Optimal Goals of Sepsis Resuscitation

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Terminology

ystemic Inflammatory Response Syndrome (SIRS)
- ✓ Temp > 38.3°C or < 36°C
- ✓ HR > 90/min
- ✓ RR > 20 or PaCO2 < 32
- ✓ WBC > 12 or < 4 or Bands > 10%

> TWO out of four criteria
> acute change from baseline

epsis
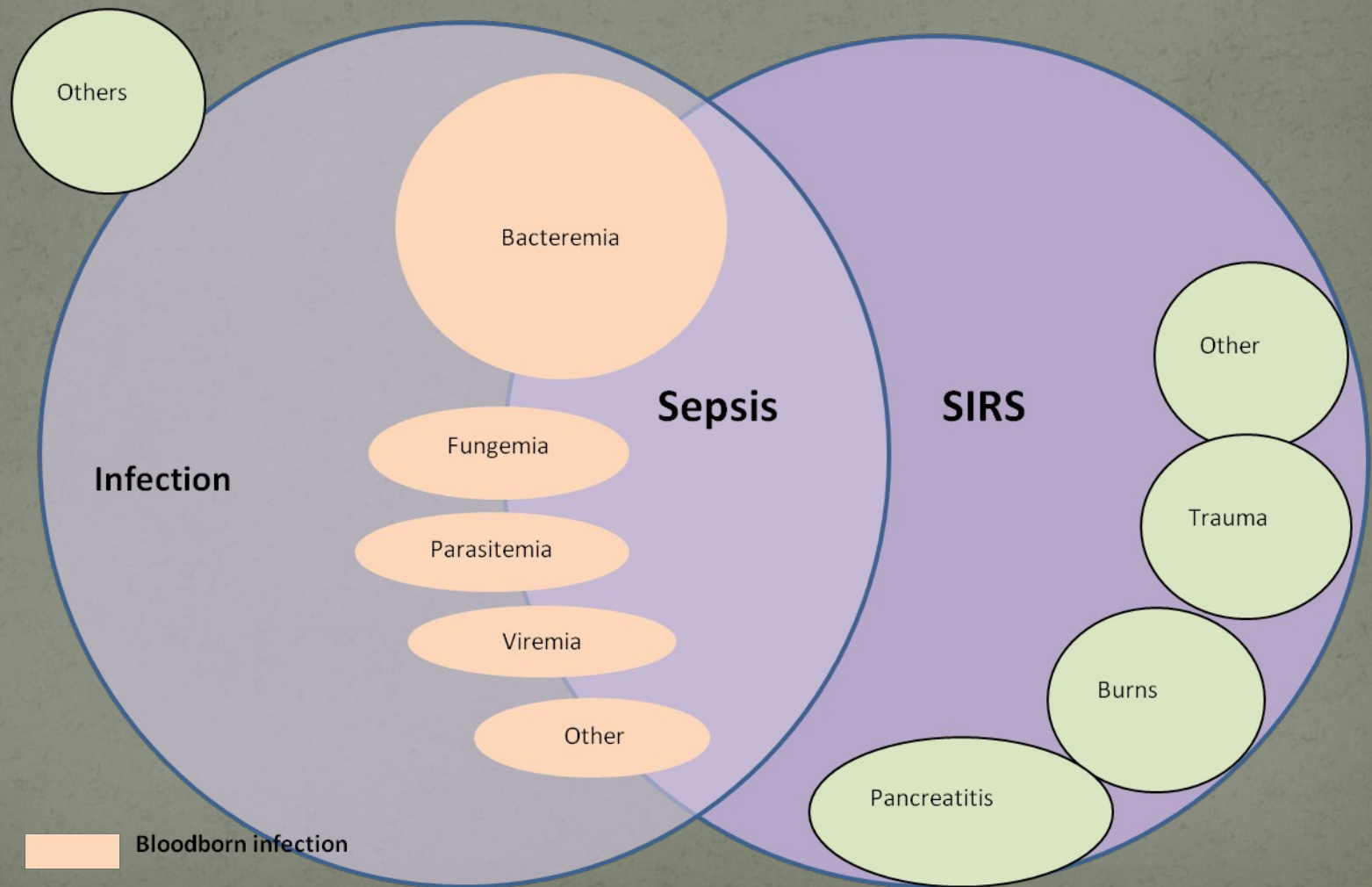- ✓ The systemic inflammatory **response to infection**.

evere Sepsis
- ✓ Organ dysfunction secondary to sepsis.
- ✓ e.g. hypoperfusion, hypotension, acute lung injury, encephalopathy, acute kidney injury, coagulopathy.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

associated with hypoperfusion

SIRS and Sepsis
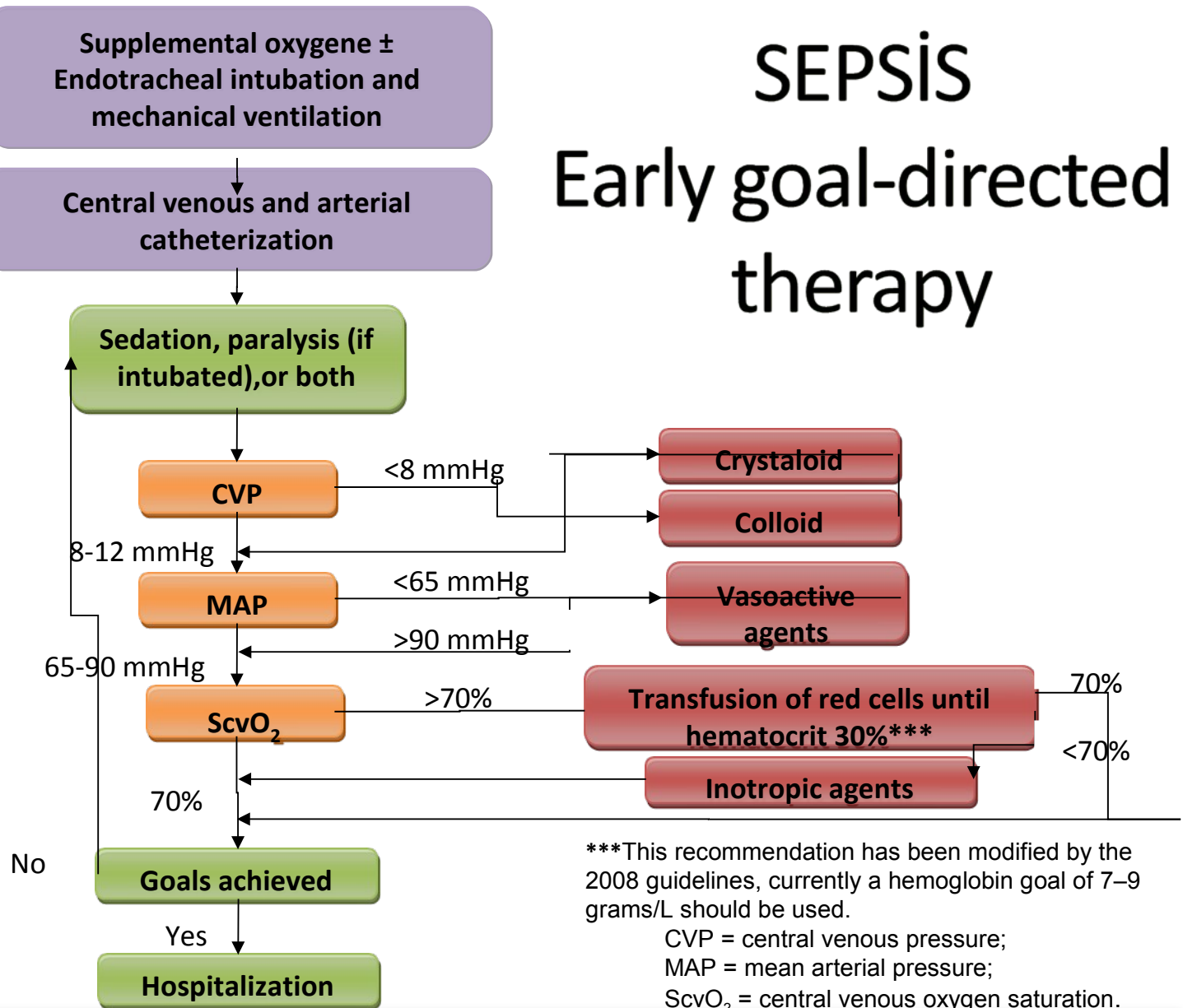
Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine, 345*(19), 1368–1377

Optimal Goals of Sepsis Resuscitation

- **EARLY MANAGEMENT**
  - **Stabilize respiration**
  - **Assess perfusion**
  - **Establish central venous access**
- **Goals of initial resuscitation**
  - **Early goal-directed therapy-targeting venous oxygen saturation**
  - **Early goal-directed therapy - other targets**
  - **Lactate clearance**
  - **Intravenous fluid**
  - **Vasopressors**
  - **Additional therapies**
  - **Ongoing management**

- **CONTROL OF THE SEPTIC FOCUS**
  - **Identification of the septic focus**
  - **Eradication of infection**
  - **Antimicrobial regimen**
- **ADDITIONAL THERAPIES**
  - **Glucocorticoids**
  - **Nutrition**
  - **Intensive insulin therapy**
  - **External cooling**

CASE

- 73yo male patient with diabetes, CAD and hypertension,

- Main complaints—diarrhea for 2 days, has onset of shaking chills, followed by a subjective fever.

- Later presents with altered mental status, fever to 39°C.

- Vital Signs:
  - BP: 80/50 mm Hg
  - HR: 130/min.
  - RR: 34/min
  - Pulse ox: 92%

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Early Management

➤**Stabilize respiration**
➤**Assess perfusion**
➤**Establish central venous access**

Airway

Breathing

Circulation

Supplemental oxygene ± Endotracheal intubation and mechanical ventilation

Perfusion—Restoration of perfusion to the peripheral tissues

Chest X-ray

Arterial Blood Gases

Early Management

➢**Stabilize respiration**

➢**Assess perfusion**

➢**Establish central venous access**

Hypotension

Arterial Line ?

Hypoperfusion signs

include cool, vasoconstricted skin, tachycardia >90/min, obtundation or restlessness, and oliguria or anuria.

Elevated lactate level

Platelet count
INR
Creatinin
Bilirubin

Early Management

- Stabilize respiration
- Assess perfusion
- **Establish central venous access**

Static measures

Establish central venous access
CVP measurement
Internal juguler vein diameter
IVC collapse

Dynamic measures

Radial pulse pressure
Aortic blood flow peak velocity
Brachial artery blood flow velocity
Passive leg raising

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- **SEPSIS GUIDELINES**

- **CONTROL OF THE SEPTIC FOCUS**
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- **ADDITIONAL THERAPIES**
  - Glucocorticoids
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Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Critical Care Medicine 2013;41(2):580–637.

- 48 pages with NO magic bullets
- Very few specific therapies directed at the early stages of sepsis pathophysiology
- Numerous important recommendations (and numerous controversial ones)
- Requires repetitive, complex assessments
- Many interventions are time-sensitive

How do you quickly deliver complex care?

Mobilization and coordination of people and resources.

System-based Approaches to sepsis

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*

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System-based Approaches to sepsis

- ## Early-Goal Directed Therapy (EGDT)
  - ➤ INCLUSION = SEPSIS AND [BP < 90mm Hg after fluid OR Lactate > 4 mmol/L]

Control	Intervention	EGDT
CVP 8-12	Fluids	CVP 8-12
MAP > 65	Vasopressors	MAP > 65
	Transfusions Dobutamine	ScvO2 > 70%
49% mortality		33% mortality

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Used to promote:
1. CVP > 8 as an initial target
2. Use of Svo2 monitoring and use of blood/dobutamine

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System-based Approaches to sepsis

Control		EGDT
49% mortality		33% mortality
Do whatever you normally do.		Use a rigid protocol with multiple dedicated team members

They did not control for the system of care.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, *345*(19), 1368–1377.

A Multidisciplinary Community Hospital Program for Early and Rapid Resuscitation of Shock in Nontrauma Patients

BEFORE (control)

AFTER (protocol)

Do what you normally do. We will be watching.

Screening Protocol,
Educational Initiative,
Shock Team, Treatment Protocols.

Sebat, F., Johnson, D., Musthafa, A. A., Watnik, M., Moore, S., Henry, K., & Saari, M. (2005). A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. *Chest*, *127*(5), 1729–1743.

Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis

BEFORE

AFTER

All physicians, nurses, and patient care technicians in the emergency department and intensive care units received formal order set clinical **education**. Additionally, all hospital floor clinical nurse specialists and advance practice nurses, along with the house staff physicians in these areas, were **in-serviced on the order sets**....These educational endeavors **included training in sepsis pathophysiology, monitoring of central venous pressures, assessment of central venous blood oxygen saturation, and the pharmacotherapy of sepsis**

1. EDUCATION
2. ORDER SET with recommendations and goals for sepsis treatment.

Do whatever it is that you normally do. We will be watching.

Goals during the first six hours of fluid resuscitation

- Central venous pressure 8 to 12 mmHg
- Mean arterial pressure ≥65 mmHg
- Urine output ≥0.5 mL/kg/hour

✚

- Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65% , respectively

Early Goal-Directed Therapy

- The mortality benefit of EGDT is derived from one single-center trial***.

- However, the general application of this mortality benefit from EGDT is unknown.

- Ongoing, are a number of large randomized trials
  - Protocolized Care for Early Septic Shock **[PROCESS]** and
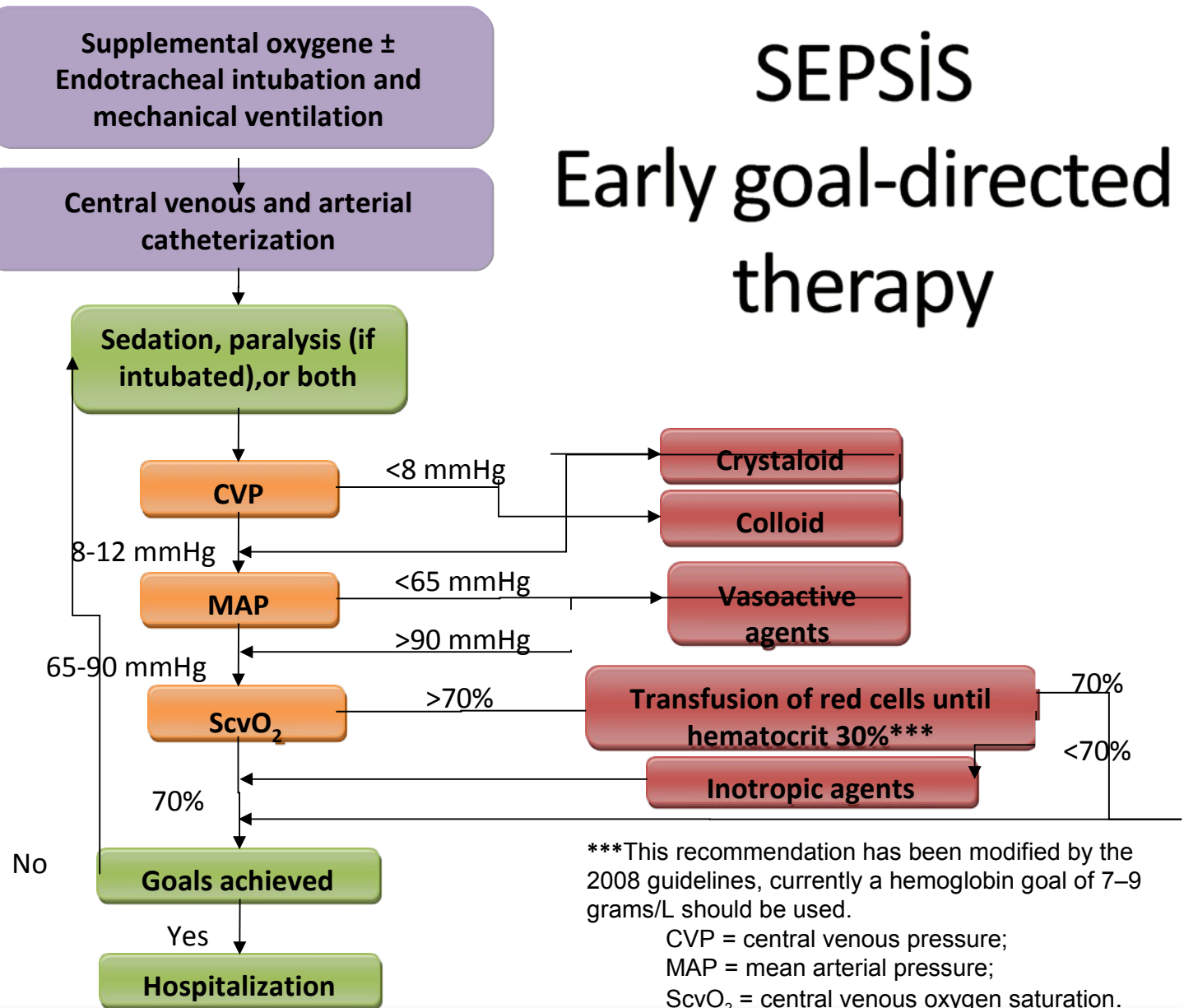 - Australasian Resuscitation In Sepsis Evaluation **[ARISE]** designed to answer this question.

***Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine, 345*(19), 1368–1377.

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SEPSİS
Early goal-directed therapy

Supplemental oxygene ± Endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP —— <8 mmHg —→ **Crystaloid** / **Colloid**

8-12 mmHg

MAP —— <65 mmHg —→ **Vasoactive agents**

>90 mmHg

65-90 mmHg

ScvO₂ —— >70% —→ **Transfusion of red cells until hematocrit 30%*** ** —— 70% / <70% —→ **Inotropic agents**

70%

No

Goals achieved

Yes

Hospitalization

***This recommendation has been modified by the 2008 guidelines, currently a hemoglobin goal of 7–9 grams/L should be used.

CVP = central venous pressure;
MAP = mean arterial pressure;
ScvO₂ = central venous oxygen saturation.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine, 345*(19), 1368–1377

Intravenous fluids

- Relative intravascular hypovolemia is typical and may be severe.

- As an example, early goal-directed therapy required a mean infusion volume of approximately 5 liters within the initial 6 hours of therapy in the EGDT trial.

- Fluid therapy should be administered in well-defined (eg, 500 mL), rapidly infused boluses.

Vazopressors

Drug	Effect on heart rate	Effect on contractility	Arterial constriction effects
Dobutamine	+	+++	- (dilates)
Dopamine	++	++	++
Epinephrine	+++	+++	++
Norepinephrine	++	++	**+++**
Phenylephrine	0	0	+++
Amrinone	+	+++	-- (dilates)

In severe septic shock, we prefer to use norepinephrine in most patients

Phenylephrine (a pure alpha-adrenergic agonist) can be useful when tachycardia or arrhythmias preclude the use of agents with beta-adrenergic activity.

Additional therapies

- When the $ScvO_2$ remains <70% after optimization of intravenous fluid and vasopressor therapy,

⬇

It is reasonable to consider additional therapies, such as **inotropic therapy** or **red blood cell transfusion**

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CONTROL OF THE SEPTIC FOCUS
Source Control

■ No randomized-controlled data

In necrotizing fasciitis, multiple case series have shown improvement with an aggressive operative approach.

Sudarsky LA, Laschinger JC, Coppa GF, Spencer FC. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg 1987;206(5):661–5.

Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: Prompt recognition and aggressive therapy improve survival. J Pediatr Surg 1996;31:1142-6.

Freischlag JA, Ajalat G, Busuttil RW: Treatment of necrotizing soft tissue infections: The need for a new approach. Am J Surg 149:751-755, 1985

Expert opinion supports identifying the source of infection and aggressively managing it when possible.

Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med 2004;32:S513-26

Source Control

- Don't be satisfied with a diagnosis of sepsis and no source.

- If a source exists and is potentially removable, get the ball rolling.
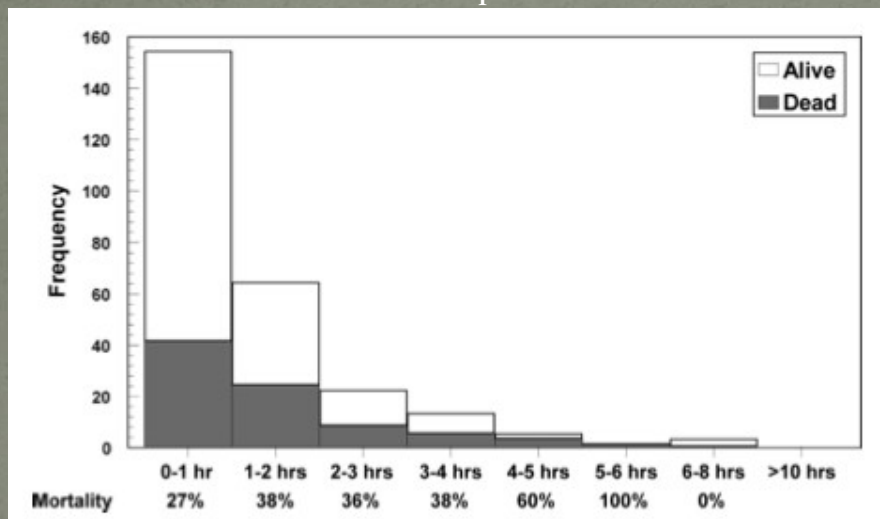
Antibiotics

- Multiple large, observational studies have shown the time to administration of antibiotics to be strongly associated with improve survival.

Antibiotics

- No randomized-controlled data

Time from EDGT qualification to ABX

Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*. Critical Care Medicine 2010;38(4):1045–53.

Time from hypotension to appropriate ABX
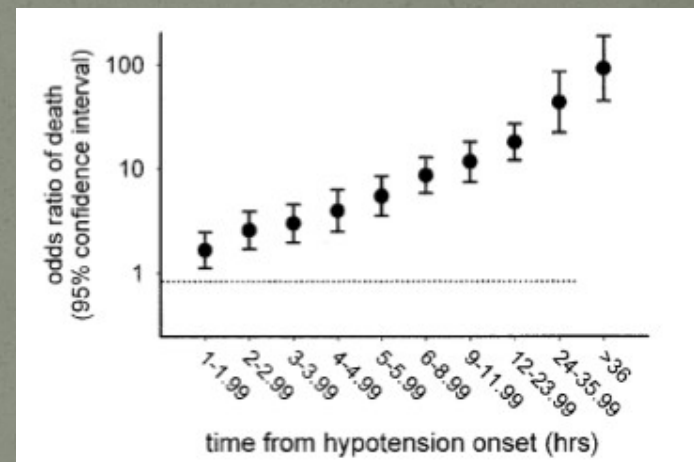
Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Critical Care Medicine 2006;34(6):1589–96.

Does everyone know what to do?

- 73yo male patient with diabetes and hypertension, main complaints—diarrhea for 3 days, has onset of shaking chills, followed by a subjective fever.
- Later presents with altered mental status, fever to 39°C.
- Vital Signs:
  - BP: 80/50 mm Hg
  - HR: 130/min.
  - RR: 34/min
  - Pulse ox: 92%

Acute Phase

- Identify Sepsis as early as possible

- Broad spectrum antibiotics and identify source(s) of infection

- Identify severity: Vitals, mental status, urine output, **LACTATE**, other labs.

- Volume and physiologic resuscitation protocols with GOALS.

- Tweak your system so these things happen **FAST**

Sepsis Identification

- Train all providers

- Vital sign/Laboratory alerting systems

- ?Biomarkers

Lactate

Evidence is clear that lactate levels are predictive of death and MODS

Clearance of lactate is associated with improved survival

Algorithms of care based on lactate clearance appear to work as well or better than other approaches.

Jones AE, Shapiro NI, Trzeciak S, et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial. JAMA: The Journal of the American Medical Association 2010;303(8):739–46.

Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. American Journal of Respiratory and Critical Care Medicine 2010;182(6):752–61.

Goals in resuscitation

Early, quantitative resuscitation goals vs. standard care have resulted in improved mortality

The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis *.
Jones, Alan E. MD; Brown, Michael D. MD, MSc; Trzeciak, Stephen MD, MPH; Shapiro, Nathan I. MD, MPH; Garrett, John S. MD;
Heffner, Alan C. MD; Kline, Jeffrey A. MD; on behalf of the Emergency Medicine Shock Research Network investigators
Critical Care Medicine. 36(10):2734-2739, October 2008.

Goals in resuscitation

- Initial fluid resuscitation:
- CVP 8-12, MAP > 65, Urine output 0.5 mL/kg/hr, ScVO2 70% and Lactate Clearance.

- Give enough volume to maximize stroke volume. Start with 20cc/kg in most patients. Goal?
- Give vasopressors to raise the MAP enough to maintain adequate end-organ perfusion.
- Assessment of Cardiac Function
- Urine output and lactate clearance are nice global indicators of success.

Resuscitation

- Crystalloids are favored as the initial fluid
- Hydroxyethyl starches (HAES) are likely harmful
- Albumin may have a role, particularly if a lot of fluid is given
- A lower Hb target (~7) is generally accepted

Summary

- System-based strategies are effective for improving sepsis care
- Processes should aim to:
  - ✓ Identify patients early and identify the severity of sepsis
  - ✓ Quickly administer appropriate antibiotics and source control
  - ✓ Establish institutional goals for physiologic resuscitation
  - ✓ Multidisciplinary care to ensure compliance