Levy M, et al. Crit Care Med 2015; 43:3-12
Guirgis FW et al. Journal of Critical Care 2017; (40)296-302

Early Identification

Systemic Inflammatory Response Syndrome (SIRS)

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- White blood cell count > 12000/mm^3 or < 4000/mm^3

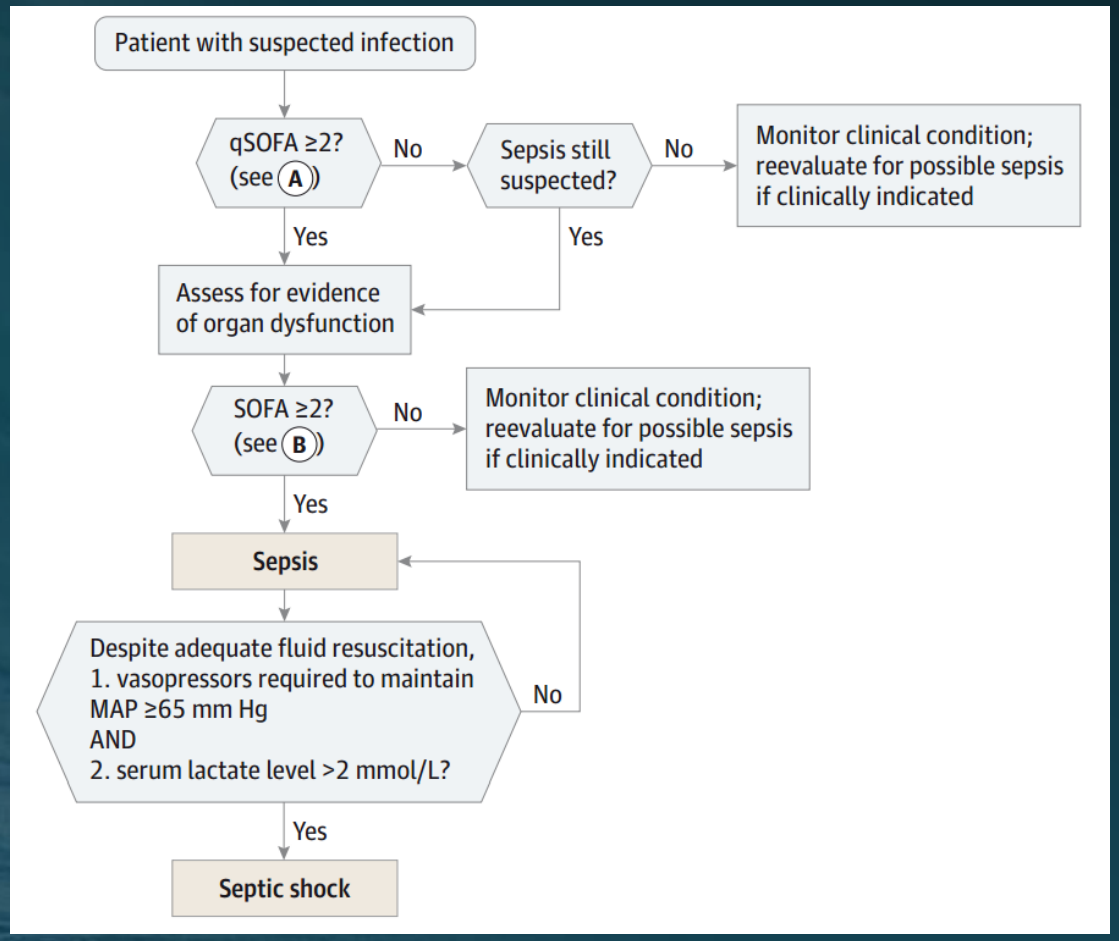
Quick SOFA (qSOFA)

- **H**ypotension (SBP ≤ 100 mmHg)
- **A**ltered mental status (GCS ≤ 13)
- **T**achypnea (RR ≥ 22 breaths/min)

qSofa ≥ 2

Bone RC et al. Chest. 1992;101(6):1644-55
Singer M et al. JAMA. 2016; 315(8):801-10

Early Risk Stratification



A qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables

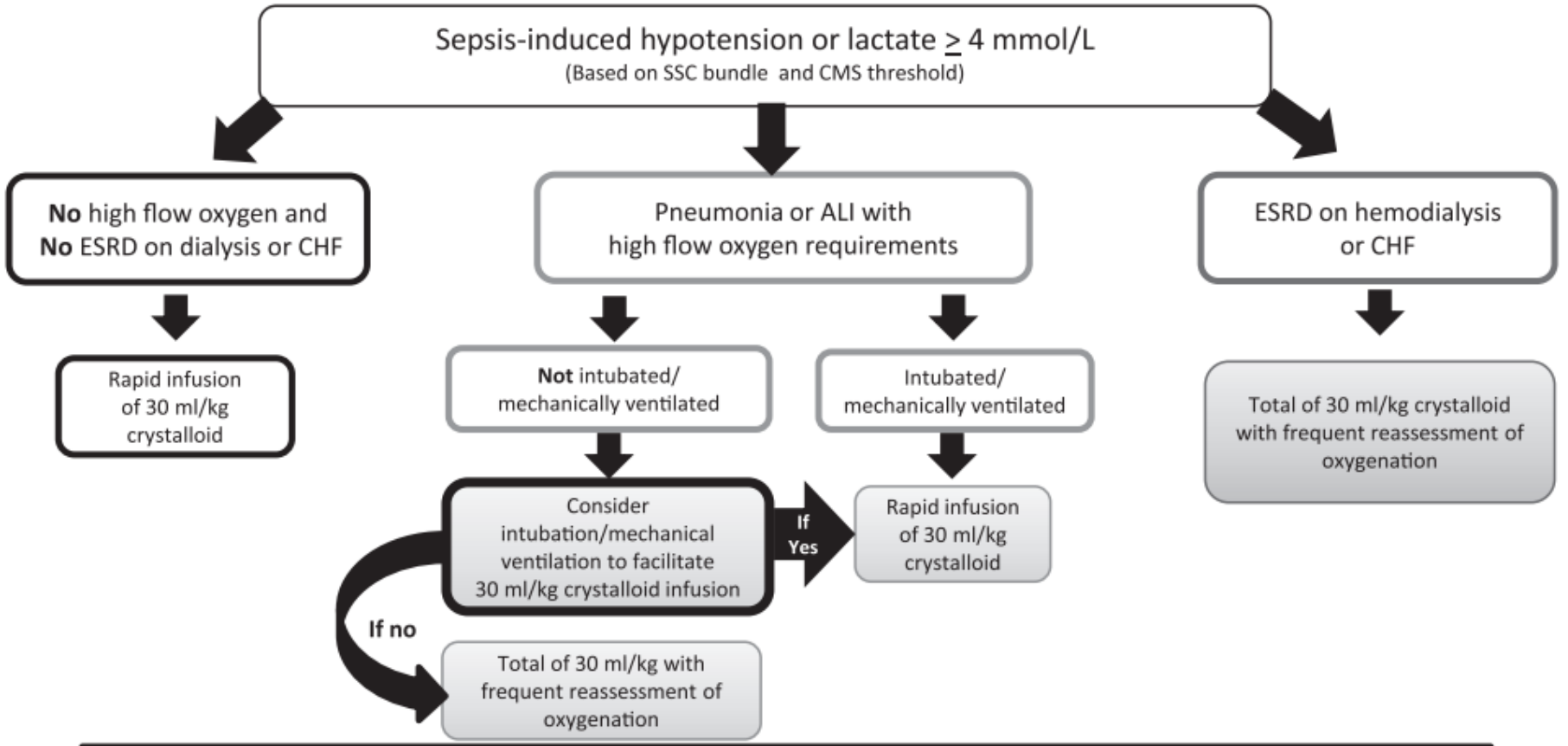
- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

Singer M et al. JAMA. 2016; 315(8):801-10

A New Chapter of EGDT Monitoring

Early Protocolized Interventions coupled with Targeted Goals

Application of Fluid Resuscitation in Adult Septic Shock



Considerations post 30ml/kg crystalloid infusion

1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize inte rstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
   - blood pressure/heart rate response
   - urine output
   - cardiothoracic ultrasound
   - CVP, ScvO2
   - pulse pressure variation
   - lactate clearance/normalization
   - dynamic measurement such as response of flow to fluid bolus or passive leg raising
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

Dellinger RP et al. Crit Care Med. 2017;45(3):381-5

Implement Combination of Monitoring

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Dellinger RP et al. Crit Care Med. 2017;45(3):381-5

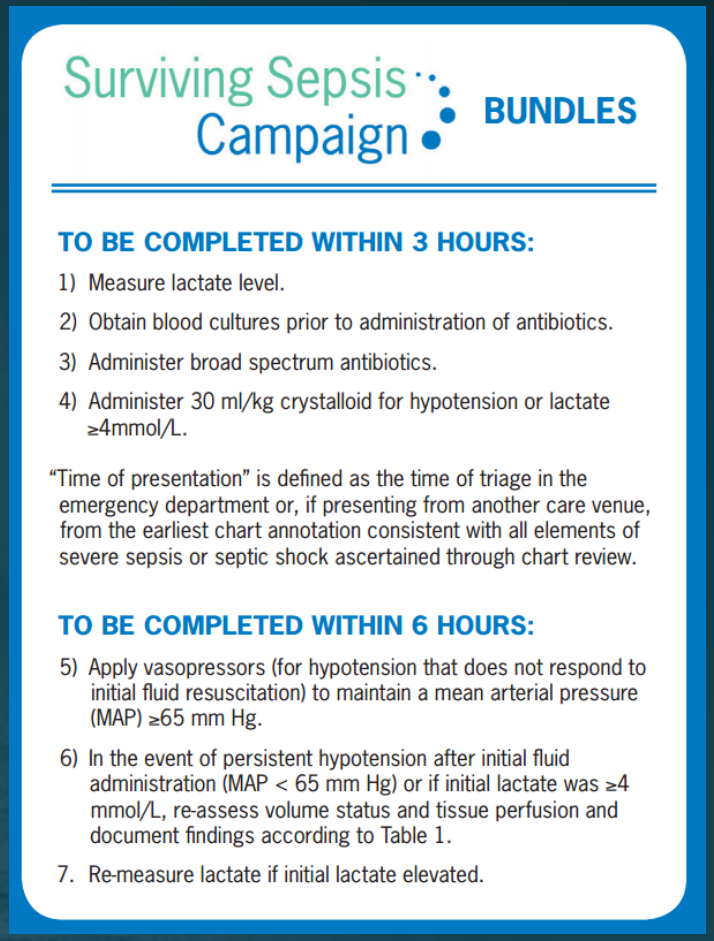
Intensity of Monitoring

- Minimalist Approach vs. Maximalist Approach

Static versus dynamic measures?

Vincent JL et al. Critical Care 2011, 15:220

Updated 6 Hour Bundles



Surviving Sepsis Campaign BUNDLES

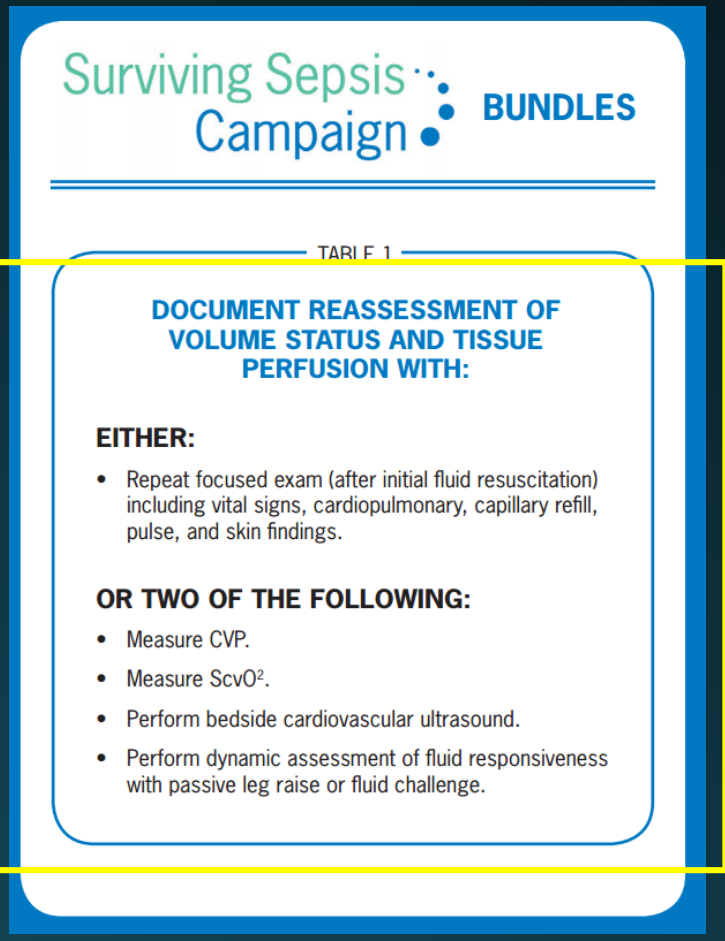
TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level.
2) Obtain blood cultures prior to administration of antibiotics.
3) Administer broad spectrum antibiotics.
4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L.

"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6) In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.



Surviving Sepsis Campaign BUNDLES

TABLE 1

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER:

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP.
- Measure $ScvO^2$.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

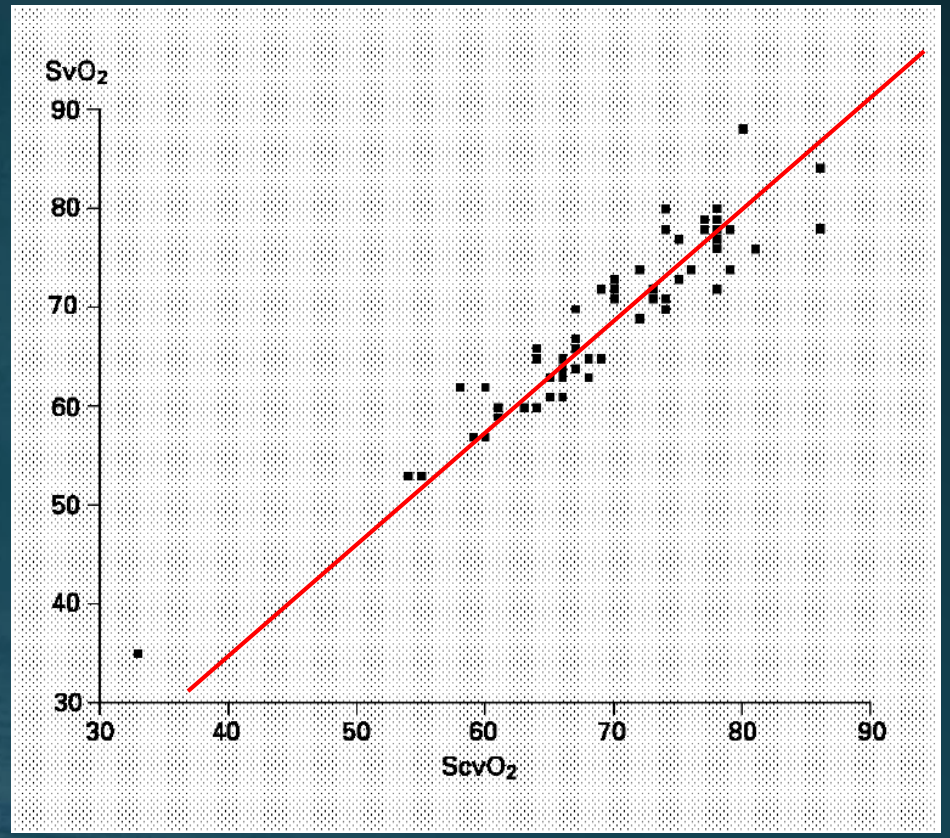
http://survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf

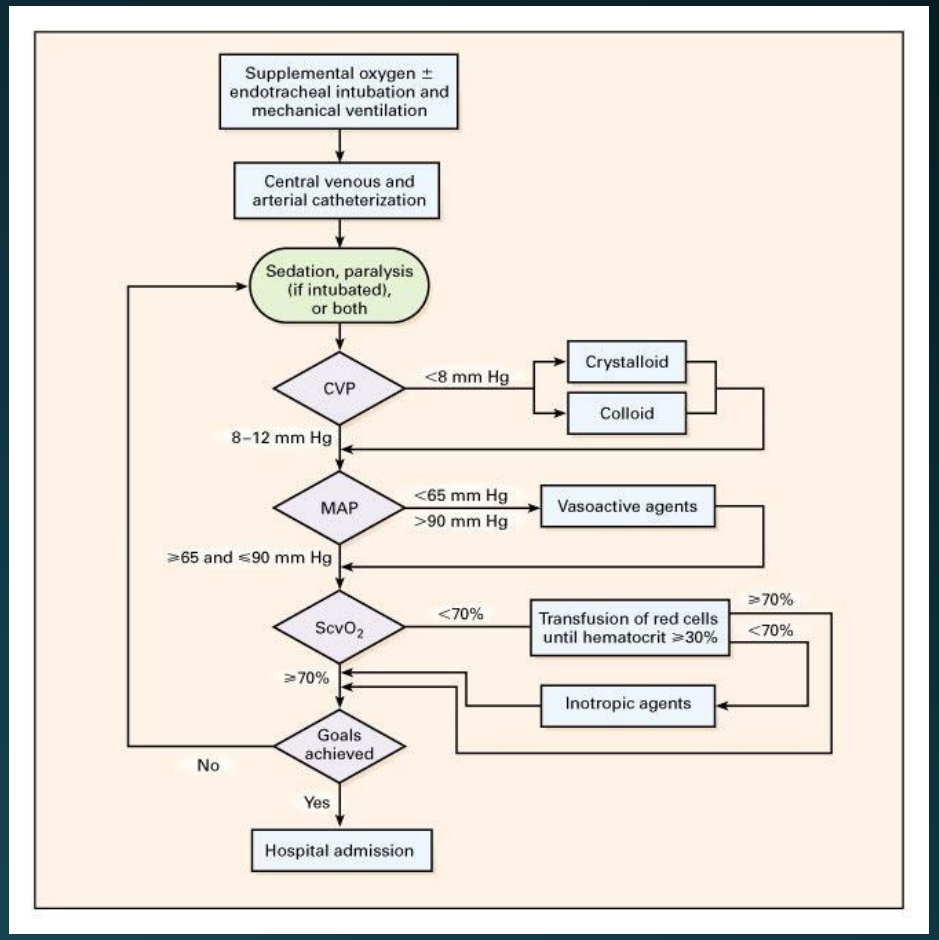
Benefits to the Central Line

- Optimal monitoring depends on the patient
- Invasive approach is often needed for initial evaluation of critically ill patient
- In addition to monitoring CVP and $S_{CV}O_2$, facilitates rapid administration of fluids
- CVC's still being utilized in > 50% of cases (despite being randomized to "usual care"), not just for obtaining $ScvO_2$

	RIVERS		ProCESS			ARISE		PROMISE	
	EGDT	Standard	EGDT	Protocol	Usual Care	EGDT	Usual Care	EGDT	Usual Care
CVC Placement	100%	100%	93.6%	56.5%	57.9%	90%	70.3%	92.1%	50.9%

$S_{cv}O_2$ vs SvO_2

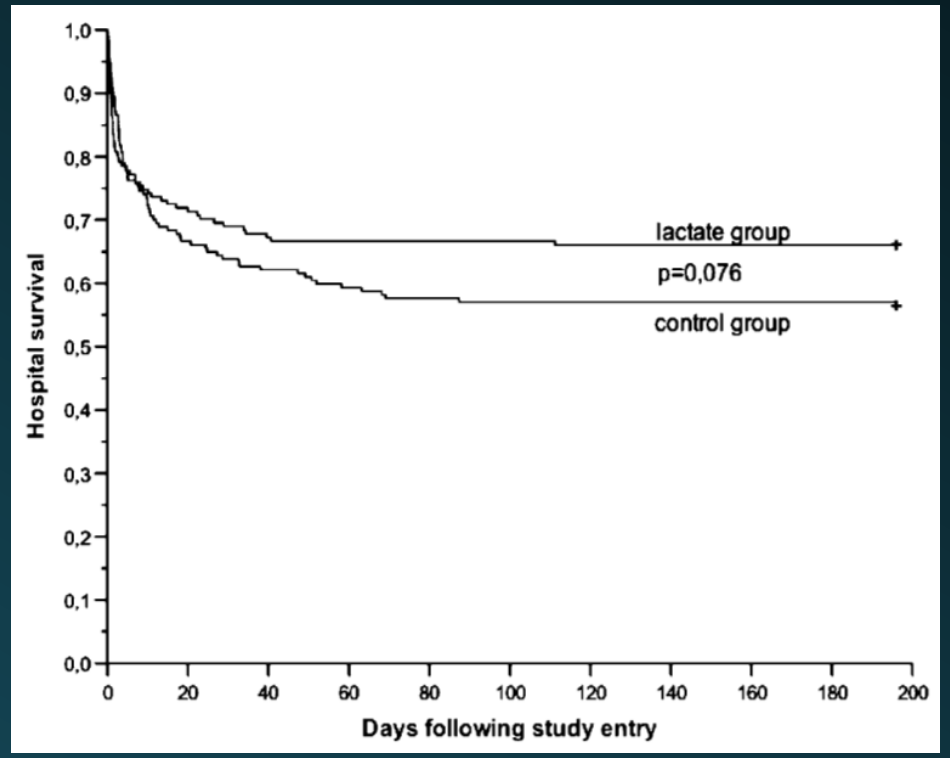




Ladakis et al. Respiration 2001;68:279

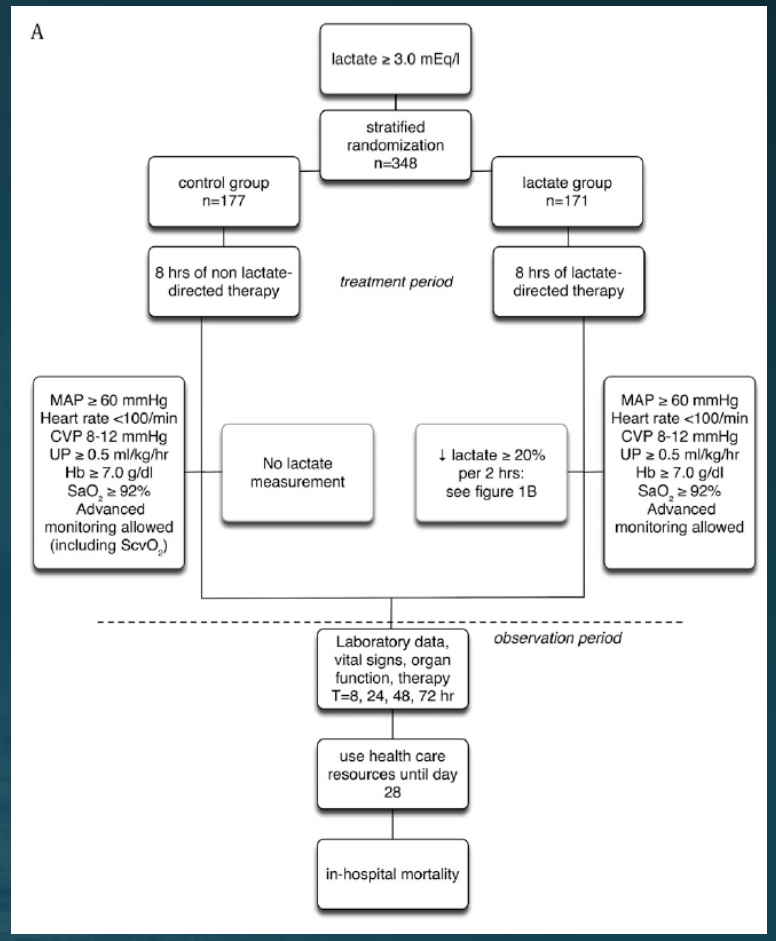
Early Lactate-Guided Therapy

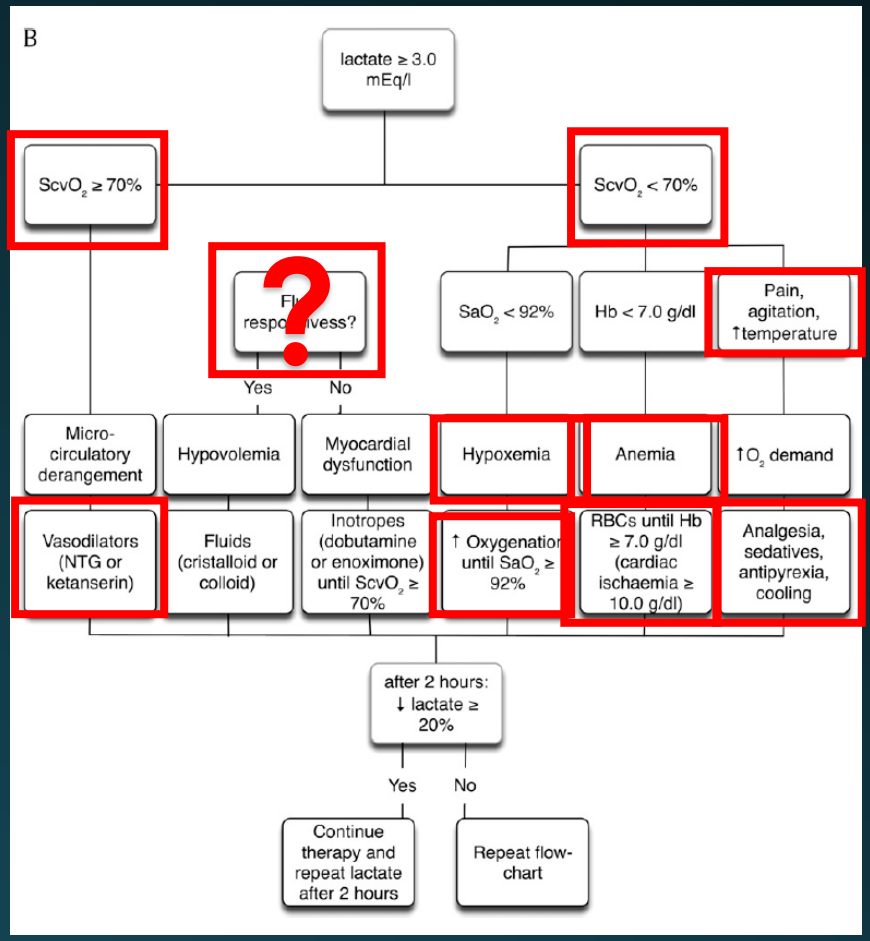
- Not a direct measure of tissue perfusion
- Objective surrogate for tissue perfusion
- Indicative of tissue hypoxia **AND** associated with worse outcomes AND standard laboratory test
- Significant reduction in mortality seen with lactate-guided resuscitation (RR 0.61; 95% CI, 0.43-0.87)



Jansen TC et al. Am J Respir Crit Care Med 2010;182:752-761

Protocol Management is Basic Critical Care Triage





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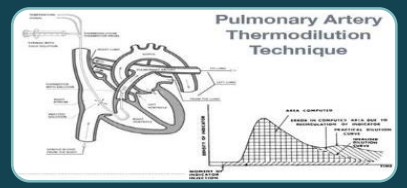
Monitoring Cardiac Output

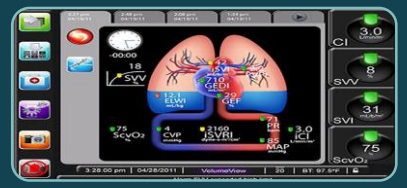


Thermodilution (pulmonary artery catheter)

- Provides simultaneous measurements of COP, PAP, SvO2
- Invasive

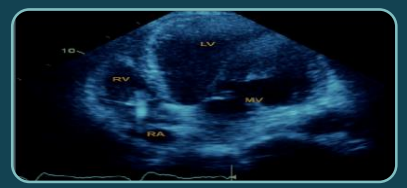
Transpulmonary or Ultrasound indicator dilution

- PiCCO, VolumeView, COstatus
- Less-invasive (may require CVC for calibration)



Arterial pressure trace-derived CO

- EV1000 (Vigileo), MostCARE
- Non-invasive but may be less accurate



Echocardiography or Transesophageal Doppler

- Non-invasive
- Requires training

Vincent et al. Critical Care 2011,15:229

Fluid Assessment: Ultrasound Utilization

- Echocardiography
  - Allows visualization of cardiac chambers, valves, and pericardium

Cardiac Abnormalities in Severe Sepsis
Left ventricular dilatation
Left ventricular contraction impairment Global Segmental
Left ventricular diastolic dysfunction
Right ventricle systolic/diastolic dysfunction
Ventricular outflow obstruction
Valvular lesions Functional Endocarditis

McLean Critical Care (2016) 20:275

Advanced Hemodynamic Monitoring Variability

Table 1 Physicians' personal opinion and attitude on advanced hemodynamic monitoring in circulatory shock

	Strongly disagree		Disagree		Neutral		Agree		Strongly agree		Total (*n*)
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	
Further hemodynamic assessment (e. g., assessment of cardiac output) is needed to determine the type of shock if no clear clinical diagnosis of the type of shock can be made	2	1	15	5	18	6	58	20	191	67	284
Echocardiography is helpful to determine the type of circulatory shock	2	1	0	0	1	0	6	2	275	97	284
Pulmonary artery catheterization is helpful in making a differential diagnosis in complex patients with circulatory shock	24	9	79	28	54	19	92	33	34	12	283
Transpulmonary thermodilution is helpful in making a differential diagnosis in complex patients with circulatory shock	8	3	15	5	36	13	102	36	123	43	284

Saugel et al. Med Klin Intensivmed Notfmed 2017

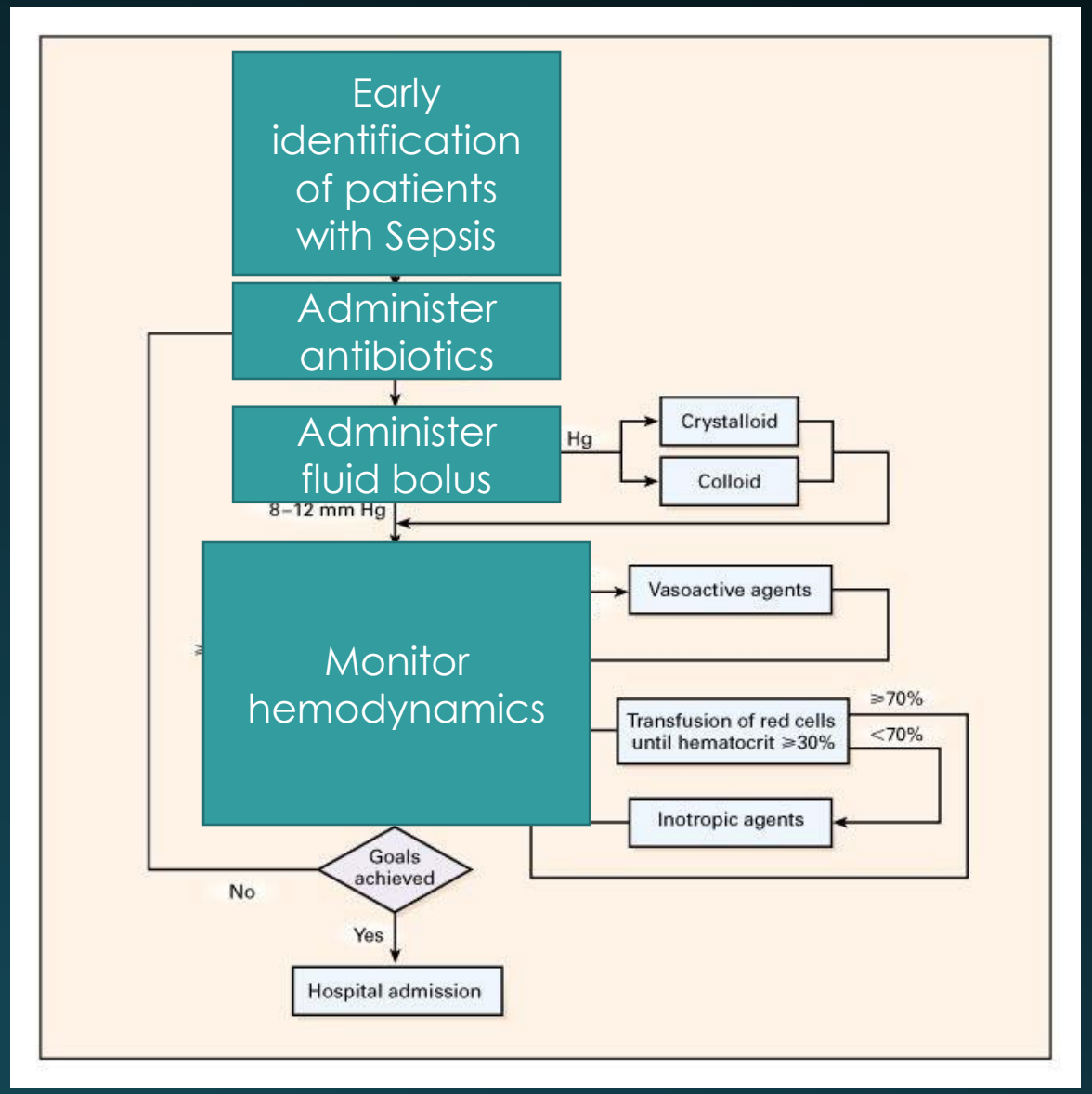
Conclusions

- Protocols
  - streamline medical care
  - reduce variability in care delivered by different individuals
  - decrease errors in both omission and commission
- Usual Care vs. Protocolized care very much depends on experience and training of health care professionals
  - For less experienced trainees, protocols minimize chance for errors and variability
- Management of severe sepsis and septic shock need to be both EARLY and GOAL DIRECTED

Rebuttal

Early Recognition will always be important

- 30 mL/kg fluid bolus
- Lactate clearance
- Early antibiotics



Hemodynamic Monitoring: Jury still out…

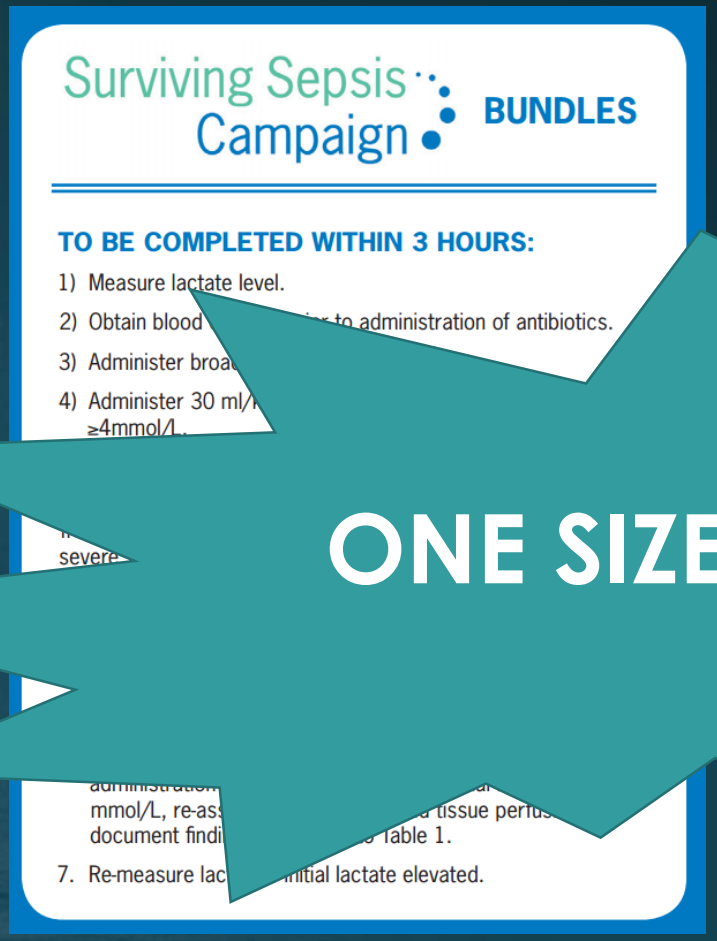
- **VOLUME-CHASERS: Observation of Variation in Fluids Administered and Characterization of Vasopressor Requirements in Shock**
- Multi-center, observational cohort study
- Etermine the variability in shock resuscitation and **modalities used** to determine the amount of fluid and vasopressor administered

DISCOVERY
The Critical Care Research Network

Surviving Sepsis Campaign

- Is not dead…
- Individualize and tailor therapy for patients with comorbidities
- Complexity and heterogeneity of septic shock patients dictates individualized approach to hemodynamic management
- Hemodynamic targets must be further elucidated for the different phases of the disease

Updated 6 Hour Bundles


Surviving Sepsis Campaign BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level.
2) Obtain blood
to administration of antibiotics.
3) Administer broa
4) Administer 30 ml/
≥4mmol/L.
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Table 1.
7. Re-measure lac
initial lactate elevated.

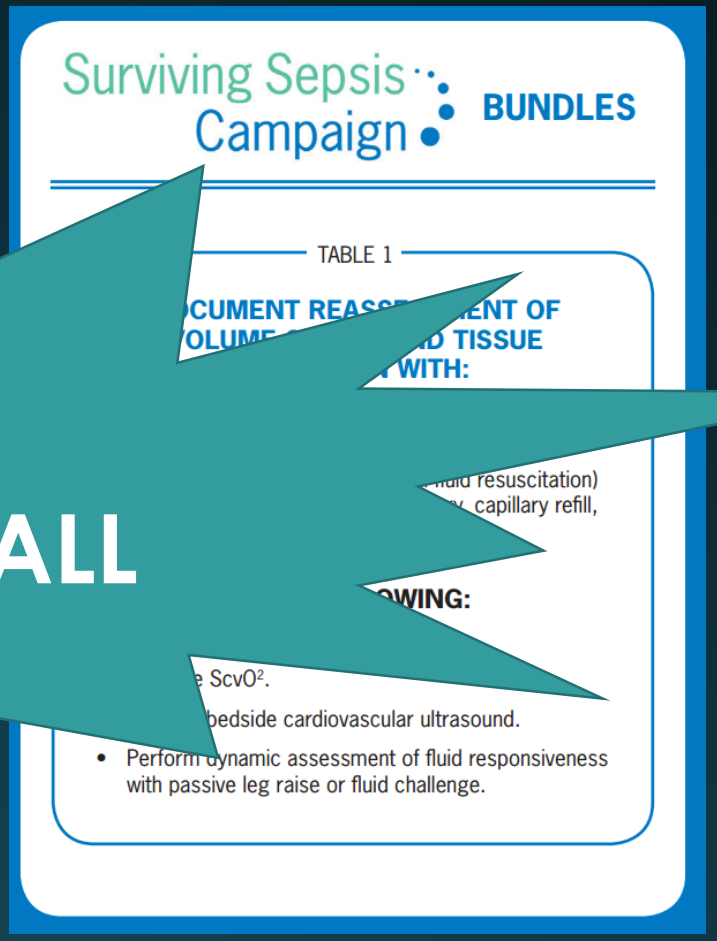
Surviving Sepsis Campaign BUNDLES

TABLE 1

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WITH:

luid resuscitation)
capillary refill,

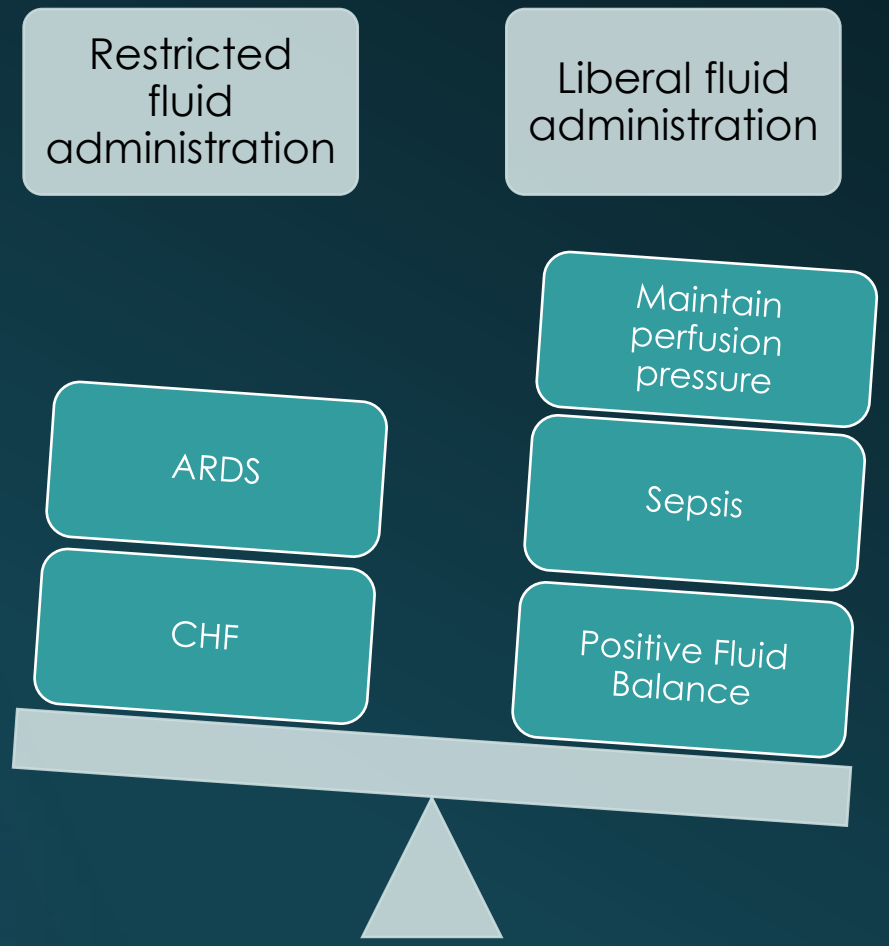
OWING:

e $ScvO^2$.
bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

ONE SIZE ≠ FIT ALL

http://survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf

Individualize Therapy for Comorbidities



Four Phases in the Treatment of Shock

Phase Focus	Salvage	Optimization	Stabilization	Deresuscitation
	Obtain minimal acceptable blood pressure	Provide adequate oxygen availability	Provide organ support	Wean from vasoactive agents
	Perform lifesaving measures	Optimize cardiac output, SvO2, lacate	Minimize complications	Achieve a negative fluid balance

Learning Assessment Questions

- Initial appropriate fluid resuscitation in septic shock includes which of the following?

a) Administer at least 15 mL/kg of crystalloid fluid within the first 3 hours
b) Administer at least 30 mL/kg of colloid fluid within the first 3 hours
c) Administer at least 30 mL/kg of crystalloid fluid within the first 3 hours
d) Administer at least 20 mL/kg of crystalloid fluid with reassessment using passive leg raise

Learning Assessment Questions

- Which of the following elements are NOT included in the Surviving Sepsis Guidelines for initial resuscitation?

a) Utilize static variables over dynamic ones to predict fluid responsiveness
b) Guide resuscitation with lactate clearance
c) Target mean arterial pressure (MAP) of 65 mm Hg in patients requiring vasopressors
d) Use frequent reassessment of hemodynamic status for additional fluids

Thank You!

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